# Innate immune mechanisms in invertebrates: Insights into the Toll pathway, the Imd pathway, and the complement system

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## SCIENTIFIC ENVIRONMENT

The work presented in this thesis was performed in the group of Prof. Dr. Andreas Hejnol, at the Sars International Centre for Marine Molecular Biology in the University of Bergen (Norway) from 2016 to 2019, and at the Department of Biological Sciences from the University of Bergen (Norway) from 2019 to 2021.

This thesis is part of the PhD program of the Department of Biological Sciences of the University of Bergen.

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When people ask me what will I miss the most when I leave Bergen, my immediate answer is the people (yes, the drinking water and the landscape are nice, but the people are even better). Therefore, I would like to write a few lines – probably shorter than what they deserve – thanking all the people that walked with me on the journey of my PhD, sharing the good but also the less good moments.

First of all, I would like to give a big thanks to Andreas Hejnol for giving me the opportunity to do the PhD in his lab, for his guidance, supervision, and discussions, especially in the last stages of my PhD. In my job interview, I was asked what I was expecting from my PhD and my supervisor. My answer was that I wanted to learn. I honestly think you have greatly fulfilled my expectations.

I am also infinitely grateful to Carmen. She started being my "mentor", showing me around in the lab, but soon it became much more. I cannot say with words how happy I am to have worked with you, learning a lot, but also having a lot of fun.

I would also like to thank my other co-authors, especially Tsai and Ludwik, for their contributions and fruitful discussions.

I also want to thank Daniel, who, patiently, introduced me to bioinformatics. For someone that was afraid of breaking the computer every time opened the terminal, this means a lot.

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I would also like to thank Sars and BIO administrations for taking care of the "boring" bureaucratic stuff, allowing me to focus entirely on my projects and for making a nice work environment. The thanks are also extended to other co-workers both in Sars and BIO, for creating such a nice environment to work.

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I would also like to thank to all the people with whom I had the luck to share my home in Bergen. Among them, I want to specially mention Aish, Carine, James, Océane, Paula, and Tarja. Thanks for all the good and crazy moments that made Bergen a bit brighter, especially during the dark and rainy winters.

However, amongst all my housemates, I would like to highlight my big thanks to Clemens. First my housemate, then friend and partner. You have supported me during all this journey, especially in the most difficult times. I love you.

Now, please forgive I will switch to spanish. También me gustaría dar las gracias a mis padres y a mi hermana. Por apoyar y animarme en mi decisión de marcharme a Bergen; y por seguir apoyándome durante todo este tiempo. Porque se que tanto mi hermana como mi madre están muy contentas por mí. Y que mi padre lo estaría. Os quiero.

## Abstract

The innate immune system is the first line of defense against pathogens. This system is equipped with receptors, named Pattern Recognition Receptors (PRRs), that recognize a broad set of molecules present in pathogens, known as Pathogen-Associated Molecular Patterns (PAMPs). These receptors are present in many immune pathways, such as the Toll- or the Imd pathways, but also in other immune mechanisms as the complement system or lectins. The Toll- and the Imd pathways are pathways that trigger the production of antimicrobial peptides, whereas the complement system and lectins are involved in opsonization, phagocytosis and pathogen killing. This thesis aimed to investigate the evolution of innate immunity and, more specifically, the evolution of these pathways and systems in invertebrates. In order to fulfill this aim, I divided this thesis in two studies. First, I investigated the evolution of the Toll receptors (TLRs), which are the PRR involved in the Toll pathway; and second, I studied the presence and role of the aforementioned pathways and systems in the nemertean *Lineus ruber,* a member of the spiralian clade. Both studies combine *in silico* and *wet-lab* approaches in order to accomplish the aims.

In my first study, I performed transcriptomic and genomic surveys in order to identify TLRs in 45 invertebrate species. The results show the presence of TLRs in 24 of these 45 species, being present in very variable numbers. Moreover, I performed phylogenetic analyses in order to reconstruct the evolution of TLR, showing that all metazoan TLRs originated from a single proto-TLR present in the planulozoan (cnidarian + bilaterian) last common ancestor. This gene later likely duplicated and diversified giving raise to TLRs that group in three clades. Further duplications and losses shaped the distribution of TLRs across the phylogeny, generating the extant diversity of TLRs in metazoans. Additionally, as TLRs are involved both in immunity and development, stage-specific transcriptomic analyses of four protostome species and *in situ* hybridization in the brachiopod *Terebratalia transversa* were performed, showing that TLRs are expressed in this species during ontogeny.

In my second study, I investigated the presence and function of the Toll pathway, the Imd pathway, the complement system, and lectins in the nemertean *Lineus ruber.* Transcriptomic surveys in *Lineus ruber* show that components of these pathways and

systems are present in this species. Moreover, *in situ* hybridization shows that lectins are expressed in the blood, the nervous system, and the gut. Additionally, in order to study the function of some of the components of these pathways and systems, I performed an immune challenging assay, in which *Lineus ruber* specimens were exposed to gram negative bacteria. Differential expression of TLRs, *imd, C3-1,* and lectins was tested, showing that all these genes, except for one TLR and *imd*, are upregulated upon gram-negative infection. The earliest immune response was detected at 6 hours of infection, with the upregulation of *Lineus ruber TLRβ1* and *TLRβ2.* Additionally, a stronger upregulation of another TLR, *TLRα3,* occurred at 12 hours of infection, simultaneously to the upregulation of lectins. Upregulation of the complement gene *C3-1* was first observed at 24h of infection.

Altogether, the two studies that compose my thesis provide insights into how immunity functions in invertebrates and how this system has evolved.

## LIST OF PUBLICATIONS

### PAPERS INCLUDED IN THIS THESIS

Manuscripts included in this thesis are the following:

**Paper I:** Orús-Alcalde A, Lu TM, Hejnol A. The evolution of the metazoan Toll receptor family and its expression during protostome development. Available in BioRxiv. Under review in BMC Ecology and Evolution. doi: 10.1101/2021.02.01.429095.

**Paper II:** Orús-Alcalde A, Hejnol A. The Toll pathway, the complement system and lectins are likely involved in immunity in the nemertean Lineus ruber.

### ADDITIONAL PAPERS

During my PhD, I have also contributed to:

**Paper III:** Gasiorowski L, Børve A, Cherneva IA, Orús-Alcalde A, Hejnol A. Gene expression in the developing nemertean brain indicates convergent evolution of complex brains in Spiralia. Available in BioRxiv. Under review in BMC Biology. doi: 10.1101/2021.03.29.437382.

**Paper IV:** Andrikou C, Orús-Alcalde A, Aguilera F, Sebé-Pedrós A, Hejnol A. Morphological, molecular, and functional characterization of priapulid hemolymph and evolutionary implications. Manuscript in preparation.

## AUTHOR CONTRIBUTIONS

I hereby declare that I have written this thesis myself, with the help and contribution of other people in form of comments and formal corrections. I also declare that I have written Paper I and Paper II, discussing and having comments and corrections from my co-authors, but also from Dr. Carmen Andrikou, postdoc in Andreas Hejnol lab.

In the following paragraphs I will detail the contribution of other authors and my contribution to Papers I and II.

**Paper I:** Andrea Orús-Alcalde (me), Dr. Tsai-Ming Lu and Prof. Dr. Andreas Hejnol are the authors of this paper. I performed the genome and transcriptome surveys; the phylogenetic analyses; the interpretation of the data obtained from the transcriptome stage-specific analyses; and the gene cloning, probe synthesis and whole mount *in situ* hybridization; and imaging. Dr. Tsai-Ming Lu performed the transcriptome stage-specific analyses. Prof. Dr. Andreas Hejnol was involved in the design and supervision of the project.

**Paper II:** Andrea Orús-Alcalde (me) and Prof. Dr. Andreas Hejnol are the authors of this paper. I performed the surveys in the *Lineus ruber* transcriptome and the *Notospermus geniculatus* genome; the gene cloning, probe synthesis, and whole mount *in situ* hybridization; imaging; and the immune challenge experiments, including the infection of the animals, RNA extraction, cDNA synthesis, quantitative-real time PCRs, and data analyses. Prof. Dr. Andreas Hejnol was involved in the design and supervision of the project.

Additionally, during my PhD, I also contributed to two other publications (Papers III and IV).

**Paper III:** The authors of this paper are Dr. Ludwik Gasiorowski, Aina Børve, Irina Cherneva, Andrea Orús-Alcalde (me) and Prof. Dr. Andreas Hejnol. This paper was written by Dr. Ludwik Gasiorowski, with comments and corrections from the remaining authors. For this paper, together with Dr. Ludwik Gasiorowski, I searched for candidate genes and cloned them. Furthermore, I performed antibody and EdU stainings.

**Paper IV:** The authors of this paper are Dr. Carmen Andrikou, Andrea Orús-Alcalde (me), Dr. Arnau Sebé-Pedrós, and Prof. Dr. Andreas Hejnol. This paper is being written by Dr. Carmen Andrikou. For this paper, together with Dr. Carmen Andrikou, I have collected *Priapulus caudatus;* fixed samples; performed whole mount *in situ* hybridization; phagocytosis assays; immunohistochemistry; EdU stainings; FACS sorting; and imaging.

# CONTENTS

# CHAPTER 1: INTRODUCTION

## 1.1 PATHOGENS

A disease is an alteration of the normal state of an organism that impairs the normal functioning of the organism, affecting humans, animals, or plants. Pathogens are living agents, including viruses, bacteria, protists, and parasites, that are often the cause of disease. Before the discovery and acceptance of the existence of microorganisms and their role in diseases, they were thought to be caused by supernatural phenomena (e.g. God, magic, evil spirits) or by geological and astronomical events (e.g. earthquakes, comets) that spread poisonous vapors in the air (Karamanou et al., 2012). Microorganisms were discovered by Antoni Van Leeuwenhoek in 1676, when he observed what he called "animacules", which are bacteria and other microorganisms, in water and infusions with one of his self-made microscopes (Porter, 1976; Van Leeuwenhoek, 1677). However, it was not until the late 19th century, when Louis Pasteur refuted the theory of spontaneous generation and proved that microorganisms are ubiquitous (Ariatti and Comtois, 1993; Karamanou et al., 2012; Pasteur, 1860). Later in that century, Robert Koch established a direct relationship between some microorganisms and the disease they were causing (Cambau and Drancourt, 2014; Karamanou et al., 2012).

Today, we know that pathogens are numerous and some reports even suggest that there could be more pathogenic species than free-living species (Windsor, 1998). Furthermore, pathogens normally infect more than one species, whereas a species can also be the host of multiple pathogen species. This entails a serious threat for animals and plants, which are exposed to the attack of multiple pathogens that can cause serious diseases and death. For instance, in the 13th century, the bubonic plague, caused by the bacteria *Yersinia pestis*, cost the life of approximately 20 million people (McEvedy, 1988); and the Spanish flu, caused by H1N1 influenza A virus, caused approximately 50 million human deaths between 1918 and 1919 (Radusin, 2012). Currently, protozoans belonging to several *Plasmodium* species are responsible for malaria disease, which killed 409.000 people only in 2019 (World Health Organization, 2020); and SARS-CoV-2 virus has killed over 3 million people since March 2020. In other animals, pathogens also trigger deathly diseases, generating, in some cases, great losses in human economy. For instance, the crustacean *Lepeophtheirus salmonis* (salmon lice) infests salmons (Skilbrei et al., 2013), while QPX (Quahog Parasite Unknown) is a parasite of clams (Whyte et al., 1994), causing both of them the death of a large number of salmons and clams, respectively. In order to counter-attack pathogens, animals and plants have developed defense mechanisms, known as the immune system. Furthermore, pathogens affecting bacteria (e.g. the bacteriophage T4 virus attacks *Escherichia coli*) and immune genes in bacteria (e.g. *cas* genes) have been identified (Barrangou et al., 2007; Hadas et al., 1997), suggesting that immunity is a very ancient mechanism. Therefore, immunity is an important mechanism present in living organisms to be able to defend themselves against pathogens.

## 1.2 Pathogen entrance and types of immunity

In order to avoid the entrance of pathogens into the organism, plants and animals have a series of physical barriers. For instance, plants have cuticles that not only prevent the entrance of microorganisms to the plant but also prevent microbe proliferation on their surface (Doughari, 2015; Zhang et al., 2019). In some plants (e.g. trees, bushes), the accumulation of lignin in the cell walls, confers rigidity and an extra layer that is very difficult to trespass by insects or microorganisms (Doughari, 2015). Moreover, many plants have developed structures, such as stomatal guard cells, trichomes, or thorns to avoid parasites or predators (Doughari, 2015; Melotto et al., 2006). Furthermore, animals have an epidermis covered by mucus or other structures (e.g. feathers, scales, cuticles, hair) that prevent pathogen entrance into the organism.

However, if a pathogen manages to overcome these barriers, the organism employs other immune mechanisms to defend itself. Immunity is a mechanism to distinguish between self and non-self in order to eliminate pathogens. In animals, this system is composed of humoral (proteins present in liquids and extracellular compartments) and cellular components (Turvey and Broide, 2010). Once these extracellular proteins and cells encounter pathogens, they trigger immune processes, such as agglutination, melanization, or phagocytosis, to isolate, kill and destroy the invading pathogens (Fisher and DiNuzzo, 1991; Nagl et al., 2002; Yassine et al., 2012). These immune mechanisms are present in many organs and systems, including the blood (Lv et al., 2017; Melcarne et al., 2019; Toubiana et al., 2013), the epidermis (Bosch et al., 2009;

Pujol et al., 2008; Rakers et al., 2013), the gut and respiratory system (Garcia-Garcia et al., 2013; Gendrin et al., 2013; Lu et al., 2013; Lv et al., 2017; Marques and Boneca, 2011; Toubiana et al., 2013), or the nervous system and sensory structures (Gendrin et al., 2013; Yang et al., 2010). Immunity is classified into innate immunity and adaptive immunity. Innate immunity is an immediate, non-specific response to pathogen invasion that is present in all animals. Adaptive immunity is constituted by molecules with immune memory and high diversification potential, in order to provide a specific immune response for the attacking pathogen. Since antibodies, which are highly variable immune molecules, are present in vertebrates but are lacking in invertebrates, the adaptive immune system is thought to be specific for vertebrates. However, several authors are challenging this view, showing that invertebrate immune systems could also have memory and other proteins with high diversification potential, suggesting that an adaptive-like immune system could be present in these organisms (Brites et al., 2008; Cerenius and Soderhall, 2013; Cong et al., 2008; Kurtz and Franz, 2003; Pancer, 2000; Portela et al., 2013; Sadd and Schmid-Hempel, 2006; Watson, 2005; Zhang, 2004).

## 1.3 Conserved mechanisms in innate immune systems

Upon pathogen entrance into the organism, the innate immune system is activated. As mentioned above, innate immunity is an unspecific response, meaning that a relatively small set of protein receptors can induce a generic response towards the invading pathogens. This is possible because innate immunity is equipped with Pattern Recognition Receptors (PRRs), which are transmembrane and extracellular receptors that recognize Pathogen-Associated Molecular Patterns (PAMPs), a broad range of molecules that are conserved in microorganisms but are not present in the host (Janeway, 1992, 1989). Furthermore, PRRs can also detect molecules called Damage-Associated Molecular Patterns (DAMPs), which are produced by the host cells only under defensive situations. These receptors are present in the main pathways and systems involved in innate immunity, such as the Toll pathway (Toll-like receptors), the Imd pathway (Peptidoglycan recognition protein receptors). Furthermore, extracellular proteins, such as the lectins involved in complement activation (e.g. ficolins or mannose-binding lectins), but also other types of lectins (e.g. galectins), are also PRRs.

### 1.3.1 The toll pathway

The Toll pathway is a pathway involved in immunity and development in metazoans (Aderem and Ulevitch, 2000; Anthoney et al., 2018; Barton, 2003; Brennan and Gilmore, 2018; Coscia et al., 2011; Hoffmann and Reichhart, 2002; Medzhitov, 2001; Nie et al., 2018; Valanne et al., 2011). The first component of this pathway to be identified was the *Drosophila Toll* receptor, due to its role in the establishment of dorsoventral polarity in early embryonic development (Anderson et al., 1985; Anderson and Nüsslein-Volhard, 1984). A decade after, the Toll pathway was discovered to be involved both in *Drosophila* and human immunity (Lemaitre et al., 1996; Medzhitov et al., 1997). Currently, it is known that *Drosophila melanogaster* and *Homo sapiens* have 9 (Anderson and Nüsslein-Volhard, 1984; Tauszig et al., 2000) and 10 TLRs (Medzhitov et al., 1997; Rock et al., 1998), respectively; but many other TLRs and other components of this pathway have also been identified across metazoans. In vertebrates and *Drosophila,* this pathway has been extensively studied and reviewed (Aderem and Ulevitch, 2000; Anthoney et al., 2018; Barak et al., 2014; Barton, 2003; Kawai and Akira, 2010; Lindsay and Wasserman, 2014; Valanne et al., 2011).

In vertebrates and *Drosophila*, the Toll pathway is activated in response to bacteria, fungi, and viral infection (Chowdhury et al., 2019; Deepika et al., 2020; Li et al., 2013; Lund et al., 2003; Schwandner et al., 1999; Tauszig-Delamasure et al., 2002; Underhill et al., 1999; Zambon et al., 2005). Furthermore, the Toll pathway also plays a role in immunity in cnidarians (Bosch et al., 2009; Brennan et al., 2017; Franzenburg et al., 2012), mollusks (Priyathilaka et al., 2019; Ren et al., 2017, 2016; Wang et al., 2016; Zhang et al., 2011, 2013), annelids (Prochazkova et al., 2019; Škanta et al., 2013), and echinoderms (Lu et al., 2013; Russo et al., 2015). Moreover, during arthropod ontogeny, besides being involved in the establishment of dorsoventral polarity (Anderson et al., 1985; Anderson and Nüsslein-Volhard, 1984), this pathway plays a role in axis elongation (Benton et al., 2016; Paré et al., 2014), segmentation (Eldon et al., 1994), muscle and neuronal development (Halfon et al., 1995; Ward et al., 2015), heart formation (Wang et al., 2005) and wing formation (Byun et al., 2019; Meyer et al., 2014); whereas in vertebrates, the Toll pathway plays a role in nervous system development (Hung et al., 2018; Kaul et al., 2012; Rolls et al., 2007; Shechter et al., 2008). Additionally, the Toll pathway is involved in the development of cnidarians

(Brennan et al., 2017). Nevertheless, although components of the Toll pathway are expressed during mollusk and annelid development (Priyathilaka et al., 2019; Prochazkova et al., 2019), their roles in immunity and/or development have not been elucidated.

The receptors of the Toll pathway are the Toll receptors (TLRs) (Anderson et al., 1985; Lemaitre et al., 1996; Medzhitov et al., 1997; Rock et al., 1998). TLRs are type I transmembrane proteins characterized by the presence of one or more extracellular leucine-rich repeat (LRR) domains, a transmembrane domain (TM), and an intracellular Toll/IL-1 (TIR) domain (Figure 1.1A) (Hashimoto et al., 1988; Schneider et al., 1991). The region formed by the LRR domains is responsible for pathogen detection; while the TIR domain is involved in signal transduction (Bell et al., 2003; Kobe and Kajava, 2001; Schneider et al., 1991). LRR domains are formed by 22-26 amino acids, in which multiple leucine residues are found (Hashimoto et al., 1988). Furthermore, all TLRs contain at least one LRR domain with cysteine residues in the C-terminal area of the domain (LRRCT), but only some TLRs contain LRR domain with cysteine residues in the N-terminal area of the domain (LRRNT) (Medzhitov, 2001; Rock et al., 1998; Schneider et al., 1991). According to the structure of the LRR region, TLRs are classified in vertebrate-type or single cysteine cluster (V-type/scc), and protostome-type or multiple cysteine cluster (P-type/mcc) (Figure 1.1A) (Hibino et al., 2006). Since vertebrates only have V-type/scc TLRs and the *Drosophila melanogaster* and *Caenorhabditis elegans* TLRs are classified as P-type/mcc type (except for the *Drosophila* Toll9), V-type/scc TLRs and P-type/mcc have been associated to deuterostomes and protostomes, respectively. However, in the last decade, sequencing of genomes and transcriptomes has shown the presence of V-type/scc TLRs in protostomes and P-type TLRs in invertebrate deuterostomes, demonstrating that these TLRs types are not restricted only to deuterostomes or protostomes, respectively (Brennan and Gilmore, 2018; Davidson et al., 2008; Halanych and Kocot, 2014; Nie et al., 2018). Furthermore, TLR-like proteins containing only LRR and transmembrane domains (LRR-only) or the transmembrane and the TIR domain (TIR-only) (Figure 1.1A) are also involved in immunity in metazoans (Bosch et al., 2009; Brennan and Gilmore, 2018; Gauthier et al., 2010; Kamm et al., 2019; Leulier and Lemaitre, 2008; Liu et al., 2020; Nie et al., 2018; Peiris et al., 2014; Poole and Weis, 2014; Wiens et al., 2006). However, only proteins constituted by the LRR domains, a transmembrane domain, and a TIR are considered TLRs (Brennan and Gilmore, 2018).

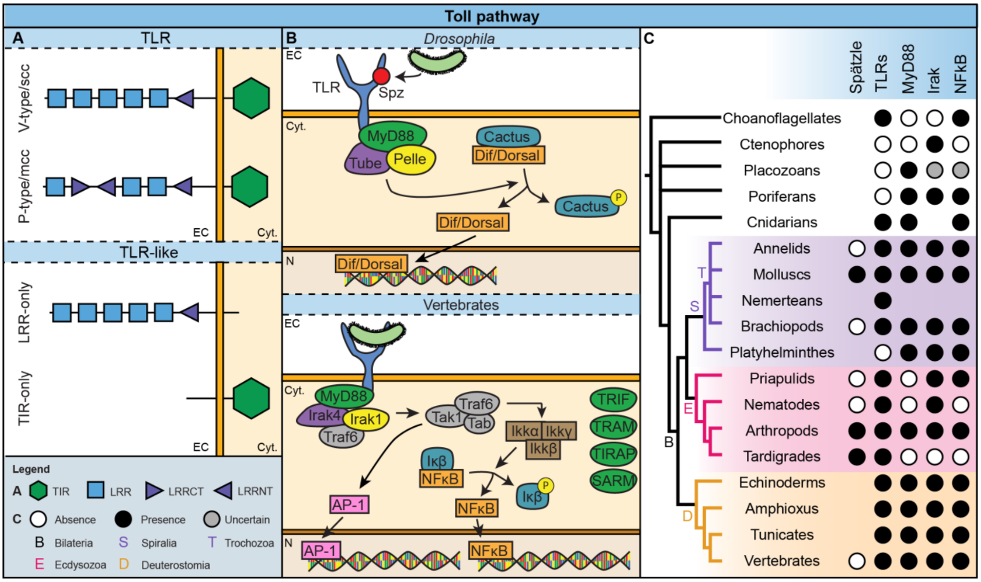


**Figure 1.1 The Toll pathway in metazoans. A.** Domain architecture of Toll-like receptors (TLR) and Toll-like receptors-like (TLR-like). **B.** Toll pathway signaling cascade in *Drosophila* and vertebrates. **C.** Presence and absence of components of the Toll pathway in metazoans. Abbreviations: AP-1: Activator protein 1; Cyt: Cytoplasm; EC: Extracellular space; LRR: Leucine-rich repeat; mcc: multiple cysteine cluster; N: Nucleus; P-type: Protostome-type; SARM: Sterile-alpha and Armadillo motif-containing protein; scc: single cysteine cluster; Spz: Spätzle; TIR: Toll/IL-1 receptor domain; TIRAP: Toll/interleukin-1 receptor domain-containing adapter protein; TLR: Toll receptor; TRAM: TRIF-related adaptor molecule; TRIF: TIR-domain-containing adapter-inducing interferon-β; V-type: Vertebrate-type. This figure is a combination of figure 1 in Paper I (for plate A) and figure 1 in Paper II (for plates B and C). References: A. (Brennan and Gilmore, 2018; Leulier and Lemaitre, 2008). B. (Barton, 2003; Hoffmann and Reichhart, 2002; Lindsay and Wasserman, 2014; Valanne et al., 2011). C. (Anderson et al., 1985; Anderson and Nüsslein-Volhard, 1984; Azumi et al., 2003; Bosch et al., 2009; Brennan et al., 2017; Davidson et al., 2008; Denoeud et al., 2010; Forsthoefel et al., 2012; Gauthier et al., 2010; Gerdol et al., 2018; Gerdol and Venier, 2015; Halanych and Kocot, 2014; Hibino et al., 2006; Ji et al., 2018; Kamm et al., 2019; Leclère et al., 2019; Lemaitre et al., 1996; Luo et al., 2018; Mapalo et al., 2020; Medzhitov et al., 1998, 1997; Palmer and Jiggins, 2015; Peiris et al., 2014; Poole and Weis, 2014; Ren et al., 2017, 2016; Richter et al., 2018; Rock et al., 1998; Sasaki et al., 2009; Sullivan et al., 2007; Tassia et al., 2017; Toubiana et al., 2014; Traylor-Knowles et al., 2019; Valanne et al., 2011; Wesche et al., 1997; Wiens et al., 2006, 2005; Williams et al., 2018; Yu et al., 2015; Yuan et al., 2009)

In vertebrates, activation of the Toll pathway occurs by the direct binding of TLRs to PAMPs (Gay and Gangloff, 2007). In *Drosophila,* however, this is an indirect process, in which PAMPs are recognized by other PRR receptors – PGRP-SA, PGRP-SD, GNBP1, and GNBP 3 (Bischoff et al., 2004; Gobert, 2003; Gottar et al., 2006; Michel et al., 2001) – that trigger proteolytic cascades that culminate with the cleavage of Spätzle by the Spätzle-processing enzyme (SPE) (Jang et al., 2006). Once Spätzle is cleaved, TLRs recognize it and the Toll pathway is activated (Chowdhury et al., 2019; Weber et al., 2003). During development in *Drosophila*, Spätzle also acts as the ligand of the TLRs, although the cleavage of this protein is conducted by the Easter enzyme as a result of a different proteolytic cascade (DeLotto and DeLotto, 1998; Morisato and Anderson, 1994; Weber et al., 2003).

Upon ligand recognition, TLRs are activated and trigger a similar signaling cascade in *Drosophila* and vertebrates. Names for the *Drosophila* and the vertebrate orthologs are different (except for MyD88). Thus, through the following section, when mentioning them, the first ortholog refers to the *Drosophila* protein, while the second corresponds to the vertebrate ortholog. Once TLRs are activated, they interact with the adaptor MyD88 by their TIR domains (Figure 1.1B) (Horng and Medzhitov, 2001; Medzhitov et al., 1998). This leads to the recruitment of the kinase proteins Tube/Irak4 and Pelle/Irak1, which interact between them and MyD88 by the DEATH domains present in these proteins (Schiffmann et al., 1999; Sun et al., 2002; Wesche et al., 1997). When the Toll pathway is not activated, Cactus/IκB inhibits the entrance to the nucleus of the *Drosophila* transcription factors Dorsal and Diff, and their vertebrate ortholog NFκB-p65. Upon Toll pathway activation and recruitment of the kinase proteins, a phosphorylation cascade triggers the degradation of Cactus/IκB, leading to the translocation of these transcription factors into the nucleus (Aderem and Ulevitch, 2000; Lemaitre et al., 1996; Valanne et al., 2011). Furthermore, in vertebrates, TLRs also trigger, by another branch of downstream effectors, the translocation of the transcription factors AP-1 to the nucleus (Valanne et al., 2011). These transcription factors induce the expression of other immune-related genes, such as antimicrobial peptides and cytokines. (Akira et al., 2006; De Gregorio, 2002; Lemaitre et al., 1996; Rutschmann et al., 2000; Valanne et al., 2011). Additionally, in vertebrates, the TLRs can also associate with other adaptors (TRIF, TRAM, and TIRAP) and trigger a MyD88-independent cascade, promoting the entrance of the transcription factor interferon regulatory factor (IRF) to the nucleus (Kawai et al., 2001). Orthologs of these adaptors have not been found in invertebrates. Furthermore, another adaptor, the SARM protein, which is present both in vertebrates and invertebrates, is involved in Toll receptor pathway inhibition (Belinda et al., 2008; Carty et al., 2006).

Moreover, the sequencing of invertebrate genomes and transcriptomes over the last two decades has made possible the identification of many components of the Toll pathway in species across the metazoan tree (Figure 1.1C). Within ecdysozoans, the presence of Spätzle has been detected in multiple arthropods and tardigrades (Mapalo et al., 2020; Morisato and Anderson, 1994). Moreover, in spiralians, Spätzle has been suggested to be present in the clam *Paphia undulate* (Yu et al., 2015). Nonetheless, this protein is not present in other metazoans, including the remaining mollusks that have been surveyed for this protein (Davidson et al., 2008; Gerdol et al., 2018; Gerdol and Venier, 2015; Mapalo et al., 2020). Toll receptors are widespread in multiple species across the metazoan tree, especially in bilaterians (Figure 1.1C) (reviewed in Coscia *et al.*, 2011; Brennan and Gilmore, 2018; Nie *et al.*, 2018). In non-bilaterian metazoans, although TLRs seem to be absent in ctenophores (Traylor-Knowles et al., 2019), placozoans (Kamm et al., 2019), poriferans (Gauthier et al., 2010; Wiens et al., 2006), and hydrozoan cnidarians (Bosch et al., 2009; Leclère et al., 2019), they are present in anthozoan cnidarians (Brennan et al., 2017; Poole and Weis, 2014; Williams et al., 2018). Due to the absence of TLRs in these metazoans (Dunn et al., 2014; Philippe et al., 2009; Ryan et al., 2013), some authors have proposed that TLRs could have emerged in the common ancestor of cnidarians and bilaterians (Leulier and Lemaitre, 2008; Liu et al., 2020; Nie et al., 2018). However, the presence of TLRs in choanoflagellates, the sister group to metazoans, challenges this hypothesis, suggesting that TLR origin could predate the appearance of animals (Richter et al., 2018). Within spiralians, TLRs are present in annelids (Davidson et al., 2008; Halanych and Kocot, 2014), mollusks (Gerdol and Venier, 2015; Halanych and Kocot, 2014; Ren et al., 2017, 2016), brachiopods (Gerdol et al., 2018; Halanych and Kocot, 2014), phoronids (Halanych and Kocot, 2014; Luo et al., 2018) and nemerteans (Halanych and Kocot, 2014; Luo et al., 2018); where they went through lineage-specific expansions in the trochozoan lineage. However, TLRs have not been found so far in platyhelminthes (Peiris et al., 2014) and rotifers (Flot et al., 2013). Moreover, in other ecdysozoans than arthropods and nematodes, TLRs are present in onychophorans, tardigrades, nematomorphs, and priapulids (Mapalo et al., 2020). In invertebrate deuterostomes, they are present in echinoderms and amphioxus, where this gene family has also been expanded, but also in tunicates, in which TLRs are present in lower numbers than in other deuterostomes. Orthologs for the adaptor MyD88, Irak proteins, and the transcription factor NF-$\kappa$B have been detected in a wide range of metazoan species (Azumi et al., 2003; Davidson et al., 2008; Forsthoefel et al., 2012; Gauthier et al., 2010; Gerdol et al., 2018; Gerdol and Venier, 2015; Hibino et al., 2006; Peiris et al., 2014; Tassia et al., 2017; Toubiana et al., 2014; Yuan et al., 2009), albeit gene losses have occurred in ecdysozoan lineages (Figure 1.1C) (Mapalo et al., 2020). Along with these findings, previous studies have shown that the expression of many components of the Toll pathway in invertebrates is altered upon bacterial exposure, showing that the function of this pathway in immunity is conserved in metazoans (Ren et al., 2017, 2016; Tirapé et al., 2007; Toubiana et al., 2014; Wang et al., 2011; Zhang et al., 2011; Zhang and Coultas, 2011).

### 1.3.2 The Imd pathway

The Imd pathway is a pathway in arthropods, that is involved in the detection and immune response against *meso*-diaminopimelic acid (DAP)-type peptidoglycans, which are found in gram-negative bacteria and a few gram-positive bacteria (Bai et al., 2020; Bao et al., 2013; Kaneko et al., 2006; Lemaitre et al., 1995; Zhou et al., 2018).

This pathway is activated by receptors belonging to the Peptidoglycan recognition protein receptors (PGRPs) family (Dziarski, 2004; Dziarski and Gupta, 2010, 2006; Myllymäki et al., 2014). PGRPs are present in multiple metazoan species (e.g. mollusks, brachiopods, arthropods, vertebrates) (Gerdol et al., 2018; Gerdol and Venier, 2015; Kang et al., 1998). PGRPs, also known as PGLYRP in vertebrates, recognize peptidoglycans and are characterized by the presence of a recognition PGRP domain (aka N-acetylmuramoyl-L-alanine amidase domain) at the C-terminal end of the protein (Kang et al., 1998; Werner et al., 2000). PGRP proteins are classified into short PGRPs (Invertebrate PGRP-S and the vertebrate PGLYRP) and long PGRP (PGRP-L) (Werner et al., 2000). Short PGRPs are extracellular proteins around 200 amino acids long, while long PGRPs can be extracellular, transmembrane, or cytosolic proteins and are constituted at least by 400 amino acids (Dziarski and Gupta, 2006; Myllymäki et al., 2014). The arthropod PGRP-LC is a transmembrane protein that constitutes the main receptor of the Imd pathway (Choe et al., 2005, 2002; Gottar et al., 2002; Rämet et al., 2002; Takehana et al., 2004; Werner et al., 2003). Additionally, the cytoplasmatic isoform of PGRP-LE acts as a cytosolic receptor sensing intracellular peptidoglycans and activates the Imd pathway (Chevée et al., 2019; Paik et al., 2017; Takehana et al., 2004, 2002). Besides the PGRP recognition domain, these two proteins have a RIP Homotypic Interaction Motif (RHIM), which is involved in signal transduction to the Imd adaptor (Kaneko et al., 2006). Other long PGRPs, (PGRP-LA, PGRP-LF, and PGRP-LB) are involved in the regulation of the Imd pathway (Basbous et al., 2011; Gendrin et al., 2013; Maillet et al., 2008; Zaidman-Rémy et al., 2006). Furthermore, some arthropod PGRP-S are also involved in Imd pathway modulation, however, the majority of them (e.g. PGRP-SA, PGRP-SB, PGRP-SD) are involved in other functions such as Toll pathway modulation (Michel et al., 2001), initiation of the prophenoloxidase cascade during melanization (Takehana et al., 2004, 2002; Yoshida et al., 1996) and bacterial degradation (Bischoff et al., 2006; Mellroth et al., 2003; Zaidman-Rémy et al., 2011, 2006).

Upon PGRP-LC and PGRP-LE peptidoglycan recognition, signal transduction to the adaptor Imd occurs via the RHIM motifs (Figure 1.2A) (Kaneko et al., 2006), triggering the Imd-Fadd-Dredd complex (Hu and Yang, 2000; Naitza et al., 2002). Then, activation of the caspase Dredd by Iap2 leads to the cleavage of Imd by Dredd (Meinander et al., 2012). Once Imd is processed, it associates with Iap2 and promotes the formation of the Tab2/Tak1 complex (Meinander et al., 2012). This triggers the dissociation of the IKK complex, formed by Kenny/IKKγ and Ird5/IKKβ (Silverman, 2000), which leads to the phosphorylation and cleavage of Relish by Ird5/IKKα-β and Dredd, respectively (Kim et al., 2014; Kleino and Silverman, 2019; Myllymäki et al., 2014; Silverman, 2000; Stöven et al., 2000; Valanne et al., 2011). Relish is constituted by two Relish Homology Domains (RHD and IPT) and an IκB-like region, formed by ankyrin repeats (ANK) and a DEATH domain, which inhibit the entrance of Relish into the nucleus (Dushay et al., 1996; Keshavarz et al., 2020; Shin et al., 2002). Once Relish is cleaved, being only constituted by the two Relish Homology Domains, it is translocated into the nucleus, where it regulates the expression of immune genes (e.g.

antimicrobial peptides, PGRPs) (Choe et al., 2002; De Gregorio, 2002; Lemaitre et al., 1995; Stöven et al., 2000).

Although the Imd pathway is characteristic of arthropods, this pathway has been lost in some lineages (Bao et al., 2013; Gerardo et al., 2010; Hoffmann and Reichhart, 2002; Nishide et al., 2019; Palmer and Jiggins, 2015). However, although the Imd pathway has not been identified in other metazoans, other components of the Imd pathway have been found outside Arthropoda (Figure 1.2B). In the spiralians mollusks and brachiopods, long transmembrane PGRPs (tPGRPs), Fadd, Dredd and Relish proteins have been identified (Gerdol et al., 2018; Gerdol and Venier, 2015; Itoh and Takahashi, 2008; Ni et al., 2007; Toubiana et al., 2014; Wei et al., 2012; Zhang and Coultas, 2011). However, the lack of the Imd adaptor and the fact that the tPGRPs do not contain RHIM motifs makes it difficult to elucidate the presence of this pathway. Within ecdysozoans, tPGRP, Imd, Fadd, Dredd, and Relish have not been identified in priapulids, nematodes, and tardigrades (Mapalo et al., 2020). Moreover, although no homolog pathway to the arthropod Imd pathway has been found in vertebrates, this pathway shows similarities with the vertebrate TNF-α pathway, which also culminates with the entrance of the transcription factors NFκB-p105/NFκB-p100 – orthologs of Relish – to the nucleus (Hoffmann and Reichhart, 2002; Myllymäki et al., 2014; Steiner, 2004). Furthermore, both pathways share multiple components (e.g. Fadd, Dredd/Caspase8, K63, IKKγ, IKKα-β, Tak1, Relish/NFκB-p105/100) and, although the Imd protein is absent in vertebrates, a similar protein, also containing a DEATH domain is present as the adaptor in the TNF-α pathway (Georgel et al., 2001; Myllymäki et al., 2014). However, vertebrate PGRP proteins are not involved in the activation of this pathway (Myllymäki et al., 2014; Sedger and McDermott, 2014).

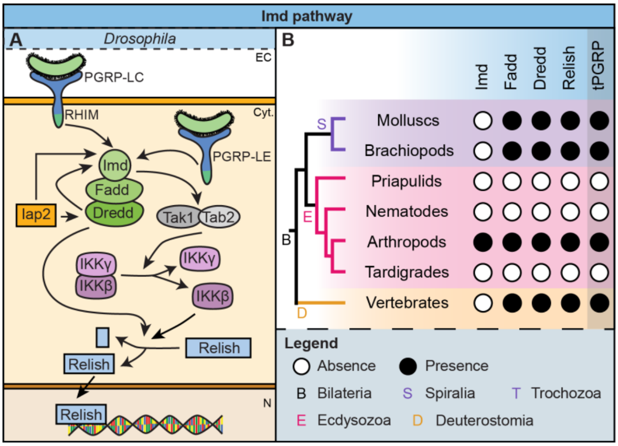


**Figure 1.2. The Imd pathway in metazoans. A.** Imd pathway signaling cascade in arthropods. **B.** Presence and absence of proteins of the Imd pathway in metazoans. Greyish compartments within each pathway compartment indicate proteins that are uncertain to be involved in the pathway. This figure is a modification of Figure 1 in Paper II. Abbreviations: Cyt: Cytoplasm; EC: Extracellular space; N: Nucleus; PGRP: Peptidoglycan recognition proteins; RHIM: RIP Homotypic Interaction Motif; tPGRP: long transmembrane peptidoglycan recognition proteins. References: A. (Hoffmann and Reichhart, 2002; Valanne et al., 2011). B. (Chevée et al., 2019; Choe et al., 2002; Davidson et al., 2008; Dushay et al., 1996; Gerdol et al., 2018; Gerdol and Venier, 2015; Gottar et al., 2002; Hu et al., 2019; Hu and Yang, 2000; Kaneko et al., 2006; Mapalo et al., 2020; Naitza et al., 2002; Rämet et al., 2002; Romero et al., 2011; Shin et al., 2002; Takehana et al., 2004, 2002; Toubiana et al., 2014; Werner et al., 2003, 2000; Zhang and Coultas, 2011).

### 1.3.3. THE COMPLEMENT SYSTEM

The complement system is a proteolytic cascade in which proteins present in the blood, the lymph, and interstitial tissues, but also in cellular membranes trigger immune processes such as opsonization, phagocytosis, inflammatory regulation, and cytolysis. The complement system in vertebrates was identified at the end of the 19$^{th}$ century by Jules Bordet (Bordet, 1895; Cavaillon et al., 2019). Since then, many proteins involved in the vertebrate complement system have been identified and how this system functions in vertebrates has also been disentangled, leading to the writing of numerous reviews (Bajic et al., 2015; Fujita, 2002; Fujita et al., 2004b; Kolev et al., 2014; Merle et al., 2015a, 2015b; Müller-Eberhard, 1988; Reid and Porter, 1981; Ricklin et al., 2016, 2010; Zipfel et al., 2007). However, it was not until approximately 100 years later that the first evidence of the presence of the complement system in invertebrates were found (Bertheussen, 1983, 1981; Bertheussen and Seljelid, 1982; Kaplan and Bertheussen, 1977). Currently, the invertebrate complement system is not fully understood yet.

The vertebrate complement system is activated by three different pathways: The classical pathway, the lectin pathway, and the alternative pathway (Figure 1.3A). In non-infection conditions, the alternative pathway is constantly activated at low levels in order to search for potential danger; whereas the classical and the lectin pathways are only activated by the presence of pathogens or during apoptosis (Gaipl et al., 2001; Merle et al., 2015a; Mevorach et al., 1998). In order to avoid the elimination of healthy cells, these cells express proteins (e.g. Factor H, MAP-1, Decay-accelerating factor (DAF)) in their cellular membranes that avoid complement activation on their surfaces (Medof et al., 1984; Skjoedt et al., 2010; Wu et al., 2009). The alternative pathway is constantly activated by a process called tick-over, which consists on conformational changes of the complement C3 protein due to spontaneous hydrolysis to generate C3($H_2O$) (aka C3u), which binds to Factor B (Bexborn et al., 2008; Li et al., 2010; Pangburn et al., 1981; Winters et al., 2005). Factor B is a serine protease constituted by 3 complement control protein modules (CCP) (aka Sushi or Short Consensus Repeats – SCR), a von Willebrand factor (vWF), and a serine protease domain (SP) (Figure 1.3B) (Milder et al., 2007). Once Factor B and C3 are bound, Factor D cleaves Factor B and forms the C3 convertase – C3($H_2O$)Bb –, which cleaves C3 into C3a and C3b. In infection conditions, the classical pathway is activated by the interaction of the C1q protein with antigen-antibody complexes and PAMPs (Albertí et al., 1993; Diebolder et al., 2014). C1q is a multimeric protein formed by subunits that consist of a globular C1q domain, involved in ligand recognition, and a collagen domain, which is the domain by where the subunits interact (Figure 1.3B) (Carland and Gerwick, 2010; Svehag et al., 1972). Moreover, C1q forms a complex with C1r and C1s (Arlaud et al., 2002; Girija et al., 2013). The lectin pathway is activated by the detection of PAMPs by mannose-binding lectins (MBL) and ficolins (Matsushita, 2010; Matsushita and Fujita, 1992). Similar to C1q, MBL and ficolins are multimeric proteins constituted by subunits consisting in a collagen domain, by which the subunits assemble, and a C-terminal recognition domain (Ichijo et al., 1993; Sastry et al., 1989). In MBL, this recognition domain is a C-lectin domain (Sastry et al., 1989); whereas in ficolins, is a Fibrinogen-related domain (FBG) (Ichijo et al., 1993). Once MBL and ficolins detect PAMPs, they interact and activate MBL-associated serine proteases (MASPs) (Matsushita et al., 2000; Matsushita and Fujita, 1992). Both, the classical pathway protein C1s and the lectin pathway protein MASP are serine proteases that cleave the complement proteins C2 and C4 to generate C2a, C2b, C4a, and C4b fragments. C2a and C4b interact to form the C3 convertase (C4b2a), an enzyme that catalyzes the cleavage of C3 into C3a and C3b (Matsushita, 2013; Müller-Eberhard et al., 1967).

The three activation pathways converge in the formation of C3 convertases and the cleavage of C3 into C3a and C3b. C3, which is the central component of the complement system, is a protein that belongs to the Thioester-containing protein (TEP) family. Its domain architecture consists of α2-macroglobulin domains, an anaphylatoxin domain, a thioester domain (TED), a CUB domain, and a C345C domain (aka Netrin domain) (Figure 1.3B) (Janssen et al., 2005). Once it is cleaved, the anaphylatoxin domain region forms the C3a fragment, while the remaining fragment comprises C3b. C3a is an anaphylatoxin that regulates inflammation, having both pro-inflammatory and anti-inflammatory functions, but it also has antimicrobial properties (Coulthard and Woodruff, 2015; Hartmann et al., 1997; Nilsson et al., 1996; Nordahl et al., 2004; Takafuji et al., 1994; Wu et al., 2013). Similar to C3($H_2O$), the C3b fragment can interact with Factor B to form C3 convertase (C3bBb), after Factor D cleaves Factor B (Alcorlo et al., 2013; Torreira et al., 2009). Thus, this C3 convertase generates an amplification loop that increases the production of C3a, C3b, and, therefore, of C3 convertase (C3bBb). Moreover, solitary C3b fragments also have opsonization properties, attaching to the bacterial surfaces and being detected by complement receptors (CR) present in phagocytes (Ehlenberger and Nussenzweig, 1977). Humans have five complement receptors: CR1 and CR2 are constituted by CCP modules and a transmembrane domain (Ahearn and Fearon, 1989); CR3 and CR4 are formed by two protein chains containing integrin-α and β domains, respectively (Vorup-Jensen and Jensen, 2018); and CRIg, constituted by Ig domains (Helmy et al., 2006). Additionally, C3b also can interact with C3 convertases to form C5 convertases (Pangburn and Rawal, 2002). This enzyme cleaves C5 into C5a and C5b, being C5a an anaphylatoxin involved in pro-inflammatory processes (Hartmann et al., 1997; Nilsson et al., 1996; Takafuji et al., 1994). C5b recruits C6, C7, C8, and C9 forming the membrane attack complex (MAC), which inserts into the cellular membrane of gram-negative bacteria and protozoans forming pores and leading to its lysis (Bhakdi and Tranum-Jensen, 1978; Rosado et al., 2008). Furthermore, these proteins also induce apoptosis in the infected tissue (Hughes et al., 2000; Nauta et al., 2002; Sato et al., 1999). Moreover, many other proteins (e.g. properdin, decay-accelerating Factor (DAF), Factor H, Factor I) participate in the regulation of complement activation, both to inhibit complement activation on healthy cells, but also to increase the activation of this process during infection (Alcorlo et al., 2013; Fearon and Austen, 1975; Hourcade, 2006; Kouser et al., 2013; Medof et al., 1984; Merle et al., 2015a; Wu et al., 2009).

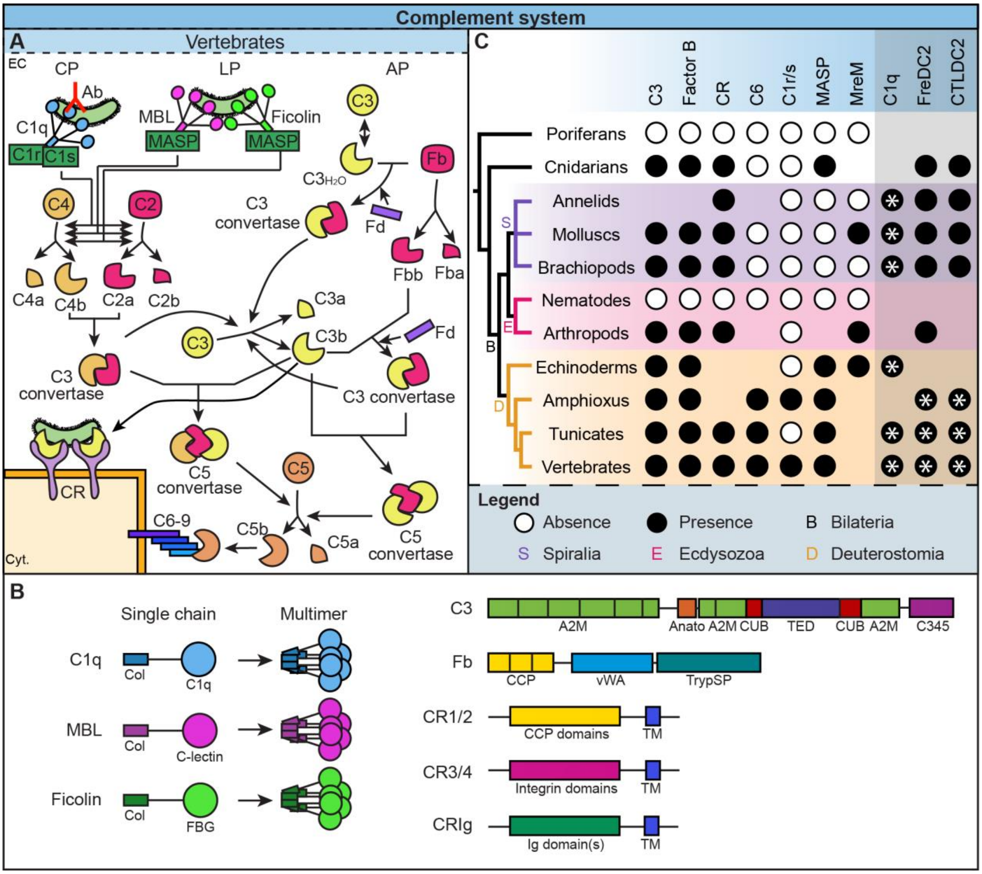


**Figure 1.3. The complement system in metazoans. A.** Complement system cascade in vertebrates. **B.** Domain architecture of proteins belonging to the vertebrate complement system. **C.** Complement system components in metazoans. Orthologs of components of the Imd pathway have been found in vertebrates, however, these components belong to the vertebrate TNFα pathway. Greyish compartments within each pathway compartment indicate proteins that are uncertain to be involved in the pathway. For C1q, FreD-C, and C-lectin proteins, black circles with an asterisk (*) indicate the presence of proteins with collagen domains (C1qL, ficolin, and MBL/GBL, respectively), while only black circles indicate presence of C1q, FreD-C, and C-lectin proteins containing coiled coil regions instead of collagen domains (FreDC2 and CTLDC2). Abbreviations: A2M: α2-macroglobulin family domain; Ab: antibody; Anato: Anaphylatoxin homologous domain; AP: Alternative pathway; CCP: complement control protein; CP: Classical pathway; CR: Complement receptor; Cyt: Cytoplasm; EC: Extracellular space; Fb: Factor B; Fd: Factor D; LP: Lectin pathway; MASP: Mannan-binding lectin serine protease;

MBL: Mannose-Binding Lectin; TED: Thioester domain; TM: Transmembrane domain; TrypSP: Trypsin-like serine protease domain; vWA: von Willebrand factor type A domain. This figure is a modification of Figure 1 in Paper II. References: A. (Bajic et al., 2015; Merle et al., 2015a; Ricklin et al., 2016). B. (Ahearn and Fearon, 1989; Carland and Gerwick, 2010; Helmy et al., 2006; Ichijo et al., 1993; Janssen et al., 2005; Milder et al., 2007; Sastry et al., 1989; Svehag et al., 1972; Vorup-Jensen and Jensen, 2018) C. (Adams, 2000; Ahearn and Fearon, 1989; Al-Sharif et al., 1998; Altincicek and Vilcinskas, 2007; Ariki et al., 2008; Azumi et al., 2003; Castillo et al., 2009; Dishaw et al., 2005; Gerdol et al., 2018; Gerdol and Venier, 2015; Girija et al., 2013; Gorbushin, 2019, 2018; Han et al., 2018; He et al., 2008; Helmy et al., 2006; Hibino et al., 2006; Huang et al., 2011; Ichijo et al., 1993; Janssen et al., 2005; Ji et al., 1997; Kimura et al., 2009; Marino et al., 2002; Matsushita and Fujita, 1992; Milder et al., 2007; Miller et al., 2007; Nagai et al., 2006; Nair et al., 2005; Nonaka et al., 1999; Nonaka and Kimura, 2006; Palmer and Jiggins, 2015; Poole et al., 2016; Prado-Alvarez et al., 2009; Raftos et al., 2002; Rosado et al., 2008; Sastry et al., 1989; Sekiguchi et al., 2012; Sekiguchi and Nonaka, 2015; Sekine et al., 2001; Skazina and Gorbushin, 2016; Smith et al., 2006, 1998; Srivastava et al., 2010; Suzuki et al., 2002; Svehag et al., 1972; The C.elegans Sequencing Consortium, 1998; Vorup-Jensen and Jensen, 2018; Wang et al., 2019; Zhu et al., 2005).

Although the complement system has been well studied in vertebrates, this system is less understood in invertebrates. C3, Factor B, and complement receptors are present cnidarians (Dishaw et al., 2005; Fujito et al., 2010; Gorbushin, 2018; Kimura et al., 2009; Miller et al., 2007; Poole et al., 2016), spiralians (e.g. some mollusks, brachiopods) (Altincicek and Vilcinskas, 2007; Castillo et al., 2009; Gerdol et al., 2018; Gerdol and Venier, 2015; Gorbushin, 2018; Prado-Alvarez et al., 2009; Wang et al., 2017, 2019), some arthropods (Adams, 2000; Ariki et al., 2008; Gorbushin, 2018; Palmer and Jiggins, 2015; Sekiguchi and Nonaka, 2015; Zhu et al., 2005), and deuterostomes (Al-Sharif et al., 1998; Azumi et al., 2003; Gross et al., 1999; He et al., 2008; Hibino et al., 2006; Marino et al., 2002; Nair et al., 2005; Nonaka et al., 1999; Raftos et al., 2002; Smith et al., 1998, 2006; Suzuki et al., 2002) (Figure 1.3C). However, these proteins were not identified in placozoans (Kamm et al., 2019), poriferans (Srivastava et al., 2010), and nematodes (The C.elegans Sequencing Consortium, 1998). C3, Factor B, and complement receptors constitute the proto-complement, which is the minimum set of proteins needed to have a functional complement system that leads to the opsonization and phagocytosis of pathogens (Cerenius et al., 2010; Gorbushin, 2018). The presence of a proto-complement in cnidarians suggests that this system was originated during early metazoan evolution

(Cerenius et al., 2010). In vertebrates, the complement system is formed by approximately 30 genes (Volanakis, 1998). However, many of them emerged by gene duplications during vertebrate evolution. This is the case, for instance, the vertebrate *C3, C4,* and *C5* are the result of duplications of an ancestral *C3-like* gene during early vertebrate evolution, and they are orthologous to the *C3* genes present in invertebrates (Nonaka, 2011; Nonaka et al., 1998; Nonaka and Kimura, 2006). Similarly, the vertebrate gene codifying for Factor B – *Complement factor B* (*cfb*) – and *C2* emerged during early vertebrate evolution, being orthologous to the invertebrate *cfb* (Nonaka et al., 1998; Nonaka and Kimura, 2006). Moreover, some invertebrates have Factor C or Factor L proteins, which are homologous to Factor B (Gorbushin, 2018). Moreover, although C6-like proteins are present in tunicates and amphioxus, membrane attack-complex (C6-C9) proteins are absent in invertebrates (Azumi et al., 2003; Dodds and Matsushita, 2007; Nonaka and Kimura, 2006; Suzuki et al., 2002). However, MACPF domain-containing proteins with unknown functions or involved in other processes than complement have been found in other invertebrates (Gorbushin, 2016; He et al., 2011; Mah et al., 2004; Martin et al., 1994; Miller et al., 2007).

Knowledge about how the complement is activated in invertebrates is also scarce. MBL, ficolins, C1q, and the serine proteases C1r, C1s, and MASPs have been identified in invertebrate deuterostomes (Figure 1.3C) (Azumi et al., 2003; Gorbushin, 2019; Hibino et al., 2006; Huang and Xu, 2015; Ji et al., 1997; Nonaka and Kimura, 2006; Sekine et al., 2001). Furthermore, although spiralians lack orthologs to the vertebrate MBL and ficolins, C-type lectins (C-lectins) and Fibrinogen-related domain-containing proteins (FreD-C) being composed of coiled coil regions instead of collagen domains, named CTLDC2 and FreDC2 respectively, have been identified (Gerdol et al., 2018; Gerdol and Venier, 2015; Gorbushin, 2019; Skazina and Gorbushin, 2016). Since, similarly to collagen domains, coiled coil domains are domains by which proteins can associate and multimerize (Kammerer, 1997), it has been suggested that these proteins could multimerize and form proteins with analogous functions to the vertebrate MBL and ficolins (Gerdol et al., 2018; Gerdol and Venier, 2015; Gorbushin, 2019; Skazina and Gorbushin, 2016). Furthermore, although MASP proteins are not present in spiralians, MASP-related Molecules (MreM) have been detected in mollusks and arthropods (Gorbushin, 2019). The presence of lectins that could form multimer proteins and MreM in invertebrates has led to some authors to hypothesize that the lectin pathway could be present in invertebrates. Additionally, as C1q is mainly activated by antigen-antibody complexes and antibodies are exclusive from vertebrates, it is considered that the classical pathway was originated during the vertebrate lineage evolution (Fujita et al., 2004a; Nonaka and Kimura, 2006). However, C1q proteins consisting of a collagen domain and a C1q globular domain (C1qL) are not only present in vertebrates but have also been found in spiralians (Gorbushin, 2019). However, C1r and C1s, which are homologs to MASP, emerged during early vertebrate evolution (Nonaka and Kimura, 2006).

## 1.4 Animals of study

### 1.4.1 The nemertean *Lineus ruber* (Müller, 1774)

Nemerteans are unsegmented, marine, free-living worms that generally inhabit in intertidal zones under rocks or buried in sand or mud (Gibson, 1972; Turbeville, 1991). These animals are characterized by having an eversible proboscis, which they use to haunt preys (Gibson, 1972; Turbeville, 1991). The proboscis is enclosed in the rhynchocoel, a coelomic cavity full of liquid that is extended from the anterior to the posterior part of the animal (Gibson, 1972; Turbeville, 1991).

Nemerteans are spiralians that belong to the trochozoan clade, together with mollusks, annelids, brachiopods, and phoronids, being the relationships among these groups not resolved (Figure 1.4A) (Dunn et al., 2014, 2008; Edgecombe et al., 2011; Laumer et al., 2019; Struck and Fisse, 2008). However, a recent study (Marlétaz et al., 2019), recovers an older hypothesis that positions nemerteans as the sister group of platyhelminthes within spiralians (Figure 1.4B). Nemerteans are classified into three major taxa: Paleonemerteans, pilidiophorans, and hoplonemerteans (Alfaya et al., 2019; Andrade et al., 2014). Within nemerteans, *Lineus ruber* belongs to the Pilidiophora lineage (Gibson, 1972; Krämer et al., 2016). Although *Lineus ruber* was described as a single species by Müller (Müller, 1774), due to their identical morphology with other species (e.g. *Lineus viridis, Lineus clandestinus*), these species have often been grouped forming a species complex (Gibson, 1995; Punnet, 1901), often receiving other species names (e.g. *Lineus gesserensis, Fasciola viridis*) (Gibson, 1995; Punnet, 1901). Morphological, developmental, and molecular analyses over the last century have enabled the classification of these species as single species

(Cherneva et al., 2019; Gibson, 1995; Gontcharoff, 1959; Krämer et al., 2016; Rogers et al., 1995).

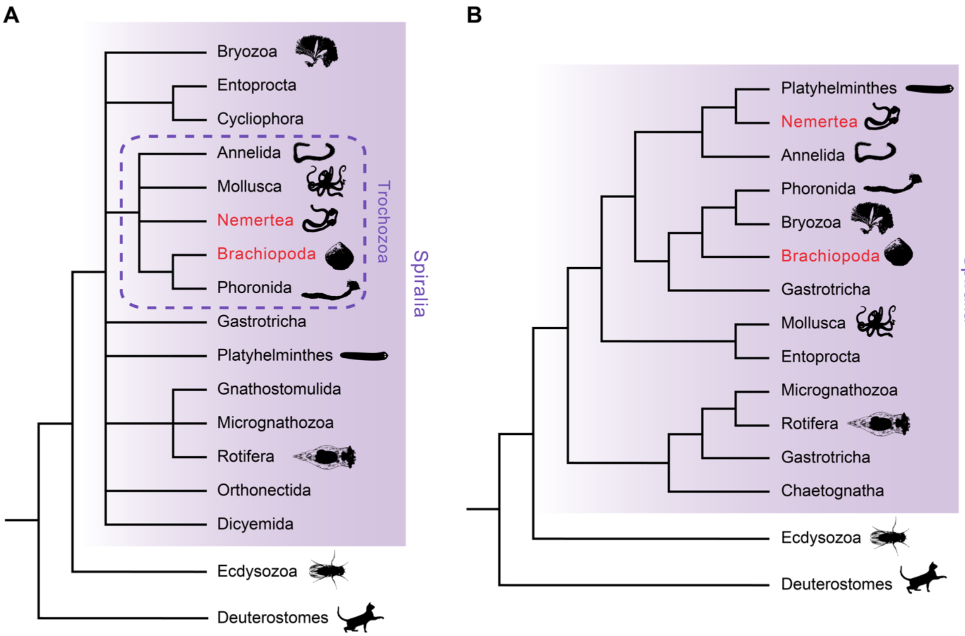


**Figure 1.4. Phylogenetic position of Nemertea and Brachiopoda within Spiralia.** A) Phylogeny according to (Dunn et al., 2014): Nemerteans and brachiopods belong to the trochozoan group within spiralians. B) Phylogeny according to (Marlétaz et al., 2019). Nemerteans are the sister group to platyhelminthes; while brachiopods are the sister group to phoronids and bryozoans. In red, it is indicated the position of Nemertea and Brachiopoda in the tree.

*Lineus ruber* are red-brownish worms which adult size vary from 3 to 7 cm long (Figure 1.5A), which inhabit underneath the rocks in intertidal zones of the North Atlantic Ocean and artic seas (Cantell, 1975; Gibson, 1995, 1972; Punnet, 1901). *Lineus ruber* epidermis is covered by cilia, and glandular cells are present ubiquitously in the skin (Cantell, 1975; Punnet, 1901; Turbeville, 1991). The body wall is formed by two layers of longitudinal musculature and a layer of circular musculature (Cantell, 1975; Punnet, 1901). The mouth is located ventrally, in the anterior part of the trunk, opening to the gut, which occupies the majority of the trunk (Ling and Willivier, 1973; Punnet, 1901). The proboscis opening is located in the anterior tip of the animal (Ling, 1971; Punnet, 1901). The gonads are located laterally from the mid-trunk to the posterior end of the animal (Punnet, 1901). The nervous system is composed of the brain, two ventrolateral and a dorsal nerve cords (Beckers, 2014; Martín-Durán et al., 2018; Punnet, 1901; Schmidt-Rhaesa, 2007; Turbeville, 1991). Posteriorly, the brain is in contact with the cephalic organs, which are involved in neuroendocrine functions (Beckers, 2014; Ling, 1970, 1969; Punnet, 1901). Furthermore, cephalic nerves also emerge from the brain and innervate the frontal organ and the eyes, located in the anterior area of the head (Beckers, 2014; Punnet, 1901). Like all nemerteans, *Lineus ruber* possesses a coelomic closed circulatory system (Gibson, 1972; Schmidt-Rhaesa, 2007) formed by a system of interconnected blood vessels and lacunae (Punnet, 1901). In the head, the cephalic lacuna surrounds laterally the proboscis, forming a loop in the most anterior part of the animal (Cantell, 1975; Punnet, 1901). At the level of the brain, the cephalic lacuna divides into a dorsal blood vessel and two lateral blood vessels (Cantell, 1975; Punnet, 1901). The two lateral blood vessels run posteriorly, in parallel to the nerve cords until the posterior tip of the animal, where they fuse with the dorsal blood vessel (Punnet, 1901). Furthermore, perpendicular blood vessels connect the two lateral blood vessels in the posterior area of the animal (Punnet, 1901).

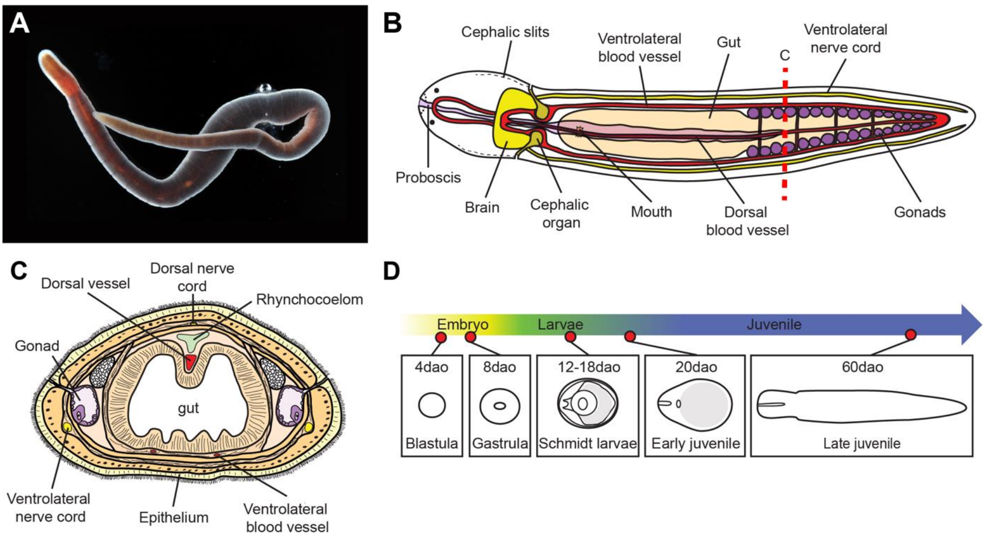


**Figure 1.5. Anatomy and development of the nemertean *Lineus ruber*.** A. Adult *Lineus ruber* alive specimen. B. Scheme of the anatomy of *Lineus ruber* adult. The red line marks the level of the cross-section in panel C. C. Cross-section at the level of the mid-posterior trunk (red-dashed line in B). D.

Development of *Lineus ruber*. The grey area in the Schmidt larvae and the early juvenile represents the yolk Image references: A from (Martín-Durán et al., 2015); B and C adapted from (Punnet, 1901); D adapted from (Martín-Durán et al., 2015). Dao: days after oviposition.

*Lineus ruber* are dioecious animals that reproduce once per year, during spring (Gibson, 1972; Martín-Durán et al., 2015; Punnet, 1901). During oviposition, the female releases the eggs inside of a gelatinous cocoon, where the embryos develop, reaching the larval stage on the 12th day after oviposition (dao) (Martín-Durán et al., 2015). *Lineus rube*r larva is an intracapsular larva called Schmidt's larva (Gibson, 1972; Martín-Durán et al., 2015; Schmidt, 1964). A gradual metamorphosis, in which only the larval epidermis is discarded, occurs at 18-20 days after oviposition (Figure 1.5D) (Martín-Durán et al., 2015). The early juvenile *Lineus ruber* is formed 20 days after oviposition (dao) and it already has worm shape (Figure 1.5D). Shortly after metamorphosis, the brain, proboscis, the eyes, the mouth, and the gut are formed, and *Lineus ruber* juveniles already have the adult anatomy by 25 dao (Martín-Durán et al., 2015). Soon after, the juveniles break the cocoon and escape from it.

#### *COLLECTION OF* LINEUS RUBER *IN BERGEN (NORWAY) AND CULTURE IN THE LABORATORY*

Adult animals are collected yearly, normally between January and March, by the members of Dr. Andreas Hejnol lab in a rocky beach in Fana, Bergen, Norway (coordinates: 60°15'06.6"N 5°19'15.4"E) during low tide. The animals are kept in a tank with constant air supply in the animal facility with 2 liters of seawater at 8°C and salinity 33. Animals were fed once per week with mussels and the water was changed once per week. Between March and April, the adults spawn and the cocoons are collected and placed in Petri dishes. Salinity and temperature for the animals in development are the same as for the adults, but they were never fed.

### 1.4.2 THE BRACHIOPOD *TEREBRATALIA TRANSVERSA* (SOWERBY, 1846)

Brachiopods are filter-feeding organisms that live in benthic ecosystems. Adult organisms have a dorsal and a ventral shell, which attaches to rocks by the ventral side or by a pedicle (Figure 1.6) (Santagata, 2015). Inside the shell, their body consists of a lophophore used for filtering food particles, a gut, and a mantle epithelia with gonads distributed in the internal walls of the shell (Kuzmina and Malakhov, 2007; Santagata, 2015).

Like nemerteans, brachiopods are considered to be spiralians that belong to the trochozoan clade and are the sister group to phoronids (Figure 1.4A) (Dunn et al., 2014, 2008; Edgecombe et al., 2011; Laumer et al., 2019; Struck and Fisse, 2008). However, other studies also suggest that brachiopods are the sister group to a clade formed by phoronids and bryozoans (Figure 1.4B) (Marlétaz et al., 2019; Nesnidal et al., 2013). Furthermore, brachiopods are divided into three lineages: the rhynchonelliforms, the linguliforms, and the craniiforms, belonging *Terebratalia transversa* to the rhynchonelliform lineage (Williams et al., 1996).

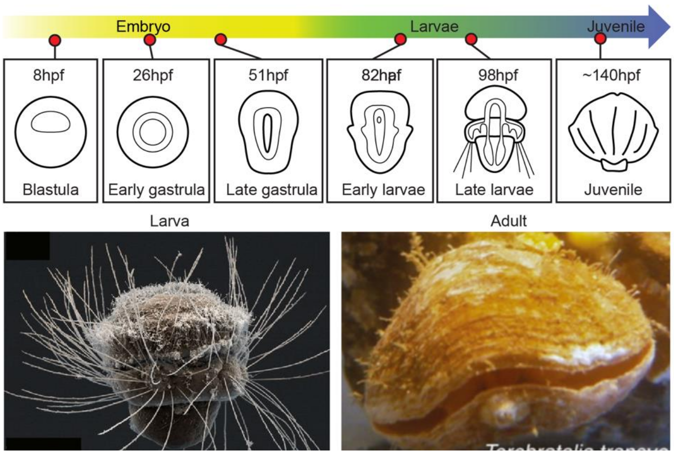


**Figure 1.6. Development of the Brachiopod *Terebratalia transversa.*** Developmental time points and adult *Terebratalia transversa* images were obtained from Schiemann *et al.*, 2017; while the SEM image of the larvae was obtained from Thiel *et al.*, 2017. Abbreviations: hpf: hours post-fertilization.

*Terebratalia transversa* reproduces during winter. Soon after fertilization occurs, a ciliated blastula is formed, which develops into a gastrula by 26 hours post-fertilization (hpf) (Figure 1.6) (Freeman, 1993a; Schiemann et al., 2017). In the late gastrula, the embryo elongates and constrictions divide it into different regions, establishing the zones that will later develop into the different lobes of the larva, named the apical lobe, the mantle lobe, and the pedicle lobe (Freeman, 1993a). At 82 hpf, a non-feeding larva is formed, containing a transient apical tuft and eye-spots in the apical lobe (Freeman, 1993b). In this early larva, the apical lobe is The mantle lobe and the pedicle lobe are overlapping (Freeman, 1993a). In the late larva (Figure 1.6), the anterior lobe, the mantle lobe, and the pedicle lobe are well delimited (Freeman, 1993a). In the mantle lobe, the larva has two pairs of chaetal sacs, from where chaeta are extended. The pedicle lobe is the area of the larvae by which the larvae attach to the substrate when it settles, prior to metamorphosis (Freeman, 1993b; Stricker and Reed, 1985a). During metamorphosis, the mantle lobe is inverted, covering partially first the pedicle lobe and then the anterior lobe, and secretes a substance that forms the shell (Freeman, 1993b; Stricker and Reed, 1985a, 1985b). Molecular studies examining gene expression during development have been conducted, assessing the expression of mesodermal genes, nervous system-related genes, Hox genes, and segmentation genes in this non-segmented brachiopod (Gasiorowski and Hejnol, 2019; Passamaneck et al., 2015; Santagata et al., 2012; Schiemann et al., 2017; Sinigaglia et al., 2018; Vellutini and Hejnol, 2016).

### COLLECTION OF TEREBRATALIA TRANSVERSA IN FRIDAY HARBOR (USA) AND CULTURE IN THE LABORATORY

*Terebratalia transversa* adults were dredged from the rocks at the seafloor near Friday Harbor, USA, during the winter. The animals were spawned in the laboratory and embryos were kept in glass bowls with seawater at 10°C. The water was changed every day and cleaned from debris. Once they developed into larvae and were able to swim, the animals were transferred into beakers.

## Chapter 2: Aims of the study

The global aim of this thesis is to better understand the evolution of innate immune response in invertebrates. In order to accomplish this aim, first, I have investigated the evolution of TLRs in invertebrates (Paper I). Second, I have studied immune mechanisms present in vertebrates and/or arthropods, such as the Toll pathway, the Imd pathway, the complement system, and lectins in the nemertean *Lineus ruber,* which belongs to the spiralian protostome clade (Paper II).

### 2.1 The evolution of the metazoan Toll receptor family and its expression during protostome development (Paper I)

The main goal of this study is to reconstruct Toll receptor evolution in invertebrates. First, I performed genomic and transcriptomic surveys in under-represented metazoan species in order to gain an overview of in which metazoan lineages TLRs have been lost or have been duplicated. Next, I performed phylogenetic analyses in which TLRs from the four main metazoan clades (cnidarians, ecdysozoans, spiralians and deuterostomes) were included. Moreover, in order to investigate the expression of TLRs during ontogeny, Dr. Tsai-Ming Lu performed stage-specific transcriptome analyses on the ecdysozoans *Priapulus caudatus* and *Hypsibius exemplaris* and the spiralians *Crassostrea gigas* and *Terebratalia transversa.* In addition, to fulfill this aim, I also performed whole mount *in situ* hybridization at different developmental stages of *Terebratalia transversa*.

### 2.2 The Toll pathway, the Complement system and lectins are likely involved in immunity in the nemertean *Lineus ruber* (Paper II)

The objective of this study was to investigate pathways present in arthropods and/or vertebrates in the nemertean *Lineus ruber.* Thus, I surveyed for components of the Toll pathway, the Imd pathway, the complement system and lectins in the transcriptome of *Lineus ruber.* Furthermore, in order to investigate in which tissues are these genes expressed, I performed whole mount *in situ* hybridization of the components retrieved in the transcriptome survey. Moreover, in order to gain insights on the function of these pathways and systems, I performed an immune challenge assay, exposing *Lineus* *ruber* specimens to gram-negative bacteria and evaluating the changes in expression of genes involved in the aforementioned pathways and systems.

# CHAPTER 3: MATERIAL AND METHODS

Material and methods for Papers I and II are described in each paper. In this chapter, I will provide a more thorough description of the material and methods for each paper and for the additional results. Following sections indicate the method and the papers in which the method is applied.

## 3.1 ANIMAL FIXATION (PAPERS I AND II)

*Terebratalia transversa* embryos and larvae were fixed at various developmental stages, whereas *Lineus ruber* juveniles were fixed at 60 days after oviposition. The animals were fixed with 4% paraformaldehyde in phosphate buffer saline 0.1% Tween-20 (PTw) for 1h at room temperature. Afterwards, the samples were washed in PTw and stored in 100% methanol. *Terebratalia transversa* samples were fixed by members at that time of the Dr. Andreas Hejnol group (Andreas Hejnol, Daniel Thiel, Petra Kovacikova, and Ferenc Kagan). I performed the fixations on *Lineus ruber* specimens.

## 3.2 GENOMIC AND TRANSCRIPTOMIC SURVEYS (PAPERS I AND II)

20 genomes (*Xenoturbella profunda, Hofstenia miamia, Praesagittifera naikaiensis, Isodiametra pulchra, Meara stichopi, Helobdella robusta, Crassostrea gigas, Octopus bimaculoides, Biomphalaria glabrata, Lingula anatina, Notospermus geniculatus, Phoronis australis, Macrostomum lignano , Echinococcus multilocularis, Hymenolepis microstoma, Hypsibius exemplaris, Ramazzottius varieornatus, Loa loa, Onchocerca volvulus,* and *Daphnia pulex*) and 25 transcriptomes (*Convolutriloba macropyga, Membranipora membranacea, Bugula neritina, Symbion pandora, Galathowenia oculata, Eisenia fetida, Terebratalia transversa, Hemithris psittacea, Limnogathia maerski, Lepidodermella squamata, Macrodasys sp, Megadasys sp, Diuronotus aspetos, Mesodasys laticaudatus, Lineus longissimus, Lineus ruber, Phoronopsis harmeri, Epiphanes senta, Rotaria tardigrada, Echinorhynchus gadi, Macracanthorhynchus hirudinaceus, Priapulus caudatus, Halicryptus spinulosus, Peripatopsis capensis,* and *Armorloricus elegans*) were surveyed for Toll receptors in Paper I. For Paper II, the transcriptome of *Lineus ruber* was surveyed for immune genes belonging to the Toll pathway (*spätzle, myD88, irak*s, and *dorsal/NF*$\kappa$*B*), the Imd pathway (PGRPs, *imd, fadd, dredd, and relish/NF*$\kappa$*B*), to the complement system (*C3,*

*Factor B,* CRs, *C6, C7, C8, C9, C1q, C1s, C1r, MASP, MReM*) and lectins (C-lectins and FreD-Cs). Furthermore, the genome of *Nothospermus geniculatus* was also surveyed for PGRP proteins.

Hmmer profiles were generated for domains of the proteins mentioned above using HMMER software version 3.2.1 (www.hmmer.org) from alignments downloaded from the pfam website (http://pfam.xfam.org/) or from protein sequences collected from NCBI database (www.ncbi.nlm.nih.gov). Next, the hmmer profiles were blasted against the genomes and transcriptomes, obtaining a database of proteins presumably containing those domains. These sequences were validated by BLAST (Altschul, 1997) (www.blast.ncbi.nlm.nih.gov). Domain architecture of proteins surveyed in Paper I was analyzed with the online software SMART (Letunic et al., 2015; Schultz et al., 1998) (http://smart.embl.de/) and LRRfinder (Offord and Werling, 2013) (http://www.lrrfinder.com). Domain architecture of proteins surveyed in Paper II was analyzed with the online software SMART (Letunic et al., 2015; Schultz et al., 1998) (http://smart.embl.de/), hmmer (Finn et al., 2015) (http://hmmer.org/) , and NCBI Conserved Domains (Lu et al., 2020) (https://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi). Both for Paper I and Paper II, sequence identity was calculated using the online software Clustal Omega (Sievers et al., 2011) (https://www.ebi.ac.uk/Tools/msa/clustalo/). Moreover, in Paper I, TLR classification into P-type/mcc or V-type/scc was performed according to the criteria in Brennan and Gilmore, 2018 (Brennan and Gilmore, 2018).

### 3.3 Phylogenetic analyses (Papers I and II)

For each analysis, protein sequences obtained from the transcriptome and genome surveys, from the literature, and NCBI database (www.ncbi.nlm.nih.gov) were aligned using MAFFT software version 7, applying the L-INS-I algorithm (Katoh and Standley, 2013). Next, the alignments were trimmed manually and using TrimAl software version 1.2 (Capella-Gutierrez et al., 2009). Maximum-likelihood phylogenetic analyses were conducted with IQ-TREE software (Nguyen et al., 2015) in the CIPRES Science Gateway (Miller et al., 2010) (http://www.phylo.org). In Paper I, the LG+R8 model was selected as the best-fit model according to Bayesian Information Criterion (BIC). In Paper II, the LG+F+I+G4 model was selected for the phylogenetic analysis of DEATH domains; the VT+I+G4 model for the phylogenetic analysis of NFκB factors; the LG+R4 model for both, the phylogenetic analyses of proteins belonging to the TED family and Factor B, Factor C and Factor L proteins; and the LG+G4 model for the PGRP phylogenetic analyses.

For all the analyses, bootstrap values were calculated running 1000 replicates using ultrafast bootstrap.

### 3.4 Stage specific transcriptome analyses (Paper I)

In Paper I, in order to study the expression of TLR genes during development, we examined already published stage specific transcriptomes from different developmental stages from the spiralians *Crassostrea gigas* and *Terebratalia transversa*, and the ecdysozoans *Priapulus caudatus* and *Hypsibius exemplaris*. Tsai-Ming Lu, co-author of Paper I, performed the analyses. More details are specified in the Material and Methods section of the paper.

### 3.5 Gene cloning and probe synthesis (Papers I and II)

Specific primers for each gene were designed with MacVector 10.6.0 software based on the sequences obtained from the surveys in transcriptomes. Fragments of each gene were amplified and inserted into pGEM-T Easy vectors (Promega, USA) and transformed in competent *E. coli* cells. Minipreps were prepared using NucleoSpin®Plasmid kit (Macherey-Nagel) and sequenced in the Sequencing facility of the University of Bergen. Next, RNA probes using digoxigenin-11-UTP (Roche, USA) were prepared with the MEGAscript™ kit (Invitrogen, Thermo Fisher).

### 3.6 Whole mount *in situ* hybridization (Papers I, Paper II and additional results)

I performed whole mount *in situ* hybridization in *Terebratalia transversa* (Paper I) and *Lineus ruber* (Paper II) as described in (Gasiorowski and Hejnol, 2019; Martín-Durán et al., 2015; Schiemann et al., 2017). For *Terebratalia transversa,* proteinase K digestion was performed during 10 minutes, whereas *Lineus ruber* samples were digested for 15 minutes. In both cases, probes were hybridized at a concentration of 1 ng/µl at 67°C during approximately 72h. Colorimetric *in situ* hybridization are shown in Paper I, Paper II and in the additional results. Colorimetric *in situ* hybridization probe detection was performed with anti-digoxigenin-AP antibody (1:5000) and developed using NBT/BCIP. Next, samples were washed in 100% ethanol and rehydrated in ethanol descending-concentration steps (75%, 50%, 25%). Samples were mounted in 70% ethanol and imaged using an Axiocam HRc camera connected to an Axioscope Ax10 (Zeiss, Oberkochen, Germany). Images were analyzed using Fiji and Adobe Photoshop CS6. Furthermore, some fluorescent *in situ* hybridization (FISH) are also shown in the additional results. FISH probes were detected with anti-digoxigenin-POD antibody (1:250) and developed incubating in TSA Plus Cy3/Cy5 Kit (Perkin Elmer, USA) during 1h 15min. The nuclei were labelled with 1:2000 Hoechst® 33342 or 1:5000 Sytox Green. FISH samples were imaged using a Leica SP5 confocal laser-scanning microscope (Leica, Wetzlar, Germany). Images were also analyzed using Fiji and Adobe Photoshop CS6.

### 3.7 Bacterial culture (Paper II)

Gram-negative bacteria *Vibrio diazotrophicus* were purchased from ATCC (catalog number: 33466). Bacterial stocks were kept in agar plates made with Difco™ Marine Broth (Fisher Scientific) at 4°C and in 80% glycerol at -80°C. Prior use, the bacteria were resuspended and cultured in Difco™ Marine Broth (Fisher Scientific) at 26°C overnight in constant shaking.

### 3.8 Immune challenge experiments in *Lineus ruber* (Paper II)

The *Lineus ruber* specimens used in this experiment were collected specifically for this experiment by Aina Børve. The animals were acclimatized in the animal facility for two weeks in tanks with 2 liters of sea water with salinity 33 at 8°C.

Before the immune challenging experiment, I tested different bacterial concentrations into which expose the animals in order to select the appropriate concentration, in which the bacteria would infect the animals but not be lethal. In order to do that, I exposed 4 groups of animals (with 5 animals in each group) to different bacterial concentrations: $10^6$ bacteria/ml (group 1), $10^7$ bacteria/ml (group 2), $10^8$ bacteria/ml (group 3) and $7.6x10^8$ bacteria/ml (group 4). Bacterial cultures were prepared the previous night in Difco™ Marine Broth (Fisher Scientific) at 26°C in constant shaking. The final concentration of these cultures was $7.6x10^8$ bacteria/ml. In order to prepare the concentrations for groups 1-3, I diluted the bacterial culture to each concentration with autoclaved sea water. Two more groups of animals were used as controls, exposing them to only autoclaved sea water (group 5) and only autoclaved marine broth (group 6). Animals were monitored during 48h. All the animals in groups 1-3 and control groups survived the 48h and no major complications were observed. However, the 5 animals in group 4 (bacterial concentration: $7.6x10^8$ bacteria/ml) died after approximately 3h of exposure. Therefore, I decided to select $10^8$ bacteria/ml as the bacterial concentration for the experiment.

For the immune challenge experiment, I distributed 64 animals into 8 groups with 8 animals per group. Prior to distribution into the different groups, all animals were injured with a sterile needle in order to facilitate the penetration of bacteria. Groups 1-4 were exposed to *Vibrio diazotrophicus* at a concentration of $10^8$ bacteria/ml (immune challenged groups); while groups 5-8 were exposed to autoclaved sea water (control groups). Animals from one immune challenged group and one control group were snap-frozen at different timepoints (3h, 6h, 12h, and 24h) in liquid nitrogen and stored individually at -80°C.

### 3.9 RNA EXTRACTION, DNA SYNTHESIS, QUANTITATIVE REAL-TIME PCR (QPCR) AND DATA ANALYSIS (PAPER II)

I performed RNA extractions for each animal individually using TRI Reagent™ Solution (ThermoFisher Scientific) and 1-bromo-3-chloropropane (Sigma). cDNA was synthetized with the SuperScript™ III First-Strand Synthesis System (Invitrogen) kit, adding 1 µg of RNA to the reaction. Specific primers for each gene were designed in MacVector 10.6.0 software and ordered to Sigma. Gene sequences for *Lineus ruber TLRs* were obtained from surveys performed in Paper I, whereas the sequences of the remaining genes were obtained from the surveys in Paper II. *Lineus ruber Actin* was selected as a control gene. The primer efficiency was tested and genes with primers with the best primer efficiency and melting curves with only one peak were selected as candidates. The master mix for each qPCR contained 1µl of cDNA, 2 µl of primers (10 µM), 7 µl of sterile RNAse free water and 10 µl of mastermix Roche Diagnostics Lightcycler 480 Sybr Green I M (Fisher Scientific) and reactions were performed in Roche LightCycler 480 real-time PCR machine. 2 or 3 technical replicates and 2 or 3 biological replicates were performed per gene and timepoint. For each technical and biological replicates, both in infected and control animals, the gene of interest was normalized with the actin expression levels. Then, values of each gene of interest were compared between infected and control animals for each timepoint, and the fold expression was obtained applying the $2^{-\Delta\Delta CT}$ method (Livak and Schmittgen, 2001). I analyzed this data using the Light Cycler 480 SW 1.5.1, Microsoft Excel and StatPlus:mac LE v7 software.

### 3.10 Histology: embedding, sectioning and Hematoxilin-Eosin staining (Additional results)

I optimized the protocol for embedding *Lineus ruber* in paraffin and then, specimens were embedded in paraffin by the Molecular Imaging Facility (MIC) of the University of Bergen. In the laboratory facilities of Dr. Henrik Glenner, I performed horizontal cross-sections of 7μm thickness using a microtome Leica RM2255. The sections were transferred into poly-l-lysine coated slides (Thermo Scientific™ SuperFrost Plus™) and dried overnight at 37°C. Next, sections were deparaffinated by immersion into Neo-Clear Xylene substitute (Sigma Aldrich), descending ethanol series (100%, 96%, 70%) and phosphate buffer saline (PBS). Hematoxilin-Eosin (H-E) staining was performed incubating the samples in hematoxylin (Sigma Aldrich) for 5 min and in eosin (Sigma Aldrich) for 30 seconds. Slides were washed with PBS after both stainings and mounted in 70% glycerol. Samples were imaged with an Axioscope Ax10 (Zeiss, Oberkochen, Germany).

### 3.11 Illustrations

I have done all illustrations and figure plates in this thesis with Adobe Illustrator CS6.

# Chapter 4: Summary of the findings

## 4.1 The evolution of the metazoan toll receptor family and its expression during protostome development (Paper I).

The aim of this paper was to reconstruct the phylogenetic relationships of Toll receptors (TLRs) from cnidarians, spiralians, ecdysozoans, and deuterostomes, in order to study the evolution of these receptors. With this objective, I surveyed for TLRs in the transcriptomes and genomes of 45 species. Then, including TLRs from other species already available in the existing literature, I performed a phylogenetic analysis and classified these TLRs into V(ertebrate)-type/scc and P(rotostome)-type/mcc, according to their structure. Moreover, with the aim of discriminate the dual role of these receptors in immunity and development, Dr. Tsai-Ming Lu and I performed stage-specific analyses in four protostome species: the ecdysozoans *Priapulus caudatus* and *Hypsibius exemplaris*, and the spiralians *Crassostrea gigas* and *Terebratalia transversa*. In order to validate these results and to gain knowledge of the function of TLRs, I analyzed the spatial and temporal expression of TLRs in *Terebratalia transversa* by whole mount in situ hybridization (WMISH).

### Distribution of TLRs in the metazoan species analyzed and phylogenetic analysis

The genomic and transcriptomic surveys conducted in xenacoelomorphs, spiralians, and ecdysozoans reveal that the number of TLRs is variable depending on the species (Table 1 and Figure 3; Paper I). TLRs are not present in xenacoelomorphs and some spiralians (e.g. Cycliophora, Platyhelminthes, Micrognathozoa, Gastrotricha), indicating that TLRs could have been lost in these lineages. Within spiralians, multiple TLRs are present in variable numbers in the species surveyed, which suggests episodes of gene expansions in these lineages. On the contrary, we found lower numbers of TLRs in ecdysozoans, detecting only one TLRs in each nematode, onychophoran and tardigrade species analyzed, and up to 4 in priapulids, 2 in loriciferans, and 5 in arthropods. Next, I did a phylogenetic analysis including TLRs from cnidarians, spiralians, ecdysozoans, and deuterostomes. The phylogenetic analysis shows that TLRs cluster in three well-supported clades (>60), named here clade α, clade β, and clade γ (Figure 4; Paper I). Clade α is present in cnidarians, spiralians, and ecdysozoans; clade β in deuterostomes, spiralians, and three ecdysozoan species; and clade γ only in spiralians. Clade β and clade γ are sister clades and together form the sister clade to α. Performing two further phylogenetic analyses we investigated whether the two different insertions/deletions could explain the distribution of the TLRs in these three clades, however, this was not the case (Supplementary Figures 2 and 3; Paper I). Furthermore, V(ertebrate)-type/scc and P(rotostome)-type/mcc were found in the three clades, not being informative about which of the two types is the ancestral form (Figure 4; Paper I).

### TLRs ARE EXPRESSED DURING ONTOGENY IN THE FOUR PROTOSTOMES ANALYZED

We performed stage specific-transcriptome analysis in the ecdysozoans *Priapulus caudatus* and *Hypsibius exemplaris,* and in the spiralians *Crassostrea gigas* and *Terebratalia transversa* (Figure 5; Paper I). Analyses of *Hypsibius exemplaris* stage-specific transcriptomes show that the only TLRs present in this species (*Hex-TLRα2*) is expressed in time windows during ontogeny (Figure 5A; Paper I). The *Priapulus caudatus Pca-TLRα1* and *Pca-TLRα2* are expressed during the whole development, while *Pca-TLRα3* is expressed only in the later stages analyzed (Figure 5B; Paper I). Next, we found that 11 (out of 12) TLRs were expressed during *Crassostrea gigas* development (Figure 5C; Paper I). 5 of these genes (*Cgi-TLRα1, Cgi-TLRα4, Cgi-TLRβ4, Cgi-TLRδ1, Cgi-TLRδ2*) were expressed throughout development, while the other 6 (*Cgi-TLRα2, Cgi-TLRα3, Cgi-TLRβ1, Cgi-TLRβ2, Cgi-TLRγ1, Cgi-TLRγ2*) were expressed at specific developmental stages. Similarly, *Terebratalia transversa* stage-specific transcriptome analyses show that 12 (out of 15) TLRs were expressed during this species ontogeny (Figure 5D; Paper I). *Ttr-TLRα2, Ttr-TLRα5, Ttr-TLRβ1, Ttr-TLRβ4, Ttr-TLRβ5,* and *Ttr-TLRδ* are expressed in time windows, being all of them (except for *Ttr-TLRβ*) also expressed in the juvenile stages.

Next, in order to validate the stage-specific transcriptome analyses in *T. transversa*, I performed whole mount *in situ* hybridization (WMISH) at specific developmental stages for the *Terebratalia* TLRs (early gastrula only for *Ttr-TLRα4;* and late gastrula, early larvae and, late larvae for all the genes). Results show that *Ttr-TLRα2* is expressed in two pairs of lateral domains and the mesoderm (Figure 6B; Paper I). *Ttr-TLRα4* is expressed in different tissues through development (Figure 6G,I,J; Paper I). During early gastrula and early larval stages, this gene is expressed in the mesoderm (Figure

6G,I; Paper I). However, besides in the mesoderm, at early larval stages, this gene is also expressed in the inner lobe epithelium (Figure 6I; Paper I). At late larvae, *Ttr-TLRα4* is expressed in the pedicle and the brain (Figure 6J; Paper I). *Ttr-TLRα5* has a uniform salt and pepper expression pattern in the late gastrula and both larval stages analyzed (Figure 6K-M; Paper I). *Ttr-TLRβ3* is expressed in the anterior part of the animal in the late gastrula stage. Finally, *Ttr-TLRγ4* and *Ttr-TLRδ* expression was detected in the ectoderm in a salt and pepper distribution for all developmental stages analyzed. Expression by *in situ* hybridization was not detected in the remaining genes and developmental stages analyzed not mentioned here (Figure 6A,C-F,H,O,P; Paper I). Stage-specific transcriptome analyses and *in situ* hybridization results are in general consistent (Figure 6; Paper I). However, expression for *Ttr-TLRβ3* in the late larvae was detected in the specific transcriptome analysis, but not in the *in situ* hybridization. Similarly, expression was not detected for *Ttr-TLRγ4* in the early larvae stage-specific transcriptome analysis and for *Ttr-TLRδ* both in early and late larval stages, but *in situ* hybridization shows expression in the ectoderm. These differences between the results of stage-specific transcriptome analyses and *in situ* hybridization could be due to differences and variation of the developmental stages of the specimens used in both methods.

## 4.2 THE TOLL PATHWAY, THE COMPLEMENT SYSTEM, AND LECTINS ARE LIKELY INVOLVED IN IMMUNITY IN THE NEMERTEAN *LINEUS RUBER* (PAPER II)

The objective of this paper was to investigate the immune mechanisms present in the nemertean *Lineus ruber.* With this purpose, I surveyed the *Lineus ruber* transcriptome to identify genes belonging to the Toll pathway, the Imd pathway, the complement system, and lectins (FreD-Cs and C-lectins). Then, I analyzed the domain architecture of the proteins encoded by these genes (Figures 2, 3 and Supplementary figures 3 and 4 – Paper II) and performed phylogenetic analyses (Figures 2 and 3 – Paper II). Furthermore, I analyzed the expression patterns of the genes obtained in the transcriptomic survey in *Lineus ruber* juveniles by whole mount *in situ* hybridization (WMISH) (Figure 4 – Paper II). Finally, I performed an immune challenge assay by infecting adult *Lineus ruber* and assessed the expression levels of immune genes compared with non-infected conditions (Figure 5 – Paper II).

### IDENTIFICATION OF IMMUNE PROTEINS BELONGING TO THE TOLL PATHWAY, THE IMD PATHWAY, THE COMPLEMENT SYSTEM, AND LECTINS IN THE TRANSCRIPTOME OF *LINEUS RUBER*

The surveys performed on the *Lineus ruber* transcriptome identified components belonging to the Toll pathway, the Imd pathway, the complement system, and lectins. From the Toll pathway, the adaptor *myD88*, an *irak* gene, and the transcription factor *dorsal/diff/NFκB-p65* were identified. Domain architecture and phylogenetic analyses of the proteins encoded by these genes (Figure 2 – Paper II) confirm that they are orthologs of the components of the Toll pathway in other metazoans, including *Drosophila* and *Homo sapiens*. I also identified key components of the Imd pathway (*imd, fadd, dredd,* and *relish/NFκB-p105/100*). Domain architecture and phylogenetic analyses of their corresponding proteins confirmed their identity (Figure 2 – Paper II). Although 2 PGRPs were found in the *Lineus ruber* transcriptome, they could not be identified as receptors of this pathway. Additionally, surveys in the *Notospermus geniculatus* genome show that this nemertean has 8 PGRP genes, but they could not be identified as receptors of this pathway (Supplementary Figure 2 – Paper II). Regarding the complement system, I found 2 *C3* genes, 4 *Cfb* genes, and up to 26 putative genes encoding for complement receptors in the *Lineus ruber* transcriptome. Domain architecture and phylogenetic analyses of the proteins encoded by these genes confirmed the identity of the *Lineus ruber* C3 and Factor B proteins as orthologs of the C3 and Factor B proteins present in other species, respectively (Figure 3 – Paper II). Furthermore, domain architecture analyses reveal that among the 26 putative complement receptors, there are proteins containing similar domain organization to all the vertebrate complement receptor types (CR1, CR2, CR3, CR4, and CRIg) (Figure 3 and Supplementary Figure 3 – Paper II). Furthermore, I did not detect any orthologs for the vertebrates *C6*/*C7*/*C8*/*C9*, *C1s*/*C1r*/*MASP*, *MASP-related molecules* (*MReM*), and *Complement factor C* (*Cfc*) in the transcriptome surveys. Additionally, I also searched for genes encoding for FreD-Cs, C-lectins, and C1q proteins in order to identify putative activators from the complement system. The survey results reveal the presence of 4 genes encoding for FreD-C proteins containing coiled coil domains and 3 genes encoding for C1q proteins containing collagen domains (Supplementary Figure 4 – Paper II). Both coiled coil motifs and collagen domains allow protein multimerization and, therefore, these proteins could be suitable for complement system activation. C-lectins and the remaining FreD-Cs did not contain a domain architecture suitable for complement activation, but they have similar domain composition to C-lectins, FreD-Cs, and C1qs found in other metazoans.

### EXPRESSION OF IMMUNE GENES IN VARIOUS TISSUES IN *LINEUS RUBER* WAS DETECTED BY WHOLE MOUNT *IN SITU* HYBRIDIZATION (WMISH)

Next, in order to study the expression pattern of the genes detected in the transcriptome survey, I performed whole mount in situ hybridization (WMISH) in *Lineus ruber* juveniles. *fred-c1* is expressed in the ventrolateral nerve cords, the brain, and the cephalic nerves (Figure 4B – Paper II); whereas expression of *fred-c5* is detected in the blood (Figure 4C – Paper II). *c-lectin2* and *c-lectin3* are expressed only in the head, being *c-lectin2* detected in nervous structures (Figure 4D – Paper II) and *c-lectin3* in the proboscis area (Figure 4E – Paper II). *c-lectin5* is expressed in a small area of the brain and the cephalic nerves (Figure 4F – Paper II); while *c-lectin9* expression was detected in a more restricted area of the brain and the frontal sensory organ (Figure 4G – Paper II). *c-lectin10* is expressed in the ventrolateral nerve cords, the brain, and the eyes (Figure 4H – Paper II); and *c-lectin11* in the gut (Figure 4I – Paper II). *C1q-1* was found to be expressed in the ventrolateral nerve cords, the brain, and the frontal sensory organ (Figure 4J – Paper II).

Furthermore, I also performed WMISH for genes belonging to the Toll pathway (*TLR1-6*, *myD88*, and *dorsal/NFκB-p65*), the Imd-like pathway (*imd* and *relish/NFκB-p105/100*), for *C1q-2*, and other FreD-Cs and C-lectins (*fred-c2, fred-c3, fred-c4, fred-c6,* and *fred-c7, c-lectin1, c-lectin4, c-lectin5, c-lectin6,* and *c-lectin7*). However, no signal was detected for these genes.

### IMMUNE GENES ARE UPREGULATED IN *LINEUS RUBER* AFTER EXPOSURE TO GRAM-NEGATIVE BACTERIA

In order to study the immune role of the Toll pathway, the Imd pathway, the complement system, and lectins in *Lineus ruber*, I exposed adult specimens to the gram-negative bacteria *Vibrio diazotrophicus* and performed qPCRs to assess the expression levels of *TLRα3, TLRα4, TLRβ1, TLRβ2, imd, fred-c5, C3-1,* and *c-lectin2*. Expression of these genes was analyzed at 3h, 6h, 12h, and 24h, in control and infected animals. I used *actin* as a reference gene.

Expression of *TLRα3* at 3h and 6h of infection does not differ significantly from the control animals (Figure 5A – Paper II). However, at 12h, the expression of this gene is upregulated in infected animals, reaching 4.9-fold levels. At 24h, although *TLRα3* is still upregulated, expression levels have descended to 2.55-fold. At 3h, 6h, and 24h of infection *TLRα4* expression does not vary compared to the controls, whereas at 12h it is downregulated. *TLRβ1* expression is similar to the control animals at 3h. However, by 6h of infection, this gene is significantly upregulated with expression levels at 1.89-fold, reaching the 2.2-fold by 24h of infection. At 3h, *TLRβ2* expression levels are similar in infected and control animals. This gene is upregulated at 6h and 12h of infection, being at expression levels of 1.56-fold and 1.89-fold, respectively. However, at 24h of infection, this gene is significantly downregulated compared to the controls. *imd* is not significantly upregulated or downregulated at any studied timepoint. *C3-1* expression levels are similar in control and infected animals at 3h and 6h. By 12h, this gene is significantly downregulated but its expression increases at 24h, when expression of 1.7-fold was detected. The lectin *fred-c5* was detected to be downregulated at 3h of infection. However, expression levels increase to reach 1.56-fold at 12h of infection, although the levels of expression at 24h were similar to the controls. Finally, *c-lectin2* was expressed similarly at 3h and 6h in infected and control animals, but expression increased to reach expression levels of 1.55-fold by 12h. At 24h the expression of this gene decreases to similar levels to the control animals.

Analysis of the gene expression by timepoints (Figure 5B – Paper II) reveals that by 3h of infection, none of the genes studied is upregulated and only *fred-c5* is downregulated compared to the controls. At 6h, the Toll receptors *TLRβ1* and *TLRβ2* are the only genes to be upregulated, being the remaining genes at similar expression levels to the control animals. By 12h of infection, the majority of the gene expression levels are affected by the infection: the Toll receptors *TLRα3* and *TLRβ2,* and the lectins *fred-c5* and *c-lectin2* are upregulated; whereas *TLRα4* and *C3-1* are downregulated. The expression levels of *TLRβ1* and *imd* did not significantly vary compared to the controls. At 24h of infection, *TLRα3, TLRβ1,* and *C3-1* are upregulated, being *TLRβ2* downregulated.

## 4.3 Additional results

Additionally, in order to investigate whether 60 days after oviposition (dao) *Lineus ruber* juveniles already developed the morphology of the adults, I did cross-sections of the *Lineus ruber* juveniles and performed hematoxylin-eosin stainings. Furthermore, in order to study hematopoiesis and localize the hematopoietic tissue in this species, I performed *in situ* hybridization in *Lineus ruber* juveniles for genes involved in this process. However, as common areas of expression where hematopoiesis could occur were not detected, the hematopoietic tissue in this species could not be found.

### Histology in *Lineus ruber* juveniles shows identical morphology when compared to the adults, except for the gonads

As the *in situ* hybridization were performed on 60 dao juveniles *Lineus ruber*, I wanted to compare the morphology of the individuals at this stage with the morphology of adult *Lineus ruber* specimens. Thus, I performed cross-sections along the antero-posterior axis of the animal in order to assess whether the organs present in the adult *Lineus ruber* are already formed in the 60 dao juveniles or not (Figure 4.1). The histological sections show that at this stage, the brain is already formed, being the dorsal and ventral lobes already distinguishable (Figure 4.1B). The proboscis and the rhynchocoelum are also formed and, dorsal to them, the ventral blood lacuna is also observed. Moreover, the histological sections also show the cephalic organs, which are surrounded by blood vessels and closely located to the lateral nerve cords (Figure 4.1C). Cross-sections from the mid-trunk of the animal also show the two ventral nerve cords, located laterally to the gut (Figure 4.1D). In the mid-trunk sections, the lateral blood vessels are also normally observed. However, in some sections, they could not be identified, probably because they collapsed during tissue manipulation. Furthermore, the dorsal blood vessel is found between the rhynchocoelum and the gut (Figure 4.1C). The dorsal nerve cord, perpendicular blood vessels, and gonads were not identified in any of the sections analyzed. However, in a previous study, the dorsal nerve cord was shown to be present in *Lineus ruber* early juveniles (Martín-Durán et al., 2018). Furthermore, although they were not detected in the sections, we cannot discard the presence of perpendicular blood vessels at this stage, as it is plausible that they collapsed during tissue manipulation, as often happened with the lateral blood vessels. Thus, the morphology of the late juvenile is similar to the morphology in adults

(Figure 4.1E) (Beckers, 2014; Punnet, 1901), as all the organs and systems from the adult are already present in the juvenile, except for the gonads.

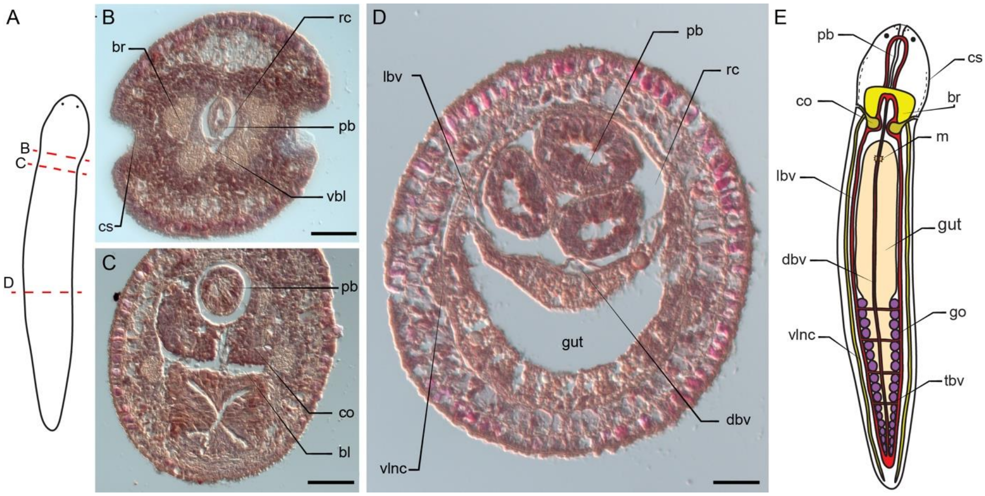


**Figure 4.1. Morphology of the 60 days *Lineus ruber* juvenile.** A. Diagram of a juvenile *Lineus ruber* showing the level of the cross-sections on B-D panels. B-D. Hematoxylin-Eosin staining of cross-sections at different points across the anterior-posterior axis. E. Diagram of an adult *Lineus ruber.* Dorsal is to the top. All scale bars indicate 100um. Diagrams are not at scale. bl: blood lacunae; br: brain, co: cephalic organs; cs: cephalic slits; dbv: dorsal blood vessel; lbv: lateral blood vessel; go: gonads; m: mouth; pb: proboscis; rc: rhynchocoelum; tbv: transversal blood vessel; vbl: ventral blood lacunae; vlnc: ventrolateral nerve cord. Schemes are not at scale. Panel E is adapted from Punnet, 1901.

## HEMATOPOIETIC GENES ARE EXPRESSED IN OTHER TISSUES THAN BLOOD IN *LINEUS RUBER*

In order to study the expression pattern of hematopoietic candidate genes in *Lineus ruber*, I performed *in situ* hybridization on *gata123, ebf, meis, vegfr, notch, gcm,* and *c/ebp. gata123* and *ebf* are expressed in the brain and the nerve cords (Figure 4.2A,B). *meis* is also expressed in the brain and the nerve cords, but, additionally, I also detected expression of this gene in the blood vessels and the cephalic organs (Figure 4.2C-C''). *runx1* expression is localized in some cells within the epidermis, most likely in gland cells (Figure 4.2D). *vegfr* expression was detected surrounding the proboscis in the head and in the posterior trunk, where the dorsal blood vessel is located (Figure 4.2E-E'). *notch* is expressed exclusively in the cephalic organ canals (Figure 4.2F-F'). *gcm* is expressed in the mid-posterior part of the head, in close proximity to the cephalic slits, including the surroundings of the cephalic organ canals (Figure 4.2G-

G'). Furthermore, although it was not visible in the colorimetric in situ hybridization, *gcm* was also detected surrounding the proboscis in the area of the head, where the blood lacunae that surround this organ are located (Figure 2G''). *c/ebp* is expressed in the brain, the lateral nerve cords, the cephalic nerve cords, and the apical organ (Figure 4.2J). Thus, many of the hematopoietic genes conserved in *Drosophila* and vertebrates, are expressed in other tissues than blood in *Lineus ruber*, being consistent with the role of these genes in other organs and systems (Alfonso and Jones, 2002; Cattenoz and Giangrande, 2016; Green and Vetter, 2011).

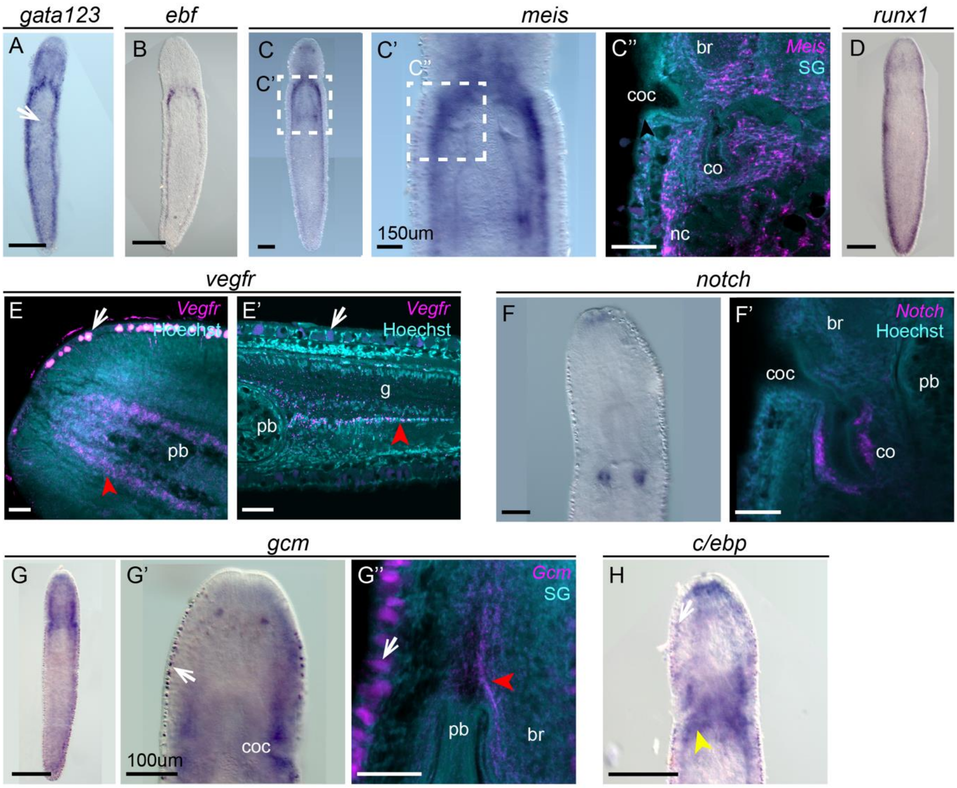


**Figure 4.2. Expression of hematopoietic candidate genes in *Lineus ruber* late juveniles.** Red arrows indicate expression or possible expression in the blood vessels/lacunae; Yellow arrows indicate localized expression in the cephalic organs or the cephalic organ canals; yellow dashed line indicates a big area of expression in the cephalic organ. White arrows indicate background, normally due to probe trapping in the epithelial glands. Black scale bars indicate 250µm and white scale bars indicate 25µm, unless another value is specified. bl: blood lacunae; br: brain; co: cephalic organ; coc: cephalic organ canal; con: cephalic organ nerve g: gut; nc: nerve cord; pb: proboscis.

# Chapter 5: Discussion

## 5.1 Gene expansions and losses shaped invertebrate Toll receptor evolution

The evolution of many gene families is driven by gene expansions and losses (Aguilera et al., 2013; Bastin and Schneider, 2019; Fernández and Gabaldón, 2020; Martín-Durán et al., 2013; Matus et al., 2007). According to my findings in Paper I, TLRs evolution has been shaped by multiple TLR losses and duplications in different metazoan lineages. In my research, surveys for TLRs in invertebrate genomes and transcriptomes and phylogenetic analyses integrating TLRs from species across the metazoan tree (Paper I) provide a comprehensive view of how TLRs have evolved in different metazoan lineages. There are few previous studies assessing phylogenetic relationships of TLRs within the main metazoan clades (Davidson et al., 2008; Luna et al., 2002; Luo and Zheng, 2000; Luo et al., 2018). These studies already provide some insights into TLRs evolution, for instance, Davidson *et al.,* 2008 (Davidson et al., 2008) show that TLRs cluster in three clades, although the relationships between these clades are not resolved; and both Davidson *et al.,* 2008 (Davidson et al., 2008) and Luo et al., 2018 (Luo et al., 2018) already show lineage specific expansions in some trochozoans. However, a TLR phylogenetic analysis, including a broader taxon sampling, was necessary to gain more insights on TLR evolution. Similar to Davidson *et al.,* 2008 (Davidson et al., 2008), my phylogenetic analysis shows that TLR cluster in three different clades (α, β, and γ) (Paper I). TLRs from clade α are present in cnidarians, spiralians, and ecdysozoans, and they are more similar to the *proto*-TLR, the TLR present in the common planulozoan ancestor, than to the other clades. Clade β is present in spiralians, ecdysozoans and deuterostomes; whereas clade γ is excusive from trochozoan spiralians. In the following paragraphs, I will explain how evolution of TLRs has been shaped by gene duplications and losses.

Due to the absence of TLRs in ctenophores (Traylor-Knowles et al., 2019), placozoans (Kamm et al., 2019) and poriferans (Gauthier et al., 2010; Wiens et al., 2006), previous studies have suggested that TLRs could have been originated in the lineage to planulozoans (cnidarians and bilaterians) by the fusion of an *LRR-only* and an *TIR-only* genes (Leulier and Lemaitre, 2008; Liu et al., 2020; Nie et al., 2018). However, this vision is challenged by the existence of TLRs in choanoflagellates, suggesting that this gene family was originated in the lineage to the choanoflagellate and metazoan common ancestor (Richter et al., 2018), unless metazoan and choanoflagellate TLRs would have been originated by convergent evolution. Independently whether metazoan Toll receptors were originated within the metazoan lineage or in the lineage to the common ancestor of choanoflagellates and metazoans, analyses in Paper I suggest that only one TLR (the *proto*-TLR) was present in the planulozoan common ancestor (Figure 5.1). This is supported by the fact that all cnidarian TLR sequences cluster together in the phylogenetic analysis (Paper I).

During cnidarian lineage evolution, mutations in the *proto*-TLR gene originated the *TLR-Cα,* the ancestor gene to all cnidarian TLRs. *TLR-Cα* was duplicated in some anthozoan lineages, as multiple TLRs are present in some species of this lineage (e.g. *Acropora digitifera* has 4 TLRs (Poole and Weis, 2014)). However, this TLR also was lost in the hydrozoan lineage (e.g. *Clytia* and *Hydra* (Bosch et al., 2009; Leclère et al., 2019)).

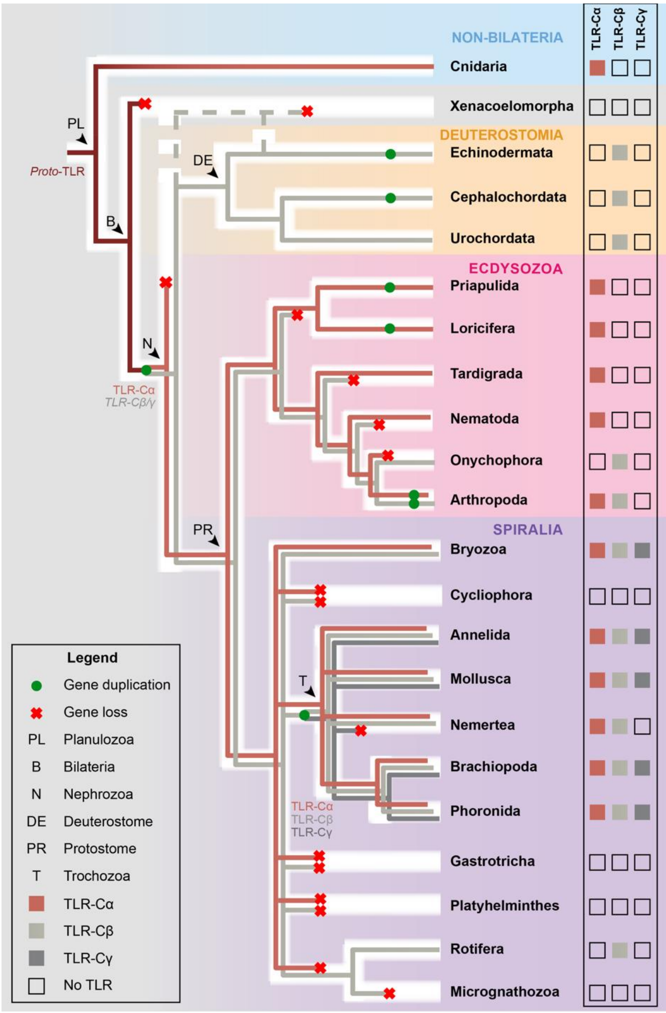


**Figure 5.1. Evolution of TLR.** White thick lines represent the phylogenetic relationships between the different taxonomic groups according to Dunn *et al.,* 2014; while discontinuous lines show alternative phylogenetic scenarios suggested by Kapli *et al.*, 2021. Thinner colored lines represent the evolution of TLRs: *proto*-TLR in dark brown; *TLR-Cα* and TLRs belonging to clade α in brown; *TLR-Cβ/γ*, *TLR-Cβ* and TLRs belonging to clade β in light grey, and *TLR-Cγ* and TLR belonging to clade γ in dark grey.

After the split of cnidarians and bilaterians, the *proto*-TLR duplicated, giving raise to two genes that would be the ancestral genes for clade α and clades β and γ (*TLR-Cα* and *TLR-Cβ/γ*, respectively). The phylogenetic position of xenacoelomorphs and echinoderms is controversial, with some authors affirming that xenacoelomorphs are the sister group to all nephrozoans and echinoderms belong to the deuterostomes (Cannon et al., 2016; Dunn et al., 2014; Hejnol et al., 2009; Srivastava et al., 2014). However, other authors consider that xenacoelomorphs and ambulacrarians (echinoderms and hemichordates) constitute a clade on their own, named Xenambulacraria, which is nested within the bilateria/nephrozoa (Kapli et al., 2021).

Considering the first scenario, in which xenacoelomorphs would be the sister group to all nephrozoans, the most parsimonious explanation suggests that the *proto*-TLR duplication to generate *TLR-Cα* and *TLR-Cβ/γ* would probably have occurred after the split of the xenacoelomorph and nephrozoan lineages; and, afterwards, the *proto*-TLR would have been lost in the xenacoelomorph lineage (Figure 5.1). Considering the second scenario, the duplication of the *proto*-TLR gene to generate *TLR-Cα* and *TLR-Cβ/γ* would have occurred before the emergence of the Xenambulacraria lineage. Therefore, *TLR-Cα* would have been lost during the early Ambulacraria lineage evolution, whereas *TLR-Cβ/γ* would have been lost in xenacoelomorphs and remained in echinoderms (Figure 5.1).

Therefore, the nephrozoan common ancestor likely had two TLR, the *TLR-Cα* and *TLR-Cβ/γ* (Figure 5.1). However, after the split of protostomes and deuterostomes, *TLR-Cα* was lost in the deuterostome lineage, being *TLR-Cβ/γ* the only TLR present in deuterostomes, which gave rise to the diversity of TLRs present today in the extant deuterostome species. Multiple episodes of gene duplications have occurred in the echinoderm and cephalochordate lineages (Hibino et al., 2006; Ji et al., 2018; Tassia et al., 2017), as more than 200 TLRs are present in the sea urchin *Strongylocentrotus purpuratus* (Hibino et al., 2006) and 30 TLRs in *Branchiostoma lanceolatum* (Ji et al., 2018). However, low numbers of TLRs are present in tunicates, being 2 TLRs present in *Ciona intestinalis* (Sasaki et al., 2009) and only 1 in *Oikopleura dioica* (Denoeud et al., 2010).

Like the nephrozoan common ancestor, the protostome common ancestor also likely had two TLR, the *TLR-Cα* and *TLR-Cβ/γ* (Figure 5.1). In ecdysozoans, TLRs belonging to both α and β clades have only been conserved in some arthropods. For instance, *Drosophila melanogaster* has 8 TLRs belonging to clade α, while only Toll9 belongs to clade β; and *Daphnia pulex* has 4 TLRα and only one TLRβ (Figure 4 – Paper I). However, this is not the case for other arthropods such as *Ixodes scapularis*, for which all TLR belong to clade α. Similarly, TLR from clade β would have been presumably lost in priapulids, loriciferans, tardigrades and nematodes. This implies the loss of *TLR-Cβ/γ* at least four times independently (one for the lineage to priapulids and loriciferans, another one for the lineage to tardigrades, another one for the lineage to nematodes, and another one within the arthropod lineage). Moreover, onychophorans seem to be the only ecdysozoan group that has a TLR from clade *β,* while they lost the TLR from clade *α.* Moreover, TLRs in ecdysozoans are present in low and similar numbers between different species, suggesting that episodes of gene duplications have not been frequent in this lineage.

Within spiralians, TLR evolution followed three different strategies: 1) Both *TLR-Cα* and *TLR-Cβ/γ* were lost in some spiralian clades (cycliophorans, gastrotrichs, platyhelminthes and micrognathozoans); 2) in rotifers *TLR-Cα* was lost, and only *TLR-Cβ/γ* was conserved; and 3) both *TLR-Cα* and *TLR-Cβ/γ* were conserved (bryozoans and trochozoans). Additionally, *TLR-Cβ/γ* was duplicated in the lineage to trochozoans and, therefore, the last common ancestor of all trochozoans had three TLR, which were the ancestor genes of the trochozoan TLRs belonging to clades α, β, and γ. TLRs are present in highly variable numbers among trochozoans, which is explained by multiple gene duplications and losses in these lineages. Some of these duplications and losses have occurred recently, causing that species belonging to a same trochozoan clade have very different numbers of TLRs (e.g. the phoronid *Phoronis australis* has 24 TLRs, while only 3 are present in *Phoronis psammophila* (Halanych and Kocot, 2014)).

Furthermore, the analyses in Paper I indicate that TLRs belonging to clade γ are exclusive from trochozoans. All TLRs from deuterostomes, onychophorans and arthropods that emerged from *TLR-Cβ/γ* cluster with trochozoan clade β TLRs (Figure 4 – Paper I). This is because the deuterostome, onychophoran and arthropod TLRβ sequences must be more similar to the trochozoan TLRs from clade β than to TLRs from clade γ; and trochozoan TLRs from clade β are more similar to the deuterostome, onychophoran and arthropod TLRβ sequences than to TLRs from clade γ. This could indicate that TLRs from clade γ were very fast evolving.

But why gene gains and losses are frequent in some lineages (e.g. trochozoans) and less frequent in others (e.g. ecdysozoans)? These gains and losses are probably the consequence of multiple factors, such as adaptation to new environments, or to be related to pathogen abundancy, pathogen diversity, lifestyles (e.g. sessility vs motility), or even with the disponibility of other defense mechanisms. Therefore, adaptation to new environments or microbe-rich environments could have driven the evolution of TLRs towards expansion, as, for instance, oysters that live in microbe-rich environments have a large immune gene repertoire (Guo et al., 2015); whereas TLR expansion might not have occurred if other mechanisms to detect these pathogens were already present. Therefore, expansion of TLRs is possibly also correlated to functional diversification and generation of a broader assortment of immune resources. Moreover, the numerous TLR expansions in trochozoans but not in non-trochozoan spiralians and ecdysozoans suggests different immune strategies in trochozoans and in non-trochozoan spiralians and ecdysozoans, as the later need to have evolved also other mechanisms to defend themselves. Especifically in ecdysozoans, the presence of cuticles could already confer some protection against pathogens that it is not present in spiralians, which could be one of the possible explanations to the fact that the TLR complement in ecdysozoans seems to be less numerous than in trochozoans.

## 5.2 TLRs ARE INVOLVED IN DEVELOPMENT AND IMMUNITY DURING ONTOGENY, BUT WHICH IS THE PUTATIVE ANCESTRAL FUNCTION OF THIS GENE FAMILY?

As mentioned before, having a wide set of immune proteins is advantageous in order to adapt to new environments or to microbe-rich environments. This is important for adult organisms, but it is also very relevant for embryos and larvae, as pathogens also can cause their death or abnormalities in their development (Balbi et al., 2019; Benkendorff et al., 2001; Deris et al., 2020). Therefore, immune strategies are already present in early embryonic stages (Balbi et al., 2019; Benkendorff et al., 2001; Hamdoun and Epel, 2007; Jacobs et al., 2014; Tirapé et al., 2007). Besides being involved in metazoan innate immunity in adults, TLRs also play a role in immunity during ontogeny. For instance, TLRs have been shown to participate in embryonic and/or larval immunity in arthropods (Deris et al., 2020; Tauszig et al., 2000), mollusks (Tirapé et al., 2007), and amphioxus (Yuan et al., 2009). However, TLR functions during ontogeny are not only restricted to immunite functions, as these genes are also involved in developmental processes. For example, besides being involved in immunity, the cnidarian *Nematostella vectensis* TLR also plays a role in early development (Brennan et al., 2017); and multiple TLRs are involved in developmental processes in *Drosophila melanogaster,* such as establishment of the dorso-ventral axis (Anderson et al., 1985; Anderson and Nüsslein-Volhard, 1984) or muscle and neuronal development (Halfon et al., 1995; Ward et al., 2015), among others (Benton et al., 2016; Byun et al., 2019; Eldon et al., 1994; Meyer et al., 2014; Paré et al., 2014; Wang et al., 2005). In onychophorans, a TLR has also been suggested to be involved in axis elongation and heart formation (Janssen and Lionel, 2018); and in mice, TLRs are involved nervous system development (Hung et al., 2018; Kaul et al., 2012; Shechter et al., 2008). Additionally, TLRs also participate in embryonic and/or larval immunity in arthropods (Deris et al., 2020; Tauszig et al., 2000), mollusks (Tirapé et al., 2007), and cephalochordates (Yuan et al., 2009). In Paper I, stage-specific transcriptome analyses showed that TLRs are expressed during development in the ecdysozoans *Hypsibius exemplaris* and *Priapulus caudatus* and in the spiralians *Crassostrea gigas* and *Terebratalia transversa*. Furthermore, whole mount *in situ* hybridization in *Terebratalia transversa* shows that TLRs in this species are expressed in the endomesoderm and the ectoderm during embryonic stages; and in the mesoderm, brain, and ectoderm in larval stages. However, although these analyses show expression of TLRs in these species during ontogeny, they are not enough to assess whether they participate in developmental or immune processes.

In a global perspective, the dual function of TLRs raises the question whether the ancestral function of these receptors is immunity or development. From my point of view, aiming to answer this question is challenging. As mentioned before, both, immune and developmental roles for these receptors are widespread in planulozoans, including cnidarians and bilaterians (Anderson et al., 1985; Anthoney et al., 2018; Brennan et al., 2017; Kaul et al., 2012; Lemaitre et al., 1996; Manicassamy and Pulendran, 2009; Prochazkova et al., 2019; Ren et al., 2016). Therefore, both of these functions were presumably already present in the Planulozoan common ancestor. Outside metazoans, TLRs are present in choanoflagellates, which are single-celled organisms in which some species form colonies (Richter et al., 2018). Richter et al., 2018 suggest that TLRs could be involved in immunity and prey detection. However, to the best of my knowledge, there are not studies addressing the function of TLRs in choanoflagellates, which could be involved in immunity but also in colony organization, having perhaps similar mechanisms than TLRs in metazoan development. Moreover, proteins containing LRR domains are involved both in immunity and development in plants (Diévart and Clark, 2004). Therefore, unless one of these functions was coopted separately in plants and animals, it is possible that both functions were already present in the *LRR-only* and *TIR-only* genes that originated the first TLR.

## 5.3 Vertebrate and arthropod immune mechanisms are present in the nemertean *Lineus ruber*

In the previous section, corresponding to Paper I, I addressed evolution of TLR in a global metazoan scale, in order to infer how evolution of this gene family and, therefore, evolution of the Toll pathway has occurred. In this section, I will discuss how immunity occurs in the nemertean *Lineus ruber*, focusing on the Toll pathway, the Imd pathway, and the complement system upon gram-negative bacterial infection.

### 5.3.1 The Toll pathway

The Toll pathway is involved in immunity through metazoans. Upon pathogen recognition, the TLR interact with adaptor proteins, triggering a kinase cascade that ends with the translocation of the transcription factor NF-κB into the nucleus. TLRs are activated either by the direct binging of pathogens to TLRs or by the binding of the Spätzle protein. In *Lineus ruber*, the lack of an Spätzle protein suggests that TLRs are activated by direct binding to the ligand, in a similar way than in vertebrates (Medzhitov, 2001; Valanne et al., 2011). As mentioned before, the number of TLR highly varies according to the species (section 5.1). In *Lineus ruber*, 6 TLRs are present, belonging 4 of them to the TLR clade α (TLRα1, TLRα2, TLRα3, and TLRα4) and the other 2 to the TLR clade β (TLRβ1 and TLRβ2) (Paper I). Therefore, on the contrary to other trochozoans (e.g. annelids, mollusks, brachiopods), no TLRs belonging to clade γ are present in *Lineus ruber.* This also occurs in the other two pilidiophoran and the hoplonemertean nemerteans for which TLRs were included in the phylogenetic analysis in Paper I, suggesting that TLRs belonging to clade γ were lost either in early nemertean evolution, or at least, in early neonemertean (Pilidiophora and Hoplonemertea) evolution (Alfaya et al., 2019; Andrade et al., 2014). Furthermore, a MyD88 adaptor protein, at least one Irak protein, and the transcription factor Dorsal/Diff/NF-κB-p65 are also present in *Lineus ruber*.

Moreover, in Paper II, I show that *Lineus ruber TLRα3, TLRβ1* and *TLRβ2* are involved in defense against gram-negative bacteria, as they are upregulated after exposure to *Vibrio diazotrophicus.* From these genes, *TLRβ1* and *TLRβ2* are the first TLRs to be upregulated, suggesting that they could be involved in a first wave of immunity. However, *TLRα3* has a later and stronger upregulation, indicating that, although in later steps of infection, this gene has a stronger response against gram-negative infection. Upregulation of TLRs upon gram-negative exposure also occurs in other invertebrates, such as mollusks (Priyathilaka et al., 2019; Ren et al., 2016; Wang et al., 2011) and arthropods (Deepika et al., 2020; Deris et al., 2020; Li et al., 2013). Altogether, these studies indicate that the Toll pathway is involved in response against gram-negative bacteria in invertebrates. Additionally, *Lineus ruber TLRα4* did not show any response against gram-negative infection, suggesting that this gene might not be involved in immunity against gram-negative bacteria.

### 5.3.2 The Imd pathway

The Imd pathway is known for being involved mainly in the response of gram-negative bacteria in arthropods, although this pathway is also activated against some gram-positive bacteria (Bai et al., 2020; Bao et al., 2013; Hoffmann and Reichhart, 2002; Zhou et al., 2018). The Imd adaptor is the key component of this pathway and, as this protein has not been identified outside Arthropoda (Gerdol et al., 2018; Mapalo et al., 2020; Toubiana et al., 2014), the presence of the Imd pathway in other organisms than arthropods is not clear. Specifically in spiralians, the presence of the Imd pathway is controversial in brachiopods and mollusks due to the absence of the Imd protein (Gerdol et al., 2018; Toubiana et al., 2014), although other components of this pathway are present (e.g. PGRPs, Fadd, Dredd, Relish). However, the presence of the Imd protein in *Lineus ruber* (Paper II) shows that this protein and, therefore, this pathway is present in some spiralians. However, expression of *imd* does not change upon exposure to gram-negative bacteria, suggesting that, on the contrary to arthropods, the Imd pathway in *Lineus ruber* would not be involved in immunity against gram-negative bacteria. However, as in arthropods, this pathway is also involved in the defense against some gram-positive bacteria (Bai et al., 2020), it could be possible that the *Lineus ruber* Imd pathway would be involved in immunity against gram-positive bacteria.

Besides Imd, Fadd, Dredd and the transcription factor Relish/NFκB-p105/100 are also present in *Lineus ruber* (Paper II). However, although PGRP receptors are present in this species, PGRPs compatible with Imd pathway activation are lacking. In arthropods, long PGRPs involved in Imd pathway contain RHIM motifs, which are involved in signal transduction (Kaneko et al., 2006). Although long PGRPs have been found in mollusks and brachiopods – but not in *Lineus ruber* –, these proteins do not contain RHIM motifs. Therefore, in case that PGRPs would be involved in the spiralian Imd pathway, an alternative signaling mechanism should be present in those receptors. Nonetheless, there is also the possibility that PGRPs would not be involved in the spiralian Imd pathway and this pathway would be activated by other receptors. For instance, the vertebrate TNF-α pathway, which is analogous to the Imd pathway and shares many components with it (e.g. Fadd, Dredd/Caspase8, Tak1, Relish/NFκB-p105/100), is not activated by PGRP receptors, but by the TNFR1 receptor (Myllymäki et al., 2014). Therefore, similar receptors could maybe be involved in the activation of the Imd pathway in spiralians.

### 5.3.3 The complement system

The complement system is a defense mechanism consisting of extracellular and transmembrane proteins that, upon pathogen detection, leads to a proteolytic cascade that triggers immune mechanisms including opsonization, phagocytosis, inflammation processes, and cytolysis. The complement cascade has been very well characterized in vertebrates, being activated by three pathways: the alternative pathway, the lectin pathway and the classical pathway (Merle et al., 2015a, 2015b). However, how the complement system functions in invertebrates has not been so clearly elucidated. The alternative pathway to activate complement is the most ancient of the three pathways, being already present in the planulozoan common ancestor (Nonaka and Kimura, 2006). The origin of the lectin pathway has been hypothesized to occur in chordates (Nonaka and Kimura, 2006). However, more recent studies challenge this view, suggesting that this pathway could be present in spiralians (Gerdol et al., 2018; Gorbushin, 2019). Moreover, due to the lack of antibodies in invertebrates, and the involvement of these proteins in classical pathway activation, it is widely accepted that this pathway was originated in the early vertebrate lineage evolution (Fujita et al., 2004a; Nonaka and Kimura, 2006).

The core complement system of *Lineus ruber* is composed by 2 C3 proteins, 4 Factor B, and up to 26 putative complement receptors (Paper II). The presence of these proteins could suggest that the complement system in *Lineus ruber* is activated by the alternative pathway, similarly than in brachiopods and mollusks (Gerdol et al., 2018; Gorbushin, 2019). Additionally, upregulation of *C3-1* in *Lineus ruber* during gram-negative bacterial infection shows that the complement system would be activated against gram-negative bacteria in *Lineus ruber* (Paper II). Upregulation of complement components occurs upon immune challenge with gram-negative bacteria in cnidarians and in invertebrate deuterostomes (Clow et al., 2000; Poole et al., 2016; Wang et al., 2009); and, specifically, upregulation of *C3* has also been detected in mollusks (Peng et al., 2017; Wang et al., 2017).

In vertebrates, C1q, ficolins, and mannose-binding lectins (MBL) are receptors that detect pathogens and activate the complement system via the classical and the lectin pathway. These proteins are multimeric proteins that associate by collagen domains. Although C1q proteins are also present in invertebrates, ficolins and MBL proteins, however, are lacking. Nonetheless, similar proteins (FreD-Cs and C-lectins) containing coiled coils instead of collagen domains are present in protostomes (Gorbushin, 2019). Since coiled coil domains are also multimeric domains (Kammerer, 1997), FreD-Cs and C-lectins have been suggested to perform analogous roles to ficolins and MBL in complement activation in invertebrates (Gerdol et al., 2018; Gorbushin, 2019). The transcriptome of *Lineus ruber* contains 3 genes encoding for C1q proteins containing collagen domains and 4 genes encoding for FreD-C proteins with coiled coil domains that could function as putative receptors of the complement system (Paper II). However, after the pathogen would be detected by the FreD-Cs or C1q, serine proteases are needed in order to trigger the proteolytic cascade. While serine proteases are present in vertebrates and mollusks (MASP, C1s, and C1r in vertebrates and MreM in mollusks) (Gorbushin, 2019; Matsushita and Fujita, 1992), they have not been found in *Lineus ruber* (Paper II) and in brachiopods (Gorbushin, 2019). Therefore, another mechanism to circumvent the lack of serine proteases is needed to trigger the complement cascade.

## 5.4 Summary and conclusions

Innate immunity is an essential defense mechanism in order to protect ourselves against pathogens. Along this thesis, I have stressed the importance of the innate immune system in invertebrate species, focusing mostly on the Toll pathway and evolution of TLRs, but also having a glimpse into the Imd pathway, and the complement system involved in immunity in the nemertean *Lineus ruber.* The Toll pathway is an ancient pathway present in metazoans that is involved in bacterial, fungi, and viral infection. The Toll receptors, which are found in variable numbers along species in the metazoan tree, have evolved from a *proto*-TLR that has originated three clades (α, β, and γ). Clade α TLRs are present in cnidarians, ecdysozoans and some spiralians; clade β in some spiralians, some ecdysozoans, and in deuterostomes; and clade γ only in trochozoan spiralians. Evolution of these TLRs clades has implied duplications and losses of TLRs since early metazoan evolution (e.g. TLR loss in xenacoelomorphs or duplication in the nephrozoan common ancestor); but they have also occurred more recently in specific lineages, which explains the high variability on the number of TLRs in spiralians, for instance. TLRs gains probably caused functional specialization of these receptors, providing a diversified tool of immune mechanisms that facilitate animals to adapt and survive to microbe-rich environments, for example. Moreover, although TLRs are of high importance in adult immunity, they are also involved in immunity in ontogeny and play a role in diverse developmental processes in embryos and larvae. The study of the expression of TLRs during ontogeny in protostomes shows that these genes have different spatial and temporal expression dynamics during development. Furthermore, in this thesis I also addressed the function of the Toll pathway by identifying components of this pathway in the nemertean *Lineus ruber* and showing that at least three TLRs are involved in defense against gram-negative bacteria in this system. Moreover, identification of components of the Imd pathway in *Lineus ruber*, showed for the first time the presence of the Imd protein, which could not have been identified previously in brachiopods and mollusks. However, the lack of response of this protein against gram-negative infection suggests that this pathway is not involved in defense against gram-negative bacteria but opens the possibility that this pathway plays a role in immunity against other pathogens. Lastly, I also show that the complement system in *Lineus ruber* could be activated by both the alternative and the lectin pathways and that this system is involved in response to gram-negative infections. Altogether, these findings provide insights into the evolution of innate immune mechanisms in invertebrates.

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# CHAPTER 7: PAPERS I, II AND III

## 7.1 Paper I: The evolution of the metazoan Toll receptor family and its expression during protostome development.

Paper I

# The evolution of the metazoan Toll receptor family and its expression during protostome development


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## Abstract

**Background:** Toll-like receptors (TLRs) play a crucial role in immunity and development. They contain leucine-rich repeat domains, one transmembrane domain, and one Toll/IL-1 receptor domain. TLRs have been classified into V-type/scc and P-type/mcc TLRs, based on differences in the leucine-rich repeat domain region. Although TLRs are widespread in animals, detailed phylogenetic studies of this gene family are lacking. Here we aim to uncover TLR evolution by conducting a survey and a phylogenetic analysis in species across Bilateria. To discriminate between their role in development and immunity we furthermore analyzed stage-specific transcriptomes of the ecdysozoans *Priapulus caudatus* and *Hypsibius exemplaris*, and the spiralians *Crassostrea gigas* and *Terebratalia transversa*.

**Results:** We detected a low number of TLRs in ecdysozoan species, and multiple independent radiations within the Spiralia. V-type/scc and P-type/mcc type-receptors are present in cnidarians, protostomes and deuterostomes, and therefore they emerged early in TLR evolution, followed by a loss in xenacoelomorphs. Our phylogenetic analysis shows that TLRs cluster into three major clades: clade α is present in cnidarians, ecdysozoans, and spiralians; clade β in deuterostomes, ecdysozoans, and spiralians; and clade γ is only found in spiralians. Our stage-specific transcriptome and *in situ* hybridization analyses show that TLRs are expressed during development in all species analyzed, which indicates a broad role of TLRs during animal development.

**Conclusions:** Our findings suggest that the bilaterian TLRs likely emerged by duplication from a single TLR encoding gene (*proto*-TLR) present in the last common cnidarian-bilaterian ancestor. This *proto*-TLR gene duplicated before the split of protostomes and deuterostomes; a second duplication occurred in the lineage to the Trochozoa. While all three clades further radiated in several spiralian lineages, specific TLRs clades have been presumably lost in others. Furthermore, the expression of the majority of these genes during protostome ontogeny suggests their likely involvement in development.

## Keywords

Toll receptor, Toll-like receptor, innate immunity, development, metazoan evolution, gene duplication

## Background

Toll-like receptors (TLRs) are involved in immunity and development in metazoans [1–7]. The first described *Tlr* was the *Drosophila* gene *Toll*, which plays a role during early embryonic development [8, 9] and in immunity [10]. The human toll receptor TLR4 was the first TLR discovered in mammals [11]. Since then, TLRs have been found in most planulozoans (Cnidaria + Bilateria) [12–14]. Both in vertebrates and invertebrates, these receptors recognize pathogens and activate the Toll pathway, which induces the expression of downstream immune genes [15–17]. In *Drosophila*, TLRs are mainly activated by gram-positive bacteria, fungi, and viruses, promoting the synthesis of antimicrobial peptides (AMPs) [4, 10, 17–21]. In vertebrates, TLRs are involved in innate immunity and in the activation and regulation of adaptive immunity [11, 22–26]. TLRs are also involved in the immunity of other animals such as cnidarians [27], mollusks [28–31], annelids [32, 33], crustaceans [34] and echinoderms [35]. The developmental roles of TLRs in *Drosophila* [reviewed in 2] comprise the establishment of the dorso-ventral axis [8, 9], segmentation [36], axis elongation [37], muscle and neuronal development [38, 39], wing formation [40, 41] and heart formation [42]. TLRs also play a role in cnidarian development [27]. Moreover, in ecdysozoans, TLRs have also been shown to be involved in onychophoran axis elongation [43]. In spiralians, TLRs are expressed during the development of mollusks [31] and annelids [32], but no further analyses have been conducted. TLRs are also involved in nervous system development in mice [44–47], although the ligands that activate them during this process remain unknown [2].

TLRs are proteins characterized by an extracellular region containing one or more leucine-rich repeat (LRR) domains, one type-I transmembrane domain and one intracellular Toll/IL-1 receptor (TIR) domain (Figure 1) [48, 49]. The extracellular LRR domains are the regions that recognize the ligand [50, 51]. Each LRR domain is constituted by 22-26 amino acids, in which multiple leucine residues are present [48]. Some LRR domains contain cysteine residues in the N-terminal (LRRNT) or the C-terminal (LRRCT) part of the LRR domain [6, 49, 52]. However, LRR domains are also found in a large number of other proteins [53], for example in the immune NOD receptors [54] and in proteins involved in developmental processes (e.g. Slit, Capricious, Tartan) [55, 56]. The TIR domain is involved in signal transduction [49] and is also present in other proteins, e.g. in immune proteins in plants [57, 58], in members of the interleukin-I receptor family (IL-1) [49, 59] and in adaptors of the Toll pathway (e.g. MyD88) [60–62]. Although the TIR domain is the most characteristic domain of the TLRs, at least one LRR domain must be present to categorize a receptor as TLR (Figure 1) [13].

Based on the structure of the LRR domains, TLRs have been previously classified as vertebrate-type or single cysteine cluster (V-type/scc), and protostome-type or multiple cysteine cluster (P-type/mcc) (Figure 1) [7, 13, 63, 64]. V-type/scc TLRs are characterized by having only one LRRCT domain, which is located next to the cellular membrane. P-type/mcc TLRs contain at least two LRRCT domains and, commonly, an LRRNT [7, 13]. Traditionally, it has been assumed that all deuterostome TLRs belong to the V-type/scc [64], and because *Drosophila melanogaster* TLRs (except for Toll9) and the *Caenorhabditis elegans* TLR belong to the P-type/mcc, they have been suggested to be protostome specific [64]. However, P-type TLR are also present in invertebrate deuterostomes and V-type TLRs in protostomes [13, 14, 65, 66]. Therefore, in agreement with Davidson et al., 2008 [65]; and Halanych and Kocot, 2014 [66], we affirm that the V- P-type nomenclature is problematic and should be avoided in favor of the mcc/scc nomenclature.

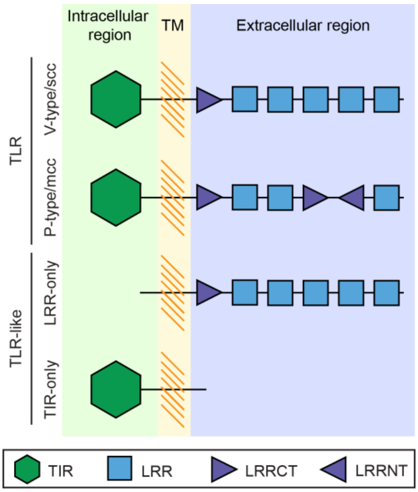


**Figure 1. Structure of TLR and TLR-like receptors.** TLRs are constituted by a series of extracellular leucine-rich repeat (LRR) domains, a transmembrane region (TM) and an intracellular Toll/IL-1 receptor (TIR) domain. TLRs are often classified into V-type/scc or P-type/mcc according to the structure of their extracellular region. V-type/scc TLRs have only one LRRCT located next to the TIR domain, while P-type/mcc TLRs have more than one LRRCT and, sometimes, an LRRNT domain. Proteins that lack either the LRR domains or the TIR domain are not considered as TLR receptors. These TLR-like proteins are classified in LRR-only or TIR-only. [Adapted from 7, 13]

Several authors consider that TLRs originated in the lineage to the Planulozoa by the fusion of a gene with a TIR domain (*TIR-only*) and a gene containing only LRR domains (*LRR-only*) [7, 14, 67]. However, this hypothesis is challenged by the presence of TLRs in choanoflagellates, the sister group to metazoans, which suggests that the origin of TLR could predate metazoans [68]. LRR-only and TIR-only are TLR-like proteins (Figure 1) involved in immunity [7, 12–14, 69–74] – e.g. in *Hydra*, association of LRR-only and TIR-only proteins activates the Toll pathway [75, 76].

The TLR complement has been previously surveyed in vertebrates [11, 52, 77–79] and in a few invertebrates, especially in arthropods [8, 14, 18, 80, 81]. Humans have 10 TLRs [11, 52], *D. melanogaster* has 9 [8, 18] and the nematode *C. elegans* has only one [82]. Recent genome and transcriptome sequencing of more organisms has revealed that TLRs are widespread across the metazoan tree (summary in Figure 2). Outside bilaterians, TLRs are present in anthozoan cnidarians (e.g. *Nematostella* [27], *Acropora* [72], *Orbicella* [83]), but not in hydrozoans (e.g. *Hydra* [75], *Clytia* [84]).

Furthermore, TLRs have not been found in ctenophores [85, 86], placozoans [73] and poriferans [69, 74]. Within bilaterians, previous studies have shown that the number of TLRs in spiralians is highly variable between species [65, 66, 87–90], suggesting that TLR genes underwent several independent radiations [13, 65, 89, 91]. However, the surveyed platyhelminth and rotifer species lack TLRs [70, 71, 92]. In ecdysozoans, besides arthropods and nematodes, TLRs are also present in onychophorans, tardigrades, nematomorphs and priapulids [93]. In invertebrate deuterostomes, the number of TLRs in echinoderms and amphioxus is expanded [64, 94, 95], which is in contrast to the limited number of TLRs in tunicates [96, 97]. Although the TLR sequences of many metazoans have been explored [7, 12–14], more protostome species must be surveyed to gain a better picture of the TLR evolution (Figure 2).

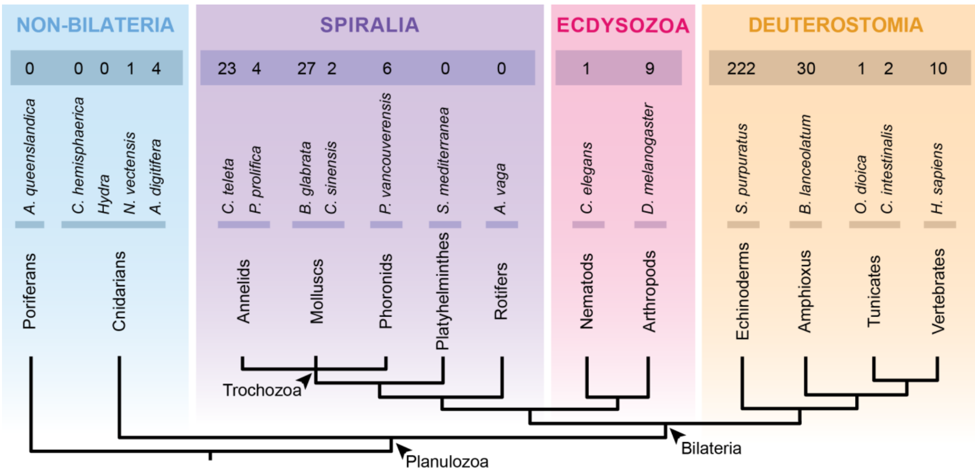


**Figure 2. Review of the number of TLRs across metazoans.** Within metazoans, no TLRs have been found outside Cnidaria and Bilateria. Spiralians show a variable number of TLRs, being, for example, 23 TLRs in the annelid *C. teleta*, but none in the rotifer *A. vaga*. In ecdysozoans, *C. elegans* and *D. melanogaster* have 1 and 9 TLRs, respectively. The number of TLRs in deuterostomes is also variable, being high in *S. purpuratus* and *B. lanceolatum*, but reduced in tunicates. References: [8, 11, 18, 27, 52, 64–66, 69, 70, 72, 75, 82, 84, 88, 92, 94, 96, 97]. Phylogeny according to [98].

Although the phylogenetic relationships of TLRs have been previously analyzed, these were mainly focused on vertebrate TLR evolution [67, 99] or including only few protostome species [13, 65, 89]. So far, the results are contradictory and are not sufficient to comprehend the detailed evolution of TLRs. For instance, Davidson et al., 2008 [65] suggested that TLRs are divided into three major clades, although the relationships between them remained unresolved. Brennan and Gilmore, 2018 [13] suggested that TLRs cluster according to the TLR-type (P-type/mcc or V-type/scc) and Liu et al., 2020 [67] suggested that both TLR types would be widespread in invertebrates. Furthermore, Luo et al., 2018 [89] showed lineage-specific expansions of TLRs in some trochozoan groups (phoronids, nemerteans and brachiopods). Thus, phylogenetic analyses including TLRs of species representing the broad metazoan diversity are lacking. In this study, we aim to reconstruct the TLR evolution by searching for TLRs in under-represented metazoan clades and performing a phylogenetic analysis including TLRs of species from the four main metazoan clades (cnidarians, spiralians, ecdysozoans and deuterostomes). Moreover, we aim to reconstruct the early TLR function by analyzing their expression during the course of development in four protostome species.

## Results

Our genome and transcriptomic surveys revealed a total of 198 TLRs in 25 species (Table 1, Figure 3). No TLRs were found in 20 species. Additionally, our analysis also revealed a large number of TLR-like proteins (TIR-only or LRR-only). However, only sequences containing a TIR domain, a transmembrane domain and, at least, one LRR domain were considered as criteria for TLRs.

### TLRs are absent in the genomes and transcriptomes of xenacoelomorphs and in some spiralians

Our surveys revealed that TLRs are absent in the genomes and transcriptomes of all Xenacoelomorpha, Platyhelminthes, Cycliophora, Micrognathozoa and Gastrotricha species analyzed (Table 1). Furthermore, TLRs are also absent in the transcriptomes of all the rotifer species investigated, except for *E. senta* (Table 1, Figure 3). Moreover, although TLRs were present in the bryozoan *M. membranacea*, they were not found in the transcriptome of the bryozoan *B. neritina*. However, although TLRs were not detected, TLR-like proteins were present in all these animal groups (data not shown).

**Table 1. TLR genome/transcriptome survey results and classification of TLRs included in the phylogenetic analysis.**

| | Species | TLRs | V-type /scc | P-type /mcc | NC | Reference |
|---|---|---|---|---|---|---|
| | **Cnidaria** | | | | | |
| | *Nematostella vectensis* | 1 | 0 | 1 | 0 | L: [27] |
| | *Acropora digitifera* | 4 | 1 | 3 | 0 | L: [72] |
| | *Acropora millepora* | 1 | 0 | 1 | 0 | L: [72] |
| | *Orbicella faveolata* | 1 | 0 | 1 | 0 | L: [83] |
| | **Xenacoelomorpha** | | | | | |
| | *Xenoturbella profunda* | 0 | 0 | 0 | 0 | G: Unpublished |
| | *Hofstenia miamia* | 0 | 0 | 0 | 0 | G: GCA004352715 |
| | *Praesagittifera naikaiensis* | 0 | 0 | 0 | 0 | G: PRJDB7329 |
| | *Isodiametra pulchra* | 0 | 0 | 0 | 0 | G: Unpublished |
| | *Meara stichopi* | 0 | 0 | 0 | 0 | G: Unpublished |
| | *Convolutriloba macropyga* | 0 | 0 | 0 | 0 | T: [100] |
| **SPIRALIA** | **Bryozoa** | | | | | |
| | *Membranipora membranacea* | 6 | 4 | 1 | 1 | T: SRX1121923 |
| | *Bugula neritina* | 0 | 0 | 0 | 0 | T: [101] |
| | **Cycliophora** | | | | | |
| | *Symbion pandora* | 0 | 0 | 0 | 0 | T: [102] |
| | **Annelida** | | | | | |
| | *Galathowenia oculata* | 39 | 18 | 12 | 9 | T: Unpublished |
| | *Eisenia fetida* | 11 | 0 | 1 | 10 | T: SRX3108745 |
| | *Helobdella robusta* | 4 | 1 | 3 | 0 | G: [103] |
| | *Phyllochaetopterus prolifica* | 3 | 1 | 0 | 2 | L: [66] |
| | **Mollusca** | | | | | |
| | *Crassostrea gigas* | 12 | 10 | 2 | 0 | G: [104] |
| | *Octopus bimaculoides* | 9 | 1 | 6 | 2 | G: [105] |
| | *Cyclina sinensis* | 2 | 1 | 1 | 0 | L: [88] |
| | *Leptochiton rugatus* | 1 | 0 | 0 | 1 | L: [66] |
| | *Biomphalaria glabrata* | 27 | 16 | 10 | 1 | G: [87]/NCBI |
| | **Brachiopoda** | | | | | |
| | *Terebratalia transversa* | 15 | 4 | 4 | 7 | T: [100] |
| | *Hemithris psittacea* | 6 | 3 | 1 | 2 | T: [66] |
| | *Lingula anatina* | 25 | 15 | 7 | 3 | G: [106] |
| | **Micrognathozoa** | | | | | |
| | *Limnogathia maerski* | 0 | 0 | 0 | 0 | T: SRX1121929 |
| | **Gastrotricha** | | | | | |
| | *Lepidodermella squamata* | 0 | 0 | 0 | 0 | T: [107] |
| | *Macrodasys sp* | 0 | 0 | 0 | 0 | T: [108] |
| | *Megadasys sp* | 0 | 0 | 0 | 0 | T: [108] |
| | *Diuronotus aspetos* | 0 | 0 | 0 | 0 | T: SRX1121926 |
| | *Mesodasys laticaudatus* | 0 | 0 | 0 | 0 | T: SRX872416 |
| | **Nemertea** | | | | | |
| | *Lineus longissimus* | 10 | 7 | 2 | 1 | T: [100] |
| | *Lineus ruber* | 6 | 2 | 3 | 1 | T: Unpublished |
| | *Notospermus geniculatus* | 7 | 5 | 1 | 1 | G: [89] |
| | *Paranemertes peregrina* | 2 | 1 | 0 | 1 | L: [66] |
| | **Phoronida** | | | | | |
| | *Phoronopsis harmeri* | 2 | 0 | 1 | 1 | T: SRX1121914 |
| | *Phoronis australis* | 24 | 14 | 8 | 2 | G: [89] |
| | *Phoronis psammophila* | 3 | 1 | 1 | 1 | L: [66] |
| | *Phoronis vancouverensis* | 6 | 5 | 0 | 1 | L: [66] |
| | **Platyhelminthes** | | | | | |
| | *Macrostomum lignano* | 0 | 0 | 0 | 0 | G: [109] |
| | *Echinococcus multilocularis* | 0 | 0 | 0 | 0 | G: [110] |
| | *Hymenolepis microstoma* | 0 | 0 | 0 | 0 | G: [110] |
| | **Rotifera** | | | | | |
| | *Epiphanes senta* | 1 | 1 | 0 | 0 | T: Unpublished |
| | *Rotaria tardigrada* | 0 | 0 | 0 | 0 | T: [111] |
| | *Echinorhynchus gadi* | 0 | 0 | 0 | 0 | T: SRX1121912 |
| | *Macracanthorhynchus hirudinaceus* | 0 | 0 | 0 | 0 | T: [108] |

| | | | | | | |
|---|---|---|---|---|---|---|
| ECDYSOZOA | **Priapulida** | | | | | |
| | *Priapulus caudatus* | 3 | 0 | 3 | 0 | T: [100] |
| | *Halicryptus spinulosus* | 4 | 1 | 3 | 0 | T: [100] |
| | **Tardigrada** | | | | | |
| | *Hypsibius exemplaris* | 1 | 0 | 1 | 0 | G: [112] |
| | *Ramazzottius varieornatus* | 1 | 0 | 1 | 0 | G: [113] |
| | **Onychophora** | | | | | |
| | *Peripatopsis capensis* | 1 | 0 | 0 | 1 | T: [114] |
| | **Nematoda** | | | | | |
| | *Loa loa* | 1 | 0 | 1 | 0 | G: [115] |
| | *Onchocerca volvulus* | 1 | 0 | 1 | 0 | G: [116] |
| | *Caenorhabditis elegans* | 1 | 0 | 1 | 0 | L: NCBI |
| | **Loricifera** | | | | | |
| | *Armorloricus elegans* | 2 | 1 | 1 | 0 | T: SRX1120677 |
| | **Arthropoda** | | | | | |
| | *Daphnia pulex* | 5 | 2 | 3 | 0 | G: [117] |
| | *Drosophila melanogaster* | 9 | 1 | 8 | 0 | L: NCBI |
| | *Ixodes scapularis* | 5 | 1 | 3 | 1 | L: [118] |
| DEUTEROSTOMIA | **Tunicata** | | | | | |
| | *Ciona intestinalis* | 2 | 1 | 1 | 0 | L: [97] |
| | *Oikopleura dioica* | 1 | 1 | 0 | 0 | L: [96] |
| | **Echinodermata** | | | | | |
| | *Strongylocentrotus purpuratus* | 8 | 7 | 1 | 0 | L: [64] |
| | **Craniata** | | | | | |
| | *Homo sapiens* | 10 | 10 | 0 | 0 | L: NCBI |

NC column indicates the number of TLRs that could not be classified for each species. In the reference column G/T indicate that the TLR sequences were surveyed and found in genomes (G) and transcriptomes (T) in this study. L (standing for literature) indicates that the TLR sequences were already published in previous studies and we did not obtain these sequences by performing a survey but by directly obtaining them from that publication or NCBI database. For further details, see Supplementary Table 1.

### The number of TLRs detected in members of Ecdysozoa is low when compared to Spiralia and Deuterostomia

The TLR survey of the ecdysozoan genomes and transcriptomes revealed only one TLR for the tardigrade, nematode, and onychophoran species analyzed (Table 1, Figure 3). Furthermore, we detected up to 4 different TLRs in priapulids, 2 in loriciferans, and 5 in arthropods.

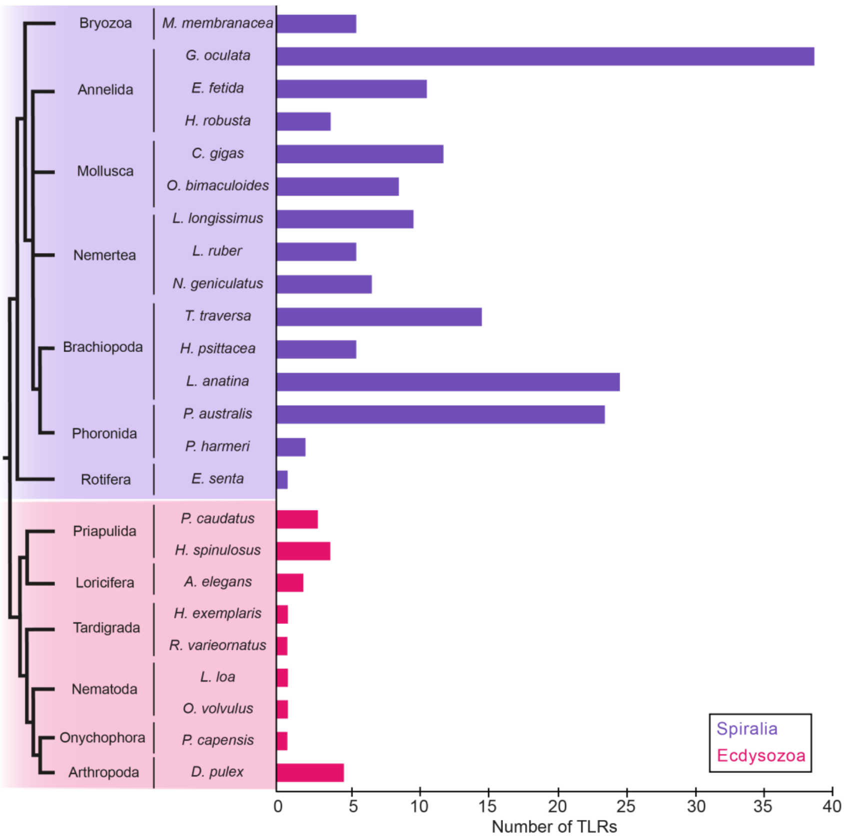


**Figure 3. Total number of TLRs in the analyzed species.** In general, the number of TLRs in spiralians (purple) is higher and more variable between species when compared to ecdysozoans (magenta). Species in which TLRs were not detected are excluded from the graph.

### Multiple TLRs are detected in trochozoan species

TLRs were found in the genomes/transcriptomes of all trochozoan species analyzed (Table 1, Figure 3). Our results reveal that, in general, multiple TLRs are present in highly variable numbers in trochozoan species. The number of TLRs is not reflected by the phylogeny, meaning that species belonging to a same clade do not have a more similar number of TLRs than species belonging to another clade. This is explained by the multiple duplications and losses that have independently occurred in the Toll receptor family during trochozoan evolution [13, 65, 89].

### P-type/mcc and V-type/scc are not specific for any planulozoan clade

Previous studies suggest that V(ertebrate)-type/scc and P(rotostome)-type/mcc TLRs are restricted to vertebrates and protostomes, respectively [64]. However, our results show that both, P-type/mcc and V-type/scc type TLRs, are present in cnidarians, spiralians, ecdysozoans, and deuterostomes (Table 1; Supplementary Table 2). V-type/scc TLRs are the most abundant TLR type in the spiralian species analyzed. However, many spiralians also have several P-type/mcc TLRs. P-type/mcc TLRs are the predominant TLR type in the ecdysozoan species included in this analysis. For nematodes, tardigrades and onychophorans, which only have one TLR, this TLR was always classified as P-type/mcc. Ecdysozoan species analyzed with more than one TLR have one or more P-type/mcc TLRs and only one V-type/scc. Although the vertebrate TLR complement seems to only contain V-type/scc TLRs [14, 67, 119, 120], P-type/mcc TLRs are also present in other deuterostomes, such as the tunicate *C. intestinalis* [97] and the echinoderm *S. purpuratus* [64] (Table 1, Supplementary Table 2). This suggests that P-type/mcc TLRs were lost in the lineage to the Craniata.

### TLRs form three clades

Our phylogenetic analysis showed that TLRs group into three clades (Figure 4A), which we named clade α (89 TLRs), clade β (102 TLRs) and clade γ (79 TLRs). Although these three clades are supported with support values >60, some of the internal nodes have low support values (<60). The phylogenetic analysis showed that clades β and γ are sister clades and together form the sister group to clade α. All three clades contain both P-type/mcc and V-type/scc TLRs, which makes it difficult to reconstruct whether P-type/mcc or V-type/scc show the ancestral state of TLRs. Furthermore, 2 deuterostome TLRs (from *H. sapiens* and *C. intestinalis*) and 11 spiralian TLRs (2 from species of mollusks and 9 from brachiopods) could not be assigned to any of the above clades. The 9 brachiopod TLRs form a clade with a high support value (>60), but do not group with either the mollusk or the deuterostome sequences. This TLR brachiopod clade is the sister clade to the three main clades (α, β and γ). For these sequences, the alignment showed brachiopod-specific deletions in the amino acid positions 150-220 that are not present in the TLRs belonging to the three main clades (Supplementary Figure 1). To investigate whether this insertion is causing the clustering of the TLRs into three clades, we performed a second phylogenetic analysis (Supplementary Figure 2) with the same parameters of the main analysis (Figure 4A) but excluding the 150-200 amino acid region. The second analysis (Supplementary Figure 2) is able to reconstruct clade α with high support value (>60). However, clade γ is nested within clade β and both of them have low support values (<60). In the second analysis (Supplementary Figure 2), as in the main analysis (Figure 4), the 9 brachiopod sequences cluster together and form the sister clade to the three main clades. However, in the analysis shown in Supplementary Figure 2, the mollusk and deuterostome sequences are included in the clade γ. In the main analysis (Figure 4A), no distinctive motifs were observed in the alignment that justify the exclusion of these sequences from the main clades.

Clade α includes TLRs from all cnidarian, spiralian and ecdysozoan species analyzed, except for the onychophoran TLR (Figure 4). Because all cnidarian TLRs cluster together, it is likely that only one TLR was present in the last common ancestor of Cnidaria. Clade β is formed by TLRs belonging to deuterostomes, spiralians and three ecdysozoans (two arthropods and the onychophoran TLR) (Figure 4). This suggests that at least the ancestral TLR of Clade β/γ was already present in the last common ancestor of Nephrozoa (Protostomia + Deuterostomia). Furthermore, lineage-specific expansions of clade β TLRs are detected in spiralians and deuterostomes. Clade γ TLRs are present in all trochozoan groups except for the nemertean species analyzed (Figure 4). Clade γ contains TLRs that radiated independently in several lineages. Our alignment shows that 159/181 TLRs belonging to the clades β and γ contain an insertion of 6 amino acids in the positions 349-354 (Supplementary Figure 1). In Clade α, this insertion is only present in Pcau-TLRα1, the sister TLR to all the remaining TLRs belonging to this clade. To exclude that this insertion causes the clustering in three distinct clades, we performed a third phylogenetic analysis (Supplementary Figure 3), in which we applied the same parameters as in the main analysis -shown in Figure 4A- but eliminated the 6 amino acid insertion regions. In the third analysis (Supplementary Figure 3), the three clades could be reconstructed with good support values (>60). However, due to low support values (<60), the relationship between the clades could not be resolved. Moreover, the clustering of the TLRs into the three clades (α, β, γ) was maintained with respect to the main analysis (Supplementary Figure 3, Figure 4A), except for eight phoronid and one human sequences. In the main analysis (Figure 4A), the phoronid sequences cluster together within clade γ, with high support values (>60). This clade of phoronid TLRs is the sister clade to all remaining TLRs in clade γ. Nevertheless, in the third analysis (Supplementary Figure 3), these phoronid TLR sequences constitute a well-supported (>60) clade within clade β, but it is not the sister clade to the remaining TLRs in this clade. In the main analysis (Figure 4A), the human sequence is not included in any of the three main clades, but in the third analysis (Supplementary Figure 3) it does cluster in clade α.

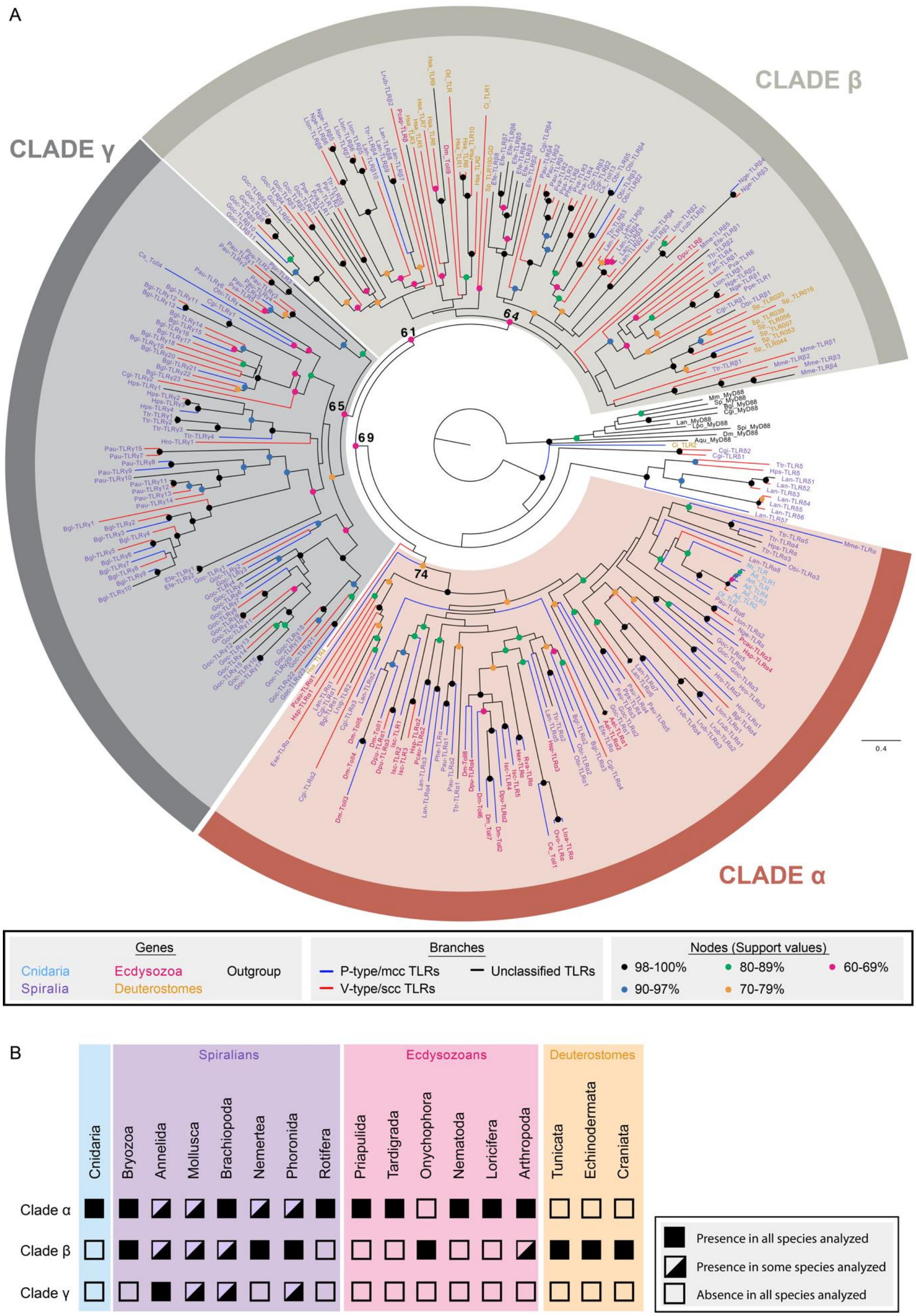


**Figure 4. TLR phylogenetic analysis and distribution of P-type/mcc or V-type/scc.** A). Phylogenetic analysis of TLRs based on maximum likelihood Bootstrap values are indicated next to the main nodes

and all nodes with bootstrap values >60 are marked with full dots (colored differently according the support values). Tip labels contain an abbreviation of the species name and the gene name given in this study (for sequences searched *de novo* here) or in the original study (for sequences obtained from the literature). Numbers in the gene name do not imply gene orthology. Species abbreviations: Ael: *A. elegans*; Ad: *A. digitifera*; Am: *A. millepora*; Bgl: *B. glabrata*; Ce: *C. elegans*; Cgi: *C. gigas*; Ci: *C. intestinalis*; Cs: *C. sinensis*; Dm: *D. melanogaster*; Dpu: *D. pulex*; Efe: *E. fetida*; Ese: *E. senta*; Goc: *G. oculata*; Hex: *H. exemplaris*; Hps: *H. psittacea*; Hro: *H. robusta*; Hsa: *H. sapiens*; Hsp: *H. spinulosus*; Isc: *I. scapularis*; Mme: *M. membranacea*; Nge: *N. geniculatus*; Nv: *N. vectensis*; Lan: *L. anatina*; Lloa: *L. loa*; Llon: *L. longissimus*; Lrub: *L. ruber*; Lrug: *L. rugatus*; Obi: *O. bimaculoides*; Od: *O. dioica*; Of: *O. faveolata*; Ovo: *O. volvulus*; Pau: *P. australis*; Pcap: *P. capensis*; Pcau: *P. caudatus*; Phe: *P. hermeri*; Ppe: *P. peregrina*; Ppr: *P. prolifca*; Pps: *P. psammophila*; Pva: *P.vancouverensis*; Rva: *R. varieornatus*; Sp: *S. purpuratus*; Ttr: *T. transversa*. B). Presence/absence in the metazoan groups included in our study.

### TLRs are expressed during development in the ecdysozoans *P. caudatus* and *H. exemplaris* and in the spiralians *C. gigas* and *T. transversa*

In order to study the temporal expression of TLRs during ontogeny, we analyzed stage-specific transcriptomes of the priapulid *P. caudatus* [121], the tardigrade *H. exemplaris* [122], the mollusk *C. gigas* [104] and the brachiopod *T. transversa* [123]. All the analyses were performed using both RSEM [124] and kallisto [125] methods.

The expression of the only TLR present in *H. exemplaris* was analyzed in stage-specific transcriptomes of 19 stages (one biological replicate) (Figure 5A; Supplementary Table 3) [122]. Expression of *TLRα* was detected (TMM ≥ 0.15) in time windows during development (zygote, morula, gastrula, elongation, segmentation and differentiation).

Three TLRs were identified in *P. caudatus* transcriptomic survey (Table 1). The expression of these TLRs was analyzed in five embryonic stages (two biological replicates) (Supplementary Table 4) [121]. Our results indicate that all three TLRs found in the transcriptomic survey are expressed during embryonic development (TMM ≥ 0.15). *Pca-TLRα1* and *Pca-TLRα2* are expressed in all developmental stages analyzed, whereas *Pca-TLRα3* is expressed only in the later embryonic stages (Figure 5B; Supplementary Table 4).

The expression of the 12 *C. gigas* TLRs (Table 1) was analyzed in stage-specific transcriptomes of 19 stages (one biological replicate) (Supplementary Table 5) [104].

Our results show that at 11 of the 12 TLRs are expressed during development (Figure 5C; Supplementary Table 5). Some TLRs are expressed throughout development (*Cgi-TLRα1, Cgi-TLRα4, Cgi-TLRβ4, Cgi-TLRδ1, Cgi-TLRδ2*), while others (*Cgi-TLRα2, Cgi-TLRα3, Cgi-TLRβ1, Cgi-TLRβ2, Cgi-TLRγ1, Cgi-TLRγ2*) are only expressed at certain developmental stages. *Cgi-TLRβ3* expression was not detected at any of the stages analyzed.

15 TLRs were found in our transcriptome survey of *T. transversa* (Table 1). Expression of these TLRs was analyzed in stage-specific transcriptomes of 12 developmental stages (with two biological replicates) [123]. Our results suggest that at least 12 of the 15 TLRs are expressed at certain stages during *T. transversa* development (Figure 5D; Supplementary Table 6*). Ttr-TLRα2, Ttr-TLRα5, Ttr-TLRβ1, Ttr-TLRβ4, Ttr-TLRβ5,* and *Ttr-TLRδ* expression is detected in time windows during embryonic and larval stages. All these genes, except *Ttr-TLRβ5*, are expressed in juveniles. For some genes (*Ttr-TLRα4, Ttr-TLRβ2, Ttr-TLRβ3,* and *Ttr-TLRγ4*), expression was detected throughout development. Moreover, expression was not detected at the embryonic and larval stages analyzed for *Ttr-TLRα1, Ttr-TLRγ1, Ttr-TLRγ2* and *Ttr-TLRγ3*. Similarly, *Ttr-TLRα3* expression was only detected in the competent larvae and in the juveniles.

Our analyses show that TLRs are expressed during the development of the spiralians *T. transversa* and *C. gigas* and the ecdysozoans *P. caudatus* and *H. exemplaris*. These analyses show that the TLRs expressed during development are not restricted to one TLR clade in the tree shown above, but they are found in all three main clades (e.g. *Ttr-TLRα4, Ttr-TLRβ3, Cgi-TLRγ1*).

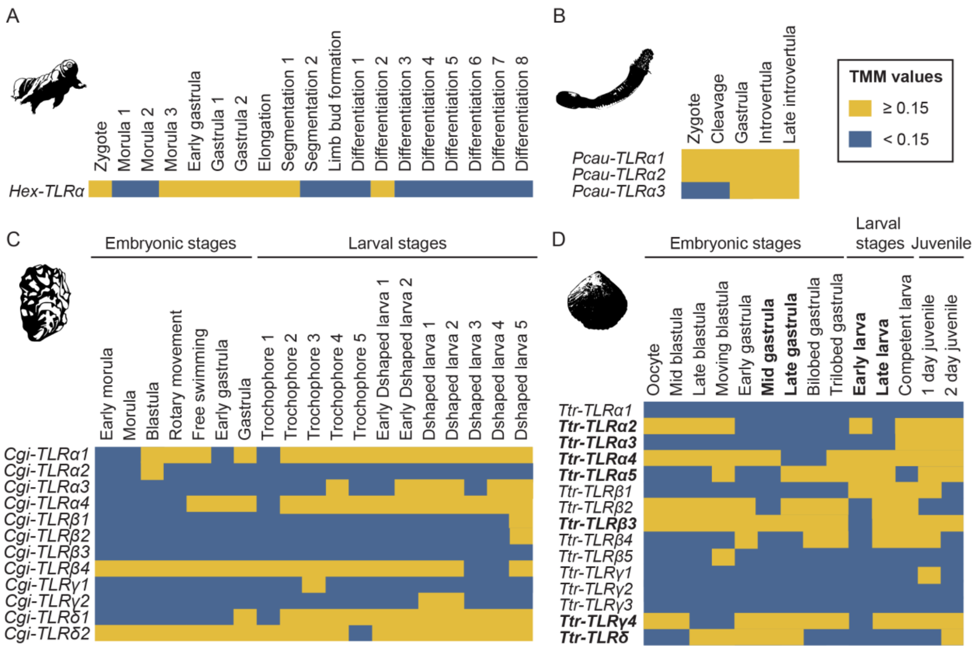


**Figure 5. TLR expression in developmental stage-specific transcriptomes of (A) *H. exemplaris*, (B) *P. caudatus*, (C) *C. gigas* and (D) *T. transversa*.** Heatmaps corresponding to the average of the RSEM analyses are shown. For heatmaps corresponding to Kallisto analyses see Supplementary Tables 3, 4, 5 and 6. Bold indicates stages and genes for which *in situ* hybridization was performed. TMM: Trimmed means of M values.

Furthermore, in order to validate our stage specific transcriptome results, we performed whole mount *in situ* hybridization (WMISH) for the *T. transversa* mRNAs of *TLRα2, TLRα3, TLRα4, TLRα5, TLRβ3, TLRγ4* and *TLRδ* (Figure 6). Consistently with our stage specific transcriptomic analysis, our WMISH results show that *Ttr-TLRα2* is not expressed at the late gastrula stage (Figure 6A), but the expression is present in the mesoderm and in two pairs of lateral domains in early larvae (Figure 6B). This gene is not expressed in late larvae (Figure 6C). In agreement with our stage specific transcriptomic analysis, we did not detect *Ttr-TLRα3* either in late gastrulae or in the two larval stages analyzed (Figure 6D-F). *Ttr-TLRα4* has a dynamic expression pattern during *T. transversa* development. This gene is expressed in the mesoderm at the early gastrula stage, but, consistent with the stage specific transcriptome analysis, it is not detected in late gastrulae (Figure 6G-H). In early larvae, *Ttr-TLRα4* is expressed in the inner lobe epithelium and in a medial V-shaped mesodermal domain (Figure 6I).

In late larvae, this gene is expressed in the brain and in the pedicle (Figure 6J). mRNA of *Ttr-TLRα5* is detected in a uniform salt and pepper distribution at the late gastrula stage and the two larval stages for which WMISH was performed (Figure 6K-M). *Ttr-TLRβ3* is expressed in the anterior region of the animal in late gastrulae (Figure 6N). However, although *Ttr-TLRβ3* expression was detected in early larvae in the stage specific transcriptome analysis, expression was not detected by WMISH (Figure 6M). Furthermore, *Ttr-TLRβ3* is not expressed in the late larvae (Figure 6P). The expression of *Ttr-TLRγ4* and *Ttr-TLRδ* have a uniformly salt and pepper distribution at the late gastrula and early larvae stages (Figure 6 Q-R and T-U). This salt and pepper transcript distribution is similar in late larvae, although it is absent from the pedicle lobes (Figure 6 S and V). These results conflict with the stage specific transcriptome analyses, as, in this analysis, neither *Ttr-TLRγ4* expression was detected in the early larvae nor *Ttr-TLRδ* in any of the two larval stages tested. Differences between the results of both analyses could be explained by differences and variation of the developmental stages of the specimens used for the stage-specific transcriptome and the WMISH.

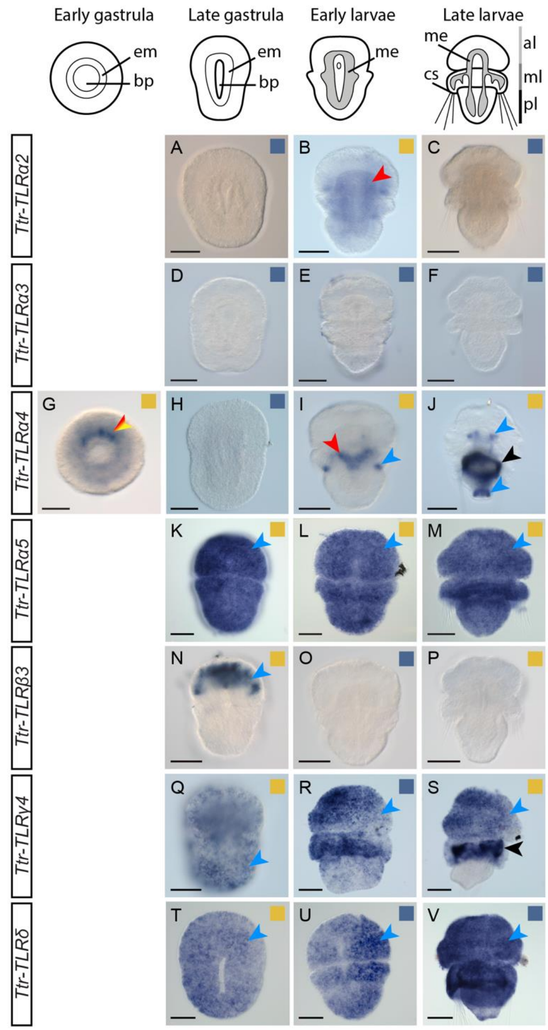


**Figure 6. Expression of TLRs during the development of the brachiopod *T. transversa*.** Whole-mount *in situ* hybridization (WMISH) of TLRs in *T. transversa* embryos and larvae. Above the WMISH plates, there are schematic representations of each developmental stage analyzed. These representations are not to scale. The name of each gene is indicated in the rectangles on the left. All panels show dorso-ventral views and anterior to the top. Squares in the top-right of each plate indicate whether the expression was detected (yellow) or not (blue) in the stage-specific transcriptome analysis. Ectoderm, mesoderm and endoderm is indicated with blue, red and yellow arrowheads, respectively. The red and yellow arrowhead indicates endomesoderm. The ring-shape staining present in the late larvae *Ttr-TLRα4* and *Ttr-TLRγ4* is background staining (black arrowhead) [126]. Scale bar indicates 50 µm. al: apical lobe; bp: blastopore; cs: chaetal sacs; em: endomesoderm; me: mesoderm; ml: mantle lobe; pl: pedicle lobe.

## Discussion

### The evolution of the TLR family is characterized by losses, expansion and conservation

As shown in previous studies, TLRs are absent in the Platyhelminthes *S. mediterranea* and *S. mansoni* [92]. Here, we show that this receptor family is also absent from the genomes of three other platyhelminth species (*M. lignano, E. multilocularis* and *H. microstoma*). Thus, TLRs are absent in species belonging to four different platyhelminth lineages (Macrostomorpha – *M. lignano*; Cestoda – *E. multiocularis* and *H. microstoma*; Tricladida – *S. mediterranea*; and Digenea – *S. mansoni*) suggesting that TLRs could have been lost during early platyhelminth evolution. This hypothesis is reinforced by the lack of TLRs in *M. lignano*, member of Macrostomorpha, an early-diverging platyhelminth lineage [107]. In rotifers, even though TLRs could not be detected in *A. vaga* [70], *E. gadi, R. tardigrada* and *M. hirudinaceus*, our transcriptome survey revealed one TLR in the monogonont rotifer *E. senta*. This suggests that TLRs would have been independently lost in some rotifer lineages. So far, we did not detect TLRs in the genomes and transcriptomes of the species belonging to Xenacoelomorpha, Cycliophora, Micrognathozoa, and Gastrotricha, suggesting that TLRs were lost in these lineages. How the immune response is achieved in animals that lack TLRs is unknown, but it could be triggered by other components of the Toll pathway e.g. TLR-like molecules [14, 70–72], similar to what has been shown for LRR-only TLR-like and TIR-only TLR-like in *Hydra* [75, 76].

Another outcome of this study is the remarkable expansion that the TLRs family exhibits in trochozoans. Evolution of this gene family in trochozoans is characterized by multiple duplications and losses, having as a consequence a very variable number of the TLRs complement in trochozoans. Moreover, in our phylogenetic analysis, TLRs of the same species and clades mostly group together, indicating the existence of multiple independent duplications (Figure 4A). The same has been shown also in previous phylogenetic analyses of TLRs (Figure 6) [13, 65, 89].

In contrast to trochozoans, our results show that the number of TLR in ecdysozoans has been relatively conserved during evolution. At least, few TLR gene duplications have occurred in this lineage, including recent independent duplications in arthropods, priapulids or loriciferans.

### The evolution of the three clades (α, β, γ) of TLRs

There are very few studies assessing the phylogenetic relationships of TLRs within the main metazoan clades (Figure 7) [65, 89]. The study of Davidson et al., 2008 [65] recovered three clades of TLRs. However, the relationships between the clades remain unclear. Furthermore, the composition of the clades slightly differs in both analyses (e.g. while our study shows that deuterostome TLRs belong to one clade – clade β –

their results suggest that deuterostome TLRs are present in two clades – clades A and B) [65]. However, their phylogenetic study is limited by the number of sequences and species included. Similar to Luo and Zheng, 2000 [127]; and Luna et al., 2002 [128], our results suggest that ecdysozoan and deuterostome TLRs evolved independently from a common TLR precursor. However, our phylogenetic analysis has also some limitations, as the support values for the main clades are not optimal (with support values 61-74%). This is also reflected by the rearrangement of the tree when the alignment is modified for the phylogenetic analyses shown in Supplementary Figures 2 and 3.

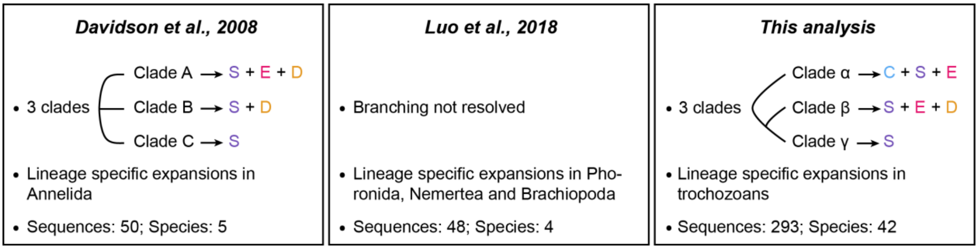


**Figure 7. Comparison between Davidson et al., 2008; Luo et al., 2018; and this study.** The main conclusions and the number of TLRs and species included in the three studies are compared. Cnidaria (C), Spiralia (S), Edysozoa (E) and Deuterostomia (D).

Previous studies suggest that TLRs originated likely by the fusion of an *LRR-only* and a *TIR-only* TLR genes in the lineage to Planulozoa (Cnidaria + Bilateria) [7, 14, 67]. However, this hypothesis is challenged by the presence of TLRs in choanoflagellates, indicating that at least one TLR could be already present in the common ancestor of choanoflagellates and animals [68]. Here, we hypothesize that the planulozoan stem species had only one TLR (Figure 8), the *proto*-TLR. This is supported by the fact that all cnidarian TLRs included in our analysis cluster in a monophyletic group within clade α, which is consistent with the results of Brennan and Gilmore, 2018 [13]. During cnidarian evolution, this gene was lost in some lineages, e.g. *Hydra* [75], *Clytia* [84], and multiplied in others, e.g. *A. digitifera* [72].

After the split into the cnidarian and bilaterian lineages, the *proto*-TLR was duplicated in the lineage to the Bilateria, giving rise to a clade α type TLR gene (*TLR-Cα*) and the *proto*-TLR gene of clades β and γ (*TLR-Cβ/γ*) (Figure 8). However, our results indicate that *TLR-Cα* was lost during early deuterostome evolution. Later, expansions of *TLR-Cβ/γ* generated the TLR diversity found in deuterostomes. Furthermore, as vertebrate TLRs diversified within the vertebrate lineage, it is impossible to make one-to-one orthology gene assignments between the vertebrate TLRs and the invertebrate TLRs [67].

The protostome stem species and the spiralian stem species had likely two TLRs: *TLR-C*α and *TLR-Cβ/γ* (Figure 8). During early trochozoan evolution, the spiralian *TLR-Cβ/γ* gene was duplicated, giving raise to the ancestral TLR from clade β in trochozoans (*TLR-Cβ*) and the ancestral TLRs from clade γ (*TLR-Cγ*). This is supported by the fact that clade β and clade γ are sister clades and clade γ is only present in trochozoans. Later, episodes of gene duplication generated the larger diversity of TLRs from clade β and clade γ in trochozoans. These expansions could have occurred due to the necessity to adapt to microbe rich environments [129, 130]. Losses of both TLRs seem to have occurred in non-trochozoan lineages, e.g. in platyhelminths and rotifers.

Our results show that the ecdysozoan stem species had two TLRs (Figure 8) belonging to clade α and clade β/γ. Although, in general, the number of TLRs is low, few duplications of *TLR-Cα* occurred in some lineages (e.g. arthropods, priapulids, loriciferans). Furthermore, our analysis shows that the surveyed priapulids, tardigrades, nematodes and loriciferan lack TLRs from clade β; whereas clade β TLRs are present in the majority of the arthropods and in the onychophoran surveyed. This would imply that TLR clade β would have been lost independently in the early branching ecdysozoans but not in the most late-branching lineages [98, 131].

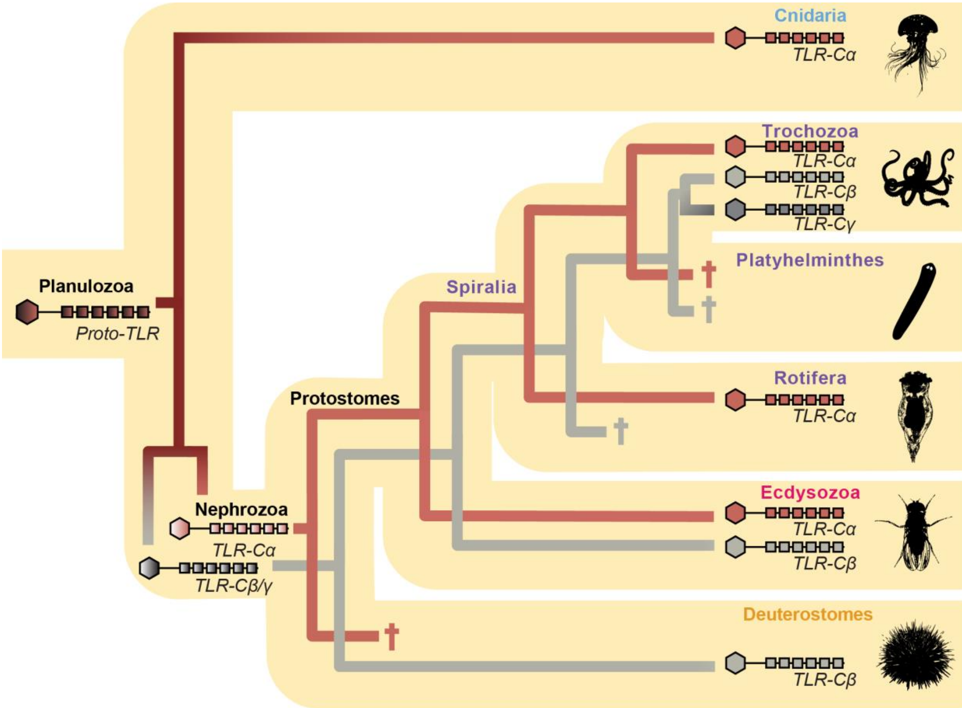


**Figure 8. Origin and evolution of TLRs.** Gene lineages are depicted in different colors (*proto-TLR:* dark brown; *TLR-Cα*: light brown; *TLR-Cβ/γ* and TLR clade β: light grey; and TLR clade γ: dark grey) within the metazoan tree. Gene losses are indicated with a cross. Phylogeny according to: [98]

## Are protostome TLRs involved in immunity and development during ontogeny?

TLRs are well known to play a key role in adult innate immunity in planulozoans [11, 22–26]. During ontogeny, this gene family has also been shown to be involved in a great number of developmental processes both in arthropods and vertebrates [2, 8, 9, 36, 38, 39, 42, 44–46]. Here, we identify TLRs expressed during ontogeny in four protostome species (the ecdysozoans *H. exemplaris* and *P. caudatus* and the spiralians *C. gigas* and *T. transversa*) (Figures 5 and 6). Expression of TLRs was observed for some TLRs in short developmental time windows (the *H. exemplaris Hex-TLRα*; the *C. gigas Cgi-TLRα2, Cgi-TLRα3, Cgi-TLRβ1, Cgi-TLRβ2, Cgi-TLRγ1, Cgi-TLRγ*2; and the *T. transversa Ttr-TLRα2, Ttr-TLRα5, Ttr-TLRβ1, Ttr-TLRβ4, Ttr-TLRβ5*), suggesting a possible role of these genes in development, as genes involved in developmental processes are usually expressed for defined periods of time in tissues in order to participate in specific developmental processes [132–134]. For instance, expression during early embryonic stages of the *T. transversa Ttr-TLRα2* (Figure 5) might suggest its involvement in dorso-ventral axis specification, as it has been shown for the *Drosophila Toll* [8, 9]. Later, in the early larvae, transcription of this gene is transiently activated in the mesoderm (Figures 5 and 6), suggesting that this gene might be also involved in mesoderm development. However, our analyses do not exclude the possibility that these genes might also be involved in immunity, as these TLRs could have a dual role, as it has been shown for the *Drosophila Toll* [10] and the only TLR in the cnidarian *N. vectensis* [27]. Discerning the role of TLRs expressed in broad time windows or during the whole development (the three *P. caudatus* TLRs; the *C. gigas Cgi-TLRα1, Cgi-TLRα4, Cgi-TLRβ4, Cgi-TLRδ1, Cgi-TLRδ2*; and the *T. transversa Ttr-TLRα4, Ttr-TLRβ2, Ttr-TLRβ3,* and *Ttr-TLRγ4*) is complex, as these genes could be involved either in immunity or in development, or both. However, detection of immune processes in our analyses is not possible with the data available. Therefore, further investigations are required to gain more knowledge on functions of TLRs during development. Immune roles of the TLRs during ontogeny should not be underestimated: Many marine invertebrate embryos and larvae live in environments rich in microbial pathogens [135, 136]. Pathogens cause mortality of embryos and larvae but also provoke anomalies during development [137, 138]. Therefore, these embryos and larvae need immune defenses to fight pathogens [136]. Actually, few studies have shown that the Toll pathway is involved in immunity during ontogeny in arthropods, mollusks and amphioxus [18, 138–140], and other immune-related genes have also been found to be involved in immunity during mollusk and echinoderm development [139, 141–143]. Additionally, in planulozoans it has been shown that TLRs are involved in adult immunity [11, 22–26]. Thus, TLRs are probably also involved in immunity during ontogeny across the metazoan tree.

## Conclusions

Based on our data we propose a scenario in which TLRs evolved from an ancestral *proto*-TLR that originated before the split into the cnidarian and the bilaterian lineage. Duplications and losses characterize the evolution of TLRs in the main metazoan groups. The *proto*-TLR duplicated in different metazoan lineages and gave rise to three

TLR clades. This TLR complement was expanded during Trochozoa evolution, while it was lost in some non-trochozoan spiralian lineages (e.g. platyhelminths, cycliophorans, micrognathozoans, gastrotrichs and some rotifers). Ecdysozoans possess a low number of Clade α and Clade β TLRs; whereas all deuterostome TLRs belong to clade β, being originated by radiations in the different lineages. Furthermore, our data shows that TLRs are expressed during ontogeny in two ecdysozoan and two spiralian species, suggesting that these genes could be involved in development.

## Materials and methods

### Genomic and transcriptomic surveys

We surveyed TLRs 20 genomes and 25 transcriptomes (Supplementary Table 1). Overall, only high-quality transcriptomes (Complete BUSCO gene values >70% - Supplementary Table 1) were selected, but lower quality transcriptomes were also included when they represented a species from a low investigated clade (e.g. the loriciferan *A. elegans* transcriptome (Complete BUSCO gene value 36.2%)). In order to search for the TLR sequences, hmmer profiles for the TIR and the LRR domains were generated using HMMER software version 3.2.1 [144] (www.hmmer.org). The hmmer profile for the TIR domain was compared to each genome/transcriptome using the hmmersearch function of HMMER in order to obtain a database of proteins containing the TIR domain. Next, the LRR hmmer profile was also compared to the TIR domain-containing sequences database by using hmmersearch. These sequences were validated by BLAST [145] (www.blast.ncbi.nlm.nih.gov) and SMART [146, 147] (http://smart.embl.de/). Sequences from the same species with >90% similarity were considered to be polymorphisms or isoforms and only one of them was considered for the analyses.

### Phylogenetic analysis

The phylogenetic analysis was performed including TLRs obtained from the genome/transcriptome surveys, from NCBI database and from the literature. The MyD88 protein was selected as an outgroup, including the TIR domain of well annotated MyD88 proteins in the alignment. All sequences included in the phylogenetic analyses are found in (Supplementary Table 2). The sequences were aligned using MAFFT software version 7 applying the L-INS-I algorithm [148]. The alignment was trimmed manually in order to obtain a fragment containing one LRR domain, the transmembrane domain, and the TIR domain. This was followed by a second trimming step performed with TrimAl software version 1.2 using the gappyout trimming model [149]. The final alignment used to perform the phylogenetic analysis contains 375 amino acids. The maximum likelihood phylogenetic analysis was performed using IQ-TREE software [150] in the CIPRES Science Gateway V.3.3 [151] (http://www.phylo.org). LG+R8 was selected as the best-fit model (according to BIC (Bayesian Information Criterion) [152]) and was applied for the phylogenetic reconstruction. Bootstrap values were calculated running 1000 replicates using ultrafast bootstrap.

**TLR classification**

TLR sequences from the genomic/transcriptomic surveys, as well as the ones obtained from the literature and NCBI database, were classified into P-type/mcc and V-type/scc. In order to do so, the number of LRR domains was analyzed with LRRfinder software [153] (http://www.lrrfinder.com). Next, sequences were classified applying the same criteria followed by Brennan and Gilmore, 2018 [13]. Some TLR sequences were incomplete and they could not be classified into P-type/mcc or V-type/scc.

**Stage specific transcriptome analyses**

In order to assess the expression of TLR genes, we examined publicly available stage-transcriptomic data of various developmental stages for the spiralians *C. gigas* and *T. transversa* and the ecdysozoans *P. caudatus* and *H. exemplaris*. For *C. gigas*, we examined 19 developmental time-points from early morula to D-shaped larvae, being the transcriptomic data previously published in [104] (accession number: SRR334225-SRR334243). For *T. transversa*, 14 stages from oocyte to 2-day juvenile were analyzed, being this dataset available from [123]. For *P. caudatus*, only 5 embryonic stages (from zigot to late introvertula) were analyzed. The transcriptomic data was obtained from [121]. The 20 *H. exemplaris* embryonic transcriptomes analyzed (from zigot to differentiation) were obtained from [122] (accession numbers: SRR1755597, SRR1755601, SRR1755603, SRR1755606, SRR1755610, SRR1755612, SRR1755621, SRR1755623, SRR1755627, SRR1755631, SRR1755637, SRR1755644, SRR1755647, SRR1755650, SRR1755656, SRR1755662, SRR1755666, SRR1755706, SRR1755715, SRR1755719). We first performed quality-trimming on downloaded RNA-seq raw reads using Trimmomatic v.0.38 [154], removing low quality or N bases (parameter settings: LEADING:20 TRAILING:20 SLIDINGWINDOW:4:20). To estimate the transcript abundancies, quality-trimmed reads were aligned to reference transcriptome assemblies (*C. gigas* [104], *T. transversa* and *P. caudatus* [100], *H. exemplaris* [112]). We applied two quantification methods: an alignment-based method using Bowtie2 [155] and RSEM [124], and the ultra-fast alignment-free method kallisto [125]. Both methods reported normalized expression values in transcripts per million (TPM), and we further executed cross-sample normalization among different developmental-stage samples by TMM method [156]. To define a criterion for gene expression value in this study, we performed *in situ* hybridization of selected TLR genes at different developmental stages in *Terebratalia*, as well as examining expression values in our analysis corresponding to *in situ* hybridization data of *Hox* genes in *Terebratalia* [123] and *Wnt* genes in *Priapulus* [121]. We considered expression for values ≥ 0.15.

**Animal collection and embryonic cultures**

Adult *T. transversa* specimens were collected in Friday Harbor, USA. The eggs were fertilized, and animals were fixed at different developmental stages with 4% paraformaldehyde for 1h at room temperature, as described elsewhere [123, 157]. Next, the samples were repeatedly washed in Ptw and stored in 100% methanol.

**Gene cloning, probe synthesis, in situ hybridization and imaging.**

Specific primers for *T. transversa* TLRs were designed using the MacVector 10.6.0 software [158]. TLRs were amplified and inserted into pGEM-T Easy vectors (Promega, USA) and transformed in competent *E. coli* cells. Minipreps were prepared using NucleoSpin®Plasmid kit (Macherey-Nagel) and sequenced in the Sequencing facility of the University of Bergen. RNA probes were transcribed using digoxigenin-11-UTP (Roche, USA) with the MEGAscript™ kit (Invitrogen, Thermo Fisher). Whole mount *in situ* hybridization (WMISH) was performed as described in [123, 159]. Probes were hybridized at a concentration of 1 ng/µl at 67°C during 72h. Next, they were detected with anti-digoxigenin-AP antibody [1:5000] (Roche) and developed using NBT/BCIP (Roche). Samples were washed twice in 100% ethanol and re-hydrated in descending ethanol steps (75%, 50% and 25% ethanol in PBS). Samples were mounted in 70% glycerol. Samples were imaged using Axiocam HRc camera connected to an Axioscope Ax10 (Zeiss, Oberkochen, Germany). Images were analyzed using Fiji and Adobe Photoshop CS6.

### Illustrations

Figure plates and illustrations were made with Adobe Illustrator CS6.

## List of abbreviations

**AMPs:** Antimicrobial peptides; **BCIP:** 5-bromo-4-chloro-3-indolyl phosphate; **BIC:** Bayesian Information Criterion. **BUSCO:** Benchmarking Universal Single-Copy Orthologs; **IL-1:** Interleukin-I receptor; **LRR:** Leucine-rich repeat; **LRRCT:** Leucine-rich repeat C-terminal domain; **LRRNT:** Leucine-rich repeat N-terminal domain; **Mcc:** multiple cysteine cluster; **NBT:** nitro blue tetrazolium; **NOD:** Nucleotide oligomerization domain; **PBS:** Phosphate-Buffered Saline; **P-type:** Protostome type; **PTw:** PBS with 0.1% Tween® 20; **RSEM:** RNA-Seq by Expectation Maximization; **Scc:** Single cysteine cluster; **TIR:** Toll/IL-1 receptor; **TLR:** Toll-like receptor; ***TLR-Cα:*** clade α type TLR gene; ***TLR-Cβ:*** clade β type TLR gene; ***TLR-Cγ:*** clade γ type TLR gene; ***TLR-Cβ/γ:*** proto-TLR gene of clades β and γ; **TLR-like:** Toll-like receptor-like; **TM:** Transmembrane; **TMM:** Trimmed mean of M values; **TPM:** Transcripts per million; **V-type:** Vertebrate type; **WMISH:** Whole mount in situ hybridization.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional files. TLR and MyD88 sequences obtained in the genomic/transcriptomic surveys and used in the phylogenetic analysis, together with their NCBI accession numbers, are available in the Supplementary Table 2.

## Competing interests

The authors declare that they have no competing interests

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## Supplementary material Paper I

**Supplementary Figure 1. Phylogenetic analysis alignment.** Regions rich in gaps located in the positions 150-220 for TLRs not belonging to the three main clades are marked in magenta. In cyan, we mark the positions 349-354 characteristic from clades β and γ; and the gaps corresponding for these positions for the TLRs belonging to clade α.

**>Mme-TLRβ3**
NYQTIKNMVYLDLSDNKISIIP----NDIFYQMVKMSHLNLIGNQIVSLDNNMFLYNANL
QSLYLSNNRLTTFDSKLLNHCKALERLMISQNKISLFDVEFVNEIDSLRSVRIDENPFDC
SCGQLFFQSWVQRSKK----KFGQDLQCVQPSNLLNQKISEY---QPQQCV-KWVVDGVA
----LVGLVLIIIVTYQLRWYLTNIPYTRSMRY------RQQDECHYDAMVIFSNKDTDW
V-KELMRELEEDRENKIYIRVRDDISGTITFEECSKVMNQSRKIILILSNSFLAETECIS
EVEFAGNELFSTANGRVMILVLEELQESRIDL-VRSLMIEANVIELLESTRKMREVWQKL
KKFVNHQKP
**>Mme-TLRβ4**
NFKTIKHLTYLDLSDNSLPSIP----NDLFDNMPKLKTLKMISNLISSLDRRQFIHNSQL
RTLDMTKNLLETFHVSVFANDTLIKALSLRTNKISMFDETFTQFVSTLTYLRIENNSFDC
SCGQLYFQKWANSSKK----QYGDKLICHSPGQLRNQRIVIY---QLFDCY----WVLVG
LA--LVGIITTVLLMYRFRWYLAHLRFALSVAE-RLVDIKQQDQCKYDAMVLFSDEETNW
V-KRLLIELEEDRENLIYIRARDDITGDVNFDSCCKIMKQSRKIILVLSNSFLREDECIS
EATFAGSELFSTAKERILILVLEELQEPL-NP-VSSLLVETHYIDLYETTRKMRAIWQKL
RRFVSHRAN
**>Mme-TLRα**
-LTAFPNIKI------------------------AMEELSLSHNTITELPEDPFYWLRHV
VHLNIQHNELTPQNIPIFDRLGKISYLFLAYNNIVYFPPSIR---KNFKALSITGNKITC
-CNGHWMKTWLQEQNE--TIWNSLTAHCKD----QAHPIIQLDPDGFS-CP-LYLAPIII
SIALTIATMMTSVAVYVYSFELKIILFKLNLHPR---SV-DSESLDYDLYLMYNYADSPW
ATEKLLPGLE-KFGYRVYVPERDMGIGEITAEARANAFASTHRVLVVVSQKFIDSGESMK
EFFHAHEHENSTTRRYLVLVKLEKI--NRTD-IFKKYMSTNFFVSVKS------KFWYNL
RYWLPREST
**>Mme-TLRβ5**
LFHGMKNLKTLLLMHNHLGLSFSDDYTGFLSRLPRLMVVNMSSNGITVLPKQMISNTSAL
EVLDLGMNHIYSWDSQTFQGAVGLKKLLLNTNRLALFNETSFSDLKNLTVLDLGNNPFAC
TCDMRWFRDWLKTT--KVHVNNSHTYTCTSPAKMQGTHLIEFELTTLQ-CVPVWIVSGCF
IS--LLLILIMVCVLYRYRWRIRFALYKCSKSCKAYQRLPQTDRPLYAAFFSFCSEDENI
IEEQILPNIDNDAGVYPLIHRIKYDPSRTYLDCLEKALLTSPATVVMLCQHYKEDRQCEL
ELAAS----LQEEDRRIILVVLDDIVQRKLPVALRVMLNRNEAIEWHRNEQQARMLKGKL
AEALED---
**>Mme-TLRβ2**
NFKAISNLEYLDLDTNNLTFIR----NHTFDHMPNLNTLILSANNLKHIDDQAFIHNYNL
ATLLLQANKFSVFNVTLLEGPKNLRKLCISTNLITHFDSSFVKFMGTLQTVKIANNPFDC
SCGRKFFSDWLNRTKL----HESVGLECTTPENMAQKKVYNY---EDLECT-PLIWSAVV
LC-LIIVTIMIAVPCYRYRWYISHMVIMQAVKD-RAMDIKHSDECKYDAMILSSEADMKF
V-KTLLLHLEEDRSNRLYHSLRDAIPGTYRFESLCEVMRQSRKIIIVISNSYLNSSECMS
EAAFAGEELFGTKKEKIVVLVLEDLNEDLMPS-IAGLLTET-VIDLPESKKTMAPVWDRL
KKFVENKP-
**>Mme-TLRβ1**
FYPQLKQLQKLDISGNSFKYLD----PNAFNEMKYLSSVIAQSNPLSILPDTIFISNMKL
VKVDFSNCFLDELDNTIVKSLPKLEHLYLKYNQFTSFAPSVISVVKALKTLSLLGNPFDC
DCNIGRLQDWLSETEK----IDVINITCGGPEHAADTSIFEY---PPPRCK----LPLII
GC-AVVGFVLLILLCICSRWYISHRKILPELKG-ILKNIRYGYKCDYDAVVCYSDIDQQW
VGGRLVPALESKKA-RLYIYERDSTIGAEKTVQIRDAMERSRNVIIVLSKSYLASEAFLP
EVDIVADVMRQNEKGRILLLALDDLDNRKMDP-IKLLTLTEKTLNVV-------------
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**>Goc-TLRγ23**
SLSCWPRMRKLLLGNIELQQIFDHGNETIFNNCTYMKTIDLQNTGIKRLPQNTFLDMENV
QYINISNNKLTSLDI--LTSTKNL-TLNISSNLLDHLSNKMTQLLDQMEILDLSYNPIMC
GCPQIDFIVWLKNT--YVEIYNLNQYQCVYQDGTK--YINDISLSQLKQCN-IIIQAVCS
IGS-VVVIGIISIIYSYRHKLEYLLLIARHAAKSKKDKHNDKTFNFHGFVSYSSEDDLW
IVEQLHMKMEQDFGLKLCIHERDFLPGYFITENISSFMEASRKTVIVLSNNYLKSKWCTF
EFELAKCKLIEATFNTMVMILLHDLDQRKVSPALHKYLKQKTYLKWPKDSSQQPAFWLRL
KEALDQKPE
**>Goc-TLRγ17**
VLNCFPSLTEVRIGGNQL----NT-HIMMFANCTKLTHLDVSHNKLVSMPKDAFHETPNL
IHLNLSGNLFANLEIHEVTQLTKLQVLDLSYNRFQAIPESWRHTIQLLGKLYISGNPFMC

SCDTVDHLIWLQSI--QDLLDDPTHLTCRDTNGKEY-TIMQIHIGRFKECIKSMVQAGCI
PSAIVLVIVGISLYIYKRRFRFQYLALVARANIN--LHAPQIPDYTYDAFISYSSLDIEY
ML-TLYQKLEQEHNYELCIDMRNFRPGNPIDDEITNGIMDSHKIILVISQNFLRSGWCLY
EMQLAHGELAVRGGDGLLLILKEPRPQELITDKLQGLLDSRIYLEWSEEGDRQQVFWQRL
RDALGMPLQ

**>Goc-TLRβ11**

VLSNSTMIESVDLSGNLLFRYTDEFLCDLLKNLVNLEEISLFDNYLTHVPSCLFRASSRI
IGIYLSRNRIAYIQKGVFDSLYQLEELDLDDNSITFIDPSNFYNTPSLSWLTIENNRFSC
DCRLTGFRDWTAEH--QDIIEGP----CETPKQLKGEAVHAYTTTWLE-CNTVFIICGSL
----LFFLLVVTGLLFYFWKDIKYIKMVHRAKGKGYIPLNDNNQVLYDAFISYHPEKKFW
VEVDLIPTLEDDVQFNIMYDER-FDTG-SIFTLTEENIAQSRKILFVVSRGWIQAGWNQF
ELDMAMIKLIDDHRDMIIVLLMEHIPKKEMPDKLKMMVKYNKCLKWSDNEHKQRIFRRDL
KLELGKE--

**>Goc-TLRγ16**

VLNCFPSLTEVRIGGNQL----NT-HIMMFANCTKLTHLDVSHNKLVSMPKDAFHETPNL
IHLNLSGNLFANLEIHEVTQLTKLQVLDLSYNRFHVIPESWRHTEKILGKLYISGNPFMC
SCDTVDHLIWLQSI--QDLLDDPTHLTCRDTNGKEY-TIMQIHIGRFKECIKSMVQAGCI
PSAIVLVIVGISLYIYKRRFRFQYLALVARANIN--LHAPQIPDYTYDAFISYSSLDIEY
ML-TLYQKLEQEHNYELCIDMRNFRPGNPIDDEITNGIMDSHKIILVISQNFLRSGWCLY
EMQLAHGELAVRGGEGLLLILKEPRPPELITDKLQGLLDSRIYLEWSEDGDKQQVFWQKL
RDALGMPLQ

**>Goc-TLRα2**

-LHNLATYP-LNVSYNNLNKIEHCLIPYLFDSLYALESLDLSFNLLTSVPSQLFSSLISL
SALYLDHNDIRFLPQGMLFNSTHVGKLTLHQNKIETLQINIFQSLQFLTTITLADNPWVC
NCSMFDFCKWLHSNWT--KVEDKSSLTCKNGSN-----LIQFT--YNCTCKQDNRIVLGI
CGSLITLLSIGLGLVYYYHDNLRFFLYLFGWRF----PVRNNGEAYFDIFICYSSKDNKY
VITKLLRYLETKPPYKVCIHERDFIPGDYIIDNIVRCINKSKTIILVLSNNFVNSMWCLG
EFQMAYHNAFENRHNNIIPILLGDLNLDHLDPTLRTFVGMNNYLRKDE------LFLQRL
LVALPEPSN

**>Goc-TLRγ10**

ALTCMESLEKLNIANNNF----NETDINIFENCTKLHILNLSYNELENIPKDTFNETTNL
ANLDLSGNKLSNIAF--LENQRNLTFLNLAGNSIQYISPPLTQDISRLMKINLDDNFLRC
GCEDIVFIDWLKNN--EDQIINWEKLKCIDDAGLY--NIQTINTEWTQQCNMNIIIAMSI
MTGFILFTTIIACCLYRHRYKVHYLYLLFRSWFH---KPDDANQYNFDGFISYSSLDKTW
ALETMYANLATKYGYNICVDERNFRPGQHLVDIIIETINTSNKIMLVITQNFLRSGWCLY
EMKMARGELATRGRDCLILILKDPIPQELITPTLRQLLESRIYLEWSEDRDRKALFWRKL
CDALGEPRH

**>Goc-TLRγ9**

ALTCMESLEKLNIANNNF----NETEINIFENCSKLHTLDLSYNELENIPKDTFNETKKL
VNLNLSGNKLSNIAF--LENQRNLTFLNLAGNSIQYISPLLTQDISRLMKINLDDNFLRC
GCEDIVFIDWLKNN--EDQIINWEKLKCIDDAGLY--NIQTINTEWTRQCNMNIIIAMSI
MTGFILFTTIIACCLYRHRYKVHYLYLLFRSWFH---KPDDANQYNFDGFISYSSLDKTW
ALETMYANLATKYGYNICVDERNFRPGQHLVDIIIETINTSNKIMLVISQNFLRSGWCLY
EMKMARGELATRGRDCLILILKDPIPQELITPTLRQLLESRIYLEWSEDRDRKALFWRKL
CDALGEPRH

**>Goc-TLRγ3**

SLDYFPSLKILLLGSNGLGPLIHDNDGRLFANLSSVVSLDIADNSIQTISPNACSNMSNL
QFLNLSQNEMFTFHL--ISHIRSLKLLNLSNNRIHLFSQDTMDMFDDLATVDLTGNLFTC
GCSDL-YIIWLTDTMIRSRWLLYEHYTCLFNNG--TITLSQVDVSQLWDCHKPYIVMASM
II-FALLVAVLVKLLHYHRWTLQYWYFMFKRAYRRQQELEQNLVKTYDAFVSYHTNSAQW
VYEHLLP-LERDENLKLCIHQRDWIPGQFISEIIVESVKQSRKTLMVVTKEFAESKYCLY
EMQMARNVLFDEGVDALVVVLIDEILSRRINSTLRYLIQRKNYIQWPDEN-----FVPKM
KAALARE--

**>Goc-TLRγ1**

VMHYFPSLKYLNMANTNLKMHLKDTNGSFFSKLSNLQTLDISKNKMETFSKKTFCHLTKL
KHINLKSNNFVAFEL--MNSV-HFLQMDLSDNKISHLTKSNLRLFELMTTINLSDNAFMC
ACEEQEFLKWLKERRIVDIMQHYSKYDCLVTQTQNKVAIRSINMDEFNQCD-AILMAKVV
AGLVAILVGVLTKVIHYNRFTIRYWKFGIAWMWRRRREEQDQVEYKYDAFVCFQNDDIDW
IYNELRPNIEQEGAFKLCIHHRDFSPGEFIIDNIVNAIEGSRYAILIISKNFLKSGFTKL
EMQLAMKVMIMRQAEMIIPVMLDDVQHPDMYRALKYHIEKKTCITTNE------HFWEKL
RAALKRE--

**>Goc-TLRγ5**

VFDCLPKLKYLNLANNKF----TNIELELFSNCSNLTYLDVSYNQLKTLPENLVAQTANL
QHLNLGGNQLRQFDV--LVPVKTLSTLNVSNNLLGYLKDEMCLQLSKMHRLDLGNNPWLC
TCDNVEFLRWVQQS--TNMLLKPDELICNDPHGNFV-LMANINISKLSGCYTTTIITVSA
TIVITLLIILLAVLAYRRRYKIQYIYLIIRAKMRGFR---QDRQYTFDGFMSYSSLDCNW
VTGVLHKTLEDELDYKICIDQRNFMPGSYIAEAIAEGINESKKVILVITQNFLRSGWCTY

EYNMARGELANRGRDCILLIMKDPIPKEHITQTLQTMLESKIYLEWSEDDDKKQLFWRKL
QDAIGEPQG
**>Goc-TLRβ10**
VMSNCRCLKIVNLKENLLFSY-EKELCRLFKWGKSLQKISIPSNYLAVLPKCIFRGLSQL
TSLYLEKNRLHVIGKGLFTDLINLEFLDLSFNAITYMDSGNFLAMTRLKSLNLNRNNFHC
TCQLLPFRNWIREK--VNLKNFRYNDTQCSLLDRKHVFVHNYTISWLE-CNKVFVVSASS
IGGIFIVVALIVTLLYNYWRDIKYYRMVHKARRHDNRQE--IAEIEFDAYVSYHPEKELW
LRVDLINNLEDDISFKVTFDDR-LEPGRSVIGSMAEAIHKSRKILFVVSRGWLRAITTQL
EIDMALVKMIDDHRDMIIVLLMEHIPKDEMPDKLKMMVKHNTCLKWSDNEKQQAKFWRDL
KLELGKH--
**>Goc-TLRγ20**
LLHCRQNLTVLKFAQNDLSPVF-NSKQPIFAGCNNLKELDISRNSISEIPNNAFVDLKNV
EEIDLSGNELTNVVV--LENCKQLRVLNLSSNPLTNLDDPTMTVLDKLQTIDLSRITLGC
GCNDVAFVHWAQTT--RVKLFNSDTYKCTYLDSSR--ALMKVSIFSLRACMKDVIIASTV
PTITLILIFIAGLYVYHKRWRIQYHCLLLREVARRYE---QLDELTYDAFVCYCSQDEDW
VAEILRPKLEDELNFKLCIHEREFIPGMDIQDNIVSFMQDSRNTILVLSEHFVESRWCQW
ETRMARNKLLDSPRDNLIMILLQDVLKQKMNPTLKSLIEMKTYLRFPQKAEELPVFWLRL
KNAMSEHVK
**>Goc-TLRβ9**
VLNHSNAISLINLKGNILFRY-DSQMCSMFKGRANLSHIDISNNYLFRLPSCIFKGLKNL
KTLYLQDNRLTYIQHDIFIDLYKLHRLNLSNNAITLISPITFAPLANLKVLRIGHNNFQC
YCEMKELRNWLGHN--IKKL-GHHKEKCSGPLTRQDEFIHSFTVSWME-CNGLSTFGSIG
IISIVLLSVITFTVLRHYWRDIQYIKMVRRARKHKSHPEN-NCLIEYDAFVSYHSDKQIW
VIRDLVNELENDVTFRVMFDER-IDLGTNIFTSMEEAIDKSRKMLFVVSRGWVAAAMNKL
EVDMALVKMIDDHRDMIIVLLMEHIPTNEMPDKLKMMVKHNTCLKWSDTERSRAKFWRDL
KLELGKH--
**>Goc-TLRβ8**
VLNNSHDIYKINLKGNLLFHYFDYQLCDLFQSKSNLSHIDISKNYLSRIPACMFTGLSKL
HILYLQENRLTYIHKDMFKDLHNLQRLNLSNNAITSIDASAFVPMTLLNRLWINQNNFDC
NCDMKGFRNWLGHN--KKILSGSIKEHCSHPLIRRNEYIHNYNVPWME-CNGLSTISTIT
ISLMVVLSVATLTVLKYIWRDIQYIQMVRRARKHGNYPLG-DIQTEYDAFVSYHVDKQIW
VMRDLVNELENDIQFRIMFDER-IELGRNIFTSMEEAIDKSRKMLFVVSRGWVAAAMNQQ
EVDMALVKMIDDHRDMIIVLLMEHIPTNEMPDKLKMMVKHNTCLKWSDTERSRAKFWRDL
KLELGKH--
**>Goc-TLRα5**
-FSSLPALPKLHIANTSLTNIN--------------------------------DYFAKV
TLLDVSNNSISHISQDVLQGMTVLKTLYLHGNKLQYIPEYMMNLK--LDHLSLSDNPWAC
DCKNAWIKPWLNANVS--ITIGFEGIKCHGG----GKQLLHYD--FEAMCNL--VVIGVP
VF-IVIFIILMVAIVTNYRQVLTLMIRHHIF--------EEPAGKTWDAFLGYATDDVEY
VQNVIIPLLE--PKYKLCVHNRDFQPGVPIIDNIAEAVDKSQRTIMILSPNFLQSQWCLS
EFRIAHMQYLNHPSKLLIPILLDDFSPAECTA-IKCHLQAHTYLEAKD------WFDRKL
LQQMPKVSL
**>Goc-TLRβ6**
LLEKSKDLIQLDLSDDMLFTYSDNELCRIFSSQSKLEILTLAGNYFSSLPVCMFQNLHHL
KDLDLRKNRIPLIQRNLFSDLRNLSVLDLRENSITFIDVTDFLKLNKLKTLYLKNNLFAC
TCDLRPFQSWVLGVSQ----KTDGPLRCSSPEQRKNNTVRNFTATWIE-CNELVMYLTIT
LSSILIITSIILLTLYNFRNDIRYRRLLQQVKRKTYTKLQDA-AIKYDAYVSYHV-EKQW
FMEEISKKLEKEIQFNL-IHDDNIVAGESIFGSMSKAINRSYNIIFVISRGWIHDPARAI
EIDEVNGILNREKRHNIILLIMEHIPPEQIPGNLKMMLRNNVVLYWNEDPKRQRIFWRDL
ILELGKTKD
**>Goc-TLRγ15**
FINCFPSLVELNLSGNQ-----GMIDVVMFDNCTNLRVLDISNNKLASLPYDMLHHVPYL
EKLNMAGNFFTHLDILNFMETKTLQSLNISSNHWRTFPDTWQKVISGLVELDIHGNPLVC
TCDTIDHLIWLQNI--QVALYKPSTLTCMDLYGQEH-NIMDINMYKYRDCL-PYLMAGFI
PCTVTLVLIGLILYAYRRRYRLLYWLLELQAKLR--QPHAEERNFVYDCFISYSSNDIDW
MIEMFQKL--EQHNYKMCIDMKDFRPGSPLVDEINQGIIQSRKVILIITQSFLTSGWCNY
EMDIAHGELALRGEDCLILVLKEPRPQALITPALQRLLEERIYLEWSNDHDRQAVFWRRV
QDALGEPLQ
**>Goc-TLRγ19**
FLACRPNLTIALLSQNNLSPIFDTPKQTIFHGCSKLKVIDISENQIKTIPFSTFIDLIQV
EIINISGNYLRQLDV--LELCTSLNLLNLSSNLLTTLSSRMTSSLDTLQTLDLTHNSLMC
GCNDIAFIDWAQQT--NVRLHNGHRYTCTDKDSHQ--QLLDISVYHLSECKKEILIASIV
PSVGLVIIFSIGLLIYNKRWRLQYRYLVAREMVRGYV---EIINLPYDAFVCYCSQDQTW
VAEQLRTKLEDEFNFKLCIHDRDFIPGMDIQENIVKRLEESRNTILVMSQHFVESRWCQW
EARLARNKLLDSPRDNLIMILLDDVLKGKMNRTLKSLLEMKTYLQYPHNEGEKQLFWMRL
RNVLMENRR
**>Goc-TLRα4**

-LTQLPTIPPLLLSKNSVSRFE-------------------------------PYLANV
SVLDLSWNGLHEIVIEALNSTRDIEQLFLDNNALTELPKSIKDMPPMLQLITMHGNHFRC
ECESAWMKSWLQAQVDNGRVNSSLKIQCADTQT----EIIH-D--FHELCL-NFLVVGVP
LA-LVSLIVFAFAVLYKFREVIILTIR----KK----PTEKPEGKLYDAFIGYATEDVLW
VQDVLIPILE--PQYKLCVHNRDFVPGTPILDNISEGIEKSQRSIMVLSPKFLDSHWCLE
EFLQAHRQYMAHSSQILIPILLDDFEPDNIVAYIRCYLQSHTYLQHAD------LFARKL
RIHMPKLTV
**>Goc-TLRγ4**
IFNCFTALRYLDIANNQL----KSKDSVFFANCSHVEHVDLSSCTIGEVPRHLLAQLPNI
TYFSLSGNRLRKLDI--LNK--KLNLLNVSSNLLSAISPGMLSQLTHLHTLDMSSNPLQC
MCDTTTFMTWVQQS--TELLHNPSDLLCMTSAGDMV-AIVHVDVAAIHQCILPTILATTL
TTTGILGIIIISLLIYRKRYRIQYIYLIIRSKLS---ES-KQARFPFDAFISYSSLDSRW
VVNTLYSTLADTHAYNVCIDQRNFMPGAYIADAIVEGINDSNKVILVISQNFLRSGWCVF
EMNIANGELANRGRDCLILIIKDPIPQELITKTLQALLESKVYLEWSEDPDRQRVFWLKL
MNAIGPKRD
**>Goc-TLRγ6**
----FPKLKTLQLRNNKV------SNVEMFANCTALAHIDLSHNGIYSLPLQLFRHTPNV
NYVNLAGNKLHTLA-FEVVFLTNLALLNLSNNNIQILTRNFQENVDQMSFIDLDNNALIC
TCDNVDFVRWIQGS--WHFLLQSNQIECKDGGGVS-HSIIDIDVNHFHGCIRSTLIASLV
PNVFFILCILLGVLFYRKRHKLHYLYLLARAQMRQRRNV-DRGNYCFDGFISYSSLDTDW
VIEHVYNELADHHGYNICIDVRNFMPGEFIADVIIESINQSYKVILVISENFLRSGWCTY
ELNMARGELSIRGRDCLVLIFKQPIPRELITPTLRSLMETRVYLEWCHEADKQQVFWRKL
LDALGQPRQ
**>Goc-TLRβ7**
------------------------------------------------------------
----MKENRLTYIHKDMFKDLHNLQRLNLSNNAITSIDASAFVPMTLLNRLWINQNNFDC
NCDMKGFRNWLGHN--KKILSGSIKEHCSHPLIRRNEYIHNYNVPWME-CNGLSTISTIT
ISLMVVLSVATLTVLKYIWRDIQYIQMVRRARKHGNYPLG-DIQTEYDAFVSYHVDKQIW
VMRDLVNELENDIQFRIMFDER-IELGRNIFTSMEEAIDKSRKMLFVVSRGWVAAAMNKL
EVDMALVKMIDDHRDMIIVLLMEHIPTNEMPDKLKMMVKHNTCLKWSDTERSRAKFWRDLKLELGKH--
**>Goc-TLRβ4**
FFTDFPSLKMLDMSNNDFSFL-HQVLAKMILGFENLEILRLSNCQLSDVP-NFFDGGEKV
TELDLSWNLIGHFRNGVLNKLRSLRKLYLQHNHITHIDPLNFERMNDLQYLDMTNNRFTC
DCEQREFINFVKGNQ-HRIIFHGRRTKCH-PDSAYNTFLLHYTSPWIE-CDGNFIMILSF
TIILVVIITCIFIFLYNYT-SIRYRSALCKIKCNQYKSL--GHQYDFDAYVIHHPTDISW
ILYELIPHVEQHFSFELCIEERNFLPGPFKTDNLARAILRSRRALLIISKDFLESDWFRL
ELEMAQLQHLNGREKYIIIIFLDEIPASQLPMKLKCLMGFTTSFVWPKNRSKRNEFWRGLLLELNKKPP
**>Goc-TLRγ22**
FFDHFPKLKTLLLGNNELGLLFASDDFLFFRNSTTLESIDLAGNNLSRIPPLLFKDTKNL
QYLNISNNYLDSFNI--LSTLSHLKYILLSNNKIRVLSSTTRHQINTLAHVDLSGNPLLC
DCNNLDFLHWLRDA--PLVFDNKDSYQCTGMNNFR--KVYDINVKDFEQCKINMIKTIAS
TAGTALITMAVVIAVYRKRYRLEYLWLVSKATVKKREGNDENGRYIYHGFVSYSGRDDLW
ICDQLHIHMEQVMGLSLCLHDRDFIPGEFITDNIIKSMEASRKTIIILSNNFLESRWCEF
ELQMAESRQAEMTYNTVITILLHDVNQNKIGPLLKKYLKQKTYLAWPRDHHQRPAFWLRLKDAIDREPD
>Goc-TLRβ5
LFRS-SNLSEVSFSGTYVGHSDVTLLKDIFHGHHNLQTLRLDTTHIQELKSGTFWSLTRL
EVLILTSNHLKTLPTDIFQGLVSLQYLDLEDNDFIHLDPNMFTQLPNLKLLWISSNSYHC
GCDLRPYREWLNHS--KVVL---PPGRCYSPSKLNNQIVDEFSLPWLE-CDDTLLISGTL
AG--LVIILSHGYAVWRFRFDMKYWYYITRAKRAAEQPLQDGGNIQWDAYVTCTPQDQKF
IYDHVIPNLEEDFKFKLCYGPRDFLGGSEI-GNRENALNNSHRAIFVISKEFMKNNWGKF
ELEMTQLKLFDDHKYMTILFFMETIPKSEMPELLKLLKRHSLCLYWKSENREQNVLWKRLKLDLFKARQ
**>Goc-TLRγ14**
VVNCFPSLKYLYLSGNNV----QGHSPRMFENCSKLKVLDISQNKLQVIPFHTFNETPNL
EEIHLSGNYFSDLEILDFKDTKSLRLLNLSHNQFHALPEFWKDTIAEFKHLDIHGNPLVC
SCDTVDHLLWLQSI--RPLLYDADNLTCKNNQGRQ--FIMEINISEFKECIKPLLLAGCI
PSAIIVITLTLALCIYRRRYRLHYLTLILRARLRKYINSEQRQDFLYDSFISYSSLDVTW
MVDILYKNLSERLNYELCIDVQNFRPGEAIVDEILAGVLESKKIILVISQNFLRSGWCNY
ELKIANGELALRGEECLILILKEPLPKELITPTLRRLLKSRIYIEWNDIEDRQQLFWRRLQDAIGEPMA
**>Goc-TLRβ3**
SFKGLLSLEKLSLARNHLDNS-DGTIVTLLKSLPRIKELDLSWNHLTYIPKSSLDSMENL
TKLDVSGNRLTSFTVDKVRTNTKLNQLNVSRNALASIEALEIGKVTLLNNLDIRYNKFKC
GCELRYLRNWLLEKNHKFSL---YSEKCFAPIEMINTSVMDFKINWIY-CDHLIISLSSA
GG-FLAIILFCIVLSFVFYWDIKYWWALRRKGLGGYLPLDEESKLSYDAFVSYHTSSESW
VADKMVKNLEDDVNFKLCLHGRDFLPGRYIADNIIVTMRNSAKIIFIITQKFLESQWCGY
ELEQAHIRQFDEEKHLVILIFLEKIPKAKLPKKIRLLMRHVTYLEWDKTSRAQNLFWKKLKLCLLDKPT
**>Goc-TLRβ2**
SFKGLANLEKLSLARNYIGSS-DDIIVMLLHLFPKVKDLDLSSNHLTWIPKTALDAMKDL

TILDFSVNRLTSFPLENVNHNTKLERLNVSRNALVNIEAPQIKADTKLNNLDIRYNKFFC
GCDLRPVRDWLLAQRFKVSI---FSERCSAPTELRGTPILYYKINWIN-CDSLIISLSST
GG-FLVIVILCIVTVCIFYWDIKYWWALRKRGVRGYIPLDQQVQLSYDAFVSYQTSSQEW
VAEYMTKHLEDDVNFKLCFHGRDFLPGRYIADNIIVSMRNSAKIIFVITQQFLESQWCGY
ELEQAHIRQFDEEKHLVILIFLEKVPKSKLPKKIRLLMRHVTYLEWDNSSRAQNLFWKKLKLSLLDKPT
**>Goc-TLRβ1**
SFQGLSSLKDLNLARNNLDFSVQSLLSKMFSALKTLKKLNVAFNHFMSLPGDVFDGLQSL
EYLDLSMNKLSFFGKRYIRNVKSLRVLNLRRNMIIKFDMNILKPPYKLVLLNISENKFIC
SCDLRGFRDWLDSKPKHITI---FDQNCSDPDTMKTSRINDFTIPWID-CDNLTISFVSA
GG-FLIIFSVTVVVLVHFRWELKYWWFLRLSRRRNYIQL-HDDGFQYDAFVSYHEESSRW
VYDYMPKELEDDMSFQLCFHGRDFIPGQSIQTNIANSISQSRKIIFVITQGFLDSNWCTY
ELEMANIHQFDKKKNLIILIFLENIPKYKLPKKVKLLMKNVTYAEWEENNRSQRIFWKRMKMALMDQPT
**>Goc-TLRγ12**
FFDCFEKLRVLNIANNDI----VNLTFTVFTGCNRLEYFDASYNNLKDIPTSAFQQVLNI
KQLVLSGNHLRDFDA--LQGLNNLQTLNLSDNILTNLPLQVRNSLDDIASIDLYGNRLSC
SCETIYFIEWLHNF--KENVYKYEGLECSYIDGVF--PVASVSIFRLWHCWAPLIMSIVS
----TIAAILFIFAIYKSRYKIQYRYLIVKGKFKRYQAAPSHDNINFDAFVSYSDHDIIW
SVETLYCKLAHEWRHNVCIEGRSYRPGGFRNEVVMEGINESNHILLVISQSFLKSGWCAF
ETRIAHGELVHRGKSCVMLILKEPKPESLIGTVLRSLLDNGCYIEWSNNPDKQRLFWYKLQDFLGEPIN
**>Goc-TLRγ2**
AFCFLSNLKMLVLNDCKLNDILTDTETSLFKNLLMLESLQLRYNNLTYFNVSHLNSLSHL
KHLDLSQNKLSKFDFAQVSK-PNFTNLDLSSNRFRMFSSDSMKSLDAIKTINLHDNILTC
ACNMLKFMLWMHNN--KGHMVQYSTYQCVFSHNDTEMNLIDIDMVSFSECHKDYIIFSVI
SVIITLLCCLIGLILYKKRWTLRYWYFILRQSWRRRRDA-DVMHYHFDAFIVFHSDDYEW
ILNELLKQSEEPHGLKYCIHLRDWRPGNFVSENIVQSVERSRHTVLIVSKNFTKSKFCYY
EMNVARSLLTSHGRDVIIAILIDEIRKAGTTATLREILRQKTYLQWPSEN-----FWERYHTMMDDNEE
**>Goc-TLRγ8**
FLTCFESVETLIIGKNYV----NGREFNVFQNCSKLHYLDLSFNGLTGIPWRAFNETPSL
IALNLSGNQISYPRF--LEAASNLTSLDLSNNKIHYMDESMRTNIGTLMSLNLDNNILLC
NCNGITFIEWLQKY--KQNIVNWDKLKCIDSKGTEK-KLIDINITLKKECLMDIIIASST
VSGIFLLVVFIAVCTYRRRYKLQYLTLLLRAWCR---KPDDGDQYNFDCFISYSSLDRIW
TLETLYTTLATKHGYNICFDERNFMPGQHLVDIINESIFTSRKIILVITQNFLRSGWCLY
EMKMARGELAARGRDCLILIMKDPVPKDLITPTLRQLLDSRIYLEWNEDVDRQQLFWRKLRDVLGEARH
**> Goc-TLRγ21**
VFHCWPNVKTLLTGGNDLSHVFYEENIDYFENCTHLEVLDLANNKINKVSKNLVKTAINLRQLNISRNQLSMFDV--
LDNNQQLELMNLSNNILGSLPISLTLTLDHINIVDLQNNPLLC
SCATLDFISWCQTT--KVHLNNLPSYTCTDGTQRQ--YLMDVSVSHVDKCKEPVVIAAVS
TSLITIIFVIIAITIYTKRWSLNYYLLLSKIFLRRRNRYSENTSYRYDAFVSYSSNDDDW
ILRNLHPILEDEHGLKLCLHQRDFIVGNDIQDNIIESIEASRKTIVVLSNNFLESKWCYF
ELQMARNKVLDGKLDLLVLVLLDDLAKDLVTATLRTLLATKTYLRAPREPQQEALFWLKLKDAISTDRS
**>Goc-TLRα3**
-LDKFPKLPTVNVRDNHITILP--------------------------------SYMPMI
KVLDASYNSIHNINIDSLSNLTALEIFLINDNDLNYLPNTWGSQTSSLKKLCYHDNPFHC
DCSSLWMEKWTTTFED-LLCSE-D-IVCQNG-----RPITDQG--INEFCHI---FASVI
IGILVTTIIV-TFLLFYFRQVIVLWTRR---RC-----ADDPANKLYDAFVCYADDDFDW
VNDNIIEHLE--PKWKMYIPDRDIQPGELRVILIQEVIETSQRTIMILSQNFLQCTELVN
TFRFAHQQYMVDPSKVLIPILAPNFEVGTMPLFVSCYLKAHTYLEASD------FFMRKL
QLQMPKIRV
**>Goc-TLRγ13**
VLNCFHSLIELNISGNVI----GQSKWKMFQNCTQMTRLDMSFNKLTSVPLGAFNELSGL
KDLSLAGNDLRSIDI--IQNNAELRFLNFSHNRLDTIPDKWREYLDEVKILDIRNNPFIC
SCQTIEYVEWFQRR--KSMIFQPNALSCVDITGKH--SLMDIDIAEYEECFHPFIIAGTI
PSVVIIIILLIALFIYKRRYRLQYLSLVLKAKMKNYVNAKESKTYLYDSFISYSSNDVYW
MVETLHNKLDDELGYKLCIDVRDFRPGNPIGDEIETGILQSRKIILVITESFLRSGWCTY
ELNIANGELALRGEECLILILREPRPEQLITPTLQRLLKSRIYLQWPEEEDKRLVFWQKLQDALGQPYS
**>Goc-TLRα1**
-LSSVPGLP-LNMTGNNFGNITNCYLNDVFNGIYNLKTLTLKDNFITTLTSGPFKSLVFL
DTLDVSNNILNTISDNAFSNVRLLKHINMVNNNMTVLKPEVFNDLSKTGTMFLSGNPYNC
-CESLPLKNWLNTHQA--QIIDIDITLCQKE--TDTVPIYSMA--DANTCDLTFYVIVII
LS--LLFIIICCILVVRFRQAIRLRLYWFKWRF---EAFEDDSKKKYDAFISYTGHDGDW
VREDLLNFLEG-NNFNICLHERDFRAGELIIDNIDRAIEDSKRSIIVLSNNFLNQDYTMY
EFEASYRDWKLGLRDPVIVILYEALNKEKIAEHLQTHLNTRTYIDKSK------YFWENL
LLAMPRQKH
**>Goc-TLRγ7**
VFNCFEKIKIINFAQNKV----YNGDLELFLNCTYLEVLDLSFNALNSVPKNTFTNLVNL
KKLNLAGNKFIHID-FDLRRFWKLESLNMSRNSMDMLSVRTRKELTDLYTVDLHGNHFSC
KCADIDFVEWIQNN--FGMVAMPDSLPCSDERYVKR-RIMLISVTHLRRCWSHTILAAVV

PVALLLLLLFVVLLAYQRRYKIKYLYLLLRAKLR---DHQDRQVYLFDGFLSYSSLDQNW
AVN-LCEKLEQDFGYNLCVDQRNFGLGYQLVDLIVESINQSRKIILVISQNFLRSGWCLF
EMNMANGELAARGRDCLLLVLKDPVPQELISPSLRALLDTRLYLEWSQDPDQEQLFWQKLRDALGDPRP
**>Goc-TLRγ11**
MLDCLQSLTVLKMRENQLEVVSNNLNNTLFNNCTQLEYVDLSFNGLTFLPKDSFIGTHRMKTLNLSGNRLQHSDM
--FPKWQYLDALDLSMNYFTTIGEELRRQMEYLKTLNIQGNPFSCDCQSLDFIEWIQNT--
QVHVTNRDGLSCSLSNQINTIKVLSLNIGQAKKCWSPIILAAVVPCVILIVMITTITIIYRSRHRIQYYYLIIRAKLR---
EQKVQDDYHFDAFLGYSSKDVGW
TIDILYKTLANEMGYNICIDQRNFRPGNYIADTIVASIAQSNKVILVITQNFLQSGWCNF
EMNMAHGELGARGRDCLILILKEPQPENLITPTLKALLGTRVYLEWSDDPDRQRVFWRLLQDALGQPKP
**>Goc-TLRγ18**
VIHCLPNLKTLLVSENNLSSLFGKYNQTVFYGCSQLQTLDLSKTLIQAIPSDAFKDLLNI
EHLKIAGNDIQTFDV--LEQCKSLILLDLSSNLLSKLSERMMSRLDALQTVDLMHNPLSC
GCRDIAFITWFQNT--HVHFLNGQEYTCTDENYKE--HLSDIYVFHLNECKMDIIIASTV
PSVCLILIFSIGLLIYRKRWQLHYRYLIAREMVQAFT---TMGNYTYDAFVCYSSQDQTW
VYEQLWTTLEEKHGLKLCIHERDFMPGVDIQENIVQSLEESRNTILVLSKYFVESRWCQWEARLARNKLLESPRDN
LIMVLLDDVLKPKMNGTLRSLLEMKTYLQFPACPDQQKLFWMRLKNAISEERP
**>Efe-TLRα**
----FPNIHSIHFEGNALTTFMYNDLPYAFLPFPNIEFLSLNGNRITHLKFGTFAKLKKL
TNLYLHNNLIKEIDSSVFDDLHLLNQLTLHSNSLELLENDTMDLLSSLSNLTLDDNPWVC
PCDNATFKYWIQQHSE--IISSPFSLKCNE----T---ILRI---DEDLCYKQYLTGPLY
TASLFCLLLLTLVLVYRYRYIIQVIVYKFELRR----KQQESESCAYDAIAVYDSSNLKW
IKDILIPRLE--PKFKLYILDRDMLPGSVQCNEVVENIKRSRRTLVVLSGAEDLQE-IGF
GFDVAHHRVTQERHHRLKLILLHNVAKQDLHANFKAYLTTGQYFSVVD------LFWQKM
LYFLPR-PP
**>Efe-TLRβ1**
IFQPLLNLQTLNLAGNRLGRVITDIDGQLFRGLSKLRWLRLDNNEMRVMQYTMFSDLTSL
QMLNLSNNYLSSWAPGIFNASGKLSIVDFSSNKISIVTEQELLTVPTNTSLNLTDNPFAC
YCDLIWFRRWIHNS--STKLAHLQSYICNSPDQMAKKPLLEFNPDDIARCHLMWILLGAC
SG-VVAIMLFFGTMMYRYRWQLRLRLYYAQRRIRGYIEVDEGYD--YDIYVSYSDSDREW
VRTELMPRFNLLGELRVFIEEADATFGFLEFDTLAEAIYKSKKIMLVVSDEYLHDGRRLF
EREWAIRSRFEKQDDSIIVVCLEPDADVKVPAVLLPIC-RNQGLEWKQDEAGQEFFWRKL
ADVIQY-RD
**>Efe-TLRβ8**
IFQEAQNIEKINMSFSRI----ESNLIAPFHHLLKLTDLDVSGTGISNLS-HMFADLPNL
KRLRLSRNPILTLERKDFEGIESLRDLDLSSGKLSTISFESLKVWKNLRVVDFSDNPFLC
DCNFIWLRRWLKRANAKVEVRGWDKYYCQTSKG--QVNMFQLSPSDID-CFQHWLLTVRL
LTSLIWITATSASALHRFRWHLRYWYFMKTVHAQRFKDEEEPDFFAFDAFVGYSSSDSNW
VITQLLPRLEQECNLRLCIHERDWLPGRDIAENILESIDNSRKTLLIVSNAFAVSHWCHF
EMTMAQTKLFEDDRDNLILVLLEEIADCNMNPRLQLLMQNKTYIEWTDNNIGQQLFWARLRQVLAKQSN
**>Efe-TLRβ7**
VFRGLSHLRVFNISRSKS------KTIYPFYYFRRIEVLILRDVGLRNLER--ARYNRRL
RYLDISQNEISVLMSSSLARL-KLEVLLVRDNWLSVIDLETLSTWTNLKRVDFSENTLNC
DCKIIWFRRWLQNRQSNVTVENLHLTQCTAPAKAKDKPVHLLEPTDLE-CFKPYMVAVFL
TAFFAYLIAPTVSMLHRLRWILKYWYFKHKTKAKEYRDIDDNKPYEFDAFISYSESDRNW
VVSQLRPRLENEFGLRLCIHHRDWLVGRDIVDNVVDSIEHSRKTVLIVSNAFALSPWCHF
ELTMAQTRLMEEDRDSLVLILLEEIADCNLTPRLQIQMQRRTYIEWTKQSVGQQLFWANLKHALAKPSD
**>Efe-TLRβ2**
----F--LEPQYSSNNPLNN--------------SMTSLDLSGTNLNTLLNGFIECYKAL
RTLNVNQNKLEILTIETFRNLPSLEELRAANNFLTQISESSLKLWTQLKTVDLSGNPFRC
DCKLLKFSQWIKENNFKKLL---DNMQCVSYSSGKRQSIVS-AENRLKLCLEWFLWALTA
TVFVTSFLSTFASIVHRFRWNIRYWIFSHKIKTRRFKQVRDKKHYTYDAFISYSETDSRW
VILQLLPRLESEYHLRLCIHQRDWLAGRDIAENIVLSIEQSRKTVLIVSNAFAVSQWCHF
EMTMAQSRVFQDDRDNLILVMLEEIPDCNMSPRLRMLTERQTYVQWDDHALGQQLFWVKLQQALAKPAE
**>Efe-TLRγ2**
LFR-ISNITSLVLINNDF----QN----------SLRPLDLSGSGTSFIPKSMFSELSAL
QFLNLSRNIIESFQV--LPPSGNLSLLNLSDNSIRILTSEMISELESLQTIDLSRNPLSC
LCNATEFIAWLKSTK-KVSFENIEEYTCLHPNGTK--SVNSLNMTELMDCKKSFFIVPLI
IGLLLLLLGVALIVIYKRRMDLRPYIMFIRYLS----PA-ESDNYEFDVFVYFHADDVLW
VRGALLEKLQ----HLKVITPDNFRIGASMADAILDGCRKSRVIVLVLSSSFKRDDWC--
-----TLRSYTSHPGSVIPVVINDTDLSDFEDDYSNLIATHS-IDLAD------FIWNEF
TSRVDRQSS
**>Efe-TLRγ1**
LFR-ISNITSLVLINNDF----QN----------SLRPLDLSGSGTSFIPKSMFSELSAL
QFLNLSRNIIESFQV--LPPSGNLSLLNLSDNSIRILTSEMISELESLQTIDLSRNPLSC
LCNATEFIAWLKSTK-KVSFENIEEYTCLHPNGTK--SVNSLNMTELMDCKRSYFIVPLI
IGLLLLLLGIALIVIYKRRMDLRPYIMFIRYLS----PA-ESDSCEFDAFVYFQDDDEPW

VSRVLLEKLQ----HVKVITPDNFPLGAAMVDAILDGCRKSRVVVLVLSSSFKRDDWC--
-----TLRSYTSHPGSVIPVVINDTDLSDFEDDYSNLIATHS-IDLAD------FIWNEF
TSRVDRQRS
**>Efe-TLRβ6**
IFNRVPNLITLNIARSRA------KSLSLLFGLKRLEVLNMRATGVTSLPY--IAKRRHL
RILDVSENEINVLQSPVLQNL-KLEVLLLRDNWLSVINITTLDTWDRLTRVDFSENTLYC
DCQVVWFRRWLRKRK-NTTVENLHLTRCTGPAEVKDVPIHLLHPTDLE-CFSAYLLSVFI
AVFMTTLVTFLVAILHRLRWMLKYWYFRYKARAKEFRELLDQQHYEFDAFLSYSETNYEW
VVDQLHPRLENEFGLRLCIHHRDWSLGSDIVDNIVNSIERSRKTVLIVSNAFAVSQWCHF
EMTMAQTKLFEDDRDNLILVLL-----------------------------------------
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**>Efe-TLRβ5**
LLWGIPKLKELNVSRSVG------RSIAPLTNQTSLEVLSVRQDDLFDEDVNMLTNVPHL
RHLDLTDNNINVLENIPFHKLKSLEVLLLGKNWLITVNATSLCTRTHLNRVDFSANPLIC
DCGIVWFRRWLNTT--QVIVDNREDIRCSAPEEVKNRILSEIHPTDLE-CFQELLALGLI
LVQMVYLLSLIVSVLYRFRWRLKYWYFRHKTQGNEFENWIETPHYDYDAFISYNESDSKW
IVTQLSPRLETEYHLRLCIRERDWLVGLDIVDNIVDSIEKSRKTVLIVSNAFALSPWCHF
ELTMAQTRLMEEDRDSLVLILLEEIADCNLTPRLQIQMQRRTYIEWTKQSVGQQLFWANLKHALAKPSD
**>Efe-TLRβ4**
IYEGMPNLEQLRLANSRR------KAAIPFSSLSNLVELNLRGVGIRAVHLNITKNLPKL
RRLDLSDNELSHVRASFFRNL-ELDILLLRRNWISTISKTTFGMWSRLKEVDFSENPYFC
DCRMVWLRQWLRNKTRATAVRNKGRMVCIGPHEAKNTKLYLLKPTREE-CFAYYRLAVLL
FTLVIWFLAPLLSIVHRYRWFLKYYYFKYKIQQRQLHDLLDKKQYSFDAFISYSESDSKW
VINQLRPHLETEINLHLCIHHRDWLVGRDIVDNIVDSIEKSRKTVLIVSNAFALSPWCHF
ELTMAQTRLMEEDRDSLVLILLEEIADCNLTPRLQIQMQRRTYIEWTKQSVGQQLFWANLKHALAKPSD
**>Efe-TLRβ3**
VFNCIPNLEELLLINVQV------SVRHPFRNLTKLKKLNMGGTSLGDVEVKMIPDLRQL
EWLSLAHNTIQKLRRGMFQNFKTLKVLSLGNNRITTLNVTSLSLWKSLERIDLSGNPFTCDCQLVWFLHWLSTT--
NVTVSDEKQYQCNSPAALKRKSLKKLHPNEVE-CFEWWLLAVLL
ISITASASSTIGSVLYRFRWYVKYWYFKYKIQQRQEALSTDNHSYQYDAFVSYSKHDTKWVVTELRRHLEIEEGLN
LCIHDRDFLVGEDIVSNVISSIEQSRKVLFIVSNAFAASQWCHFELIMVQTRMLENDRDNLVLILLEEIDDATLSPRLK
LQMEKQTYLEWTSSEVGRQLFWDRLRQAVSRPPE
**>Hro-TLRα3**
-LKTLPLLP-LTFSRNMISSMD--------------------------------FYLSST
TVLDLSYNELNQFDLSTLMFSTTLEELYLHSNNLVSVPPEFLQKSPKLKVLTLHDNPWDC
SYENKFLKSWMMNGNV--SLLHENSILCRTP--LSGKSIFFVK--DEEANDP-RNRVILC
ILIPLFAIEIFALAIFLILKKFKVKLYYLNIHPR----ECTDEYMEYDAFISCAFSDRCR
AIE-LVSTLEN-RGYKVCYPERDFIPGEPTTSFVSK----SRRVIYLLTLDFVNTPRCLF
EFQISLQRNLEVKHKRIIVLLDSSLKVQLLPNDMFNFLTTHHCIDLLK------NWTNQL
FYSLPIKPL
**>Hro-TLRα1**
-YESLPLIPLLYFNKNLLTSFN--------------------------------HVFNDT
KILDLSENKINEISPHTWVQLIQEDSVFLHNNNLSYLPRILEKMNTS-KRVTLHGNPWSC
TCQNAWMLDWLKSHVH--VV-KPEKMVCAYP--HESKSLFEVDF-----CYS---ISCVT
VGIVVLIVAVT-----------YVWYRRFGPQKK--PPVPPNPKLTNDVFIFCSDEEQVP
LVKEIIRWLENEHRFSTICGLRDFDSK-PKVVNINEALTTSKRIIFIVSKDFLKDNWCIS
GTMSA-FSLVEDKRRFIVIFCGVHLQSTNIPVELEIYIRTYTYLSFDD------SFWKKL LRAMPKE--
**>Hro-TLRα2**
-MSNLPMLP-LTFSHNSIETID--------------------------------FYFNNT
VVLDLSYNKITKIDLQVFKSLKVLQELHLHSNFLTTVPRDFLKNDRMLKHISLHNNSWDC
SCGNKWLKQWMMNQSI--TLLTPDSVLCRTP--LSGRSLFSVS--EEECPKP--SRLLIS
LLIPLLTGVLLLLALFVLIKKFKVELNYLNIHLR----ECIGENMIYDAFVSCSYSDRRR
GIE-LVRLMEG-KGYHVCYHEKDFIGGQSIAANIVEAITFSKRVVCLLTSNFLKSTYCMF
EFQTSLHRNIELKRKRLIVLLDESVEVEVLPNDVHNFLTTHTYIELSS------KWTHQL
FYSLPLNPI
**>Hro-TLRγ1**
FLNFIS-LGELNVEKNELGEQMSDMFGLTFQCYSNLTILNLSNNKIKKLHKLSFKNLRQL
RILNLAENSLQTIE-FEISHMKYLQYLDLSRNLLVSLADDTCYVLSGLSSTSLYGNPLQC
NCETIKFMKWVQSK--KVTINNKNHTNCQNRSS-KFITLSNLAVNELRFCNLPLIIGGSL
VG-LLIICSFLGFVLYKYRWDIRYFLMSMQKSKRRCTSFERNRYYKYDAFVCYEKSDRRW
VVTELLYNLEADDRFLLCIHDRDFELGLGIKHNISMAIHASRKTLLVLTNNFLKSKWCRH
ELEMASLESLDRECNLVVPVFLEPV---ETWDSLSWLTKRYTYLEW--------FAYDKL
VVALN----
**> Cgi-TLRγ2**
AFASLRKLEYLDISNNEH----------------GLAVLGLNQTNIKVLKVNI-------
----LQRHHLSYLDN------TSLLELSIATNRIETLEPCVLSRLKSIKRLSIARNRLIA
AAYVLEYHSLV-----NVEVINA--------------SLRNFTIS---GCKE--------

---LILKNTVYHPALYRNRWKIRYMRYTLFQRAR---SSSSDDLFLYDAFVSYTSKDRDF
VIKDMIQKLEQDNGVQLLIRDRSFIPGEFKCQQIVRSIQESRKTICVVSKRYLKSAWRDY
ELNMARVEGVEVRKRYVILILLPEVCSGGYPKKISDFLKRDCFIEYPDDPAGYEEFWQRLCSALQENQD

**>Cgi-TLRα4**

-LTKIPGFP-VSLDRNNISEIYHSTLNNSFIGLLQLKTLYLNNNELQEINRGVFNKLWNL
TELHLEYNNIAYIEEGAFSALTSLSTLFLDHNLLISLPQSATNHF--LSNIRLGENPWSC
SCDVMAFIPMVMNRSM--VISDYSDMFCKETGE--NFSMKDVLVK---RCTSNILKILVI
VAAIILTTFFIIIVICLWR---PIVLFHRKCKCR---RYPEDGDKSFDAFLAYSHKDDDY
VTREFIPRLENELKYRLCVYYRDFPIGGTIADTVASSINRSKRTILLVSKHFNDHEWRNT
AFQHSFGGLFKQKDNHLIIVLLDDAKGMKLDRQLKVLVKSHHVISYRD------CFWEQL
QYKMGSSKR

**>Cgi-TLRα3**

-LYNIPSLRH------------------------------------------WRLNFPKL
KVLDLTNNHISDLIIDHDPDSSDKGVINLQYNNLTSVSDNQLKNFHSF-YIDVQNNPFSC
GC--MRVKHFILNNTKSSEYSYLRGLKCQNP--VAGRELITLS--DADGCGSQ-SGPIII
LCVLVFVLFVCLVVIIRYRVEIKILAFRFNI---PCQQQDNLDNKKFDAFVAYSQQDSDW
VLKNLVWQLETLQRFHLCLHQRDFTVGAPIAENIINSIERSRHTILVISSNFVRSEWCLM
EFRTAFHQSLIEKRRHMIIIVMGDLPHGELDTDIKRCLKTLTYLETHD------LFWDKL
VYALSDKQR

**>Cgi-TLRα1**

GFQDMPNLEMFGILDRKI--------NEIFGSFQKLHTANFSDANLEFIPANWFRQFRSL
RIIDLSHNRIKEIPYRR-NHFGKLIKLILRHNNISRITKTLIEKLSNM-AVDFSKNKFVC
ACESLEVLQFVRNQIEAINYHYLANETCYYPSSLQGMPLRSL---DSLLCPNSWTFQELY
IGLIVLTFITIVCLVVKFRKEIKILTYRLGIRF-PHR---SGRLKEYDAFVSYSALDESW
VMGTLCKRLEG-PPLRLCLHHKHFVLGACISDNIIESVEKSRHTIIVLSQNFLQSEWCLL
EFRKAFHQTLLERRRHLIVILMDQINLDTLEPEMNYFLQSHTYLKRTD------LFWDRL
IYAVSDP--

**>Cgi-TLRα2**

SFKNLQ-LETFLTESNRF----------------ELRILNISHSSLYYVPENWIIYFPKL
EYLDMSHNKIQDIVLSMYDPTSARLTLDLTFNDIRQISVRFLEKIARL-YVIIDNNPINC
SCTDMRVLEYIRNSVK----QYIRDLKCQFPENIKGRRLRDL---DNDGCG-KMLPIIVV
LSILICFLLIFLFLIIRYRLQIRLFCARLSGISN---DMDAEKSFKFDALICHGLFDEEW
ARSTFIENRHK-SHLKLGFYREDATDQKNNFEKLIDQMKSSKYVVVLLSRQFLEGEFLTP
GFQEALQQSNEHTRKRSILVLMDDIPTQEETICLRRSLQTFTCIHKND------RFTDKF
LYLLSSK--

**>Cgi-TLRδ2**

ILQGVKNIRQLRAVNVQFN--FNLISESLFKNLKYLTNLDISRNSLNFLPQSLRDQKLSL
KELNLDHNMFSSLS-SSLKQFTNLRKLYVRYNLISKINEKDQELFKSLTLIYIEGNPISC
TCSNIQSLKWMKDH--QHLFSDLSKTKCVGSNNL-TVELNEW-LLKFEICQADWLIFSIV
LIVSTLTMLIILAAIKKYHVHLEYVILRVKQRLMPVGHVCVEGDFQYDVYISYNDDDTSW
VANNLNPKLE---NIKAWFKEKDSIPGGWESEEIVNCINDSRKVMFIVSESFLDKGWHSY
AVQMAITHAFHNQRRSIMVIIKDGLPLERLPKEFKHIWWCIEHLRWPEDETNDETLLLNL
SNVLVSE--

>**Cgi-TLRδ1**

MFQGVRNLHHLYVLDVGLNNTAHSISNSLFKNLKNLLTLDFSKNGLAFLPSLLMDQKHSL
TEIRLDHNRFSAVP-SVLTELKELKTLYVRFNLISKFSRNDQRLFQSLSSIYIEGNPITC
ACTGVQSLKWMKAH--QNIFYDLNKVLCVESKIP-IVQLYEW--RKFENCQTDWLVFSVC
LLFFTIVSLTIIASVKRYRVHLEYVILRLKNRWKGV-QKSNEDMFLYDVYISYNDADCSW
VIETLYPKLE---NIKTWFGDKDSIPGRWKSEEIVGCINESRKVMFIMSESFLERGWHSY
AVQMAITHAFHNQRRSIVLIIKDGLPLDRLPNEIKNIWWCIEHFRWPENEQHDEMIFSTL
SKILKPK--

**>Cgi-TLRβ4**

LFK-APNITNIELFDNQIS---GSTLKTLLWNLIKLQKLNLQGCGINYLARGTFDRMPDL
RTIILKGNSLYGWDPTMFNKLFNLRALYLSGNSVAVVNRTSLIGKINLKFIDLADNPFAC
TCQQLWFRDWLKTAKNITVAFYPKRYVCRSPPKWDNTLVALFNYTEED-CREPWILIGSV
LGSVVFVCMVVVIVIYTHLPTVRNIIYLIRLRRKGYVRLVNSEEYMFDCYVVSCETDEQW
VFQTLSSTLEVKHSYRLCIPTRDFDIGASIADQIEEKMRECKKIIIVMSNDFAQDEWCQF
QLEKAQERIRNQGEEAVVSIMLHDIDHKHMTSTIKNLLRKSSYATWVKGKIVSKLFWDIV
VAAIEK-PP

**>Cgi-TLRβ3**

LFNNTRNLRVLDMTGVQFSHNLEEKMFQLFKPLTGLEELTLKKTSLSTFPVSVFQFMPNL
TKLSLQDCYFNQSYLRKLSAPASLKVILLDNNLITSINETNI---NNIDQMSLKSNPFLC
TCDLVFFRKWIETNS-KRLLGWPNDYTCNLPQEWKGKNLADFHLSYLS-CHPPYIIMAIS
ISFAVLAIATVSCIIYKKRWHIKYYLYLLRAKKRGYEVL-GGDDFAYDVFVAYNSDDRIW
VISEMIPRLENEEHLKLCLHDRDFQVGKLIVDNITDAMHRSRKILIILSNSFAQSHWCRF
ETMMAQLRSINHGENTVVVVILENILTKNMNNSLHMLLKSTTFIEWTNERAAKEMFWTRLVSSIKT---

**>Cgi-TLRβ1**

SFNHLQSLKHLKFDDNNLGGLISDNIGTLFAGLHKLETLSLSKNFLHNLPISIFKDLSSL
QTLTMKSNRISGWNNGLFKQTSALRSLDLSDNSISLVNSSSLADLSNFQMLNLSNNPLACTCDLRWFRDWVNQT-
-RVNIANVGNYVCNSPNVWKGKPFLSFDRTKIN-CV-LYFVVGVS
IA-SGLAVLVFCVIIYKKRWWILYRCYRLKNCC-RYQPIQDGQELVFDAYISYADDDYKW
VLEQLLPDIDSKGEFKLYFHDRDSVPGSSMISSISDNIEMSRKVIIVLTEKYLSSARHKF
EIDLAVMLKSQGVIDDIIVINVCGVSFACIPKSLQRKVSKDEFLLWKDDVDAIWLFKQRL
KAELKR---
**>Cgi-TLRβ2**
IFRYCRGLNVLDMTRIRLTTYDGVMLYELLHHLTNLTKLVLQSTLVLTLPENLFSRMPFL
GSLHLDHCYLSQWKLGVFRNVASVKTLYLDHNEIAIINQTSFELLRGLKQLSLGYNPYLCTCDMVWFREWTGNNT-
KVMLNWPYAYKCKSPREWATKLFSDFSLSYSY-CHPPYVIAAIS
TAAGVVLIVIVVGLFYHYRWHIKYFFYLMRARKRGYEPLPGDDDFIYDVFVAYHSDDRVWVISELIPCLERKEKLRL
CLHDRDFEVGKLIVDNITEKINSSRKVLLLLSNNFIQNRWCKF
EMAMVHARNVEEDRSDIVVVILENIRTQNMSNSLHVLLKTTNFLEWSNKKSAKELFWKRLVASVK-PES
**>Cgi-TLRγ1**
FFIPFVGLEILNLSNNALSQMFSDENGDFFQSQRRLTDLDLSLNRIAHLPGHVFQHNSKI
SRLNLSFNSLSDFNV--INHMKHLSQLDLSHNQLTQLSKNVRASLDAIAKVYLLGNNLKC
ICGTLDFLKWLRDSK-SIYFVGINNYTCLFENA--AASFNEIIVQVLEKCSSTLIIVLMT
TLIIVTMTTTVSRILYRYRWKLRYMYYVAKEKYKTHSEEKDRSSFRFDAFISYAEEERLF
VFK-LVKYLEEKCNLRLCIHHRDFIPGTGIADNITNAIHCSRHTVCFMTSHFLQSHWCMF
ELNMARMEAIYARQNVLFLVALEK-TMKHLPLQLMDLVDSNSYLEYPGEESGIEAFRTKLGETLAS-SD
**>Obi-TLRβ5**
IFKSCPQLTNLILKNVSN------YPNDLLKPLTKLENLMITDGQVSKVPD--ICNMNNL
TELSIFYTTVSKWNNANCSVMRVLRKLVLKDNKIIYVNPKLFSHLSNL-HIDLSRNPFVC
DCKALWFRDWSRKN--AGRLKNYRNYRCFSPNSLGHIHLRNFSLSWDY-CENSIAIAGVS
VGVLAVMFVFLAILSYTKRWSIRFCIYQSLVRKRKYKALVNNGRYKYDAFICYCSTDVSWVLNKLLPIIEEENHFNLC
LHDRDFLVGNDIVDNIVDSMQQSRKVVLVLSNDFAQSSWCQFEASIAQQKILEEHYDIIIPVLLNEIPSNLQTKRLGV
LLKQKTYLEWPNDEQYEGMFWERFIGRLNANNE
**>Obi-TLRα2**
-LTQL-GLP-IDLSGNKLNYLYNSIVNKTFIKFTNLKKLYLQNNLIEALQQKSFEGLKNL
LELILYNNKIQYIPENTFSETPKLKYLDLRNNKLQTITSEMF---KALQKIYLSDNPWSC
ECNDISFEKIFAKDTE--LLVNGEQIFCRKYDA----NIFNYGQE---FCQNVLISSVSA
VSSVIILIFLITFLVYAYRQEIQLLLFHFGYRFK---LIIDEENKLYDAFVSFDNSLDLF
VLNELLPQLEQNPPFKLCVHFRDFEVGLQITENIINSIENSKRTILLITDNFLKSEWCKY
EFQTAHYDGLSQKMNTLIVVLFENINEELLDPDLKLYLKTKTYLKYDD------WFWNKL
RFALPAKKD
**>Obi-TLRβ4**
IFKSCPQLTNLILKNVSN------YPNDLLKPLTKLENLMITDGQFSKVPD--ICNMNNL
TELSICYTNVRKWNKPNCSVMRVLQKLELKHNKIRYVNQELFSHLSNL-NIDLSNNPFVC
DCKALWFRDWSREN--AGRLKNYRNYRCFIPDTFHHISLENFSLNWDY-CENFIAIFGGI
IAVLVVIFVFFAILSYEKQWSIGFCLYHSLVRKRKYKTLVNEVQYKHDALVCYCSADVNWVVNKLLPIIEEENHFSLC
LHERDVVVGNDTVDNIVDSMQQSRKVVLVLSNDFSQSSWCQFEASIAQQKILKDHYDIIIPVLLNEIPSNLRTESLV
DLMNQKTFLKWPNESKYE-------
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**>Obi-TLRβ2**
LFR-FPSISLQLIVTTLLSD--SKSINQSLAFLPNLVTLQMSFSNLKTIP-KVICNMVNL
TSLNLKGNAIVWWNDTNCFVMKKLHFLSFSENRISIVGDKTFLLINNL-RWDLSLNPFLC
NCENAWFKSWVEKNHQKFLYYPK-DFTCDTPADLRGKQLSDIDLGNNI-CGVVGITIGIV
LGSLMFVFVVVASISYYKRWALRYICYLLKSRKKQERSQQDEKSYVYDAFICYHNSDSKYLLEKLQPKLEEENNFR
LCIHDRDFVPGWDIVDNIVESIEKSHKIVLLLSNNFALSEWCQFESTMAQQRLFNEKKNTLIPILLEPIKIKNQTSRLTI
LLKEKTYLEWTDDKNGQKLFWARL
LNTMRGP--
**>Obi-TLRγ**
FFTFFTGLRLLNIENNAIGQVAEEGFSKAFLNLTNLEELYLSNNHIRYLSNNSLLQLKNL
RILNLHINLLESFDV--ISHMLNLSYLDLSKNILQELSENTFNAIEKISTVNIQSNNLKC
GCAQIRFLTWLHKVRNHLKI---MYSKCTHPNGTV--KLTDLIITYLNSCS-SFIIITVA
CLIVLLGCFSFGALVYHFRWKLRYLYYMIRERY-AYQRI-QTGEYLYDAFVSYAEEDRGC
VFEYLIPELEEKDTFKLNIHHRDFPAGKQIAENILSAIQSSRKCLILLSRSFLSSEWCMF
EYNMAKMECVHAERDLVIVIMLEELSVDILPLQLQHQIKMQSYICFPTTNPTSDVFWNNLKKSIQE---
**>Obi-TLRβ1**
FSKELTRIRKLYLDSNKLGKFLTDKKGFLLSG---------------QLSKKIFQNNKHL
KYVYFRGNKITGWENNTFVTNLTLMELDVSNNFIFTFDSDSLKYINRKKKFNVTGNPFAC
DCNLRWFRDWLNTT--TVDIVDKNGLTCNSPPDWQDKQLLDFTRSKID-CTDLYYILGGV
GG-GFLLTVVIVLFAYTKRWYIRFKIFKLYQYVQEYEAI-PGDDMYFDGYISYSDKDADW
VEKYLMHTFDNNGNFKLCFRNRDFAYGKYIIGMIESSLAVSKKMIMVLTPYYKKDKRCEFELQLGIMKLNI---
KNVMPIVLKNLQPNQIPNSLKEIFETNKFIEWDNN-----------
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**>Obi-TLRβ3**
IFNACRHITLLKFQAVSI----NASINELLMDLKNLEYLELTGNTMRNVPD--VCDMKRL
HTLILSRTWIRKWQTTNCTVMNILRVFSLSYNRIFNVNKTSFALFSNL-KWDLSHNSYIC
NCRILWFRDWMRQN--SARLHYPKSYLCSNPAPVRFLQIAKYYVSWDY-CANPIAVSGCV
LGTLSVIFIITGLVSYIKRWSIRYWVYLFFARRRKYQLL-ETSEHNYDAFVCYCGSDVGW
VTKYLLPILEEENDLHLCLHDRDFAVGNDIVDNIVDSIQQSRKVVLVLSSDFAQSQWCQFETSLAQQRLFEEKKDII
VPILLEEIPTELQTMRLALLLKQKTYLEWSNETRGQMLFWERLVEILLETKE
**>Obi-TLRα3**
-ITVFPTMP-VWLQFNNITKLV-------------------------------PYLSQI
THLNLTKNSITSLNYTVMRNMVNLKQMILDWNLLTTLPKGIQNVQ--FEVLSINHNHFFC
DCTNIWLKKWLQKSRE--SILNWRRIVCNTV--DKVLDIVVVP--NDKICNPKTLTLGLS
LALAILILLVCLFLLIHYWLEIKVILYYLNIHPSLGSANTLNEQKKYDIFISYPDQTYQF
ATGPLLSTLQS-RGYSICLPDRDFVVGSAKEENILRAIKSSVRTLIVITKSHVEDEWQLF
TLRTAVQCSLKKPFNYLLCILDG-VDKSKLDLETQAYVTSHVVIDKDD------LLWKKL
FRSIPPART
**>Obi-TLRα1**
-LSD-SMLP-IYLSGNRLISLSRSNINGTFMTLINLKQLYMHDNDLTILTKETFQGLENL
EVITLNSNSISYIAPGMFAPMPKLKIVDVSSNRLHILDNSFL---KYLESIAIHNNPWIC
KCPFVMLQELYINKPD--LVVLSESVICDHEDV--AYPLFEF---DVQHCL-KVICALAI
FSAVFLTLIIAVISIACYREELKVWLFQYGWRIP---AKLDDSNRRYDVFVAYTSKNAMF
VEHELTPRLEREPPYQVCLTYRDYDVDISYAQNTINCIQNSKRTIMLVSNDFFQTEWFRYDFQINNHDILKTLSERLI
VILMEKVDRKKLECDLMFYAKTKKFLKYQD------HFWDKL
YYMLPKVRG
**>Bgl-TLRγ10**
----------------------------FENLSDLKKLHLI------------------
--------QMRDI-------------------------------------TVNGATLSV
----------IKI---SLSGDHAGDST--------------------------------
------------------SLALPSSLFAFT---------QD---YKIDVFLGYSDTDYRF
PCQDLRAYLEDTLKLTTFLNDRDLLATLNKASGIVEAINSSWRVLLVCSEGFLKDEWSLF
TMRSAMYAQSPANPGRVV-VMVHQRCLRLLPTELLSAVEEDNILV---------SEWK--
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**>Bgl-TLRγ3**
FFDSFPEVEVLVLDHCELDSEFSQHSYSLFRNLVKLKQLDLSYNALDILLPNTFSANLNL
RSLNLAFNRFRTIP-FDLSQTLGMNKLDMRQNSLETLSSKDMALLDELQKLLISGNVLSC
GCEHIQFLQWLHLT--DVRLDENRNYTCINNQG--LSSTSAYNIEVLWECWGYFNIALGM
FAFVNIGFVFVFMLTKNKTLIISGVLQLFT-EFKKRP--V---DYQYSVFIGYSDFDYQF
ACLTLRKFIEDDLKLSTFVGDRDLLPSIAMAEGIMAAMDSSWRIVLVVNKSFVNNNWFLF
MVRSAVFSVSPANPLRVV-ILVEECCLPRLPSELLSSVPEDNVFVV---------TEWK--
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**>Bgl-TLRα2**
-LTDVPKIP-LRLDGNNLPSLRNSTVNNTFKGMKSVRSLFLNNNLLTIISPGVFSGLENL
ERIFLQNNFISLIDPQAL--LPYLYLINLRENDLNTLPIDGLGFVRELKRFSLSQNPYSC
QLDFVCFVLFIRDSAD--CIEDISDIKCSSNSL--GFTLLDFQIE---LCSE--TYALIA
ACVVIAFGLALLIVAYMNRDFLQVLCFRFGLRVM---KATEDNDRPYDAFISYSSKDEDF
VIHQLAPRLENDKKFQLCVHYRDFPVGACIAETIVRSVEASKRTILVVSDNFLDSEWCRFEFQTAHQQVLNERRNR
VILILMHDLDTEKLDSTLKVYMRTRTYLKYDD------WFWEKL
MFAMPDVQH
**>Bgl-TLRγ23**
FFDTLSTLKKLNISNNLLGSFLVLVSPRIFSSLRNLTVLDLSENFIIDFTCDLFSNLTSL
EYFNISKNALIRFEV--ISRMSNLIFLDFHLTRMTGLTSEFRDSIDRLSSIDMSNAPISC
NCKNYDFMTWMTSS--KAFSQGFKNYICVYPDQTGHV-VNDFDMNLLNQCASVLLFSMIA
IAMIVVVGAVVGGIVYKYRWKLRYLYNAAYLQFKSSRRG-EDDEFDYDAFISYDQEDGVF
VTQTLVPELEKR-EIHLCIHASEFTAGEYISSNIVKAVNRSRKTVVVLTQNMLSSYWCNF
EIQMANMEALHTGRRVLVFLLVDNIPTKDLGLELLYYIRSNTYIPFPKDFNGMSWLWDKVANDIRND--
**>Bgl-TLRγ20**
FFKNLPTLTYLNLSINLLSRCHNVKKKYIYEALVNLEVLDLGLNNIDEFTPHILDHLISL
KKLFLDYNPLKSFDV--ISNMPQLEYLSLRHSRLHRLSVYTMKAIDEITSIDMAFNPILC
ECSNLDFIRWMTAS--SAFDPKFESYFCMYSDGSMQF-IDDFTLMILSECASVIIFFSVS
SGTTFLIILILIAILHRFRWKLKYMYYAAYLHYKSAR--DNGKAFSYDVFLCYHEDDESF
VLDTLCVELEKR-GLKTLVHKRDFVSGKPIVSNIVEAVNCSRKTLVVLTDNMARSKWCQF
EVQMATMEAVSYKRPVLIFLLMSDVPCCIMGAELSYCVQNNTYLQYPSPSSEMDNFWIKLVSDLKN---
**>Bgl-TLRγ19**
FFENFASLEFLDLSANTFGRKVRKGSKPIFSSLKNLRELNLRFVDLITVDKNVFEGLENL
EILHLQLNGIYYFEV--VSYLKKLQFVNFSFTELTGLRPQVTNFFDSIATLDFSETPIHC
YCANLEFISWLSRALQYIRFQRLKWFKCVYEDTTEKY-FHDFLHQFLGECTPVTLFFIVT
SATFLLVCIIIALVVYRFRWKLKYFYYSAYLYFKSYKRFHDDKDFEFDVFVSFANEDERF
VLKEILPELTTR-GLKVHIHTTNFRAGEYITTNIVNAVQCSRRTLIVVSSNLQKSQWCHF

ELQMANLESVHTGRPVMVFLLMESLPEDVLSREMLYHIQNNTYLQLPDEVRVMDIFWTKLCSDLKD---
**>BgI-TLRα3**
-LEKVPEIP-VYLDGNSLNKLTRSYLDGLFDNCTSLLHLRLDYNYLISISKSLFDKLIEL
RSLYLNDNLINFIAKEAFANLNSVEIITLDKNRLIMLD-------SSLKSLTLSGNPWQC
QCNTSTVLRVLHALND--IIVDRGNMCCYYVGTVQ--KLSELDRTPYELCVDTLLVCLVV
AMFVLLLIVVVLVIIFKGR-EVQAWVYNLGVRVK---DKTDAGNKYFDAFISYSNKDSEF
VSKVLVPALDE-KGYRLCVHYRDFPVGQNITDTIFRAIEESSRTIMLLSRHFVESEWCRF
EFQTAHYHILKEGSHRLVFILLDDLSDDELDPDLKVQLKSKTYLKFGD------WFWEKL
FFALPDVRK
**>BgI-TLRγ22**
FFDSFTSIRELNLSNNLLGEFFQSNETLVFSKLKNLEILDLSSNGIHLLHFDLFMDLPRL
HHLNLAFNTLTTFGV--ITKLSKLMYLDLTKTGISKIPETARTFIDGL-SVFMGKCSISC
ECDNLDFLLWMVNS--KAFDKTFKNYMCFYMDSSS--PITDYTIEILRKCTSEMLFFMVG
CGTLFLFFLLLFGIIYRFRWKLRYLYYAAYLHYKKSGGE-GGAKFKYDAFVSYDHADEET
IVIHVCNELEARGLKLCVHGRDFRAGDYIASNVVKAVCSSRKTLVVLTKNLMNSYWCKYELQMANMEAVHTGRQV
LIFLLVENIPQGELGVELLYNIRNNTYIPYPTEPAFWDALWNKLANDIRD---
**>BgI-TLRγ21**
FFSELSSLLHLNLSSNLLGSFFRYESETVFYPLTNLMTLNLSFNDISELRPNIFANLINL
RQLQLQKNNLQKFDV--ITSLIKLVRLNLKLNRLSTMSSNITDHIDTLKVVDLSFSPISC
QCNNLAFINWMVNS--KAFHPNFINYQCVDSNTIQ--NITDYTVEKLNECSSVTIFLISS
GFSFVILCFVIGSVIYRFRWRIRYLYYAAYLYYSKTNSG-RDSDYKYDAFISYDQNDWKF
VVNKLMPEMEKR-RLKVCIHSKDFVAGDYIASNIVKAICSSSRTVVVLTRNMIKSYWCGY
EIQMANMEAVHTNRKVLLFLMMEDIPSSELSVDLLYNIRNNTYLQYNQDGVHMSRLWDKLAYDIKH---
**>BgI-TLRγ18**
FFNNLTSLKHLSLFQNLLGDCLNDKNGLIFSQLTELKVLNLSFNNLYYLGWEVFQGQADIEVIDLSVNRLDHITF--
VSHMRKLRHLDLHKNDIETLPTGLTDHISSLKTLDMRQNPISC
GCENLDFLQWVVNT--RVFGSDLYLYYCKFPDSDRAVRVPGYVVKRLVSCSSAVLYTVVS
CVTVLIMLILLAAVIYRFRWTLRYWYHAAKLKISSNQQM-DSDQFKYDVFVSYASKDIDF
VVKELCPRLKER-NITVYVHGEKFKVGCYIADNIYTGIRKCRKTLVVVTQNMLASRWCNY
ELQIAREQARNTGRNVLVFLFLEELPTSRMGMGVLTHIKSSTYIMYPKLPQHRGAFWDKLADDLRSS--
**>BgI-TLRα4**
-FLEMPIIPNLYLDHNPLQSLN--------------------------------PYLSRL
SEIYIDNCLLTTVMPSAIAALKNIRVMTLHNNLLQKLPTSTRNITEKATNITLHNNRWAC
SCESLWLPRWISRHKA--VLWKPGNILCDYFQK-----LEDVS--EADNCK-SAMDNFLT
VILFVLSTVATVILFFCYNTDICAIVYKLGIEFR----LYGDQYCPFDILISYGQDNYKW
VVDTLVPYLEKPGGYRVCLNHREFPSSDCVLETLPTAVRLSRSAILVLSKEFLQKEWCML
EVRVAIQRLLLVGS-KLLIICMDKVNVDELSPELRAYIHTHHYLRYDE------DFWVKL
DLFLPRKLI
**>BgI-TLRα1**
----IK-LRHLDESVAKL--------VTLFDALYVLEHMNFSTIGITTFPREWRRFFPKL
TYIDLSNNFISQVQFQNFPS-KTVVTFNLQRNNITVINMDVLNSWEKL-EVDIRNNPIHC
GCELESFLPHLQDTTTLAPYEYVKEMECSTPDALKGRKLYSL---HSSPCP-VYQVALIA
LGVTLSFLLVLVIILVRYKFEIRILLYRLHVRL-PCDADE-RHSKTYDAFISYSNDDDSW
VFENLVKFLENEKPFRLCIHQRDFVPGKTIFDNIVDSIEASRHTIIVLSPSFMKSHWAME
ELRQAYRQSLVEKTRHLVVLLLHKV---NL--N---------YCSF-----------------------
**>BgI-TLRγ16**
FFMNFSSLDQLFLGHNTLGDFLSHYNITPFIYLKQLTRLDLSYNGLTKVYRNLLSGLNAL
QELHMEENIMWDFNI--IDHMSNLRLIDLSHNQIKELPIHVREHIDNLKLIDLSFNPIRC
ECQYLYMILWMVSS--RAFNPAFENYMCVYPDGSYKI-IDDYTLQYLNACADYSVLLVVI
FSTLTMIILVIAGILYRFRWHLRYLYYAAYLKVKEGHHNQETRSYVYDVFVSYAHQDETF
VVQRLMPELSNR-GLNVFVHGRDFVVGHYIASNILTAIRESRKTLVVLTKNLINSTWCNY
ELQMANMESVHTGRQVLVFLIKDSLDITDLKTDLLYHIKNNTYIDYPHGPLALNLFWDKL
SLDLKN---
**>BgI-TLRγ14**
MFQYLDELQELRLRNNQLNNFIK-TRKPVFQYLKQLKILDLTNNALTVVQSSIFEELGSL
EIIDLSRNNMRHFNL--LTNMSSLNFLNLSHTQLSSLSVETRQNIDLLTRVDMSRNPVRC
ECDNIDFLKWMVSS--RAFDVNLTDYMCQYKDTST-IVIKDYTLVYLARCADSTLFLVVL
SVTLCMVSFVVAAVVYRFRWRLRYMYYAAYLVVKGKRKDNEAELFRYDVFISYASEDEEFILGKLLPEFDSR-
DLRVLVHGRDFAVGEFIASNIVTAVKESRKTLVVLTRNLLNSTWCNFELQMANMESIHTGRPVLLFLIKESIPTTELT
SDLLYHLNKNTYIVYPQ--EITDVFWDKLARDLLQ---
**>BgI-TLRγ8**
FFDGFFGLEKLFLSKCELQRDFALHSSRVFQNLSNLQSLDLSYNYLNDLSQGTLYYNPKLVWLNLSDNQFNRIP-
FDLKDTPNLLELDVRNNAISTVSKSITTELDQLANFWLSGNILSCGCQDLNFLHWLSST--
MVTLDQQGGNFTCMDRNG-ERSYTMRYHVDTLWECWGFLYLAIII
LCFYVTGVFLLVLVQRNKTFLVSFFLQLLG-NFKLKR--G---DYPIDVFVGYSDEDYHF
PCRDLRLYLEDVIKLKTFLNDRDLLASLSKASGIVDAINSSYRILLVCSESFLKDDWSLF
TMRAAMYAQSPANPSRVV-VVVHESCLHLLPTELLSVVNEENILVV---------SGWK--

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**>Bgl-TLRγ7**
FFDELTGLEYLALSKAGLNRDFSSFSRRLFQNLSNLTRLDLSINYLNALSKGTFSPNSKL
QWLDLSGNQFKDIP-FDLQYTPNLLELDVSSNALTTIDDDIARDLDHLVHLSLGGNILSC
SCSDLRFLQWLNLT--SVTFDHSRNYTCLNKDG-EKAYTLFYDLDSLWECWGFLYVAVII
VCLYVIGFFVILLLLRNKHFLVSYFLKILG-NIKLKR--T---DYPIHVYIAYSDIEYKF
SCSDLREYIEGTLKLNTFLNDRDLISSLNSAADIVKAMNSSWKILLVCSASFLNGDWAMLTLRSAIYAQSPTNPARI
M-VLVHQNDLLLLPHDLLSVVDDENMLII---------SEWK--
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**>Bgl-TLRγ6**
-------MENLALSNCRLERDFSQHSHVLFKNLTRLRQLDLSSNSLNYLSKNTFLFNSHL
QFVNLSRNLFREIP-FTLRYTPELRALDLSVNSLSSIDVSTTKDLDHLVKLYLQGNVLSC
GCNDITFLQWMKTT--LVTFDLNGNFTCINEKG-ERTYILFHDLESLWECNGFLYLSVII
MCLYFIGLCIVFIIYRNKQFLISYLLQTFV-GFKSTR--K---DYKIDVYIGYSDRDYKF
PCKDLREFFENSLGYKTFLIDRDLIASVDKASGIVDALNDSWRILLVCSESFLKEDWSMF
TMRSAIYIQSPANPARVV-VLVHKDCLHLLPTTLIGSVNEEKIIVV---------SEWK--
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**>Bgl-TLRγ1**
FFDDFSSLRYLILQSMMNEDFFRVSIDRIIQNMPELRYLDLTDNKLNFLPPNLFSRNSHI
THVILAKNRFSSFP-ITMDLVPNLKTLDLSGNAIIYLTEEETSSLTKHSYLLLAENNIAC
VCSQIKFLLWLNI---TF-LDNKGAYSCTSQDG-QLILTVLWDVLGFYQCYGYFMISIVL
LLVMSFIFLMAYLVHRFRTAIEAYLVRIFIKAVRMKS--SD---YKTHVFIGYADEDVGF
VRHILLRYLEEDLKVSTFVHHRDLGPGYTDQQ-MFESISDSWRILLVITQRYLNNYLSDI
IMKYASHSMSPANEKRLV-LLVQESQLYNIPGYLYDVLEDSRIIV---------SDLSA-
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**>Bgl-TLRγ5**
YLDTLPALENLALANCQLDREFSIHSGRLFQNLTRLQQLDLSSNLLNYLSTDTFMYNKHLKWLTLAQNQFREIP-
FSLKYTPELEVLDLRQNSLNTIDMASIHQLENIVKLLLSGNDLSC
GCNDLQFLQWMRST--AVTFDQDGNFTCTNKDG-KTTYTLAYDIEYLWECTGYFYIVLIV
FCLYLIGCSIVFIMMKNKHFITVYILKRIF-GIEHTR--R---DYPIDVYIAYSDTDYQF
PCNELRQFIEQSLGMTTFLIDRDLNASFDLALGIVNAINKSWRVLLVCSESFLREGWSMFTFSSAIYAQSPANPARI
V-ALVHRDCLPLLPMELFGCINEDNILYV--------SEWA--
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**>Bgl-TLRγ13**
FFPQ-SSLISLNISNNILGEYFALGRKKIFLGLGYLRFLDISMNLIYKLPRDFLSGLKSL
EVLLATKNRLQALNV--LSQMSSVWFMNFSQNSITWIDKVTRDDLDLLASLDISFNPLPC
TCDGIEILNWLAFT--NVRLVNQMYMKCQTSTG-ETVSLGDLRAQQVQACASAIILVISI
SSTVVVTLMVSLATLYRFRWKLRYLRNIALTKY-GFRPKKTGKKFQHDAYILYEDQTIKF
VFRDFIQELEVKRGHRLLLVDRDIMPGTIMTTAILSAVQNSYKTIPVVTPYFFDVWYSEY
AVQMAIMEEHYEPRQILHLCLYQATDPKDMPKDLLSVMKRNRYTEFPPETEMVKQFWDQLSSTIQQE--
**>Bgl-TLRγ2**
FFDSYPALELLALESCRIDGLLSQHSFRVFQNLHSLQSLDLSFNSLDMLSPQTFSTNPNLTSLNLAGNRFRNVP-
FDIKLTPNVKFLDIRQNALTTIDISSRKALDELNRLLLSGNILSC
GCENLLLLQWLQET--RVELDGNRNFTCMNIKG--LSSTLAYNLDGLWECWGFFNLSMAL
LCFTLLAYILFFTWIKNKTVILSSILQIFT-DFKKKP--S---DYQSGVYLGYAESEYKF
PCSELRQYIEDELCLNTFIRDRDLLPSLDIAQGVMDAINSSWRILLVINERFLHQDWFLF
TIRAAIYSISPANPSRVV-VLVEKNKVHSVPTELLSSVPNENIIVVSQ------------
-----Q---
**>Bgl-TLRγ9**
FFDGFSGLETLALSKCLIQRDFAFHSHRLFQNLKELRQLGLSFNSLNAFSNATFSFNSNL
QFLNLSDNQFNYLP-FNLKHTPELRVFDVTNNSIITINVDARHELDRLARLFLRGNILSC
GCSDLLFLQWLKNT--LVELDQGGNFSCIDKDG-ERSYTLCHDLESLWPCWGFLSIAVII
VCLYVIVFFIVFLYIKRKTFIITYFLQLLG-HFHRSR--Q---DYKIDVFLGYSDTDYRF
PCQDLRAYLEDTLKLTTFLNDRDLLATLNKASGIVEAINSSWRVLLVCSEGFLKDEWSLF
TMRSAMYAQSPANPGRVV-VMVHQRCLRLLPTELLSAVEEDNILVV--------SEWK--
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**>Bgl-TLRγ15**
FFHNFPNLKKLMLGNNKLETYFNLPNYTLFSKLKKLKTLDLSDNAISKMPTDILAGLTSL
KVLYFEHNTLWTFNL--LSHMMNLRYVYLRHSQVNSLSEDVRQHIDSIGRFDLSFNPIHC
DCENYDFLKWMMNS--RAFDPKFTNYMCQYPDSSYK-NITDYTLRILRKCTDSFIFLFVL
AATFVMIAFVLAGIIYRFRWKLRYIYYATYLRLKSVDEE-NSEQFRYDVFISYAHQDEEF
ILKVLYPELGSR-GLNVHVHGRDFVAGEFIASNIVTAVRESRKTLVVLTLDLLKSKWCNY
EIQMANMESVHTGRQVLVFLLKDSLNNKQLGTELLFHIRNNTYIVYPQNDEELAVFWDKLYKDLRK---
**>Bgl-TLRγ17**
FFSCLNSLRNLTLSVNMLGDFIGSSKERLFENLSSLSYLDLSFNSIDKMQVYFFHGLSNVTEIDLSRNKISEFNV--
ITKMNQLRRLNLSDNKISRLFSNVTDQIDRIKQVDLSKNPIDC
TCANLEFLKWMVNW---VNVSQSQGYLCKQDDGSI--AMPDYTVLSLNQCASVVIFLIII

GATLVLACVIVGMIIYRFRWSLRYWYHVAYLNYQQKRKSDRRQKFEYDVFISYVHNDETFVAQTLSTELEKR-
HVKVYMHGQKFVAGNYIASNIVQAVKSCRKTLVVLTNKYVRSQWCYY
EVQMANMEAISAGRPVLVFLIKEKIPNHKLG-EILTFIKTNTYIPYPQEDRELKIFYDKL
ASDLL----
**>Bgl-TLRγ11**
------------------------------------------------------------------------------
HITRLQLLDFSRNSITWITESTRDDLDALAELDLTFNPLPC
TCSGIEFIKWLATT--KVKLIDQVNLRCRLKDG-GSTSVGDLMLLFLQSCISSWILSVSI
LSAVFMAVVLGLVLMYRYRWKLRYLRNVAIAKF-
GFEPKKHQGLFKYDAFLVYDSDDMQFVLNECVQELEVRRGIKLCIGDRDFMPGTYVASDIVSAVQNSYRTVLLVT
PEFYDDDYVEYAVNMAINEEIHTSRQVLYLCLYQPVALAEMPRDLVAILKRNEFIEYPPEEGLIENFWDQLTAAVRQ
E--
**>Bgl-TLRγ12**
FFRP-NSLISLNISNNILGESFALDSGKVFSRLGYLRFLDISMNLLYRLPRGFLSGLKSL
EVLLATNNKLQALNL--LSHMSSVWLMNFSQNSITWIDKVTRDDLDFLASLDISFNPLPC
TCDGVEVLNWMAFT--NVRLVNQMYLKCQTNTG-EIVSFGDLRAEQVQACASAIVLVISI
SSAVVVTLMVTLALVYRFRWKLRYLRNIALAKY-GFKPKKTGKKFQHDAYILYEDQTINF
VFNDFIQELEVKRGHRLLLVDRDIMPGTYMTTAILSAVQNSYKTIPVVSPYFFDGLYSEY
AVKMAVMEEIYEPRPVLHLCLYQPTDHEGMSKDLLSIMQRNHYTEFPPDPELVKQFWDQLSNVIQQD--
**>Bgl-TLRγ4**
FLDELYGLENLALSKCQFDRNFALKSARILQNITKLKVLDISNNSLNGLSKGTFSRNSEL
LYLSLSGNQFKDIP-FDLKFTPNLKILDLSSNIITTLTTDTTDALDLLNQLMLNGNILSC
GCHDLSFLQWLNST--LVSFDNNRNYTCMNKDG-
ERTNTLTFDLESLWQCWGFFYVAMITLCLYVTGAVLIFLMLKNKNFLVSYFLQIFG-NFKHTR--S---
DYKTDVYIGYSDEDYRF
PCIELREHLERNLKLSTFIIDRDLLASLDKASGIVDAINSCWRVLLVCSKSFLKDEWSIF
TMRSAMYAQSPANPAKIV-LMVHTSCLSLLPADLLSVVNDENILVV---------SEWK--
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**>Ttr-TLRγ4**
FMSSFPNLKYLSLAYNNLGHMFDDVSKCVFLSLTELQTLDLSHNQIAKLPVDLFLNQHNLKELILNHNKLKTMG---
VASMASLQYMDLSYNEIRD--KSML---ESIATINLTKNAVSC
TCLNVVFLTWLINT--HINISGKETVYCLQQQK----MLIHFNFN---DCKKDYVIIGSV
VG-LVLVLIVIAVIVSNDR--VKYHIYLLKYKLR---NISRN-TEEDRIFISYCSEDRIW
VLRKLKPELEA-MGYKLFIHELDFEVGNFIADNIVHAIDTCFKTILVLSDNFVSSGWCMF
ELKMTLAK----S-DCAIPIYYKPVTKKNNTLLLKYLNKVKTYMKWPEDDREQYYFWQRL
KHALDKQED
**>Ttr-TLRα5**
-LTVMPQAP-LLLDNNNIEHLE--------------------------------YYLNDV
TKLILRHNAIADVPPNFVKLVTDMTLLDLSYNRIRYIDDDVLSSLKPTLSIAINHNPLAC
DCHSHSLKQWVSDHRK--RIVNLADITCFGG--AGGISILEAS--DLSICLD---IILPS
VIVPVVFICILILLVYIFRNEIKVILYKFNLHLN-----EEDETAVHDAFISYCSTDENW
VIKELANKLEMN--YKVCHHQKNFEPGVAIADNIVKSIDQSRRTILVLSNDFLNSDWCKY
EFQAAHYRALKNRQKYLIIVMLHKIDVSKLDNTLRLYVKTNGIIKVNE------LFWQKL
FYEMPIRTL
**>Ttr-TLRβ3**
LFEDLGLLKELVLKAADIANFRSKDIRAMLNVLIGLEHLNLEKVRLYSIPPTTFHHMHNL
SKLVLSDNFLSHLPEDLFFNLTNLKVLQLNHNRISQVSTKTFGFLDSLESIDLSGNPFAC
GCSLHWFLQWMNSTNVKVVGSQRFSYKCSSPPALRGKSLHEYYYKYRQNCLPIILVASVSGSCFLALLVSVICIVY
RSRWYIRYLFYLLRARRKRQRKRNDEKDFAYDAFVCYNKDDQDWVVRRLLPELEYNGEFKLCLHDRDFMPGIDII
DNIIESMEQSRRTILILSNSFAQSQWCQWELSMAQHKVLQDEGDILVLVLLEQIRSDNMSLKLHYLMRTKTYIEWTD
NEDGRKLFWEKLKGTLKAKPE
**>Ttr-TLRδ**
SLSGMEKLTTICLASNCLGSVP----PEIM-SARNLKQLDMSYNKISSIPP--IGGLKEL
RYLNMKSNRLRQLPN--LCQLKHLEIVCFSENTISDPNVDELLDMSKIKMLCLHSNRIPA
N---K-VQNLLKKASRDIRLEN-----C----------VEETHVKYLKKCL---------
-------------------------------------AMDENAVHKWDVLILHDDKDEEI
IENEIRPKLEEEMDFRVCIPYRDETMGMSKVAERSNLINFSKTIMLVITEKFNSSK--IL
GLDEVMLNGLDSETKCLIPVLWSKV---QVPKELKGRTMVRR----DS--VQEKYFWQKI
RKAIQSH--
**>Ttr-TLRα2**
-LNKIPKIS-IDLSGNNIPLIRHSHIDGSFTNMSNLLLLYLNNNNLKVLSRYTFEALPVL
EELYLHGNKLTFIEDETFLGLKKLRIISLKSNLIKTLPYTDF---SHLTSVSLAENPYDC
DCNFSRFKSWIFSSLA--TVIDSNDVFCVFYGLFPGSRLFNF---DLNYCELSSMIAIII
ILIVFVVIVALATVAYYYRNLIKVWLYNYGLRPR-----PDDSDKIYDAFVSYSSFDEST
VVHTLAPKLETNPKYKLCLHYRDFPIGSSIAETIVESVENSKRVIMLLSENYLSSEWCIY
EFKTAHHQVLKDRTNRLIVILYDEINMDNLDPDLRLYLKTNTYLCWKD------WFWQKL
YYAMPDVSD

**>Ttr-TLRα3**
-LTSLPFTEDLDLQNNSIRELT--------------------------------PYLKHV
KILNIANNKLEIVSAEAIQSLKTVQKFNLSGNRLTKL--NVNHFKTNLETLDIQDNQFTC
NCEDQWFQEWLLQINN--AVVNADSVRCHNK----DVAILSAS--HTDCGLANHTILTIC
VSVGAVMVCVAVVMVYIFRKEIKVLINHFSWHPR--RENDDNRHYLYDAFISYNLLNLDF
VRNSLIKNLE--PRYQLCIHNRDFLLGNEIADNIVTSINASKRFIAVVSKAFIESEWCQY
EFQFAHNDAMKDKRNNIIIILMEDSDLGEIDNCLKIYLRTHTYLSYKD------LFLQKL
LYSMPQVRT
**>Ttr-TLRγ3**
LMSSFPNILYLSLANNKLGELQEKQFKDVFYPLTKLEEINLSGNNITYFPVNVFLAQTKL
KRLLLHDNSLKVWH-INMSTMTSLEYLDLSENQITIIGQMSMNYFKTIVSINLNDNKIDC
LCFNLEMITWIQK-S--KFIHQRDNLKC--GDTK--KSILSYDPK---SCEVAELVIGVT
LGISALFIGVLFLIFYKIHW-LKYKLHLLKWRWRGMMA--DQNIEQEMIFISYENRDRCW
VINTLLPKLEG-MNYKTYIHNRDFTVGRPIADNIVHAIDICARTVLILSDHFAQSEWCVF
ELNMALV------KNSVVPIQYAP-----------------------------------------
**>Ttr-TLRα1**
-VEDVP----------------------------SLEELSLQFCNFSVITRNMLQNYPNL
KTMYMHNNRINYIETAALTRKVRINVITLDNNRLTHID-------KQVIIVRLQGNPWDC
QCHLKPLSDYVRNHIK-------GNITCYSPPS-----LASTPLQQVNTCEQGLLFLPIM
LGLLLALVLASTCCVYWYRYEIKIMWNKY-------RKAYKTEKHTYHAFVSHSSVDFKF
VKDNLLVSLE--PTYKLYVYYRDSIPGSTIVEDIVKAIDDSAITIILLSQNFLHSDWTKL
EFKQSYFKAMKSKSNNMIIILMEDIPLDSIKPQIKAYIRTKTYIHKND------RFFEKL
TSSMPKEEM
**>Ttr-TLRγ2**
-------------------------------------------NDISYFPDNIFIHQTKL
KKLILRRNAFQVWN-VNMSTMLSLRYLDLSKNLLTVIGETSLTFMDTFMTINLEDNLFIC
SCPYLPTISWIQEN--NKSIRQAQNLKCKMGEN--EIKLMSYNAE---SCHVIYDIIGIT
SSISVIIVMATIFISYKFHW-IKYKFHIIKWRLRNCFGIHDQPANNERIFISYENRDRRW
VLDTLVPKLENTMNYNTCIHAWDFMPGYPIADNIVRAIDICTKTIVVLSDHFAESNWCQL
ELQMALV------KHSVIPIRYAPIEKQNKTRLLKYLTKANVYIDWYDMHNKEDAFWDKL
KYTLDRDDE
**>Ttr-TLRγ1**
-------------------------------------------NDISYFPDNIFIHQTKL
KKLILRRNAFQVWN-VNMSTMLSLRYLDLSKNLLTVIGETSLTFMDTFMTINLEDNLFIC
SCPYLPTISWIQEN--NKSIRQAQNLKCKMGEN--EIKLMSYNAE---SCHVIYDIIGIT
SSISVIIVMATIFISYKFHW-IKYKFHIIKWRLRNCFGIHDQPANNERIFISYENRDRRW
VLDTLVPKLENTMNYNTCIHARDFMPGYLIADNIVRAIDICTKTIVVLSDHFAESNWCQF
ELQMALV------KDSVIPIRYAPIEKQNKTRLLKYLAKANVYIDRYNMHNKEDAF----
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**>Ttr-TLRβ5**
-----------------------------------------------------------LTHLIVTGNKLTTLSPELF---
THLKYLDVSNNSITSFSREIVGDLGYIERFIFDDNKIECDCELSHFQQWLLTTLI----DTSKTERCYN---
YEGVRIIDYQPTWID-CDNTYVVVGSI
GS-FCLLVATVAALLVYYRWDVKYWFILRKIKAKRYHNMHDENNVMYDAFVSYSSLDEGW
IYNELIPNIEDDIKFQLLMDQRDFLPGHYIIENIVQGIDSSHKVLLIISLNFIESQWCTF
ETRFAEQSSIETG-QRLILIFLEPLKKSEMSRHLQRL-----------------------S---
**>Ttr-TLRα4**
-LNALPYVP-LYLQDNHITHLT--------------------------------DYLALI
TELNLDHNAISEIPLAFLNSIPKMKTLKLAYNQIKYFPEEIEETR--AFNWSMHHNPIAC
NCYSLWLKKWVSANRK--RIDNLHDIVCFSG--AGGVAILEAS--DHLICID---IILAA
TITPASIIIIMVLLGCIFRKELKVILYKFNWHPK-----RENESLPFDAFVSYCSADEHW
IVTQLAKKLESNPPYKLCLHYKSFEPGVAIADNIVTSIDNSKRTILVLSDKFLESEWCRY
EFQAAHYRALKNRRKYLIIIMLNKIDPSKLDKNLRLYLKTNGYIKPTE------LFWEKL
KYELPMKSS
>Ttr-TLRβ2
IFMNLTQLQWLVANHNNIGMCLTKGMSKLFQNLKSLQWLDLSSNQIETLPKELFQNLKSLKYLNLSSNRISYWASE
QFTALKKLQTLDFNSNVITTINKSSIGQLENV-HLNLSNNLFSCDCDLRWFRNYINYT--
KIDFTYIKDYLCAAPPDFQGKHFLKFHSNMII-
CSPYLIRYISIGGAVVLIVLMISLATYNWRWYLKLKLFRLKNTLRGFQ--
EDDDIVTYDAYLSFAEEDRDWVTRTLLPKIDNEGRYRIYYDDRDDMPGDNIINAIDSGIEKSEKSIVVFSKKYATNGR
IDVDLTLI----LDKPHQRVILIMLEEVPLRMIPRCLHSTLWSNQHLLWTEDVNGQALFWEKLNNKLMED--
**>Ttr-TLRβ4**
------------MGDNSLYR--PNDLPALFAPLHSLTYLSISKNKLDYLHEDTFNGLYNL
EKLILTTNKLEYLSTDLFKNTTKLKTLYLAKNSLKTINAGTFEKLTFLKDINLGENQFDC
HCDIRPLRDWLKYKQKKKAIKIQGDLNCTTPPNLRNSLIVDYNPSWLD-CDNEYLLISSS
C--SMGFVLITITVIYIFHWNIKLFFAIRKANRKIDGENNPLLRKRYHAFISYANDSLWW
IKKHLLPNLQDNFEFNLCIRDRDFRAGQAEVDNIIDGMQNSTCTIFLITAEFIDSGWRQF

EMNVILRGLIDDPNNRFILVFLEDIPNNKLPIVLSTLKKNVDCLYWP--KVKRIQFWAKL
KVRILGK--
**>Ttr-TLRβ1**
IFFNISTLQILNLNKNLLSELP----DVLFTNLENLQCLDLSSNLLEVIPEKLFANLKSL
TDLNLANNMLYNTN-GIFHPLIHLTFLNLSSNSLTMITKDTLAGPKKLKTVDLNKNVFKC
TCDLQWFVDRLRQSKQCPYIVQLREYKCTN---LPGTCVANFMPSQWE-CHSIFIVVISV
LGS-ICITLLLMGCCYRYRFYLLHFCFVLKRLRETYEELYDNTQYRFDAFICYNDEDLNW
VQSQLLPKLRE-ATIKICINFMHFRIGAPRIDTIMEGIQTSRKTVLVISRHFLDDDWCLF
EMNVAAHRLFEEGKDNLVIIFLEPIQYSEMPLTLQAVVRTKRYLEWSTNEQGKDLFWETLCYLLKTRPS
**>Hps-TLRγ4**
FMSSFPNLAHLSLAKNKL----KK---NVFWPLKLLEYLDLSDNQISMLPKGVFSQQSSL
KYLILKDNALTKLS-LGLKNMKCLKYVDVSVNKLETLEPQTRSFLEKKMFIFMEDNVFQC
SCSNIDMLYWMRNMNLKSSVQRWSQVKCHNYEN---VNLTDYDIS---KCDSIRTLVVTL
IGVLV-LMLVMGVVIYKSDR-LRYKWHLLKWRLRNNR---D-HRQNFKIFFSYGSRDRQW
VWEVLKPKLEQ-DGYSLFIHEIDFHVGECIADNIVYAIDVCDQIVFVLSDNFVSSEWCMF
ELNMALV------KHCIVPIRLSPIMKRN--RLIKYLTKTRTYLEW-KDKESADEFWARL
YSRLNRK--
**>Hps-TLRγ3**
YLSSLPNLAYLSLAKNKL----NI---DVFTPLKLLEYLDLSGNQIAILPKNVFSQQDNL
KYLIMKNNALKTLN-FQLKNMNSLEYIDASENKLGTLGQQTRFFLEMMMSISLEDNVFQC
SCSNVDMINWMTKTSLKVSRQRWSQIECFNLRS---VNLTDYDIS---KCDSVTTIIATI
VGVLAPAMFCMGLVIYNYDR-IRYKWHLLKWRIRNYQAVVR-HRERFQIFLSYDSCDRQWVWKVLKPKLER-
EGYSLFIHEIDFHVGECIADNIVYAIDVCDQIVFVLSDNFVSSEWCMFELNMALV------KHCIVPIRLSPIMKRN--
RLIKYLTKTRTYLEW-KDKQSADEFWARLYSRLNRK--
**>Hps-TLRδ**
DFSNLEKLRTVILLCNRLEKFP----TSLL-DVKSLAQLELANNRIREIPP--IGQLREI
KFLSVKCNRLTSLPE--LAKLEVAEVICFSENMIVDVPVESLLRFKNLKTLCLHSNRIQN
H---K-VMQLHE----DVRLEN-----C----------IGD-DIQ---KCR---------
----------F---AYHVR--------SSNFRL-KCRNM-DKTTWKWDVYIAYAEAAEHI
VDEELVPKLTN-MGLTACVYYKDSQPGKDIMADRRDMIDRSKKILVLLTKDTSYSDF-IS
EIQHIVSEGPKDQTARLIPVQWDE---AIIPDELKKVVVTSR----RT--AQEKVFWSRI
EKALKS---
**>Hps-TLRα**
-LTSLPQVP-LYLSNNRITELS--------------------------------SYLGSL
TKLHLDHNSLREINPNFLSQLKNLTFLSITWNNIKYFPESIKGT---LFNLSIHHNPIAC
DCHSLWLKKWISRSRN--RFDNLKDIVCVDG--AGGSPVLEAQ--DNQICL---KMILLG
TIVPFVVIIIIVMLVFIFRKELKVILYKFHWHPR-----REDYTLPYDAFVSYSSGDEHW
VVSQLTKKLEGSRPFKLCLHYKSFEPGVAIADNIVTSIDSSRRTILVLSNNFLNSEWCKY
EFQAAHYRALKNRKKYLIIIMLNEVNTDKLDKNLKLYLKTNGYIKPSE------LFWEKL
QYEMPVLEP
**>Hps-TLRγ1**
ATSAFPDLTYFSLAKNKLEMMFNINSTDVFHPLEKLQFLDLSENGIIDVPSNVVEKQVSL
RMLNLSNNNMQTFKV--LFSLRNLTYLDISNNLLKTIDVISTIGLDQILRINMDKNDFEC
VCSNVRTIDWIRKDSLRSTILRRDDLQCKVIKEGGWNKIVDY---QLNDCDTDLIVLPIA
SA--LAVITFIFGIIFWKRNQIKYKLHLLKWRW-GFLKT-NPHVERGQIFISYDHRDGDW
VRNTLRPNIQE-MGYRPYLHEIDFVPGESIADNIVHAIDVCDKTVVIISDYYAESQWCQF
ELQMAITKGL----GYVIPIKYAKLKRK--NKLFQYFMKCVTYLEWPADDDTRAKFWIRL
GRAIAKE--
**>Hps-TLRγ2**
YLSSLPNLAHLSLAKNKL----NI--TDVFTPLKLLEYLDLSGNQIAILPKNVFSQQDNL
KYLIMKNNALKTLN-FQLKNMNSLEYIDASENKLGTLGQQTRFFLEMMMSISLEDNVFQC
SCSNVDMINWMTKTSLKVSRQRWSQIECFNLRS---VNLTDYDIS---KCDSVTTIIATI
VGVLAPAMFCMGLVIYNYDR-IRYKWHLLKWRIRNYQAVVR-HRERFQIFLSYDSCDRQWVWKVLKPKLER-
EGYSLFIHEIDFHVGECIADNIVHAIDTCDQIIIVLSDNFASSEWCMF
ELHMALV------KHCIVPIRLSPIVEHNN-RLITFLTKTRTYLEW-KNKPSGEIFWARL
YGTLNRE--
**>Lan-TLRδ7**
EVENF-ELRSLCLACNVIDNLP----GKFF--MKQLQELDVSYNRLTQIPA--IRNLKNL
EFLRLTGNRLQTIPS--IESLDRLLYLCLSENALVDIPTNALHRLINIKSLCLNSNRLPC
E---V-VIQVIQESSPKVSLREN----C------K--EIRD-------------------
--------------AFRAK---------------QYFEK-DGKDFESDVYVMHADEDYAL
VDQEIVPHLEER-NLKVTVNIQALRPGLPVSDQLVHFIESSRKILVVFTKNDVFEHTCLT
KVKAALEKRKKES-ETSPIVLVE-CPKSKVPHEFKDLYVIHR----RT--THEKHFWPNI
INAITQ---
>Lana17091
-LIHMSKID-LDVSNNYLETIP-------------------------------SD-TMY
REVYLDNNSISTFPTSQV--LPHLTTLSLRYNSIRTISMRQIEKDT-VNDLYLGGNPWRC

DCHARSIKHWLLNNSN--IIRDLDDITCVSGELTLGKSIKNVP--DNNGCPI---IAAIV
GGLVFVVIIACMLLLYKCNLKVRIWLYKFRFRFK--D--KQDSDKIYDAFISYSSLDEKY
VVQTLVPGLENTPPFKVCVHYKHFIPGASIAESIVEAVENSKRTIMLLSQNFIHSEWCTY
EFKTAHHQVLKDRSNHLIVVVLGDIP-SDLDSDLKLYLSTNTYLRADD------WFWEKL
LYAMPKLEN

**> Lan-TLRδ1**

DFKC-LKLKALYLNANYIRELT----PNIL-KLEELIIFDGSYNELQVLPN--IDQLQSL
KYIRLKQNQLRRLPE--LGNVKSLEVICVSENRLQDIPAEKLAKLPKL-RLCLHSNRLGQ
----K-VVRTLKEAKFEVRFDN-RSVD---P------KISKI---KVEGCH---------
------MTVLT------------------------------RETPVFDVFMLYSEEDEKV
ITDEFLPKLEKKAELKVCFASRDYIPGHFELKEALTNMRKSRKIIALLTEHFDEQK--AV
EINHAVDADLARQSCSVIPVVWGNV---KMPVQFKRIVPLRR------------VDWDRL
ITAIKE---

**>Lan-TLRα2**

-ITTLPAMP-IYLQNNKLEIIT--------------------------------DYFSRV
HTLVASNNSIAKITSRIFWY---ISHVQLDGNNLKSLPQDIESMKHNITSLSLSRNPWTC
SCENLWLKSWLLKKRK--VI-HMDSVICTNE--VKGKPISQVT--EEMLCHPSYIQVAVS
LGVLLLLTLITIAVLYKYRFEVKVILHRFNWHPR-----QEMTEKLYDAFISYSSEDRLW
VHTTLAPTLENQLPYRLCMHCRDFLPGEAIDNNIIQAIQNSRCTILVLTKNFLRSNWCIF
EFQQAHYQMIHNAHFKVIVILKEDIPAEEMDDDLRAYLRTHTYLEAKD------WFWKKL
LYVMPTMNK

**>Lan-TLRβ6**

----------------------------MFRNLTQLRKLYIQNTGLSFLPPNVFVNNGMM
SELQLQSNFLSTWDPIVFQPLLSLRKLFMDHNNIRILNETSFFIWDNLTDLNLAGNPFSC
TCENLWFRNWIQST--NVKLLQLHAYLCYEPKKLSKSPFLDWHPTKAQ-CTPAWVIASAI
GVPTLLFLALVIVVSHRYRWYIRYWCFTLRSRYKRLEPFEDNGTYVFDAFVSYNCHDRPWVIQRLLPKLEYDAGFK
LCLHDRDFIVGHDIVDNIVDGIDVSRKTILVLSNNFAQSQWCQLELTMAQHKLFDENKDILVLILLEDIKPENLSNRLT
LLLRKQTYIEWPSEEEGQDLFWERVKAALQKPSG

**>Lan-TLRβ9**

IFNNVPTLTELCLDNNQFYRILLDILRDLLRPLRHLRCLSLTANKLTELPLGMFDGLANL
TTLDLNLNSLRSLPVEIFRHQRQMTDLHLDRNSIFTLSGHMFANLTALKNFNYARNKIIC
DCNIRSFQSWLATT--SVNV---PRELCFGPEWAQKTPIKEFRPSWFA-CDD--VYLAAI
SGGCVFFVIFLSAVLYSFRWDILYIYAIYRASGKKSKLGRREPHKTYDAIAMYSPTSVTW
IKKHLIPNLEEDIRFKLCINDRDYIVGDPLVDNVETNMEKSRRILFLLTREYFESQLHET
EINLAQVKLFDGFVDKIIFVFLEEVPKTTFKEPLKTMMRHGNCLHWPRKKRERTIFWKRLKLALLEAKT

**>Lan-TLRβ8**

IFKNVPTLTELYLDNNQFYRILPDILKDLFRPLRQLRHFSLG------LPP---------
------------------------------HQSMYRVPGNFA-----L---DPNGHK---
-RQLKSFHGSLA----MTTV-------CIWPPYREDA------------CF---------
------FVIFLSAVLYSFRWDILYIYAIYRASGKKSKLGGREPHKTYDAIAMYSPTSVTW
IKKHLIPNLEEDIRFKLCINDRDYIVGDPLVDNVETNMEKSRRILFLLTREYFESQLHET
EINLAQVKLFDGFVDKIIFVFLEKVPKKTFKEPLKTMLRHGTCLQWPRKKRERTIFWKRL
KLALLEAKT

**>Lan-TLRα4**

FLTSLPNFPNLEVQRNQL----------------------------ERFPN---IALPNL
WILSLKDNSITEIKNESLQHVPNLRYLSLEGNGITHIPEGFFNHTPHM-TANLTGNPIKC
DCSQRWIKDWMLQQEKRTIF---VEAFCSNSSG--AINIKDF---DFEACVPTFYVTLLV
VLVLLIIVAILILLIYICRKELQVWIIRGWWKA-NVLTNSAQRTYKYDAYIAYCDNNYSI
IRDHFIPRLEQKHGYRLFIRDRDSEAGQPIAENVANAISKSYCTIALLSNSAMESEWFPV
EFELTHSLSVEDKSRRLVIVKVGHLSKEALQKSIQLYLTTKTYLSWTD------DFWDKM
HKILPDKRE

**>Lan-TLRα3**

-LTGFPSLP-LYVNRNQVETFP--------------------------------TLFSDL
QELQAADNNIGSISNSSFTAFPKLQYINLDRNGIAEVVVGTFDSL--LSMVSLKGNSLHC
DCSQRWIQDWIIRNLT--FI-----ATCNDT--------------DFTQCDT-NVVALAV
VLVVLAVFIALVAITFFYRTEVEVLIYRYKQ--R-----DSDTDKDYDIFISYSNDDSVF
VRNVIIQKMETEWGYKLCIHERDFLPGEYIADNIANAVEKSRRTLTLLSDSYLHSEWCVF
EFAMAHQQSLKDRCRRLVVVKLSDLDSNLLAKEVGIYLKTNTFLHKGC------MFWEKV
RGTLPAKPL

**>Lan-TLRα8**

-LTALPFAP-LEMAGNLIEVLE--------------------------------PYLANA
TKLILSNNAIQTIDPAVFGLFAELRTLHLDGNHLTHLPKEITSVN--ISEIKLDKNYLSC
DCKSTWLKRWLNENGK--NIPRFTELTCAVG--QNGQRIIDVP--DSSTCDPLIVPIAIC
LAVVLVILAVNLIV-YRFSIEIKVLVYKFNWHPR--D--DDGPEKIFDAFVSYSSQDYKW
VVHNLRHTMENVPPYRLCVHDRDFIVGETIFDNIMNSVQQSKRMIMVLSQNYVDSEWCMMEFRTAHQKVLKERS
KYLIIILFDDVNKDQLDEELLAYLNTSTYLEVSS------WFWKKL
FYAMPDLSK

**>Lan-TLRβ5**
VFSHAPHLQELYMSDNHLDKIDDAALEKLFRNLTKLRKLIISQTRLTHLPPKLFETKPFL
RELQLGSNQLSSLDPVVFQSLFSLQMLYLENNLIRTIYESSLFVWKNLTKISLAENLFSC
TCDNFWFRTWMDTT--QTTIVALNSYRCYEPKELAKSPFLDWHPSKAQ-
CTPAWVIASAIGVSIMLFLALVTVVSHRYRWYIRYWCFTLRSRYKRLEPFENNGTFVFDAFVSYNCHDRHWVIQRL
LPKLEYDAGFKLCLHDRDFIVGHDIVDNIVDALEVSRKTILVLSNNFAQSQWCQLEMTMAQHKLFDENKDILVLILLE
DIKPENLSNRLTLLLRKQTYIEWPREEEGQDLFWERVKAALQKPYG
**>Lan-TLRα1**
KLNGQPNMEIVEFSNYAY------VFITIFHGYPALHTLIAVRNNITVFPQATLLNFPKL
RYVDLRYNSIKELKI---PR-GSNRVFDLRHNDIQDLTIENVNAMRYAAHVDFRNNPIDC
GCNNSDAVKHLRSEVVKSTYRFLYDIPCHHGET--TTTIRSINLDDLNECF-IIIIPWIV
LGLLACLVVLTAILTVYFRREIQILLFRLKCRCR------S-PPKRFDAFVSYNSGDEHW
IVHTLAPKLENKPPFRLCLHYRDFIVGAAIAENIIESIEASRHTIMVLSENFLKSEWCLM
EFRAAYHQGLRERNKHLIAIVLEDILLDDIEADLRSHLRTTTYLKVSD------WFWDKL
IYCLSRNPH
**>Lan-TLRα6**
-ITTLPAMP-IYLQNNKLEIIT--------------------------------DYFSRV
HTLVASNNSIAKITSRIFWY---ISHVQLDGNILKSLPQDIESMKHNITSLSLSRNPWTC
SCENLWLKSWLLKKRK--VI-HMDSIICTNE--VKGKPISQVT--EEMLCHPSYIQVAVS
LGILLLLTLITIAVLYKYRFEVKVILHRFNWHPR-----QEMTEKLYDAFISYSSEDRFW
VHTTLAPTLENQLPYRLCMHCRDFLPGEAIDNNIIQAIQNSRCTILVLTKNFLKSNWCIF
EFQQAHYQMIHNAHFKVIVILKEDIPAEEMDDDLRAYLRTHTYLEAKD------WFWKKL
LYVMPTMNK
**>Lan-TLRβ7**
IFSAVPSLNTLSLANNSLGQT-PAILKKMFKNLGQIWKLRLSGNGLVELPLGMFDDLVQM
TDLHLQVNQITTLPAGIFNKCKKLAHVNVENNKIISISEGVLWAIGSLRQLDLSGNKWTC
DCDIRWFVHWLRNT--RVLLSKGKQEHCNLPSDLRQLKLVDFCPAWIE-CDNLHLTAGLTSS--
VVAITLTSYLIFIFRWDIKYAWVIRKTRRNGYVEI---
PDERYAAFVSYCSKNTKWIKDELLKNVEDDMGLRLCIYERDFICGNPIVDNIEEYMNQTTRVVFVVTGDSLQSRLC
DHEFKVAQNKLFEKRITSIIFILHEDVDKKTIPDNMQTMMRHTTCLCWPENGRQKTVFWKKIRLALLR---
**> Lan-TLRδ3**
DFKD-LKLKELYLNGNKIRTLP----PNIF-KLRELTHFDGSYNELQSIPD--IDQLQNL
KYIRLKQNRLRRLPE--LGNVKSLEVICVSENCLQDIPAEKLAKLPKL-RLCLHSNRLGQ
----A-VFQTLKKAKFHVRFDN-RLVD---P------KIKD----KIEGCH---------
------MTVPS------------------------------GKMPIYDVFILYSEEDEKL
INDVFLPGLEEENELKVCVAFRDYIPGQYVSEEAISNMKKSRKIIALLTEHFDEQK--AV
EINQAVGADQGRQSCSVIPVVSGNI---KIPAQFEKIVPLRA------------VDWDKL
LTAIKA---
**> Lan-TLRδ4**
AIKKLTKLESLALNANEIRELN----IGIF-DLEHLIFLDASHNPIFAIPK--VQKLKKL
EYLRLKMCRLQALPE--LGDLPRLETICVSENMISKVPAEKFQKMRQLRTICLHSNRLSV
E---LKLRQ-LK----DVRLLNDQSLNC-------------------GCY---------
----------------------------------------K-KPTEKDVLIIYSGTDDRV
VDDEILPILEEELRFSAVVDFRDFIVGKPVFTQYAANRKSCRKILFVLTADFCSGK--RM
HLNEALQAVADDKRSRIIPLIWND-PNFQLPEELRSYVQLHK----NE------SRNEKL
WKALA----
**> Lan-TLRδ2**
DFKG-SQLKALYLNANYIRTLP----QNIL-KLKELIIFDGSYNELQFLPD--IDQLQNL
KYIRLKQNQLRRLPE--LGNMKSIEVICVSENRLQHIPAEKLAKLPKL-RLCLHSNRLGQ
----A-VVQILKTAKFEVRFDN-RSVD---P------KIPKI---KIEGCH---------
------MTVLS------------------------------RETPVFDVFILYSEEDEKL
ITDKFLPQLEDKAELKVCFASRDYIPGHFELKEALNNMKKSRKIIALLTEHFDEQK--AV
EINQAVDADLARQSCSVIPVVWGNV---KMPAQFKKIVPLRR------------VDWDRL
LTAIKE---
**>Lan-TLRβ1**
LFKGTSKLKILFLSDNELGYVFNDPNGMLFKNLYKLENLTLERNRISQLWPAQFQNLTSVKNLSLSDNQVSFFTSQ
LFAPMTSLRALNLSQNMISLVNSSSIGGLGRLQTLDLSGSPFACTCDLVWFRRWINQT--
NITLSQLDVYTCNTPAERRGMPLLQFDPDAID-CVNPIYLASAVGG-
TLALLVVVFISLYRWRWFLKLRYYRFKRLAKGYERV-EGDDIVSDAFVSFCDADREWVAVELLARMDSAGRFNL-
VCDLNFLPDKSELESVVEAIECTRKAIVVLSDAYIGDPRCQF
ELEQIYESSVERQRYEMILVLKG-LPNGKIPKVLRQRLERGEFLEWTEDANGQQLFWDQLGEKLEQRPH
**>Lan-TLRβ10**
DIRNLTRLKILHFCDNTISLTRPD--NNFFTGMVSLESLNLAGKELEGVDLTLFNPLINL
KVLNMTYTGLTKVTPGTFKPLQNLRTLDLSDNKLVEIDGDIFKYIPKLATFLFNNNRFSC
DCHLVRFVGWLKHT--SIQI---EDQPCFSPSKLSAVKVGDYSPGFLE-CK-QVLLYALG
--TLVL--LIFTAVITFYRWDIRFWWQKVRPKKQGYIPI----DGEFDAFVSYSSKDEDW
VVGTLVRNLEEEARFQLCLDNRDLIPGNFIIDNLIQGMEKSKCCLFVITRNFVKSEWCNF

ELNTAISKMLDERKNVVILIYLEHIPDKDLPKNLRRLKKHVTHLKWPNDERKIDIFWKKL
QLVLYHKKE
**>Lan-TLRδ5**
NIKKLTKLESLVLNANEIRELN----IGIF-DLEHLIFLDASHNPISAIPK--VQKLKKL
EYLRLKMCRLQALPE--LGDLPRLETICVSENMISKVPAEKFQKMGQLRTICLHSNRLSV
E---LKLRQ-LK----DVRLLNDQSLNC--------------------GCY---------
----------------------------------------K-KPMENDVLIIYSGTDDTV
VDDEILPILEKELRFSAVVDFRDFIVGKPVFTQYADNRKSCRKILFVLTADFCSGK--RM
HLNEALLAVADDRRSRIIPLIWND-PNFQLPEELRIYAKLNR----KD------YFWKKL
QKALA----
**>Lan-TLRβ4**
IFSNSPNLHDLSMHDNQLNDMNSTALETVFRNLTKLRKLYLQNSKLANLPAKMFVNNGMLSTLQLQSNYLSTWDP
IVFLPLLSLKHLFMDHNHIRILNETSFFIWTNLTEVNLAGNPFSCTCENLWFRNWIQST--KAKVLQLHKYICYS----
AKTPFLDWHPTKAQ-CTPAWVIASAI
GVSIMLFLALVIVVSHRYRWYIRYWCFTLRSRYKRLEPFEDNGAFVFDAFVSYNCHDRHWVIQRLLPKLEYDAGFK
LCLHDRDFIVGHDIVDNIVDALEVSRKAILVLSNNFAQSQWCQLEMTMAQHKLFDENKDILVLILLEDIKPENLSNRL
TLLLRKQTYIEWPREEEGQELFWERVKASLQIHSG
**>Lan-TLRα5**
-YTSVP-LG-LTLANNGITELKNNSINQSFTGLFQLRTLNLSFNLLEDLKEYSFSGMTML
ENLYLDHNLLTSIDPSTFASLSRLKILTLHSNRLEYLLPDVF---TSLVHLTLSHNRWPC
DCDVIYFKHWVVSYKA--IIFDVGNINCTFKRIVQGKRVLYF---DEDYCNRTHVAALVS
VSILFFLTVIVTSLLLYYRTEIKVWIFKFGCRPK-----PDDDEKIFDAFISYSSKDEHL
IVHELAPRLENHPSYKLCLHYRDFPVGASIAETIIDAVEASKRTILVLSQNFLDSEWCLY
EFQTAHHQALQDRTNRVIVILLEDIPLKNMDNELRAYMKTKTYLRWDD------WFWDKM
AYALPDVHK
**>Lan-TLRβ2**
LFSHTPNLHELNLNSNHLRHLNSTAMETMFRNLTQLRKMYIRNAGLSVLPPNMFVNKGMLSELQLQSNSLSTWDP
FVFQPLISLKKLYMNGNRISVLNETSFHIWNNVTEMDLSGNPFSCTCGNLYFRNWMQTT--
QVKLLEIHRYQCFEPKDLEKTLFLDWHPTIAQ-CT-
VWIIASAIGVSTMLFLALVIVVSHRYRWYLRYWCFSLRARYKRLEPFEDNGTYVFDAFVSYNCHDRSWVIQRLLPK
LEYDAGFKLCLHDRDFIVGHDIVDNIVDGID---------------------
---------------------------NLSNRLTLLLRKQTYIEWPSEEEGQELFWERV
KAALRRPPE
**>Lan-TLRδ6**
NIKKLTKLESLVLNANEICELN----IGIF-DLEHLIFLDASHNPISEIPK--VQKLKKL
EYLRLKMCRLQALPE--LGDLPRLETICVSENMISKVPAEKFQKMGQLRTICLHSNRLSV
E---LKLRQ-LK----DVRLLNDQSLNC--------------------GCY---------
----------------------------------------K-KPMENDVLVIYSGTDDRV
VRRRILPILEKKLGLSAVVDFRDFTIGKPVFTEYADKLKNCRKILFVLTADFCSGM--KL
HINEALQAVADDKRSRIIPLIWND-PNFQLPVELRSYAKLNR----KD------YFWKNL
KKALA----
**>Lan-TLRβ3**
IFSNSPNLHDRSMHNNQLNDMNSTALETMFRNLTKLRKLYIHNSKLANLPPKMFANNGMLSTLQLQSNYLSTWDP
IVFQPLLSLKKLFMDHNNIRILNETSFFIWTNLTEINLAGNPFSCTCENLWLRNWIQST--
KVKLLQLHYYQCYAPEKLAKTQFLDWHPTKAQ-
CTPAWVIASAIGVPTLLFLALVIVVSHRYRWYIRYWCFTLRSRYKRLEPFENNGTFVFDAFVSYNCHDRHWVIQRL
LPKLEYDAGFKLCLHDRDFIVGHDILDNIVDALDVSRKTILVLSNNFAQSQWCQLEMTMAQHKLFDENKDILVLILLE
DIKPENLSNRLTLLLRKQTYIKWPCEEEGQELFWERVKAALQKPYG
**>Llon-TLRα2**
-LSAIPRMP-LHFENNRIEELS--------------------------------
GYLKFVVGLWMSRNDITAISREVVELLSKAKGIYFQYNKISRLSKSVMSLWKGVSKLDLTYNLLVCDCHSEWLRH
WIIEASY--LV-NGWKLRCASDETARGRAILTVE--SHEVCKT---
IIAIIFGTVFILLIVAFALVVRYRQEIKIWLYKYDWHPK--D--DSDPSLIYDAFICYSSLDYDW
AVHTLWNKLENTPPYKLLLHQRDFIPGQMTMDSIYEGVNSSKRMIMLVTQNFVRSDWCMAEFRTAHHEVLSKNT
NYLIAILGEDLDIECVPEDFKVFLKNTTYLKKDE------NFWDRLFYALPQKGP
**>Llon-TLRβ8**
AFLGLEHIEELDLNDTDIGAV-REDLKYVFKPLKGLKRLNLADSLFKHYPVVIFQNQAEL
EELDWSSNAITAIGSVVFSTLRRLRRLDLRNNQLIYISGKVFTTLTNLQTLLMWENSFAC
NCKLRGFTYWLSRSKFKDAICESYSEPCRSPPKHVGHRLESFLPTWLD-
CENAIVALSTSLVLLFCLSVSLSVVAYRKRLSIRYWYVIRKLKRKGYIPL--
SRRHSYDVFIAYMPQEQRWVEHTFRPELEKDVAFRVATVDREFQVSGEVIDLVEGGFRHSSHVIFIVTDEFLSWE
KSDYMMTQAEVMYLEKGCPEPILVLKERITMDQAPLSYKRLIRHVVRLHWPQGQGYTEDFWKNLRLVLLGERT
**>Llon-TLRβ4**
EMEHLTKLEKLFLSCAGTTVLP--------STLATLKQLEISEWSFREDSIQIISSLKNI
EILSLQQSNIHHFPYQELMMLDNLVTLDLSRNRISALDHKRIWKIPKLRKLNVASNNFEC
NCSMLPFSEWLRRPRPRIEIISLFNVKCASPSKYYNMALFNFDKD----CRSPIILPSTL
GP-IGLLIAIVIFVTVRYRGYIRYGLMLIRARWRGYGSI-EGCKFKWDAFVSFNGADYDW

VYNQLKPKLEDEAGYRICLHHRDFTIGEFITDNIVKCIDRSRKTLLILSDDFAKSQWCQL
ELSVAQHKLFYDDRDVLILVKLNDVSPENITGTMQVVMRTKTFITWSDALAEQDLFWKQLILALKRPPG
**>Llon-TLRβ7**
AFTGLENLEQLELNDTDIGAV-IEDLKYMLRPLKSLKRLDLDKSRFSHIPEDTFLNQVNL
EELHLADNEIRVIGHSAFRTLVRLKYLDLRNNRIEFIHGEAMGHLTSLLTFLFTENNFGC
HCDLAGFTKWLKEHTFHENRCEWRSERCTVPLHLKDTPILDYQPGWTD-
CDNLILTVSSIFSVFLILSSSIAIHSYRRRLSIRYWYVLQKLRRAEGGTQ-
NSLDEPFDVFISFELNDRYWVEETLLPNLEDDIRFRVCTVDRDLDPGRPEVMNIARGIRNSRNVIFVVTRELIQTAW
CEYEICLAETQSLQEGNCRLIIIFLEKFTWEELPLCMKRLLSHVNFLRWPETAHEQEDFWRRLRLVILGETT
**>Llon-TLRβ6**
AFTGLENLEQLELNDTDIGAV-IEDLKYMLRPLKSLKRLDLDKSRFSHIPEDTFLNQVNL
EELHLADNEIRVIGHSAFRTLVRLKYLDLRNNRIEFIHGEAMGHLTSLLTFLFTENNFGC
HCDLAGFTKWLKEHTFHENRCEWRSERCTVPLHLKDTPILDYQPGWTD-
CDNLILTVSSIFSVFLILSSSIAIHSYRRRLSIRYWYVLQKLRRAEGGTQ-
NSLDEPFDVFISFELNDRYWVEETLLPNLEDDIRFRVCTVDRDLDPGRPEVMNIARGIRNSRNVIFVVTREFAQTS
WCEYEISLAETQYLQEGNCRLVVLFLQKFTWEELPLCLKRLLSHVNFLRWPATAHERNEFWQRLRLMLLGELT
**>Llon-TLRα1**
-LNKLPSIKLIYLNQNNF----------------SQISLDHSENLLTEILE--RSIKGHV
KVLDLSYSSIADIDNEFLEKLSHLTHLYLNGNKLTKLTEHTLSLQERLTELHLYNNTWDC
SCSAMLMIKLLNRLIARKTLVRPDEIVCVTPERNRGRMVYMV---DDELCE-TKLAFYIE
QHFVLNMTLALLVLKFFKRETIQLLTL------RAIVNDDD-TSMVFDAFVSYCEDDRVW
VEQELIPCLQQEPPYKICQHRLNFVPGFTVQQNEFNAIKHSRRTIIVMSNAYLGREHCQYEFKTAYNYWITEKEPRL
VVVKYPDVEDRN-QETCHAYFRKFTYLEKDE------NTFDRL
LAFMPRR--
**>Llon-TLRβ5**
AFVGLEKLEQLELNDTDIGEI-TEDMKSVFHPLKGLKRLDLDKSRFSNIPDGMFMNQVN
LVELHLADNKLRAIDHSVFRTLLRLKQLDLRNNRLGFISGEVMARLPSLQTFFFTGNNFGCHCDLAEFTRWLKKND
FRENQCELYNEKCVVPPSMKDTSILDYQPTWLG-
CDNLILTVSSAFSFFLILSTSVAIHAYRRRLSIRYWFVVQKMRRAEYEAL-
DNSDIPFDVFVCFEKNDRFWVEKTLLPKLEDDIRFRVCTVDRDLDPGRPEVMNVARGIRNSRNVIFVVTRELIQTA
WCEYEICLAETQSLQEGNCRLIIIFLEKFTWEELPLCMKRLLSHVNFLRWPETAHEQEDFWRRLRLVILGETT
**>Llon-TLRβ2**
ALHGIPNLEVLDIHGNKFDDMTQD--
ANFLSMFRNLKRLSMGKMGLFFLEGWIFDNLTKLERLELSFNALGNITARWFKNLKYLKKLEMRDCRIATVNVKSF
AFLNQLNSLDLRDNPFSCDCSIQWFLNWSKHHGNQLYMFNRKDYTCASPQWLHRMPLRKFTIP---
SCYKTLLTGLSV
AGVAIIVCFFVLAFFSRYRWHIKYKLFKLKIWF-QYEEL-DGSKYEFDYHVHYDDQDVSW
VVNTLIPELEDKRGYRLYIKHRDSSLCQYIIENIRYSIEHSYKTVLCLSNQFTQNPGTQF
LLSFIINKLVNEKKNILVCILLEEIQGENLLETLEEVLTEKSYIRLPEDREAMEYFWSRV
DEALH-PRN
**>Llon-TLRβ1**
VFQNLKRLKILRLTNNDLGPQLKDTKGELFAGLENLEELYIEKNDIQELTGDVFRHLKGA
KMLELGENAISQWGTSTFSQNSTLKHLNLSRNRIATINEPSLADLKLLTTLTLTANPFSC
DCGLVWFRRWINST--NVTFPELELYTCNSPVRMAGIPLLKFDPDSLT-CKDPYILGGSL
GG-VVILILVISLVIYRYRWFIKLRAYRIAKAVAGYEPI-PGDDLRFDAYISNHRDDRRF
VLDELLQNYDNNGGFRLCFNERDFVPGEYDLTNVTENMSQSQRGLIVLSLQYIQDHFQDFELHLLLKEANLRA-
FGLIVIELEEIPPNRIPNGLRRIFEEGDHLSWSEDPNQQQL FRERLTNKLQRRPQ
**>Llon-TLRβ3**
PIAGLNKLYKFGTTGADF----IN--RGLFINKTELQSLHIGSGRITMNHLDILRNVTSL
KSLRLEKMDIREIPH--ILHLKHLKSLTLVSNKIEMIPQHFIPKLDGLKTVDLAFNPFAC
NCSLMPFSNWLRNASRLATVTNLDVTLCFSPASYKNTPLFNFEKD----CRNPIILPSVL
IP-LVLLILVVTAVSVQYRGYIRYACMLVRARWRGYDALNEGRSFKYDTFVSYNREDA
AWVLRVLRPKLEDEVGYQICLHDRDFTVGEDIVDNIIMSIDESRKTILVLSDNFAKSQWCQLEMSLAQHKLFEDNR
DVLILIRLGEVAEENMTRTMRMLMRTKTYITWPQNEEGIDLFWRNLIFALRRPPG
**>Lrub-TLRβ2**
FFKGLTNLQNLSLSWTDFGEVDHSQGADIFDQANTLRSLNFLGGFITHISAGLINDLHNL
THLNFQSNSIGYLFSEWFENLTNLKVLNLNDNKITTVVGANGRFFRSLSQLTIGENAFDCDCQLRFFSEWLRGLDD
QIRVSDMDKAVCLTPIAYENKRIKDF---KSAVCS---GIAFTS
AAAALLFIILSVIVGCYCRHDIKYMMAIRRLHHR---TLR-GSKLIYDV----NDTDRQW
INTNIGNITDKD--FNITTNHPDIVPGEARSNPLSKQINQCYYTLLLISNHFKDDLWPEV
HANLTVQEI---HNIRFVIVLIDNLRLRDLPRELKALAKQRPCFKWPTETLRRRLFWRQL
ILALIKRRA
**>Lrub-TLRα1**
-LNKLPSIKLVYLNGNNF----------------SQINLDHSEKLLTEILD--KSIKGHV
KVLDLSHSNISDIDKQFLEKLPYLSHLYLNDNMLTKLTLNSLRIADRLTEIHLYNNTWHC
SCNMTQMTILLNHLIARKTLVRPDEILCATPERHRGRRVYML---DHELCG-TDSMSFVV
LTSIIAITLATLILKFFKPKTLQVALP------RAIEDDDD-TGMVFDAFVSYCEDDRVW

VEEELIPRLK--PSYKICEHKKHFVPGITVQENEYNAIKHSRRTIIVMSNAYLERGHCRY
EFTTAYTYWIIEMKPRLVVVKYPEVVDQNK-ETCHAYFRTFTYLAKDG------NTFDRL
LDFMPEK--
**>Lrub-TLRβ1**
ELHGIPNLDVLDIHGNKFDNMVQD--ANFLSMFPNLKTLQMGKMGLFFLKDCIFDNLTKL
EKLELSFNALGNIPARWFKNLKHLKTLEMRDCRIATVNEKSFEFLNQVTHLDLRNNPFSCDCSMKWFLNWSKYHN
NRLVNYNQKDYTCASPPTLHGLPIKNFTIP---SCYKTLLTGLSAAGVAVLICFFSLALLGRYRWHIKYKLFKLKIWY-
QYEEV-
DGSKYEYDYHVHYDDEDVTWVLNTLIPELETKRRYRLYIKHRDSPLCEYIIENIRYSIEHSYKTVLCLSNKFTRNPGT
QFLLSFIINKLVNEKKNILVCILLEEIEGENLLDTLEEVLTERNYIRLPEDREAMEYFWTLVDQALH-PRN
**>Lrub-TLRα3**
-LKAIPHLTNFIHKDVQV----------------ESSILILSHNNINSLNP--YEHLKHF
TQIDLSHNNLSFIDPSWFNLFKGVSQLHLNDNNLTQINPKDIETFRNLEELHLYNNPWDCGCNKIWFKSWLSYLAD
AGVVMKPHLITCASHHWNKEKIVHNL---YVSFCQ-TFIAMVLI
--VLVTIFFIFILM-----YKLRLYIFSFNVHLR-----EEGENMESDAFISYNGADYDW
VKNKFNIRL---MKYKLC-NLRQAVDGRDFLENIETALMTSKRTIVVLTKHYLEDEECTR
EFKIAREYWVDIKRHRLIVLKH-GVDIDEIDNEIRLFLKRYKLIEMDR------NLWRNL
SYAMPNP--
**>Lrub-TLRα4**
-LKAIPTLNGLIKPDNKI--------------------LLLTGNNITNLNA--VQYLDSF
TTIDLSHSNISAINEYTL--LGKVSKLFLNDNNLTHLLVQGLKIFTNLEELHLYNNPWNC
SCDQKWMKLWLLNYIDAGIILKPHMVTCGSQNWNEGKVIHTL---PEEFCFPTILYIFLV
---LLVCILVG---VKQFIYNNKYQLFEFNLHPC-----EHGENMNYDVFISYCENDRSK
VLKDLIQSRD--PPYKICDPDDSFPRGRPINESIADAVTKSKRTIIVLTKAYALKSYCCE
EFRTALDHWSMDERHRLIVI--KDIETNTIDDKLRQYLREYTYLELDV------NLWKRL
SYILPQP--
**>Lrub-TLRα2**
-------------------------------------------------------------------------------------------
TNWPGHIQSFEDKVTEIHLYNNPWDCSCNKLWMKKWLNKLIV--ILVKPDKIICGTP--NKGQMFYMV---EDSFC--
TDKKIIIIL--VISIVLAVLILRH---VFHKLWPDPLPPNRI---
DDSNTSGMTFDAFVSYCEPDSEWVEQELIPNLQQNPPYKVCHHKQYFQPGMPSEWNEFMAIIHSRRIIIVMSNSY
LEREHCRFEFSTAYSYWIHTKNPRIVIVKYPDLEIVN-REACSAYFKRFTYLAKDE------T-FKRLFQFMPLE--
**>Nge-TLRβ6**
VFLGLGHITELELNMTDIGKI-TEDLEFVFRPLKNLERLNLANSALKDFPRDLFLNQVNL
KILDLSYNRITIIGDVILSTLKKLRYLDLRRNEITEISGDALRKLTYLQIALIAKNNYAC
TCALRGFTKWLLEHKVTDDVCADYSAGCRSPPQFVGKRLDKFQPSWID-
CDNAIVTLSTLFTIIFCLFTILSIYGYRKRLSIRYWYVIRKIKRKGYLPL-
PALHDLHDAYVAYADNDHAWVEGTLLPNLEDDVTFKICTNERDFQVSDEIIDIVEKGIKCSDRIIFLITNAYLQATKSD
YVMAQAERLYLETGRPHIILIMKEKINFDRVPLSFKRLISHAARLHWPENQGQRNDFWKNLRLLLLGERT
**>Nge-TLRβ5**
VFLGLGHITELELNMTDIGKI-PDDLEVVFRPLKNLKRLNLANSAINDFPRDLFLNQVNL
EFLDLSYNRITIIGDVVFSTLKKLRYLDLRRNEITEISGDALRKLTHLQIALIGKNNYAC
TCALRGFTKWLLEHQVGGEVCADLSASCRSPPQFVGKRLDRFQPSWID-CDNTIVTLSTLFIII----
VCLSIYGYRKRLSIRYWYVIRKIKRKGYLPL-
PALHDLHDAYVAYADNDHAWVEGTLLPNLEDDVTFKICTNERDFQVSDEIIDIVEKGIKCSDRIIFLITNAYLQETKSD
YVMAQAERLYLETGRPHIILIIKEKINFDRVPLSFKRLISHAARLHWPENQGQRNDFWKNLRLLLLGERT
**>Nge-TLRα**
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-------------------------------------------------------------------------------
NSLDYVWVVHTLWNKLEKRPAYRLLLHHRDFIPGGMIMDNIVEGVTKSKRMIMYVTDNFIKSQWCMVEFRTAHHE
ALSKNMNYLIAIVDEELDIENVPEDFKVFLKNTTYLKRNE------HFWDKLYYALPQRGP
**>Nge-TLRβ2**
VFKNLKHLKKLKLGKNELGGLIDDKKGELFAGLDHLEQLDLRMNSVKELTDGVLKPLKGMKKLELGRNSISAWGP
ATFSQNRTLQHLNLSNNNIATISKSSMSTLTSLVTLTLTGNPFSCDCGLVWFRRWIDHA--
NVTFPGLKSYQCNSPPVREGLLLLKFDPNSLT-CIDPYVLGGSIGG-
AVILCLVMTLVMYRYRWFIKLRAYRFGQAMREYEPI-
PGDDLHFDAYISNRDSSREFVLGTLLPVFDNNGAYRLCFDERDFEPGEYVLTNITNNIAQSQRGLIILTPEYIHDKFY
ELELHMLLEEANKRP-FTIIVIELVEIPPNRVPNGLRRIFEARNQLTWSENPDEQALFKDRLTNKLERRPQ
**>Nge-TLRβ4**
------DCGYLNISYFKFDDQLELANPVPFRLTPNIAEFMVSAARCFVQPQYK-------
---------LVSLLRAILRDEYITWHKKMFLLRVVAVVLPLLADGRRASDVEYVKKGVNV
NCTEKGWKDVPKNLPKKIASIRRAFVGLTKLESLDLTANKIRXIPQ--RCHKRLLAGLCA
FGVLLIVTALGLGLFSRYRWKIKYKIFKLRLWFYQYEEL-
DGSKYEYHFLVHYDDSDFPWVRDMLIPELEHKRGYRLYIKDRDSRLCEYILENIQYSIENSYKTVLCISNQFTQNSW
CQFLLRLLIQKLVNEKKNILVCILLEEIGGENLLDTLENVLTQKNYIRLPEDREAMAYFWTCVVEALH-PRN
**>Nge-TLRβ1**

VFKNLKHLKKLKVGKNELGGLIEDKKGELFAGLDHLEQLDLRMNNIQELTDGVLRPLKGMKKLELGRNSISAWGPA
TFSQNRTLQHLNLSNNNVATISKSSMSTLTSLVTLTLTGNPFLCDCGLVWFRRWIDHA--
NVTFPGLKSYQCNSPPIREGLPLLKFDADSLP-CIDPYILGGSIGG-
AVIICLAMTLVMYRYRWFIKLRAYRFGQAVREYEPI-
PGDDLEFDAYISNHHSSSEFVLGTLLPNFDNNGAFRLYFDERDFEPGTHDLTNMGKKISQSQRGLIILTPEYIQDKF
HELELHLLLEEAKKRP-FTIIVIELVEIPPTRVPKGLRRVFEARDQLTWSENADEQVLFKERLTNKLERRPQ

**>Nge-TLRβ3**

---------------------------------PEFEDFEVVSRKVFEVERWSFDKAVHICGWVLRF--
VYNLRHPNLRHSGPLSHEEMFLLRVVAVVLPLLAHGRRASDVEYVKKGVNV
NCAEKGWKDVPKNLPKKISSIRRAFVGLTKLESLDLTANKI-------------------
---------------SRYRWKIKYKIFKLRLWFYQYEDL-DGSKYEYHFLVHYDDSDFPW
VRDMLIPELENKRGYRLYIKDRDSRLCEYILENIQYSIENSYKTVLCISNQFTQNSWCQF
LLRLLIQKLVNEKKNILVCILLEEIEGENLLDTLENVLTQKNYIRLPEDREAMAYFWTCV
VEALH-PRN

**>Pau-TLRγ14**

LFRAVGKLEHLFASRNMFGLFKPGDLVTTLSGLPNIKTIDLSINRLSYLPRGIFSECPNL
THLDLQRNGMKSVHL--FSSLPSLKYLDLSHNEIKGFSKEQTEDF----FLKLENNSFEC
SCDNIPFIEWIQSDGSNDTVLNKSKLICEFADG-RMTALVDVDLNKLYDCMKIIIAVATM
----AVVLLSTSLIMWRYQWYIKYWIYVLRLRHR------DDGTEPFASYISYADNDYDL
ANT-VCTKLEE-SNLPVFFRDRDTSLGTSIFDEYFRGIESSRKCILCLTDSHLNCAERYF
ELQMSMVR----GKGFLIPVVVGNLALEKLPKPLRRLLRDDVYFEWPKTDLEEEDFWKSL
IAAVLTRKG

**>Pau-TLRγ6**

-----------------------------------------------------------------------------------------------------------------------NCRRSLLGF---------------
----------E-EH-QICIKRTWGIAKCHRS---LDAVFSYCLH------------------------------
HQHLILAAFTGKMVTCLSSEDRHWVHDVLRARLEENSDFGLCIHYRNFL
PGRNIEENVIDAIESSRHSMLVVSRNFLKSEWCIFEMHMARNIFRRQQKDVLLLILLEDI-
VQDAPLTLVNLLRSRTYLKWPADDVGQEAFWERLKETLKREPE

**>Pau-TLRγ5**

RYKAFPALKKLILAGNKLYIMLRDRKTKHFRYLNNLTHLDLAYNSINELYPETFNDLPAI
KEVLLRGNRLISVTSMNITGMPSLKNISFAKNNVRFVSENVLHLWHG-
KSVDFSQNPFNCSCLFLPFLRWFNNVSSTVTLLNSDHYRCGDEKKT---
YVRKISLDALTKCTSAWMIISIAMSICVALCITLGSVLYRHRWTISFWINFAARKSHSYSPH-
MRQRFQYDAFVIYSSEDRHWVHDVLVTRLEDESDIGLCIHYRNFLPGRDIEENVL
NAIENSRHSMLVVSRHFLKSEWCIFEMHVARNVLRQQRKDVLVLILLEDIPVQDAPLTLVNMLRTRTYLKWPANDV
GQEAFWEMLKETLTQEPE

**>Pau-TLRγ2**

IFQNLTSLKTLDLSHNLLADKLKDEYGTIFQNMTTVVKIDLSGNGIYKLHINTFHHLKKV
REVILRNNRLASLPAVHIEYLTALKLVDMTSNRVEYLSKASLDSLDK--TVLLADNPFNC
TCEMLVLFRWLHEYLEGLHIKDNHSVYCSHNTSLR---LSNFQFDDLQKCT-LWIWLSLS
TILLLTALIVGLGVAYRRRWTIRFWLIAAR---QGYHRL-PMPEYKYDAFLCHSGENTWW
A-KRIQDHLEDDIGMKLCIYYRDFPVGVPIVECVNDAIVDSRYIILLITKSFIKSQWCIY
EFFMAKSKVFCENRSRLIVLVMEKLTDDVLPRTLQNLMKDSVYLEWTDNALGQEQFWKRLRERLRTEPP

**>Pau-TLRγ13**

QFKAFGNLEHLMASRNRFGLFRSEDLVTTFSNLPRIRTIDLALNSLTSLPEGMFSQCPLLEYLNLERNGIKVVNI--
FATLPSLKLLDLSHNEIKGFTKDQTDDL----VLQMNNNSFEC
SCGNIPFIEWIQSDASDGIVLNKNNLTCQYEDG-KITSLRAVQ--GLYQCIKIIITVSSL
----TSVALCTALIVWRYQWHVRYWIYILRLKRR------DEVSKCFDAFISYSDEDHNL
AAS-VFRKLEE-MGLQIFFRERDTVIGACVLDESFRGIESSREIVLCLTESYLNSDQCYF
ELRMSMLR----GKGFVIPVVVGDVALEKLSKPLRHLLREGVYFEWPTLESEE KDFWKSMKKAVLTAKG

**>Pau-TLRα2**

-LTETS----ISLAKNNLSNIGHNYIVNTFKDANCLKELRLDNNKLTQLKRYYFESLNNI
VELWLQNNDITSIDKDSFIHLTHLQRLFLHRNHLHTLPESKL---DSIVEVTLAQNNWSC
ECSFASFRHWLLDHID--IMADITNITCTATSTSRGEELVSF---DINFCNQRLISGLIA
SILTLVTITLSLSLLLKYRDTIKVWLYRYGWRPS-----SADVRKKYDIYLSSTNTEA--
-CRELLAELEDLPRYVVFFPQRDLIPGGVTTNDITEAIKESWRTIVVLSPAYLQDSWRMF
EFLRAHYCSVHTKTNRIIVLLSEPMKADDMEKDIQAYLTSKSYIKLWE------RLYDKI
RYRLPDGRK

**>Pau-TLRα1**

-LSGIPE---VSLANNEITELNNNDIPNTFRELACVKVLRLDHNQIAHLAAYIFTGLRQL
RELDLQSNLISSIDNRTFHQIIHLEKLQLHDNRLVSLPEPNT---TSMKHITLSGNPWTC
GCDFAQFRRWLILHMD--IIPDILEVKCTLKQTSNNRKLIDLSLINIEYCYESIRNALIS
TIIIFICLIITTIVVYTNRMEIKVWIFRYGRRPY-----KDDFSKPYDAYISYSDKQLNF
VIHELLPKLEQSPHYKLHVRARDDLPGGVRANDIISTLENSCRTIAVLSENYVADEWCLF
EFQRAHYNALHSKMHSIIVVLLHDVKA-DVDKEIQLYIKTGSYMRRDD------KLWQKI
RYALPDTRK

**>Pau-TLRβ3**

YFKGLKKLDEILLGRNDFSEFDRKSPIEIFSDLRSLRKLNLNYVNLKYLHDGFFAALKNL
TKLILDGNGFSGWSPRAFQYLVSLQHLSIINCQVFTINSSMLQPVATLTRFEGYGNPFACECKLRWFISWLEMMNS
STHV---KPYKCLTPKKWHGHSIFEYNTTDDD-
CSDWLLITATASGTVVFVTAAISGIAYYHRWSIRYWMFLARSRRKKEISLRRREDFEYDCFVTYSSLDTDFVVQEM
LSHLEGENDLRVCIHERNFQVGGDITDNIVQSIETSRKIVVVLTENYVKSEWCKLELNMAHAKLLDERRQALIIIMKE
KVSVKLMTPILRHLVRNQTYILWNGSDILQTAFWGKLVQAIMKP--

**>Pau-TLRβ2**

YFANLTSLEHLSLNFVDLGIDIDSKPECLFEGLVKLKVLDLSSTALNGLPERLFKDLTSL
ERLILRKNQLSGWNGAVLENLKNLRSLDVSMNQIRTINQSSLRPVSTLNHFQGFHNPYICDCNLAWYVDWVGQM
HATLKISHKISYKCSN---LKNKSLLQYRPTFFE-CHRLAILCGSGFG-
LFTVIFTVIGLLYKHRWYIRYWIFLLRSRRSTHLEETDGLLYTYDCFI
TYSGEDSNLVTQQLLPKLENEFGYKMCVHERDFKLGREISENIAESIEKSRKVLVVLTQNFVQSEWCKFEVNLAHA
NALHNARQSLIIILVEDVSFEHMTPILRFLMRKKTFLEWTNDAQGQTLFWERLKNAIQQYGQ

**>Pau-TLRγ10**

----------------------GKGLSTIPRNLPNATVLILRRNSITSIPANIF------
--VLLQRNNIAVVD-ATFKKLPFIKLMDLGHNYIKKFSFEQVEDL----TLRLTGNLFEC
SCKTVDFITWIQAPGTSNVIENKKDLKCASPDG-THQRVVEVSLQGLGYCVQLIISSAVV
S----AMGICVAVVIWRHKWTIKYWMYLL----KRRR--GIDRIRPRHAYISATDDDLEK
ANMIFQQ-IEDKLENSVFWKHRDTVPGRSTFDEIFRGVEESRKVILCITQSYSTCTQ-NF
EVEMSF----ARGKGFIIPVLIGDVPLERLPRPLRRLLRDDIYLEWPNNVAEMPNFWVSL
HEAVMTQKG

**>Pau-TLRγ7**

LFSHFPSIKVIELQDNLLGLEMPDQFADVFENVRTLLEIDLSSNYLNKLAAECLAGNAKL
TRIHLANNKLDKLG-LRLENFPMLEFLNLSKNAILFLSSNETSALDSI-ILDLSGNILLC
SCATLNFLDWLRT---SVIFSGRNTYTCSY-KG-KPRNLEDVDLENFRECMSVTVLTSSL
VA--GTILVMLATVGWYRRGHIRYVIY------KFRQ--HPNDDLRYDAYLAYESRDCDV
AVEMAAI-LEGDHGLDIYIHDRNAPVPGDHYDSIFDGLGRSKKVILLITDHALRSESWSF
ETDLSL---SIKGKGKILCVVKGHLSIGRLNRKLRYLMADDTYLVWPEDNDVEKTFWRHV
AVAITSKNG

**>Pau-TLRγ15**

FLAYLPSIEVIELQDNLLGLEMPHQFARVFENVTTLTEIDLTRNYLHNLTAECLTGNENL
AKIHLANNKLDKIGL--VEKFPMLEFLNLSKNAILFLSSSETSALDSIAIVDLSGNIMLC
SCATLNFLEWLRTA--SVTFPKKSSYTCTYKGK--TRNLEEFDYEDFRECFSITVLTSSL
VA--GTVLVLSVVIGWYRRWHIRYIIY------KFRQPPEPNDGHRYDAYLAYESRDHDK
ALE-MTAVLERDHGLKIYIHDRNAPLPGDHHDSIFDGVGRSKKVILLITDHALRSQWWSF
ETDLS---LSIKGKSKILCVVKGHLSIGRLNRKLRYLMADDTYLLWPDNENAANTFWRNV
ALAITSKNG

**>Pau-TLRα6**

-LRSFPKLP-LHLEDNFLEHVE--------------------------------EYLKRV
TKLFASRNNISDVSEKVLKKMEKITVLYLDSNKLTTLPEYIKKMTRRLTHVNIKHNFFEC
DCNTLWIKYWLRENIA--KVIETQNILCSSG--TKGKSIIYVP--DNKVCEL---VAAIV
LAVTLTIFLVAVVSVYKHRQEVKVLLYKLQWHPK--E-LDEDETKIYDAFISYCQKDYRF
VCNDLRSSLEQNPPYKLCIHERDFMAGAPIYENIMNSVKLSKRMIMILSNDFLLSEWCMLEFRTAHQKVLKEHSRY
LIIIALGDIVSRNTDEDLQAYLKTNTYLTVDD------LFLERL
RYALPRPTS

**>Pau-TLRα4**

-LTSLPKLPRTNFSNNHLTEVT--------------------------------
AYFPNIIDLDISGNNIRNVSDAALIQLRNIKVLNVAKNKLTTMPRRLLESSANSTAISLSGNSWNCTCSEVWFIKWVL
SKSS--VVTDSHGLFCSHP--MRGKRFSDDV--
VTERCDADYTAVAVSVGVSSTVLLIVIVIVTVFSEDIKVILFKWNIDIR--N-
VDNCSDRNFDAFVSYSSLDGDWVRNHLLPLLENDPPFKTCFHERDFIPGLPITENIIQAIQKSKRTVLVVSKNFIDSE
WCQFEFLTAHKTFLETKENKLIVIVVESVNLRSLNPKLRAYFNTKTFLKVTD------LFKEKLYYAMPRLME

**>Pau-TLRα3**

-LTSLPAAP-FHLSKNSINKIE--------------------------------DYLTRV
FNMDLSYNNISVIDEDAFQNMKQVQSVDLRGNGLTTLPLLLKQGTRNLQKIFLGENKYNCSCENAWMKNWLKRN
SN--ISAGLEDIVCDSP---KKFRAIKVI--EADNCREKFTQEVVV
SICLCLLVLVLSIIIIIYRDLFRVLMYHFNVRIH-----EEETDATYDAFIAYSSLDGEW
VRNKLMPLLENRKPFKVCIHEREFLPGLSVADNVHRCMDLSRRNVMVVSQNFINSEWCRFEFQAAHAATMRNKS
KRLLLIMLEDIRQDNLGDDIKSYLKTNTYLEAEE------WFKPKLFYFMPSVKS

**>Pau-TLRγ4**

RWQATPSLKKLLLTGNRLYVMLRDKKTKHFKYLKNLEHLDLADNNLAEIYPDMFRELPVIKEIVLRRNRLFSATNLD
VSGMPLLKKVNFVNNKIRFVSEGALKLWHG-KSIDFSGNPFNCSCHFLPFLEWFNNASPTVTLLNSDQYLCRS-----
GAYIKNVDIKRLNQCKKTWRVISITVAIGVALSITFGGVLYRYRWTIKFWIVFAARRSR---
EVDRCRKFRFDAFVIYSSEDRYWVHDVLRTKLEDGNDFGLCIHYRNFLPGPPIEENIIGAIENSRHCILIVSRNFLQS
EWCIFEMHMARNVFRQQQKDVLILILLEDVPVQDAPLTLVNLLRTRTYLKWPADDVGQEAFWETLKDTLRQEPE

**>Pau-TLRα5**

-LTNLPKLP-LQLSDNRIEELK-------------------------------DYFHRL

LELDLSNNGLRTMSDIALVKLTNITTLKLNGNRLRTLPRSTETWSQSLRQLALHDNLWECTCDTMWFRDWLIQLGS
--VVQEPDSIMCFKD--EEWKPIKKA-----ILC--DYIPLAIT
VSSVSAVLMLAAVLMYIYRMEMKLLIFRLNWHPR-----TEILNKKYDAFISYSEEDSMW
VRRLIQLLEVDDPPYITCFHHRDFIPGVSTAANIEMAVHDSQCTIIVLSPAFVQSEWCMF
EFQVAHACLMDNEIGKVIIIIKEDIEVKKLQPDLKSYLRTMTYVKASD------WFSEKL
YYALPQKDK
**>Pau-TLRγ1**
ILQNMTSLRTLILSDNSLADKLADEYGSLFQNMTSVVEIDLSYNGIYVLHSNTFYHLKNV
RKIILRNNRLASLPSEHTENLTVLSFVDMASNKIQYLSKAFLDSLNR--TVLLSGNPFNC
SCGMLVFLHWLADYDDEDKIQDYRKLHCHRKPRLH---LSDFRFADLEECT-LWIWLSII
TMCTLAVLTVCFGVTYHKRWVIRFWLVATR---KKYNRL-PTTQYTYDAFLCHSSEDVRC
V-ERMRERLEEGSRLKLCLYYRDFPLGVPIIECVNEAIADSRYILLLITKNFIKSQWCIY
EFFMAKTKVFCENLSRLIIVVLEELTNDVLPRTLQSVMRDNVYLEWTDDVQGQEHFWQRLEECLGTEPP
**>Pau-TLRγ12**
LFRAIGKLEHLFASRNRIGLLTSQDLSATFSSLPNIRTIDLSLNQLSSIPESMFSLCPHL
ERLNVQRNGMKSVNL--FANLQSLKFLDFSHNEISGFTKEQTIDL----ALQMNNNSFEC
SCNNVPFIEWIQHESSNDTVLYKENLTCLYKDG-REEAVISVDLGGLYECIKIIIIISTL
----ISVVLCTALVAWRFQWHIRYWVYILRMKRR------DDV----------SKKXYDLALS-VLHKLEE-
MGLLAFFRDRDTDLGVCVLDECFRGIESSRKSIVCLTENYLNSGQRYF
ELRMSMLR---GKGFVIPVVVGDVALEKLSKPLRHLLRDGVYFEWPTLESEEKDFWKSM
LKAVLTPKG
**>Pau-TLRγ11**
MFRAIGKLEHLFASRNRIGLVTSQDLTATFSSLPNIRTIDLSLNQLSFIPEGMFSLCPHL
ERLNVQRNGMKSVNL--FANLQSLKFLDFSHNEISGFTKEQTIDL----ALQMNNNSFEC
SCNNVPFIEWIQLESSNDTVLNKENITCLYKDG-REEAVISVDLGGLYECIKIIIIVSTL
----ISVVLCSALIAWRFQWHIRYWVYILRMKRR------DDVSKNFDAFISYADVDYDL
ALS-VLHKLEE-MGLLAFFRDRNTDLGACVLDECFRGIESSRKSIVCLTESYLDSDQRYF
ELRMSMLR----GKGFVIPVVVGDVALEKLSKPLRHLLSDGVYFEWPTLESEEKDFWKS MLKAVLTPKG
**>Pau-TLRγ9**
FFRDFPSLQTLQLASNRFGLFTESYLEAIFSNLPSIRKIDLADNLLTTVPKAMFSNCTSL
VTLNLRYNPLVTFEF--FSLFPQISYVDVGDCKIQEFKAYQVKFFSSL-KVNVSGLDLDC
NCENKEFYEMIQKNKSLADLEGKQELACTRDGV--RVKLAHLGLSGLESCMYIFVILCVT
---VVSAILISVVIVLYCRWNIKYLVHLTKRKLK-----NQANALYYDVYLSFSEDDRDT
AFQ-LFTGLNN--GLEVFYWPRNSRPGTCQFEEIFEQMGLCKKIVILITASTENSAMQNF
EIRMSLPR----GKGFVIPIVKEDYVIGKLPGPIKNLLRQDLFFLWPEQEKDQEMFYRNV
KRAARSKDG
**>Pau-TLRγ8**
LFRAVPSLQTLLLAVNRIGLFTETELVAIFSNLQNIKEIDLTDNMLTTIPKVMFSNCTSL
VILNLQKNPLLTFEL--FSLFPGFTFIDLSNCEIQEFKYFQTAFFSSFRVVNVSGLSLSC
NCNNKEFYDMIRNNKSLVDLEGREELTCTHGTE--RIKLVDLDLSSLESCWYTFLIVCVT
---LTSVVIIGVVVVLYCRWNIKYLVYLTKNKLR-----NNANIFEYDLYISFSEDDRDI
AFQ-LFTGLHNK-GLDVFFWPRNSRPGSCVFDEIFEQLDGSKKVLVLVTSSTEN SVTQNFEIRMSMAR----
GKGFIIPVVTEDFVVCNLPQGIKHLLRHDLYFLWPEEDEEKE EFWKNLERAITTKRG
**>Pau-TLRγ3**
SYLPCPNLRKLILAGNRLYVMLRDKGTKHFANLPNLEYLDLANNNLTELYPEMFSELPAI
QTIVLRGNRLFAVANMDISDMPSLKKIIFARNRIQFVSEGALQLWHG-KKLDLSQNPFNC
SCQSLSFLRWFKNVSSTVTFLSPHGYLCRDKFHQKSEYVGEVDLKRLEECRKDWIVISITVSTGVALLITLIGMIYRH
RWTIKFWIVFAARRG-PINSLDRQRRFHYDAFLIYSSEDRHW
VHDVLREKLEEDNEFGLCIHYRNFLPGQPIEENIMYAIENSRHSILVLSRNFLKSEWCIF
EMHMARNIFRQQRRDILILILLEDIPVQDSPLTLINMLRTRTYLKWPADDVGQEAFWEML
KQTLKKEPG
**>Pau-TLRβ1**
---------------------------MFEGLVKLKVLDLSYTNLKGLPERLFKDLTGL
ERLILRQNQLSGWNDVVLRNLKNLRSLDVSMNQIRTINQSSLRPVSTLNHFQAFSNPYICDCNLAWYVDWVRQMH
GTLKISYKIPYNCSN---LKHKSLLQYRPTFFE-CHRLVILCG SGFG-
LFVVILAVIGLLYKHRWYIRYWIFLLRSRRSNHLEETDRLLYTYDCFITYSGD
DSDLVTQQLLPKLENEFGYKMCIHERDFKLGREISENIAESI-------VVLTQNFVKSE
WCKFEVNLAHANTLHNARQSLIIILVEDVSFEHMTPILRFLMRKKTFLEWSNDTQGQRVFWERLKDAIQQRGQ
**>Phe-TLRα**
-LNGIPE---VSMANNNLAVLNNNTIPDAFMNVDCILVLNLSQNKLTYLDASMFNGLKDL
RELHLQENNISTIMKDTFQRLQKLEILHLHKNSLTVLHEPSI---GSLKKLTLANNEWVC
DCEFAPFRQWLIEHMN--IIQDLINITCVIKEKSKNRKLIDLSLTNIEFCYESLRNALIS
VIIIFISIGVTSTLVYKYRNSIKVWLFRYGWRPY-----QDDFSKTYDAYVSYSDKQLNF
VLHELLPKLERAPQYKLYLRDRDLIPGGVQANDIIEAIEDSCRTLVVLSENYTTDEWCLF
EFQRAHYNALHNKNHNVVVIKLHDIQTEDIDKEIQLYIKTGSFFKRED------KLWEKV
RYALPDMRE
**>Phe-TLRβ**

--------------------------------------------------RFFKDLSQL
LTLELGQNKLQGWDPEIFKNTTKLQYFSVYSNNIGTLNKSSMHLLPSLKRFDAYSNPYVCNCDLIWYCDWLRNMQ
RKVTIRSDRPYNCSN---LKKRTLLSYNPTFFD-CHQLKIILPSG
FG—FVFVVFIAGLAYRYRWYMRYWLFLLRSRRNKHLEEHERLCYEYDCFVTYSG
EDSEWVIQEMLPKLEQEFRLRACIHERDFELGHDIYENIAESIENSRKVIVILTKNFVKSEWCKFELNLAHANTLHNA
CQKLIIVMKECVPMNIMTPLLRYLVRKRTFLEWSNDEQGRTLFWNRLNIALTTAAG
**>Ese-TLRα**
----L--LNNLDLSSNRISYIP----PRLFYKLEYLATLNLRSNQLTELDI--YFYLPRI
QTIDLTFNRISRFTNEVINNLPSLKQADLRNNLITSFDDYVLRLYRSL-TMRLDNNPLNC
DCAKI-FTQLLRNSVDTTNI---FRALCQT---FNGKSIFNFSLN---ACSSLFQIAGYV
IGLLLLLLMILYCLILAICFNCIPFFYVCPCKS-GVK-----RDKEYDLFISYNRANEKW
VKEQLVPFIKENENYILHYNNEN-KLDEVFGPYVKDIMSKSSCILFILSDAFLLKEWNNK
DLRQHLRYLITKEKTRFICVQMHDICDEEVEEYFTDKLQIPRFVSLENDE----LFWKKL
AYYLPKPKS
**>Pcau-TLRα2**
-QSEIPNVS-LRLDGNNVTTIHNSVIPGSFRDLNNLIALYLDGNEIEEIGDDQFNGLADI
KELHLENNMLVNISTTWIDVTPMFSMLALHGNAFSKAPEAIY---IRSSEYTLRQNPWIC
DCTDEFFLDWLRSNVD--NISDIGEMMCTIPRAITVIEILDF---EMVYCTAGFIAGFVM
LGVLFLTTVLCIALTHHYQHEIKLWLFKYGVRVR---DPESDKAKKYDAFISYHNSDEDI
ILREFVPQLEHETPYKLCVHNRDFLAGEFIAENIVYAVENSRRTIVLLTASFIDSEWCRY
EFQAAHNQAISEKVNRIILVVFEDIPKGKLDKNLEAYIKTNTYLRYDD------MFWSKL
RYALPAVRA
**>Pcau-TLRα1**
CLEKIPGLTKLSIAHTTIRSVV--YMRDFFKYHPNLTYLDMTGTRFSSLTTEAISSLDHL
RVLRLRDTGISSIPD--FARL-QLKELDLSYNNLMRIPVALL---DSLKHLDLRENPLIC
ECSTIDFMHAAQRFGLVGYLDDPDALSCTFSDQ--SIALRKVHIQ---DCG-VINIFAIV
MASLIL--LAIVVVTYRRRRYIAYYFHVTAVRLKRYEPA---GEYEYDAFVGYST-ELNW
IINFLLPKMENENPYRLFLEERDMPAYGMQVSNIVAFMDKSHTVILVITQTFLTDVYCNF
MLKTAAM------RNNVIIIFLETIATEEFPAELRVLQLHSTCLHWSENRNSQERFWKAI
EYAMPQDPS
**>Pcau-TLRα3**
-ITEFADWAEIFLDGNFLDDFN------------------------------GLNLEKPL
TILSLSQNNIDEGGLSLKEILTHVTYLGLTENNLTQLPDKDFMLAASVQVISLNGNPFRC
DCETSYLKRWFSNNAQ--RINKPNETFCTSGPLYRRTAIADLP--DDVTCDSTFPYVYLS
LLVVALLAGVA---------GVGVYVC------RGDDGDESTG-KEYDAFIAFSSQDFEF
VARTLVPGLEGRPPYRLCVHDRDFHAGKLIMDSIIQAIEVSRSTVLLLSNHFIQSNWCKL
EFQASFIEVLANPRYKLIVIVCEPIEMDSLEPDLRFYIKTHTYLEIKD------KFWEKL
CAALPRPLA
**>Hsp-TLRα3**
-LTKVPYVP-LFMDGNDVNRLPNSVINGSFVGVSNLRILRLDGNLLQNLNGFEFLPLGNL
HELYLHDNLLEFVAKATFAALGHLKVLTLHNNRLHRIPSDLF---QHLTELTLSVNSWIC
DCENSTVQVWAESISD--IISDINLTYCLLGIT--GENLSEFNDS---LCMENFLYLILI
LVLIFIICVILAFLLYRFCYEFKVCLYRYGWRIN-----MEDYHKKYDAFVSYSTRDELF
VLEEFVHRLE--PQFKVALQYREF-PSSSVADGIMDGAHKSRRFVIFITENFLHYVWKEP
ESKSAHQQVLWDTRNQVIIVMLTERPDDKFEPDLRLYMKSKTCLRWND------MFWDKL
YYTMPDIKR
**>Hsp-TLRα4**
-VSDLKEFEFMFFDGNFLEAFF------------------------------NLNLTKPL
LVLSLMDNNLRADSLSLKDILLHVTHLSLSGNNMTELPDKKFMQKRDVENFIITGNPFRCDCHTLYLKNWFQQNSD
--VIVHANATFCKFGPYYQQTPIMDLP—DEVTCGATLPDV QVNLATLLFAAPVT---------GVVVFLYNYRR—
QSVKENE GVGIKEYDAFIAFNSNDFDL
VAYTLVPVLESNPPYRLCVHDRDFPAGKLIMDSIINAVEQSRATILVLSNNFIKSHWCKL
EFQASFIEVLGNPKYKLVVILCEDIPIDSLDADLRYYLKTHTYLELND------DFWPKL
IAALPPPMG
**>Hsp-TLRα1**
GLFNIPNLKVVDLCSNNLTRVP----QKLFHDVPTLESILLVNNSISFIHREDFKNLPAL
QLVNMSLNVIEGISPDGFIGVDNLNTLDFEANSLVSFAANNIGFLSKLREVDLQGNVMKCGCFEISFSELLSSQ--
RLTF---TDIHCVTPENLE--QV--F------HCPKSWLLYVCI
VG--VLFLFVILIIIVRFCSRVKIACHRYGIRIR-----QQPKGKTYDAYICYSRSNEHW
VSSTLVPVLESRPPYKLCVHNRDRPAGDSSSNSMVNAIKQSKVTVLVLSDDFMTSDWCMVEFSPLHQSMSSY-
TNNIIPIVLENIESRNVNTEMKRILRNKQALHVDD------YFWDKL
YYMLPDAEA
**>Hsp-TLRα2**
--TAVPEIS-LHLDSNDLSTIGNSEIAGSFRDLSKLTLLDLEGNSLTDVGSGVFTGLQSL
QRLHLSRNDISHVDERAFEGLSRLSALFLDGNALALPAAALY---ANASQFTLSGNPWIC
DCSMEFFFSWLKVNVD--RISDIGSTLCTV-----EMPIMDF---ETAYCSSAFIAGLAV
LAILFLLTVVGMAVVYRYQYEIRVWVFRYGIRRR---YPESDKNKLYDAFLSYHNGDEEM

ILKEFIPRLEYERKFLLCIHARDFVPGEFIAENITQAAENSRRTIVLLTKRYLESEWCRY
EFQAGHNQAICDQVNRIILVVFGDIPKDKLDSNLQAYINTNTYIRYDD------RFWDKL
LYAMPDPPI
**>Rva-TLRα**
-LTTIPMLP-VYLDGNRLPSLPNSRINHTFNGLSQLRNLHLHHNQITILRGGEFSQLVSL
EVLDLSWNDIHSIHEHTFLTLTKLRVLNLAGNQLDSLITLPL---PTVSQLFLANNVWEC
WCNEERLTEWLVRFTA--RIQDIHHMHCYDRSQ--AL-LRDMPRE---RCSASFVVVGIV
LGCVCFLVIVLVAFVLRYRYEIQVRLYRFRLRLS-----EEDYEKICDAFISYSDLDEHL
VLGELAPRLEFSPKYKLFLHYRDHPLGMRTPESIIQGVQLSKRTILVLSENYLKREWAKL
DFKTAHQQVFKDKKNKIIIVLLGDIQMKDLDVDLRIYLKQNPCLQWGE------LFWKKL
YYALPDPEP
**>Hex-TLRα**
-LTSIPMLP-VYLDGNVLPSMPNSRINHTFNGLSHLKVLHLHHNQITVLRGHEFDQLVNL
EVLDLSWNDIHSIHPATFSQLTKLRVLNIAGNQLDSLVALPL---PSLTQLFLANNLWEC
WCNDDRLTDWLVRHSG--KILDIHHLHCYDRSQ--AL-LRDMPRE---RCSASFIMVGVI
LGCVCFVVILAIALILRYRYEIQVRFYRFRMRLS---SQDEDYEKMFDAFISYSDQDEHL
VLGELAPRLEYVPKYKLFLHSRDYPLGTRTPDSVIQGVQMSKRTILFLSENYLKREWSKLDFKTAHQQVFKDKRNK
IIIVLLGDIQMKDLDVDLRIYLKQNPCLHWGE------LFWKKL
YYALPDPEP
**>Pcap-TLRβ**
MFSNF-SLKELYLGDNKLGPAFEGNLGHLFDNLTVLSLLDLSFNDIDIFSIDQFSSLSAL
KVLNLNHNKVSIFPPDVFDGLKSLERLNIKANKITVLEAGSFQLMKKLKEIDFSENPLQC
QCDVMDFFHWINFT--NLTITHWNDYFC--PQR--NTSLKEFLIMEAEECLHNIVIICAI
TISSLVIFVLLCVLAFRL-YRFIYVRASVEVNTQKSTTIKKNKVKCYDAFICYTSKDADW
IPALFKEHLGEARKLRLYFHDNHKHIERTTSWDVMNKVDSSYKVVFISTKNFVQTDWFQWESMMLMF-----
QDCAIIVGLEDIPTMNMSYTLQWLVRTKPFITWPVLDTDIGLFWDDL
AIYIKER--
**>Lloa-TLRα**
-LEPSPDIP-IYLEHMEIPVVRHSEIPLAFNTLPSLQLLDLSGNYLMRLTGDELYRTNKI
TTLLLHNNHLMSLGDRLNEVMPQLKTITLHNNKLQDLPLSIEQ--KQITDITLGSNLFRC
DCSPRFIQYWFSSNLD--MIHDVSDIFCVENISNFGDDIFKIP--MTQIATASFLIITAL
LAVALITIGLICLAVLFLRKTKSVIVQRYKVPPF--GTHTTGSSPLFDAFISYSKKDEKL
IIDTLYRQLES-EEYILCLLHRDSPNYSTISDELINQMECAQSLILVLTQHFLNNEWKTL
QIKTSHQIFAKNRHKKLIALLGDGIEPNQLDAELGQILRKNTCIRMND------LFWNLL
HSALPVRIA
**>Ovo-TLRα**
-LKPSPDIP-IYLENMEIPIVRYSEVPLAFNTLPSLQLLDLSGNYLMRLTGDELYRTNKI
TTLMLHNNHLMSLGDRLNEVMPQLKTITLHNNKLQDLPLSIEQ--KQITNITLGSNLFRC
DCSPRFIQFWFSRNLD--VIHDMSDIFCVENISNFGEDIFKIP--MAQIATASFLIITVL
FAVALITTGLILLAMLFLRKTKSVIVQRYKVPPF--GTHTTGSSPLFDAFISYSKKDEKL
IIDTLYRQLES-EEYILCLLHRDGPNYNTISDELINQMECAQSLILVLTQHFLDNEWKTL
QIKTSHQIFAKNRHKKLIALLGDGIEPNQLDAELGQILRKNTCIRMND------LFWNLL
HSALPVRIA
**>Ael-TLRα1**
-LEH------LLLTNTSIDRVP-------------------------------------LAQLSLGRNAITEIGVETFAN
ASRLSFINLSHNGARSFRKNVTDSLESSTEIK-ADSSLECECLG--EREWLGSSAE----
TSVTNLHCLAPQINGGEKRHRLQV-NQEIADAWTIVLIAIFSILLVFIIVAIIVILRFKVE IQAFVFNFGVRIK---
LPNDVGDKIYDAFLIFSADDEDWVVNTLLQKLETAPPYR
ICIHYRDFVPGNPIIQNVMDSVANSKSTLAVISDGFINSQWCKYEFVTAFQQTLKNAAHKLCAILTQKIEPQLLKSNL
QFYLKTNTYLEKSD------MFWEKLFFSLPDP--
**>Ael-TLRα2**
-LEH------LLLTNTSIDRVP-------------------------------------LAQLSLGRNAITEIGVETF
ANASRLSFINLSHNGARSFRKNVTDSLESSTEIK-ADSSLECECLG--ERE WLGSSAE----
TSVTNLHCLAPQINGGEKRHRLQV-NQEIADAWTIVLIAIFSILLVFIIVAIIVILRFKVEIQ AFVFNFGVRIK---
LPNDVGDKIYDAFLIFSADDEDWVVNTLLQKLETAPPYRICIH
YRDFVPGNPIIQNVMDSVANSKSTLAVISDGFINSQWCKYEFVTAFQQTLKNAAHKLCAILTQKIEPQLLKSNLQF---
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**>Isc-TLR3**
-LTQLPTLP-LDLSGNKLESLDSN----------------------TA---GLAKKAPFL
RLLNLSDNLLSSIDPSEIPQ--GTDELFLRGNRLSRFPIDLVSKF-NMSILELAGNPWSC
DCEDYAFRQWAEAYTD--VVEDAEEITCAKGPN--LKRFMDL---GQKLCPS--LSYGLP
LLVLLIISLAASTAYLRHKRAIKVWLYRGVCSS-CIKEDDLDEDKIFDVFLSFSSKDSMW
AYEQLIPGVEA-HGFSVCTYDRNFKGGFLLQDIIHEAVSCSRRTLLLLTKNFVESEWCRW
EFRVAHHQALEDKINRLILVLVDELAPGLVDEELQLYMQATNYLRWGE------HFWDKL
IYSLPKKDA
**>Isc-TLR2**
-FTQLV-LRKLMLRNNRI------YIDGTFRNNGNLKYLDLAENRIEWLGKRAFSGLVNL

DLLSVSDNFLLHLNGSV-SHMPQLRILNFSHNA--------------IQ--TLYGNDFYN
DPELT-FYAYG-NNLS--TI---GAFQ-TSPKL----RM--F------ACA---------
--------LTASTAYLKYKREIKVWLYRGLCSR-CIKEDDLDDDKLFDVFLSFSSKDSNW
AYNELIPKIES-HGFSICTYDRNFKGGYLVQDIIHEAVACSRRILLLLTENFVESEWCRW
EFRVAHHRALEDNTNRLIVVLVDEVTSDAVDEELRRYMQVTNFLRWGE------HFWDKL
LYSLPKKDS

**>Isc-TLR1**

-LTDLPTSP-LYLQSNSISSLV-------------------------------APRWENL
TEVYLDENLLSNLDLTT---MRRLQILSLTNNRLRSLTPQLMGMLSSL-SLSLSGNPWIC
DCSTFSFKTWLRGHVY--MVKDYPDIACGD-----GVRINEI---PDSYCPVKQLAAVTA
ICVLAVLLVVVSVLYYRNRQTIIAYVYHFHNVFE-----DLDEDKTYDAFVSYSSADRDI
AMG-LLNSLESEEMFKLCIHERDWLPGYNISWNIVNSVQNSRRTILVVSKDFLE
SVWFQVEFHTAYYQMLEDRVDRLIVIVRGELPAETLDKELKFLLTTKTYLVWGE------WFWEKLKYAMPHRRQ

**>Isc-TLR5**

-YGAIPRVP-LYLDGNDMSHLSNSTINRTFNGLVGLQVLHLDHNKVTALHGFEFENLTNL
RELHLSHNRLATVSNRTFVSLKSLTILYLDNNYIVEFQVWNF---PSLSDLRLGHNPWSC
GCRFMEFQDWVHMFGA--PLKDSVAIRCRQNQT--GP-LLEF---NATACT-NYMPLLIV
LPSVVVLLLFVLVLVLVYRKQMKVWVHKYGVRLR---QYAPEVDRLFDAFVSYCK
KDEAFVAQILAPELECHPPFRLCLRYRDLPMSGYVAEAITEAVECSHRTLVVLSEQFLKSEWCRFELKTAHHELRC
NSRHRLVVVLLDDVAVKEMDADARQCLRSAVLLRWGD------RFWEKLRYALPDAAR

**>Isc-TLR4**

-HIAVPQLP-LYLDGNDIPALSSSTVNRTFSGLRTLRVLRLERNRLATLHGYEFDGLGEL
KELYLSYNHLTHVNNATFVPLKSLEVLHLDHNYILEMAIWNL---PRLNDVRLADNPWSC
DCHFAQFTDFLQNKGA-ELVRDLFSIQCVHNET--ALPLWEL---NTTSCT-DLVPLLVV
LAALFLLLVCIVVLAFVYRRHLSVWFYKYGVRMR-----PAEEEKLFDAFVSYSKKDEAF
VAQILAPELECQPPYRLCLHYRDLMAGGYLTDAITEAVESSRRTIVILSEHFLKSEWCRY
EFKSAHHEVLHSCTHRLVVIFLGRVSYKELDPDIRLWLKSSTFLRWGE------RFWDKL
RYAMPDTRH

**>Dpu-TLRβ**

TFYGLNSLEYLNMDRCKL----TD--EAIFAGAPRLRHLSMRDNQIVSFGSNPFADATSL
VSVDLFKNRIRGWDTQLFAGSPDLDVLNLAENQISTVSKAMMADIANLSEVDLLGNPIDCDCNLEPLRRYLEDTED
NLLI---KADHCSSPDKWRFQPITSFDPD---HCYYSFVIALYI
LIPTVCLSMLVGYAIYRSRWVIRYYMFRKRLSQ-SSSSMAEEGNFKYDAFVSYS NVDHAFVAR-
MVGMLENPPHYKLCVYERDFTAGNVLNDCIMQSIATSRKVVLVISE
NFIQSHWCLWELHLAQHSLLEDKRNGLVLVVVGKLKLNQCPPTLRFLMKTRIYLEWDLDPSKQRVFWERLRDALA
QKPD

**>Dpu-TLRα3**

-LNEIPRLPRMNLSSNSI------QIPNSS------------------------DCYPDVTWLDLSHNGMDESS
MSDWQNLPKLNRLDLTHNNFNSIPNGVVDSWHNL-TYNLNGNPWKCDCTNLALL NFIYGSWK--
RLEDFNQMKCDN-----GQKISEL---SVELCP-SVKYYTIPLPILALLIVCVGIIV YRNRRVIRAWLYRQLCLWK---
EEEENDERIYDAFISFSHHDEIFVNEVLVPQLERPPHY
QLCIHYRDWLAGEWIADQIVRSVATSKRTIVVLTENFLDSLWGKLEFRTAYKQVLTDKRMRLIIIVKGELPPDKMDQ
ELQTYLSLNTYLKYDD------FFMDRLRYALPHNTS

**>Dpu-TLRα2**

PLNDLPGIP-LYLDGNNLTELSGSTLNRTFHGLGALQVLQLADNELEELRGSEFEPLDHL
RELYLQNNKLRFISDTAFVHLRSLQVLRLDGNRLLTFPLWRL---PHLNQLSLGLNPWSC
ECRFLAFQQWIAAHPQ--QLVDSDSLHCLMGDQ----QLIGF---EFNSCSADYLPVMAA
GICLFLLGLIAVVLVFVYRQTVRIWIFRYRIRLS-----EEDKDAMFDAFVSYSLKDEQF
VSQVLAAELEHESSFRLCLQHRDFPTSHPGGDPLTLGLAASRRIVLVISQSFIESEWTRPEVRTALTGFLRLPRSRL
VAVLLTPWTDDQSDPELSLLLRSSIIIRWGE------NFWSKI
RYYLPDPTP

**>Dpu-TLRα1**

-FDDLN-LKTLWLDSNKL------KIGKIFKNIPQLISLQLGSNVIKQLEIGAFSNLPNL
FQLNLQNNQLDILPSDVLQSLANLKYLDLSNNKLTIID-------RNL-TYSLSGNPWRC
DCSNLALLKFIYGSWK--RVEDFNQMRCDN-----GLFFFEL---SVELCP-SLKYLTIA
MPVLALLVFCICTIFYRSRRVIRAWLYHQFCLWQ---EEEENDDRIYDAFISFSHNDEKF
V-DELVAQLERPPNYQLCLHHRDWLAGEWIPDQIVRSVASSKRTVVILTENFLDSF
WGKLEFRTAYQQVLKDKRMRLIVIVKGELPPDKMDTELQTYLSLNTYLKYDD------FFMERLRYALPHKKN

**>Dpu-TLRα4**

-HPNLPRIP-LYLDGAQLRALSSSIINRTFNGLRGLYVLHLEDNRIRTLEGFEFSDLESL
RELYLHNNAITSIQNRTFSALKHLQVLRLDGNRLVDFPVWNL---PELNALTLNDNPWSC
DCLFLALRTALHTAGP--KVSDASQLICGGSNR--NRSL---------LCV-DYLPLLVT
TLVAFIAVTLIILFVFIYRQPVRVWCHRYGLRLS---SAATPDSKLFDAFLSYSAKDDAF
VQQMLATNLEYSPTYKLCLQHRDCPSGGGLSETISQAVDSSRRTVMIISPNFIKAEWCRFEYKSALHQLFGTSRKR
LIVILIGDVTHKDLDADLKLYLKTNTYLQWGE------GFWDKL
RFALPDPVQ

**>Ppr-TLR1**

-----------------------------------------------------------------------------------------------KSHIDSL
SSLEYLDVRDNEFACSCDLRWFQTWMTQVP-KMIIPNKNSLHCRSPTDMTQDSVA NYTTPWIK-
CDNFIVVGGVSV--FVVLAIVITLLVGLKRWEIKYWWVFKKARM-GWRK LRDS---
EFDAYVCYHSEDEEWVTQTLQENIEGNVNFKLCIEERDFILGRQHLENF
TDLLNKSHKVLIVVSQNYLKSLWCRFEVGMAQLKLYEDNRDLLIFILLDNLKRKDMPRALKCLMLNSRVLPWPKSS
QMKSVFWMKLKLALQE---
**>Ppr-TLR2**
ILTKLPNLSKLDLSSNELGS--SSILPYLFKNLSTLRELDISDNILRTMHEDMFNSLLHL
EKLVIRHNYFKTLPTNIFKRLVNLRSLVMSTNNLCGLYKDQISPLISL-RLDVRRNSFYC
SCSLRWFQNWLQTT--RVWVDDKYKMRCNSPSDQWSNTLINFTIPWYR-CDNTIMASTSV--
SVLFLIISIVILLIFFRWDIKYWWVFSKVSIRGWHHF--
SEEKEYDAFVCYEHSDEDWVMKELLENVEKNNTFKLCIHERDFIPGKRIVDNIERGINLSHKVIIIVSSAYLSSQWCE
FELDMAHIKLTKKKK----------V-----------------------------------
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**>Ppr-TLR3**
----------LLLGMNNLTGFINSETPPLFDKNSYLKSLDLATNGLHVVHEKTMKSLPNL
QYLNLSDNFLSDIS---ISGMLQLIVLNISKNNWKDTPTELIQSLQKLNCLDISSNPLTT
ECEIQEFIQWSLYT--NVTLTKYNKFECILKNN----HV--FSETVIKTCNSGMFLAIGL
CTSFFILSVIVLTITYRNRWTIKWWLFLARKYLRLREELAEQRNYQYDAFVAFSADDITW
LKSDLIPELEMDRGLKLCIHHRDFQLGVPIEENIVNAIANSRKTILLITNKFVHSNWCMF
EVHMARQRLFDEGKNVIIAILLEEVNIGKLNRTLRNILTSNTYLEYPKNEDGQQLFWIKL
VDALRSNKD
**>Ppr-TLR4**
LFSCLKNLATLLLQGNNLGGVITDLHGDLFSSKSNLVDLHLDDNNVETLPVNLFKNATSLKRLSLSKNTIRHWHERL
FRKTTSLEYLNLAHNQISLMNKTSLPNLNILKTLNLTANPFACTCDLIWFHDWVQNT--
KVNLPGVEDYTCDSPQIFQGVPLKEFDPNKLV-CWEKLIMY ISFPS-
LIAVILVSFLIVYKKRWSLRRYWFIMKMRARRKRLMEE—GLEFDAFISYCTA DKDWVEQTILSKLDKKA-
FKFYYDARDDIPGKGIYDNLQYGFEHSRKILIILSTEYFEDK
HADLELQLIPEIEVDAREDKVIFVFKEDVYVNKIPRSIRRKVDNDDFLTWTDDQAVQDLFWGRLHEELSK-PQ
**>Cs_Toll4**
SLIDMDNLTTLLLQNNHLGDSLRDVIGQTFSSQKKLKVLNLSKNSIKALPYLIFKNQVSL
KNLSLARNAMTDVS-FSLKTMKMLQFLDLSDNQIEYVTSENMGYLDQIAH LNLSGNILACMCDNQQFLSWIATT--
KVHIIDRGQLKCLYRNKT-TLSLSRIIRSQLKDC
SLWIVMTSCVTGFGLLLILSLITLLYHRRWQLRYLWYIGRKKIDPFH--HDSRLPQIDVY
ISYEQHDVQTVTDYVYPFFERRG-YIVKIRE-EFEATDKLYRVIPDTVNKTRKVV
VFLTPSYCKDYWNTFEFNIAAYEGIYTKRNIIIPVLIGDFSDQNFTPEIRSFVNSKIVLRFPSQAHRINTFNEQLEHWL
Q----
**>Cs_Toll13**
TFKYLPKLIALEVSYFNMFDMPAQSINTLFSPLSNLKYLMCYNCQIRDDPKLFLSNKSQL
NRIKLDRNYIENISNDTFKSNPLLKTLSINMNKIGHLKASEIDFLNSLDSLDLSHNPFIC
DCDLEWFITWLKST--KTAKVEYQNYVCAYPANMAGTKLTDVHYTYRE-
CHPVWEWVGIVGGPIAVVLAIVSFVLYRKRWSIKHYIYLMRKRR-NYILV-
DGENFLYDAFVAYNQEDSDWVREHLLPVLEDEHQLKLCIHERDFRAGILINDNIVTCIEQSKKIIIILSNEFAKSGWC
MFELRVAHSKHIEDE-MELVVILLERINGRNMNN SMKTLLETTTYIEWTEDQHGQLLFWNQLKASMNK---
**>Lrug-TLR2**
-FLRIPELQK-------------------------------------------WRYDIPKLIYLDLSYNDIDRIDINGFPDDG-
LGRINLQFNNITTIRSEDIRA-LEA-IVDISNNPINCGCG-IKLYEF------LGNYEYIR DLVCHSP--LKGRKIRNLT--
QKEICPTH-MVLIVSLCAVVVILGIIIIILL RYRREVVILVYRLHI---
PCQPVDTYDSKNYDAFISYSSKDDDWVLRTLVQRLENEE
KFKLCVHHRDFEIGAAIADNVVQSVEDSRHTVMVLSRNYVDSEWCIY
EFRTALHQSLIERQKHLIVVILEDVPKSELDPDLRKCLETFTYIQVGD------LFWDKI
RYSLG--HR
**>Ppe-TLR1**
VFKNLSSLKTLNLSKNRLKYMVEDKYGGMFEGLDNLVTLNLENNDIEGLSPVIFLHLTNVQNLLMSGNRMAHWDK
ELFTNTQHIKNLDLSRNKISVIDEHALNNYSNFKTLNLEDNPFACNCELVWFCKWANRT--
KVTLVKFNNYTCSSPKSRQGVLLINFDWRSLV-CFNPYI IAGSVVG-
GVFLMTLIVVMLYRCRWRISLCCYRCGQRC-DYHYL-E-
EDKRFDAYISFDKKDNSFVQEVIMNQFDRNGKYQLCFEPRDFRLGSSIVGSMCVAVENSHRAIIVFTNAYLASGRF
QMELDLLHNEHLDRSFGMIFVTTGPQLDFRLLPKWLHKSYEDGKFLVWDENSSAQEEFRQRLDRKLRTPPP
**>Ppe-TLR3**
VFQRLNSLKHLDLSLNQLGRLTQLQFVRLFQPIRTLEYLHLGHNDLTFLNAPIFEDMLAL
KTINLVENSLKVVQSNLFESSPSLERVLLSDNQISFLDAGMFRRMTNLSFLSIEENEFEC
DCALRQFRDWGHGD--GVMILGLHGERCFASDKRLDSRVTEYETEWIE-CDHEYIIAGALGL-
FFAFATLLAGLVYRYRYDLLWWLLKRRRRR----PT--TAGERYHAFVSYNSRDSRFTLS-MIRYLEDDIRFKISFDG--
FDPASFISDCI
VQCIERSEKIIFVVSRTFLQSEWCSYELRMGELKCFEERRNIMILIFLEKIPVKELPRSLRTLVRQINYLQWPVDERA
RDVFWKRLKIALSKDAK

**>Pps-TLR3**
YFANLTWLEHLNLEGVNLRDVNVDTPDCLFEGLDNLKVLDLTNTNLKGIPTRFFKDLRSLQELILRQNRLSGWNDV
VFDNLTALQFLDVAVNQIRVVNMSSLQSVKSLNRFQAFSNPYICDCNLAWYADWLRRMHATLKVTYQLPYNCSN--
-LKRVSVLSYRPTFFE-CHRLIIL SASGGG-LFILVMLTVTVLYQYRWYIRYWMFLLRSRRAKHVEEADRLIYKYDGF
VTYSGEDSEWVIRTLLPKLEKEYGFSMCIHERDFTLGRDISENIAESIEQSRKVLVVLTNNFVRSYWCKFEVNLAHA
NTLHNSRQSLIIILAEDVDMDLMTPILRYLIRRKTYIEWTMNDQGQILFWKRLKEAMQKRGN
**> Pps-TLR2**
ILKNMTRLKTLILSDNMLSDSLVDESGRMFKDMNSVETLDLSGNRIFILHVNTFKHLINV
KTILLKDNRLASTPAVNVESLESLEQVDLSSNRIQYLSNEFLQSVTK--SVRLTGNPFNC
TCEILVLLQWLAGSEDAMKLVDNTTLACSGDNIIRGAKLVDFHYKSLQRCI-LWIWLSVS
TILTISILTFCIGLAYRKRWSLRFWIIAAR---RKYERL-PSTNYTYDAFVCHSSFDAKW
M-NTLQKELEQEPNFKLCLHYRDFPLGLPIVECINDAIVNSKYIILLITRNFIESQWCIY
EFYMAKTRVFCENRSRLIIVILEHLPEAVLPQTLQNVMKDHVYLEWTDDPVGQQAFWERLRENLAAEPP
**>Pps-TLR4**
-LTDFPTLPDLNVSNNDLTQLP--------------------------------IYLTQLVELDATGNNI
GDISGTALLQMSNIKALYIRNNNLRKLPKALLDSHGNASVLTLGENPWDCSCPNEW FLKWMTSRGS--
VVTDVGDVTCDIP--VRGQRFSDDV--IKQNCETDYMVMAST
VGSITALLIIALVLVVIFRHDIKVILFKWDIDLR--A-EEQSKDRPFDVFVSYSSLDGEW
VRQKLLPMLERNPPFRTCFHERDFLPGAPIAENIMRAIQASKRTLMVVSKNFIASDWCEFEFLTAHKSFMETKQNKI
IVVMLEDVDTKSMDPMLRAYFTTKTFIRAAD------LFKEKL
YYAMPR-TE
**>Pva-TLR1**
----------------------------------------------------------------------L-----------------DLSHNSLGYMESS
VFQNLSGLKFLNISKNKFKCDCDLRPFRDLLHEA--TFHF---GQNPCYYPTSLKKQL VSNYSLSFIA-
CDHEMIIVLAVAG-FIFLTIPIPALIAYYRLNLKYWWYFGRRRA-GYRPL-
DGGVHRYDAFVCYSKNELSWVVRELVEELENNERFQLCIHDRDFDLGGDIVDNIIRSIDCSRRVIFILSREFIRSYW
GTFELNLALMEAIEKRINFIILIFFENIPKKEIPRHLQCFMRHVTYASWPQQARAREMFWMKLKLALRNREE
**>Pva-TLR2**
YFANLTSLDHLILNGVYLRALNDDKPECLFQGLGKLKVLDLAFTHLKGLPERLFKDLTRL
ETLILRHNQLSGWNDVVLENLKNLRSLDVSGNQIHTINQSSLRPVSTLNHFQAFSNPYICDCNLAWYADWVRQMH
ATLKISYQVPYNCSN---LKNKSLLQYRPTFVE-CHRLIILSASGFG-
LFIVILAVIGLLYKYRWYIRYWIFLLRSRRARHIEENDRLL
YTYDCFITYSGEDSDLVTQQLLPKLENEFGYKMCIHERDFKLGRDISENIAESIEKSRKVLVVLTQNFVQSEWCKFE
VNLAHANTLHNARQSLIIILVEDVGFEHMTPILRYLIKKKTFLEWSNEEQGQRVFWERLKDAIQQRGQ
**> Pva-TLR3**
YFAGLLTLISLKMSDLDMGKLS--DKVCLFEGLTELKYLDLHKVMLKNLPANIFVDLKSL
VYLRISGNKLLAINPVVFSSMLSLERLDVSSNLIQNINQSSLQPFKGLNYFEAYNNPYAC
TCDLQWYTDWLRQMKRKIIRKNMQYKCASPKKFKKKNLLTYNPTFID-CYEPFIIGTTV
GS-FAVLATIVVAVGYHYRWYIRYWLFLFRSRFAKNLREDERLVYRYDCFVTYCE-
DDGWVLETLRPKLEDEFGFRVCLQDRDFELGKSKVDNIDEAIQNSRKVLIFLTANFAMNSWCNFELSLAHANCLE
NDQQHLIIIMMEDVSPKYMTPILRYLVRKRTYIEWTGDEVGQNLFWQKLPDAIRSPNQ
**> Pva-TLR4**
YFSGRPSLVSLKMPGVNLHKQT—KSSCLFRGLFRLKHLDLHDVQLKRLPSDMF
QDLQSLVYLRLSGNMLHEINPVVFSML-SLARLDVSSNQIQNINQSSLQPFKGLNQF
EAHYNPYACTCDLQWYTEWLRTMIRKVTIRKYMQYKCATPKQIERKNLLTYDPTFLD-CYEPFIIGTSVGS-
FAVLVIIVVTVGYHYRWYIRYWLFLFRSRFAKNLREDERLVY RYDCFVTYCE-
DDGWVLETLRPKLEDEFGFRVCLQDRDFELGKSKVDNIDEAIQ
NSRKVLIFLTANFAMNSWCNFELSLAHANCLENDQQHLIIIMMEDVSPKYMTPILRYLVRKRTYIEWTGDEVGQNLF
WQKLPDAIRSPNQ
**>Pva-TLR5**
RYKIAPSLKKLILSGNKLYIMLRDQKKKHFKHLNNLTHIDLSHNSINELYPEVFSELSNV
KEIILRRNRLLAVTSMNITEMPSLKNVSLVANNIRVVPETSLRAWRG-KSFDFSRNPFNC
SCQFLPFLRWFNNVSSTVTLLHAENYRCGDEQKI---FVREVRLDELVKCTSAWIVISIA
LSICVALCITLGSILYRHRWTIRYYIVSAARRTRGHPPQ-MLRRFQYDAFVVYSSEDRHW
VHDAMRTRLEDGSDFGLCIHYRNFLPGRHIEESVIDAIENSRHSILVVSRNFLRSEWCIF
EMHMARNIFRQQRKDVLIVVLLEDIPVQEAPLTLVNLLRTRTYLKWPADDVGQEAFWEMLKETLKKEPE
**> Pva-TLR6**
LLKGLGNLKWLFLNNNQLGKNLLQEYSLLFGDTLSLKELHLDRNDISSLPGNLFHSMKNLEILSLRDNKISHWSPKL
FAPLKSMEALDLSNNLIALINQTSVHNING--AFNLTGNPFAC
TCDLMWFRQWVNIT—NISFPCIGQYACNSPHSLQNTKFLDWYPDPRD-CINPFYVG GSVCG-
TVLLMLVISGATYRRRWFIRLSWYKLTHRRRGYRSLNNADVPSFDAFVSFCE
EDRQWVFDTLMKTFDEDNNFNICHDERDFPPNLSTAGCIFGCIENSRKFIVVVSEDYD
YCGRLEIELHYALQEIMEDAEFEIIVLLKDNPHPSRIPKHVAHLVSDPEFVEWPSDNDGQQLCLRRLQTMLERD--
**>Ce_Toll1**
-MVPVVELP-IILSGVTLPQLRGTSIPKAFHTLPALKTLDLSDNSLISLSGEEFLKCGEV
SQLFLNGNRFSTLSRGIFEKLPNLKYLTLHNNSLEDIPQVL----TALSKISLSSNPLRC
DCSGEHAAEWFSLHRH--LVVDFPKVECWENVTNMGNDVFVMP--IEELRDYSILFVIIT

ISIAVLLCVLVILAISFIRKSHDAINQRYKA--S--NCSTSGSSPLYHAFVSYSKKDEKM
VIDQLCRPLED-EDYQLCLLHRDGPTYCAISDELIAQMDSSQCLILVLTKHFLENEWKTL
QIKTSHQLFAKNRAKRVIAVLGDGVDANLLDDELGQILRKHTRIEMRS------LFWTLL
HSSLPSRLP
**>Dm_Toll1**
-LTHVP-LPNLHLENNTL----------------------------LRLPSANTPGYESVTSLHLAGN NLTSIDVDQ---
LTNLTHLDISWNHLQMLNATVLGFLMKWRSVKLSGNPWMC
DCTAKPLLLFTQDNFE--RIGDRNEMMCVNAEM--PTRMVEL---STNICPAVFIALAVV
IALTGLLAGFTAALYYKFQTEIKIWLYHNLLLW----EEDLDKDKKFDAFISYSHKDQSF
IEDYLVPQLEHPQKFQLCVHERDWLVGGHIPENIMRSVADSRRTIIVLSQNFIKSEWARLEFRAAHRSALNEGRSRI
IVIIYSDIDVEKLDEELKAYLKMNTYLKWGD------WFWDKL
RFALPHRRP
**>Dm_Toll2**
-LAALPRIP-LYLDGNNMPELEASTLNGSLAQLVNLRVLHLENNKLTALEGTEFRSLGLL
RELYLHNNMLTHISNATFEPLVSLEVLRLDNNRLSSLP-------HSLQGLTLGRNAWSC
RCQQLRLAQFVSDNAM--VVRDAHDIYCLDAGI----K-RELELIANGDCS-YRLPLLAA
VL-VLIFLVVVLIIVFVFRESVRMWLFHYGVRVP-----FEDAGKLYDAIILHSEKDYEF
VCRNIAAELEHRPPFRLCIQQRDLPPQA-SHLQLVEGARASRKIILVLTRNLLATEWNRI
EFRNAFHESLRGLAQKLVIIEETSVSAEAEDAELSPYLKSVPSLLTCD------YFWEKL
RYAIPIESP
**>Dm_Toll3**
-LLQMPSLSS--------------------------------------------------s----------------------RVTYVDLRNNNL TALSQKNRSSINRL-
KLHLLDNPWSCSCNDIEKINFMKSVSS--SIVDFTEIKC-SN----GEKLVSIN--QHI-CP-
SDLFYYLALAISLVATIIALNFLIWFRQPVLVWFYHGVCLSA----RELDKDKRFDAFLAFTHKDEALL-
EEFVDRLERRPRFQLCFYLRDWLAGESIPDCIG
QSIKDSRRIIVLMTENFMNSTWGRLEFRLALHATSRDRCKRLIVVLYPNVKNDSLDSELRTYMAFNTYLERSH------
NFWNKLIYSMP----
**>Dm_Toll4**
-LSEIPQLPTLVFERNSLKKWP--------------------------------PGYSSV
TRFYLAHNRLSDIDQ------DKLEYLDISNNNFSALDDRVRGFLKRL-QLSLFGNPWTC
RCEDKDFLVFVKEQAK--NIANASAIQCIDT----GRSLIEVE--ETD-CP-SVLIYYTS
LAVSLLIIALSINVFICFRQPIMIWFYHEICLSA----RELDEDKKYDAFLSFTHKDEDL
I-EEFVDRLENRHKFRLCFYLRDWLVGESIPDCINQSVKGSRRIIILMTKNFLKSTWGRL
EFRLALHATSRDRCKRLIVVLYPDVEHDDLDSELRAYMVLNTYLDRNN------NFWNKL
MYSMPHASH
**>Dm_Toll5**
-LEELP-LPRLKVGNNSL----------------------------TSLPTSEHSGYANV
SGLFLSDNNLTSLGS---DQLPNLTHLDVRGNQIQSLSDEFLLFLNNTMTLSLSGNPITC
GCESLSLLFFVRTNPQ--RVRDIADIVCTKQKK----SFQQM---EAFLCP-SYLLISCV
VGGLVIVICLLTVFYLMFQQELKIWLYNNLCLW----EEELDKDKTYDAFISYSHKDEEL
I-SKLLPKLESPHPFRLCLHDRDWLVGDCIPEQIVRTVDDSKRVIIVLSQHFIDSVWARM
EFRIAYQATLQDKRKRIIIILYRELEHNGIDSELRAYLKLNTYLKWGD------LFWSKL
YYAMPHNRR
**>Dm_Toll6**
-YSEMPRVP-LYIDGNNFVELANSHINTTFSGLKRLLILHLEDNHIISLEGNEFHNLENL
RELYLQSNKIASIANGSFQMLRKLEVLRLDGNRLMHFEVWQL---PYLVEISLADNQWSC
ECGYLAFRNYLGQSSE--KIIDASRVSCIYNNA--SV-LRE----KNGKCT-GLLPLLLV
ATCAFVAFFGLIFGLFCYRHELKIWAHTNCLMNK---VDQLDKERPNDAYFAYSLQDEHF
VNQILAQTLENDIGYRLCLHYRDVNINAYITDALIEAAESAKQFVLVLSKNFLYNEWSRF
EYKSALHELVKR-RKRVVFILYGDLPQRDIDMDMRHYLRTSTCIEWDD------KFWQKL
RLALPLPNG
**>Dm_Toll7**
-TTELPRVP-VYLDGNNFPVLKGSAINRTFASLASLQLLHLADNKLRTLHGYEFEQLSAL
RELYLQNNQLTTIENATLAPLAALELIRIDGNRLVTLPIWQMHATTRLKSISLGRNQWSC
RCQFLQLTSYVADNAL--IVQDAQDIYCMAASSSGSLK-RELDFNATGACT-SYIPLLAA
AL-ALLFLLVVIAMVFAFRESLRIWLFHYGVRVP-----CEESEKLYDAVLLHSAKDSEF
VCQHLAAQLETRPPLRVCLQHRDLAHDA-THYQLLEATRVSRRVVILLTRNFLQ
TEWARCELRRSVHDALRGRPQKLVIIEEPEVAFEESDIELLPYLKTSAVIRRSD------HFWEKLRYALPVDYP
**>Dm_Toll8**
-YEQLPHIP-LYLDGNNFRELQHSVLNRTFYGLLELEVLQLQSNQLKALNGN
EFQGLDNLQELYLQHNAIATIDTLTFTHLYHLKILRLDHNAITSFAVWNF---SYLNELRLASNPWTCSCEFIDLRDYI-
NRHE--YVVDKLKMKCISGNSPASLPV--V------QCSNDYIPILVAILTAFIFVMICISLVFIFRQEMRVWCHRFGVRLN---
VDKNEREKLFDA
FVSYSSKDELFVNEELAPMLEMEHRYKLCLHQRDFPVGGYLPETIVQAIDSSRRTIMVVSENFIKSEWCRFEFKSA
HQSVLRDRRRRLIVIVLGEVPQKELDPDLRLYLKTNTYLQWGD------LFWQKLRFALPDVSS
**>Dm_Toll9**
AFDGIATLKYLYFERSNIKDLE--------KSLKNLQVLGLAGNNINALTPAMFQSLESL

EILDLSSNHVGNWYRSAFHN-SALRVLNLRSNTINMLSNEMLKDFERLDYLSLG
DNDFICDCHLLWYIPWLQRSYSKLRFEDYMVAKCSAPYHLDGDTLLDFQLQVDENCQSELHVTNTVIAVMLVGACI
LGFIIYLKRWHIHYYYSSLKSAAKKFTNIQRDPSAVYDIFISYCQNDRTWVLNELLPNVEETGDVSICLHERDFQIGV
TILDNIISCMDRSYSLMLIISSKFLLSHWCQFEMYLAQHRIFEVSKEHLILVFLEDIPRRKRPKTLQYLMDVKTYIKWP
TAKEDRKLFWKRLKRSLERE--

**>Ci_TLR1**

AFKHV-NLTC--IKFNQV----EQ-NGIMFSGL-MVKQLYFIRSNIRSISSSAFTGSVHL
RLLDVSYNKITGLEKDIFTNL--LEELNLRGNQIRVLDPSTFSSLVNLRSLDIENNRFLC
NCDIIPLQQWIIDKLYRILL---RNVTCSLHSSRSYVDIIEW---DSELCWK--KIVGIV
LGC-LLLSTACAVFGFSVRFQALFWYEMIKSKV-SYHPRNRSDVYEYQAYISC
DSVDEAWVVRQLLCAIENETPMKLCFPSRDFKPGCPKMVSAANNLRLSKHALVILSKDYVANSWTRFELSMVSE
MWRNSERESLIVVYLKEV--ERL---PVLGVRRNAWLV WPTDVADRPSFWMKLRRSLAK---

**>Ci_TLR2**

RFNVLPTIPRLDLSNLQL----NE--KISLTQLTRLTTLNLTGNKLTSIPL--QGLPRSI
ENINLSRNKISTLPATTLTCLPNLKQLDLRNNSFSTIQTQEVSIFLAVTSVLLKGNPLEC
NCKLRPLITWIQTNEKDLSTHDLKDLICFTPKRFEGRFIINLSES----CP-NLLIGGLV
TALLIIIIIIVNIYLYKKRKKQERRDI-------GFKDLEED-TYEYDAFVSYSSDDVEF
VYK-MLEEMEEKRERKMCIHERDFTPGRGIADNIVECISTSRRMVLVVSRKYASSA
WCQYEVQIALTELHAKRRRLLVPILLEDVTREQYAGSVTTILSAITAIQAPKAQRTWANFWNKLDKTLT----

**>Od_TLR**

QLKNL-NLRGVDFSMNKITHFC----IDDFVNLEDLEFFNASLNQITDIPNNTFSFAREL
RVLDLHANSIQELN---FANLPELRMLDVSENQIRTSVDPYL---GALEQLDASYNPFQC
DCQLKKFVQFVQEPGRIVGIQAQSRYKCQIPRLLGNLNLLRL---QDKVCENEFYLSILA
IS-IVVILVVVAVVSKNRRQRMKMKELSGRNRVR---AAKN-NIVKNDAAILCHINSQKW
VTDVMLPTLKQKPQEKLYI---DFIKSQVKNEKLRRCVEQNKRVIIIITTEFASSDACLF
CLQAIYDLTRRNRKDGIVLVVLEPIPWNSMPHALKILMAEKTFIQYPVEDVGRQYFWDALRASIYQERT

**>Sp_TLR020**

VFRQLSVLQELNLEYCQIGNL-----PLVFSGLESLQKLSLKGNNIQHIHDDVLSGLGQV
NIIDFEGNQIIYLDELIFSNNRNLTNLSLADNKLTRFNQKTFKPISSISSLDLSMNPIDC
NCDLKWLIYWINKP---IHLIDRDKTICSSLEPFREKPLLDVDPNEL--CILGLLFL-IP
LASIGL--VVISVLLYHFRWQLRYKLFLLKLAA-GYKEMRDHNDYEFDVNIIFGEDDEEW
IREQLRPALGERLQ-RNVFGDEDLVLGMHYLDSVHYVVSHSYKTIIVLSRAAVQDRWFIL
KFRTAMDHVSDTLTEFVVVVFLEDIPDDEMPFLARLYLNDGRYIHWTEDARGQECFWDELTKNLT----

**>Sp_TLR007**

VFQNLSQLVYLDMTNSRIHTLR----SGLFSPLSSLRYLYIGENNLGEVPGDIFNGLFRL
NVLTFQNNILSSLDPKTFAQTLRLTDLYLPGNQISTIKPGTV---NTS-RFDISKNPFSC
TCSLAWFRQWLDSAD--IDFKHADQTLCSGLKGLSKQPILSFHPD---HCGVIFLIAGIS
FTGIFL--FFITLLAYNRRWWLNHKLFLLKLAV-GYKEMAEADNYEFHLNLMFLEEEEEW
VDRVMKPALEERFHQNIIYGDKDLHLGMFYINAINDALDNSFKTVLLISNQSIRDAWCMT
KLRMALEHLNETGLDKIILIFLEDIEDENLPYLVRLFMSRNKYMLWTDDEDGQELFWAQFEKSMRAN--

**>Sp_TLR053**

IFTPLRNLVELDLTSCCIKQVA----SRTFANLTTLLQLSLQDNDLTSIPKDAFQGLQNL
QVLRLQNNLIKFIHQGLFMGTNELEQLYLQNNHISTVASNTF---SSL-RFNIAYNPLTC
DCQLAWFRQWLNEVEGKIDLAPKNQTRCSSLKVLVNQIIWSFHPD---YCGITMIIVSAC
FAPILV--LTLGILVYLNRWWINYKLYLLKLAI-GYHEITEPEDYEFQLNLMFHDDDEWW
VNDCMKPFLEQRMHERVIFGDADLHPGSFYLNAIYDVIENSHKTILLLSNQSVDDTWYMTKLRMTVEHMNDTKLE
KVILIFLEDIDDDHLPYLVRLLLSRNKYLLWTEDEEGQEVFWAKVQKSMRQN--

**>Sp_TLR039**

ILTDLLLLQELDLSDCQLTEI-----VNAFEGLQSLQILHLEGNQLLDLPHGVLWNMAHL
RNVYLEGNKLKYLDRDLFFNSSRLRNLTLARNQLTGLNHSTFKPIKTLLSIDISENEITC
TCNLKWLPIWLSGS---ITLLNEIDTRCSSLEELELKPLMSFKPAEL--CGPIALYCSLP
IVTTWI--IIVLVFAYRHRWFLKYKLFLLKMAV-GYREIRDFDDYEFHLNVMFAEEDEGW
VRYRLRPVLEELLE-RNVYGDNDLPLGMHYYDAVHYVVEKSYKTIVLVSRAAIQDNWFII
QFRTAADQVNDTQIENMVVIFLEDIPDVELPFLVRLYLSDRKYLSWKEDERFQEYFWQKLIKMLKRN--

**>Sp_TLR056**

IFQNLSNLQILRLDKCSLSVL-----IGIFIDLKSLVSLHLENNHLKVISTGLFDKLYDL
QYLLLNGNELTYLDSNLFKYLSSLRCLDASENRISGLNHSTIEPL-RLTTLGLSLNPLVC
NCNLKWLPGWLKGT---IELIDSMGTTCNTLEPFRGKQLITFDPRYE--CGPITLYSCLA
MIGFVL--IFAVGLIYYQRWWVRYQLFLLKLCF-GYEEVHDRGEFQYDIAIMLDEIDNEW
VNQHLRPALMERGD-RIVCGDEELMLGMFYLDAVHYATEKSFKTIFVISHAA
LQDQWFMMKFRTVLDHVNDVGTEKMILVFVEDVEDDELPFLIRLFLSDHRYLVWPDDERGQEYFWEELIRDLTRH
--

**>Sp_TLR044**

TFQGLQNLQNLEMDNSDITSLN----EDIFLNLTSLQHLSIDVNHIAELTSRHLADLRSL
VGVSIKSNEIKGLASDVFTNNPHLSYLYISHNHLTTVKEGTV-----LRTLDVSNNPFSC
NCEFTWFLNWINKA--EVSIIHPDQTNCSSLAPFKNQPILAFDPT---VCGPVWVYIITI
--FVIVTCIMICVVAYQRRWLINYKLFHLKILL-GRRDDHDR-DYEYDINLAFDDDDEQW

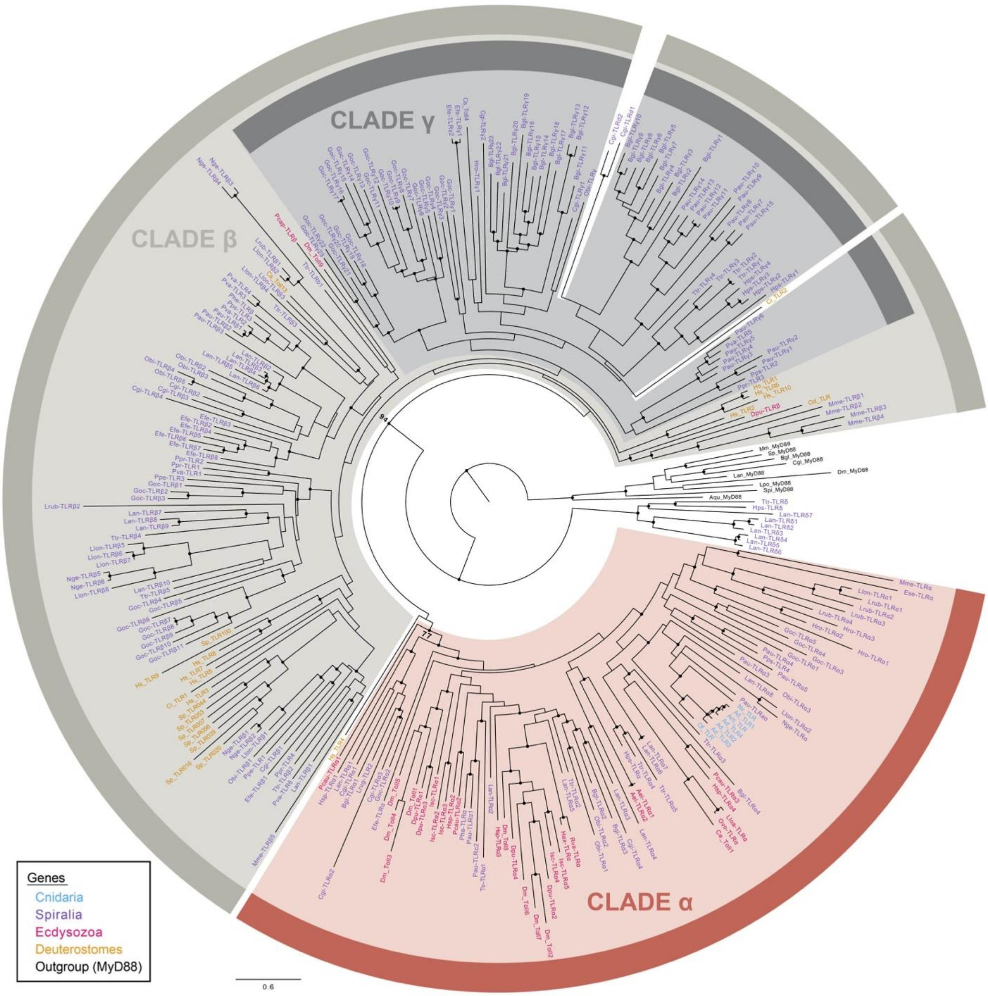
VRGILKPGLEERLDDRIVCGDDDLPLGMYYIEAITEVFEQSYKSILIVSNRAVDNHSFIS
KLRLAVDQMNEVELEKVILIFKEDIPDGRLPYLVRLFLSKNKYFRWSEDKYGQKIMWEKLVRELGKD--
**>Sp_TLR016**
VFNNLSALQVLNMSDCQISTI-----SGAFASMTSLTILSLQNNDLQILPLHIFDNLIHL
SIFSIGNNVLVYIDEALFAKMQMITSIDLARNQLSTFNQTTFSQITTLSSIDLSQNPIEC
SCKSKWLIKLLRGA---IDVQNGKDTTCSFMKPFGGEALESIQPNDL--CTAFPVYFSAV
FFAVIF--VIFIIFVYHFRWQLRYKHFLLRLAI-GYREILDREDYDFDVYVISTDDDENW
IHDQLKPSFQRFLYSRNVFTEDDLPLGMHRTEAVDHVLTRSFKILVLVNKAACADDWFLTCFRMAMDQVADTQTE
NIIVVFLENIEEDEMPLNVRLYMGGQGYVEWVEDDEGQKYFWKRLEKCLSKH--
**>Sp_TLR100**
TFSSLGNLGTMYLQHNNLYNMWETIHVPFLKSLRRLKYLNLCYNGFQNIPNNSLSNLPELKALFLCHNKISHLQDNI
INDL-PLTTLDLGHNQINLINQTLLEPLGTLKALTVSGNPFSC
GCDLQWFREWLDVT--QVHVDDNSHMICSSPPDMRGKLVIDFHPETLN-CDHTWVLVGVG----
SCMVFVTVALAVKFRFHINYCFNLVNARRRKYQRIKEDLPFLY
DAFVFFSHKDEEWVYNELVRHLEDDSGLRLCVHNRDFTLGRKILDNTIEAVDSSRFTLCILSADYLDSHWCKMEQ
EFAMANLIDR—DVLIIIALGEIPENKITKKLHKVMMKRTYLKW PMEPVQRNDFWMKLKTVLREPNN
**>Hs_TLR1**
----TKSLLSLNMSSNIL--------DTIFRCLPRIKVLDLHSNKIKSIPK--VVKLEAL
QELNVAFNSLTDLPG—CGSFSSLSVLIIDHNSVSHPSADFFQSCQKMRSIKAGD NPFQCTCELGEFVKNIDQV--
SSEVEGWDSYKCDYPESYRGTLLKDFHMSELS-CN-
TLLIVTIVATMLVLVTVTSLCSYLDLPWYLRMVCQWTQTRRRARNPLEEQRNLQFHAFISYSGHDSFWVKNELLPN
LEKE-GMQICLHERNFVPGKSIVENIITCIEKSYKSIFVLSP
NFVQSEWCHYELYFAHHNLFHEGSNSLILILLEPIPQYSIPSKLKSLMARRTYLEWPKEKSKRGLFWANLRAAINKK
--
**>Hs_TLR2**
----WPKMKYLNLSSTRIHSVT--------GCIPTLEILDVSNNNL-----NLSLNLPQL
KELYISRNKLMTLPDASL--LPMLLVLKISRNAITTFSKEQLDSFHTLKTLEAGGNNFIC
SCEFLSFTQEQQALA-KVLIDWPANYLCDSPSHVRGQQVQDVRLSVSE-CHRTALVSGMCCA-
LFLLILLTGVLCHRFHWYMKMMWAWLQAKRKPRK--
APSRNICYDAFVSYSERDAYWVENLMVQELENNPPFKLCLHKRDFIPGKWIIDNIIDSIEKSHKTVFVLSENFVKSE
WCKYELDFSHFRLFDENNDAAILILLEPIEKKAIPQKLRKIMNTKTYLEWPMDEAQREGFWVNLRAAIKS---
**>Hs_TLR3**
MLEGLEKLEILDLQHNNLARLWHANPGPIYKGLSHLHILNLESNGFDEIPVEVFKDLFEL
KIIDLGLNNLNTLPASVFNNQVSLKSLNLQKNLITSVEKKVFPAFRNLTELDMRFNPFDC
TCESIWFVNWINET--HTNIPELSHYLCNTPPHYHGFPVRLFDTS---SCKDPFELFFMI
TS-ILLIFIFIVLLIHFEGWRISFYWNVSVHRV-GFKEIDQTEQFEYAAYIIHAYKDKDW
VWEHFSSMEKEDQSLKFCLEERDFEAGVFELEAIVNSIKRSRKIIFVITHHLLKDPLCRF
KVHHAVQQAIEQNLDSIILVFLEEIPDYKLNHARRGMFKSHCILNWPVQKERIGAFRHKL
QVALGSKNS
**>Hs_TLR4**
IFNGLSSLEVLKMAGNSF----ENFLPDIFTELRNLTFLDLSQCQLEQLSPTAFNSLSSL
QVLNMSHNNFFSLDTFPYKCLNSLQVLDYSLNHIMTSKKQELQHFSSLAFLNLTQNDFACTCEHQSFLQWIKDQ--
RQLLVEVERMECATPSDKQGMPVLSLNIT----CQMKTIIGVSVLS--VLVVSVVAVLVYKFYFHLMLLAG-------KYG----
RGENIYDAFVIYSSQDEDWVRNELVKNLEEGPPFQLCLHYRDFIPGVAIAANIHEGFHKSRKVIVVVSQHFIQSRWC
IFEYEIAQTWQFLSSRAGIIFIVLQKVEKTLLRQELYRLLSRNTYLEWEDSVLGRHIFWRRLRKALLDEQE
**>Hs_TLR5**
-----PSLEQLFLGENMLQLAWTELCWDVFEGLSHLQVLYLNHNYLNSLPPGVFSHLTAL
RGLSLNSNRLTVLSH---NDLPNLEILDISRNQLLAPNPDVF---VSLSVLDITHNKFIC
ECELSTFINWLNHT--NVTIAGPADIYCVYPDSFSGVSL--FSLSTEG-CDEKFFIVCTV
TLT---LFLMTILTVTKFRGFCFICYKAQRLVFKDHPQGTEPDMYKYDAYLCFSSKDFTW
VQNALLKHLDDQNRFNLCFEERDFVPGENRIANIQDAIWNSRKIVCLVSRHFLRDGWCLEAFSYAQGRCLSDLNS
ALIMVVVGSLSQYQLHQSIRGFVQKQQYLRWPEDLQDVGWFLHKLSQQILKKQT
**>Hs_TLR6**
----VESIVVLNLSSNML--------DSVFRCLPRIKVLDLHSNKIKSVPK--VVKLEAL
QELNVAFNSLTDLPG--CGSFSSLSVLIIDHNSVSHPSADFFQSCQKMRSIKAGD NPFQCTCELREFVKNIDQV--
SSEVEGWDSYKCDYPESYRGSPLKDFHMSELS-CN-
TLLIVTIGATMLVLVTVTSLCIYLDLPWYLRMVCQWTQTRRRARNPLEEQRNLQFHAFISYSEHDSAWVKSELVPY
LEKE-DIQICLHERNFVPGKSIVENIINCIEKSYKSIFV
LSPNFVQSEWCHYELYFAHHNLFHEGSNNLILILLEPIPQNSIPNKLKALMTQRTYLQWPKEKSKRGLFWANIRAAF
NKEKS
**>Hs_TLR7**
VFDGMPNLKNLSLAKNGLKSF-----WKKLQCLKNLETLDLSHNQLTTVPERLSNCSRSL
KNLILKNNQIRSLTKYFLQDAFQLRYLDLSSNKIQMIQKTSFNVLNNLKMLLLHHNRFLC
TCDAVWFVWWVNHT--EVTIPYLTDVTCVGPGAHKGQSVISLDLYT---CELLILFSLSI
SVSLFL--MVMMTASHLYFWDVWYIYHFCKAKIKGYQRLISPDCC-YDAFIVYDTKDPEW
VLAELVAKLEREKHFNLCLEERDWLPGQPVLENLSQSIQLSKKTVFVMTDKYAKTENFKIAFYLSHQRLMDEKVDV
IILIFLEKPFQKSKFLQLRKRLCGSSVLEWPTNPQAHPYFWQCLKNALATDNH

**>Hs_TLR8**
AFLNLPSLTELHINDNMLKFF-----WTLLQQFPRLELLDLRGNKLLFLTDSLSDFTSSL
RTLLLSHNRISHLPSGFLSEVSSLKHLDLSSNLLKTINKSALKTTTKLSMLELHGNPFEC
TCDIGDFRRWMDHL--NVKIPRLVDVICASPGDQRGKSIVSLELTT---CVSVILFFFTF
FITTMV--MLAALAHHLFYWDVWFIYNVCLAKVKGYRSLSTSQTF-YDAYISYDTKDADW
VINELRYHLERDKNVLLCLEERDWDPGLAIIDNLMQSINQSKKTVFVLTKKYAKSWNFKTAFYLALQRLMDENMDVI
IFILLEPVLQHSQYLRLRQRICKSSILQWPDNPKAEGLFWQTLRNVVLTEND
**>Hs_TLR9**
TLRNLPSLQVLRLRDNYLAFF-----WWSLHFLPKLEVLDLAGNQLKALTNGSLPAGTRL
RRLDVSCNSISFVAPGFFSKAKELRELNLSANALKTVDHSWFPLASALQILDVSANPLHCACGAA-FMDFLLEV--
QAAVPGLSRVKCGSPGQLQGLSIFAQDLRL---CLDWDC FALSLLAVALG—
LGVPMLHHLCGWDLWYCFHLCLAWLRGRQSGRDEDALPYDA
FVVFDKTQSDWVYNELRGQLERGRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFL
LAQQRLLEDRKDVVVLVILSPDGRRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH
**>Hs_TLR10**
-----PTVVNMNLSYNKL--------DSVFRCLPSIQILDLNNNQIQTVPK--TIHLMAL
RELNIAFNFLTDLPG--CSHFSRLSVLNIEMNFILSPSLDFVQSCQEVKTLNAGRNPFRC
TCELKNFIQLETYS--EVMMVGWDSYTCEYPLNLRGTRLKDVHLHELS-CNTALLIVTIV
VIMLVLLAVAFCCLHFDLPWYLRMLGQCTQTWHRVRKTQEQKRNVRFHAFISYSEHDSLWVKNELIPNLEKEGSIL
ICLYESYFDPGKSISENIVSFIEKSYKSIFVLSPNFVQNEWCHYEFYFAHHNLFHENSDHIILILLEPIPFYCIPTKLKAL
LEKKAYLEWPKDRRKCGLFWANLRAAINNEQT
**>Nv_TLR**
-LHRLPKMP-VNLRGNAIRELP--------------------------------HYLGNI
TVLELSNNEIKELNMTFVDSLARVVNLAINDNKLKYLPRGVTNLTEGFRSLSISHNFFVC
DCYASWMRDWLANNTD--KIEDTSSILCASG--LEGLPIISVP--LSDNCSALSLLLAIV
LAVLLVLSVVAFVMTYCFRWEMKILMYHFNWHPR--D--DTDVSKIYDTFISYSSQDASW
VRETLQRTLESVPPYRLCIHDRDFEIGASIHDNILNSVRLSKRMIMVLSNHFIASEWCRL
EFRAAHQKVLEDRTNYLIIILFDDVDPSTLDDETKLYLRTNTYLSVSN------WFWQKL
FYALPKPLA
**>Ad_TLR1**
-LVAMPSVP-MFLQSNNIREIP--------------------------------GYLENV
TSLYLSHNQIQRLDEKTIDRLKRIETLFIDSNKLTTLPRNIENVS--FTKISLQHNFFRC
DCETKWMKQWLLREEA--HVDNIENILCHSD--VQGKAISRLP--DEELCLEAFKITAYT
LGGLLFVSLVAFAVGYKFRSEAKVFMYHFNWHPR--N--DLDPNKPYDAFISFSGNDYEW
ICNTLCVRLENDPPYKLCLHHRDFLVGAPIQQNIFDGIERSKRMIMTLSKHFVRSEWCLL
EFRAAHQKVLEDRINYLIIILFDDVDMAEVDDEIKLYMRTNTYLSVKN------WFWEKL
FYALPQNTN
**>Ad_TLR2**
----MPSVP-LFLQSNKIEEIP--------------------------------SYLENV
TALYLSHNNIERLNEKTIDRLKRIEILFIDSNKLTTLPRNIENVS--FIKISLQHNFFRC
DCKTKWMKHWLLRQEA--HIDNIENILCHSD--VKGKAISRLP--DEEVCPAAFKITAYT
LGGLLLVFLVAFAVGYKFRGEVKVFMYHFNWHPR--N--DLDPNKIYDAFISFSGIDYEW
ISNTLCARLENDPPYKLCLHHRDFLVGAPIQQNIFNGIEKSKRMIMILSKNFVKSEWCLL
EFRAAHQKVLEDRINYLIIILFDDVDMAEVDDEIKLYMRTNTYLSIKN------WFWEKL
FYALPQNSK
**>Ad_TLR3**
-LVAMPSVP-LLLQSNNIREIP--------------------------------GYLENV
TQLYLSHNNIERLDEKTIDRLKRIEKLFIDSNKLTTLPRNIENVS--FTKIALQHNLFRC
DCKTKWIKHWLSRQED--HIEHIDNILCHSD--VKDKVISNLP--DEEVCLEAFKITACT
LGGLLFMFLLAFAVGYKFRSEGKVFMYHFNWHPR--N--DSNPNKTYDAFISFSGNDYAW
ISNTLCARLENDPPYNLCLHHRDFLVGAPIQQNIFNAIEKSKRMIMILSKNFVKSEWCLL
EFRAAHQKVLEDRINYLIIILFDDVDMAEVDDEIKLYMRTNTYLSVKN------WFWEKL
FYALPQNSN
**>Ad_TLR4**
-LVTMPSVP-LFLQSNDIQEIP--------------------------------RYLENV
TSLYLSHNQIERLDEKTIDRLKRIQVLFIDSNKLTTLPRNIENVS--FTKISMQHNFFRC
DCKTKWMKQWLLREEA--HVDNIENILCHSN--VQGKAISRLP--DEKVCLEAFKITAYT
LGCLFLVFLVAFAVGYKFRSEAKVFMYHFNWHPR--K--DSDPNKIYDAFVSFSGNDYEW
ISNTLCVRLENDPPYKLCLHHRDFLVGAPIQQNIFNGIEKSKRMIMILSKNFVRSEWCLL
EFRAAHQKVLEDRINYLIIILFDDVDMAEVDDEIKLYMRTNTYLSVKN------WFWEKL
FYALPQNSN
**>Am_TLR**
-FVAMPSLP-LFLQSNNIREIP--------------------------------GYLENV
TSLYLSHNQIERLDEKTIDRLKRIQVLFIDSNKLTTLPRNIENVS--FTKISLQHNFFRC
DCKTKWMKQWLLREEA--HVDNIENILCHSD--VQGKAISRLP--DEEVCLDAFKITAYT
LGGLLLVFLVAFAVGYKFRGEVKVFMYHFNWHPR--N--DLDPNKPYDAFISFSGIDYEW
ISNTLCVRLENDPPYKLCLHHRDFLVGAPIQQNIFDGIERSKRMIMILSKHFVKSEWCLL

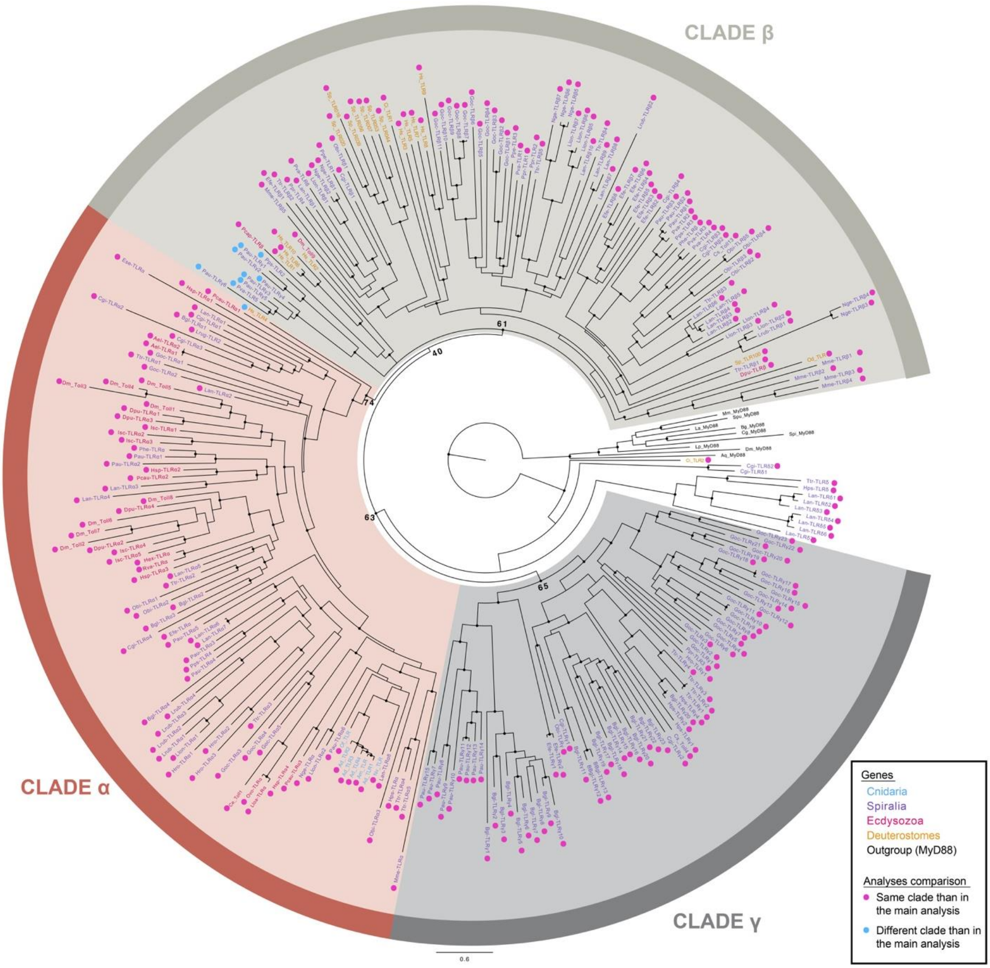
EFRAAHQKVLEDRINYLIIILFDDVDMAEVDDEIKLYMRTNTYLSVKN------WFWEKL
FYALPQNSN
**>Of_TLR**
-LTAIPKVP-LKLEDNNIREIP--------------------------------PYMENV
TALYLTHNKIQVLNKSTVRRFTRIKVLFIDSNKLTYLPKNIENLN--FTSLALHHNFFKC
DCTTLWIKHWLQRKQS--KILHIKNVLCNSE--TQGKAIYTLP--NEEVCKKTFKIIALT
LGGALVLTFIAFIVAYKYRGEMKVLMYHFNWHPR--D--DSDPRKIYDAFVSYSGSDHQW
VVNTLQERLEHDPPYKLCIHHRDFVVGAPIQENILNSVDQSKRMLMVLSRNFLKSEWCLLEFRAAHRKVLEDRMN
YLIIILFDGINMDELDDEMKLYMRTNTYLSVSY------WFWEKL
YYAMPQSTD
>Mm_MyD88
----NPTV----------------------ADWTLLAEE--------------FEY-LEI
RELETRPDPTSLLDAASVGRL-ELALLDRE-DILKE-----------LK--RIEEDC---
-------QKYLKQQNQ-----------------SE--KLQV-RVE-SVQ-----------
LG-G----ITT--------------------------DD-LGTPELFDAFICYCPNDIEF
V-QEMIRQLEQDYRLKLCVSDRDVLPGTCVWSIASELIKRCRRMVVVVSDDYLQSKECDF
QTKFALSLSPGVQQKRLIPIKYKAMKK-----DFPSILRFITICDYTN--CTKSWFWTRL
AKALSLP--
>Dm_MyD88
------KLRS----------------EEGYRDWRGISEL-------QKVDE---------
-----ANNPMLVLISQTVGHLEHLGIIDIQENLAKDTQ----RFI--MKAL------EAC
-C----FNNY--SSSNNITV---QSVQ-----------I--L---DEDRCV---------
MG--------------------------------------Q-PLPRYNACVLYAEADIDH
A-TEIMNNLESRYNLRLFLRHRDMLMGVPFEHVQSHFMTRCNHLIVVLTEEFLRSPENTY
LVNFTQKIQIENHTRKIIPILYKDM-------HIPQTLGIYTHIKYAGDS----NFWDKL
ARSLHRQPS
>Bg_MyD88
----DIDVMH----------------N-GYPNYGGLAEL--------------FSG-LEI
MEFERAKSPTALLLEPKIGKL-ELFQLDRI-DVLTD-----------CH--AINDEA---
-------KLFIKESKA-----------------LL--KIQD-TVTPGSTPPQ--------
L--------------------------------------TGKKTYYDAYICYNPKDLEF
V-RELISRFESKYRFTLFVPFRDDLPGMNEHAINAKIIERCRHMIVVLSKNFLQSEACEF
QSTFAQSLSPGARNKRIVPIKIEDC-------VIPNILRIMACCDFTK--DLWDWSWDRL
ARSITAQQS
>La_MyD88
----NPSVLT----------------DSGFKDWKGLAEL--------------FMN-DDI
SNFESMRDSTLILKDSMIATL-DIQQLERY-DILEDPT---------IK--QVENNV---
-------KSYLRQSKE-----------M-----IE--KLQD-EVSMEYD--E--------
YK-Y----MTT--------------------------DV-TGKAMYYDAFVSYAEEDIGF
V-KKLISELEKEYGLKLCVQARDLIPGASTNTVCAKLIERCTRMVIILSPKFLNSAQCDF
QIKFAQSLSPGSRGKKLVPIMYKCC-------DIPSILRHIAICDYTK--DLQEWFWNRL
AMSLKAP--
>Aq_MyD88
-----QNL----------------------SDWRTLVEL-------------GFTY-EMV
MLLRAKNSPTSLLEEATLESL--IVMMELENV----------SALQQVK--SIH-D----
RPPP--RK---PNSCS----SDPSTMVA--P-AVPSLKYVDVNLQTNSDCEQ--------
LSS-----LSL----------------------------DHGDGSDFDIFLSFAPADAEF
A-DEMRLRLIN-AGISVYIASEGLMPGQSFIDEVADKIRGCRKTIIILSPDYNQCSWCNY
EARLAHHKNPDPKRHTLIPIVYRKC-------EVPDFMSHLFYLDFSRDHQCEKYFWDRL
YKSVRHQ--
>Lp_MyD88
----NPQLTT----------------LTGLRDFRGVAEL--------------FDY-WDI
QNFQMTSDPFKLLIQNTVGKL-DLEEIERT-DVIDD-----------VK--YAEIDA---
-------HNYLRKQKW-----------C-----KE--SLQD-NVS---SCTA--------
--------LTV--------------------------DVNEGEVSLYDAYVCYTDEDIEC
V-HILSRQLESE-GIRLFIRDRDLLLGQMEYEAFARLIERCNRVLIVLSPEFLKSVECEF
QTRYATSLAVEQQQRKLIPIIYRSC-------DVPHLLRYLSKIDFTK--HIHDWVWHRL
IHSIKGERE
>Spi_MyD88
----RPCL----------------------NDYRLLAAK--------------YTN-EEI
KYLESLREPVELMTRRTIAEL-SLQQIDRP-DVVQD-----------LQ--YI--DS---
-------TPFEKEREQ------------------------------------------
--------RTN--------------------------NVQRTVRKSYHAFVCFAEEDKAF
V-DNLVKKMENNRNLHLCLPVRDFLPVGSHLETTALAIQRCKKFIVILSKNYDSSQGAIY
QAQIATSLAPGAKEKRIIPVLIDEC-------SIPRTLSHITYLDYLR--DEKH-FWNLL
CDTLTRN--
>Spu_MyD88

----RPRG----------------------CDWRDMAEE--------------FSYQLHI
QNFALESDPVKVLSASNVGKL-DIEKIERH-DVLHE-----------LP--FLEEDC---
-------KRW-KRTQA-----------------AR--DIQV-EVT-NFS--S--------
LR-G----ITL--------------------------DS-SGPPEMFDAYVCFAMADLEF
V-QQLRSQLESPHNYKLCIDQRDLLPGGSHALVTAEIINRCNKMLVILSPEFLQSPSCDF
QTKFAVSLEPGAMKRRIIPILVKPC-------DLPLIIRHITLCDFTK--DLRPWFWGRL
RKAMSIR--
>Cg_MyD88
----DPGVTG----------------D--YNDYQGLAEV--------------FTF-QDI
TNFQRQSKPTEMLYQPTVDNL-KLQPIGRSDDVITE-----------CA--LIKKDV---
-------DRYCKDITG-----------------SK--DIQD-SVSPNRSCDS--------
LG-L----VTI--------------------------DVEKGDTLYYDAFVIYNPKDLEF
V-KELAGKMEAPYNLKFCIPWRDDLPGGSRYEVSAHMITRCRRTLVILSSDFLKSAAADF
QLKFAHCLSPGARSKKVVPVFSAPC-------KMPGILRAVSFVDFTN--GLRDWNWPRL
NAVLRCPRD

**Supplementary Figure 2 – Second phylogenetic analysis, excluding the 150-200 amino acid region.** Parameters applied for the construction of this phylogenetic tree are the same than the ones applied for the main phylogenetic analysis (Figure 4A). Bootstrap values are indicated next to the main nodes and all nodes with bootstrap values >60 are marked with full black dots.



**Supplementary Figure 3 - Third phylogenetic analysis, excluding the 349-354 amino acid region.** Parameters applied for the construction of this phylogenetic tree are the same than the ones applied for the main phylogenetic analysis (Figure 4A). Recovered clades are named α, β and γ. Comparison with the main phylogenetic analysis is represented with blue and magenta dots. Bootstrap values are indicated next to the main nodes and all nodes with bootstrap values >60 are marked with full black dots



**Supplementary Figure 4. TLR sequences included in the phylogenetic analyses.** Includes the sequences obtained in the transcriptomic and genomic surveys, sequences from the literature, and sequences obtained from NCBI database.

>Mme-TLRβ3
MVESLSIFLKLVWLFCPYLVDGSVCPQYCHCSEASTDCTIIKGNPFPLSLDPKTKILQIDYKGNESFTLTGEMLDYY
PHLVELTIKGNLDHVAERAFQRSKLLRNLTIHYSTLKVLHYNIFGDENDLDTLILSDNRLLPQLPFEIFSSLTELRSLD
LSYNDFRVCNGKDSIGEEFKQLRQLQSLNLAGLGSEEDCKGISHNFFAPIEHVTHLNLSESGFFHGDLSILKPLSGL
TFLSLNNVSPFNKCPSKVQSLFGNLSTTLQLIEAERWRYQGPLDTLCYFNNETLSGLQNMTDLAFISFEYGDRPFA
TVLRKGVFRFLTHLQSLNFGWSRIATIEDGALDGLKISKLRLQHNPIGQQPIWGAGRNQPMESVLELDLSDCGIFTD
ASFNYNASFLLQSFPNLGKLGLSRNMLLSLPIFSNPEALASPSSIHTLDLFSNLIKRLSYQEMSALCHVMPALNNLYI
PQNEIVSIELLCPTLKALHAKENAIEFSQNPEDTFKYHNYQTIKNLTNMVYLDLSDNKISIIPNDIFYQMVKMSHLNLI
GNQIVSLDNNMFLYNANLQSLYLSNNRLTTFDSKLLNHCKALERLMISQNKISLFDVEFVNEIESKDSLRSVRIDEN
PFDCSCGQLFFQSWVQRSKKLKFGQDLQCVQPSNLLNQKISEYKQPQFQCVYKWVVDGVAGLVGLVLIIIVTYQL
RWYLTNIPYLTRSMRYLRQQDECHYDAMVIFNSKSNKDTDWVKELMRELEGGDYPQPINIQEPDGRENKIYIRVR
DDISGTITFEECSKVMNQSRKIILILSNSFLAETECISEVEFAGNELFSTATFNQGRVMILVLEELQESRIDLVRSLMIE
ANVIELLESTRNDPRKMREVWQKLKKFVNHQKPSAVRSRRDGYQPLLS*
>Mme-TLRβ4
EIYNIAPFNECPRLAKDLFGNLSSSIKFIQARSWRTDRKLKPNCTITGETLSGLTNLKQLSTLDFEYGDSIFGNTLLK
GVIQQLTQLRQLHLGWCRITELEDGALAGLQLTNLELTGNPLGNDQFWPNGYNRSMDTIDLLVLKQCTITAEDNFP
FYANFIVQNFPSLLQLDLSKNIMYRLPTFLKNGSLYTSNLSLSLNLHSNVLHQIKEGEVTALCQTFPNLKKLDLSDNY
MTLIETMCVSLQELHINGNNLYVNPEPNFKTIKSLRHLTYLDLSDNSLPSIPNDLFDNMPKLKTLKMISNLISSLDRR
QFIHNSQLRTLDMTKNLLETFHVSVFANDTLIKALSLRTNKISMFDETFTQFVDSTSTLTYLRIENNSFDCSCGQLYF
QKWANSSKKLQYGDKLICHSPGQLRNQRIVIYKQLFFDCYFKWVLVGLAGLVGIITTVLLMYRFRWYLAHLRFAAL
SVAERLVDIKQQDQCKYDAMVLFNSKSDEETNWVKRLLIELEGGEYSQPINLQEPDGRENLIYIRARDDITGDVNF
DSCCKIMKQSRKIILVLSNSFLREDECISEATFAGSELFSTATLKPERILILVLEELQEPLTNPVSSLLVETHYIDLYET
TRNDERKMRAIWQKLRRFVSHRANPDRSVETHNGEYEPLV*
>Mme-TLRα
SSQECYVSECRMTKFALLFLLALFTDTRAISTGCNIECESLPLVPPRWGHNSREVSNLAQKCVVQEKCNLDINDILF
NKTTHDVQDPDSVYISIDLHITCLDQASLEFTDTKMLNHSILATIRHEDCDITWESLAYLGTRVHLLHIETVVTPQSPP
PPPQLPADTAIPDGLTEISHLQLTFVNITDTLDIEPYLMTTQSSLRSVGSLSIQCFEGDRRANHNCTTPVVNFNHTKL
PDMLPNLQALTLTGVFPLNTTANLSFPWDLKSMALPLNLTHSKFKKQLYSDGFITQKGDNKFSRDLVVAGNMLIDI
SQICPYERHLNVLSIRYYGLRSIPADCFTPDHGEKSQLFYIDLSRNYLTELPSTLFRGLECLTDLYMAHNPITKLEIGT
FDDLSKLRTLSMDYNDIREVKNGTFTKLISLKSLFFHGNFKLTHIEPGSLPTYSHNLTFIDLRWCNLLKFPVDCVTLP
NLDLCDCDHNVNLSIKNLMEIISYFDPVRMYLVQPLAYYGGTYSHSDVAPMHETDQSGIGLRDCAVTSIDYNSSWP
IDQKKQLAAFLSFFQISLGKLHTDAPMLQCDCNLYDLQQFVYHNQATAPVSLLSGSKYSHALLLSASNFQTWKCH
VHPVLMLNFTEGSFLLMNSKNFVCQQDPTIICPERCTCYKGANDSRLIVDCYNRSLTAFPENIKIPSAMEELIVSLSHN
TITELPECDDPRFYWLRHVVHLNIQHNELTPQNIPIFDRFLRCMGKISYLFLAYNNIVYFPPSIRQKNFKALSITGNKI
TCCNGHWMKTWLQEQNETIWNSLTAHCKDQAHPIIQLDPDGFSCPGVVLYLAPIIISIALTIATMMTSVAVYVYSFE
LKIILFEKLNLHPFDRSSVDSESLDYDLYLMYNYADSPWATEKLLPGLEKFGYRVYVPERDMGIGEITAEARANAFA
STHRVLVVVSQKFIDSGESMKEFFHAHEHENSTTRKRYLVLVKLNEKINYRTYDIFKKYMSTNFFVSVKSRKFWYN
LRYWLPMVRERLPDISTHNNEQHDENQYHQNEAEDNQSDYNETEHNECSPLLGASNGHANMVV*
>Mme-TLRβ5
MKLLRSVITHSLWMAVLVETVQCGSRYSRESELCPTGCHCQGCVVDCKSRHLHSIPSPFSPDTCSIKLSKNFISSI
QAGAFSNLPNLTSVDLSNNRITEVDNKAFTNSPSLSSLSLASNSLQTVETSFFYPIPNIQILDISQNQLKSIPEIRSTG
KLKYLYLAGNQLTEFKFGPGYLTATYLTRITLSNNPKVTEIRRDDFKSLSKSTKVASLKLSRCSISSVESGSFLPFSP
YLVTLSLSQNPQLNSSTLQTILADFKDSTKLKSLDLSKLGLEGYVNASTFIALGSSSALMKLDLSFNAQMRGIDEGA
FDALTDLQVLYITSANLANQPQLSSNHKLTDLDMSYNNFKILHETRFPKSLTRLRLGRNRITDLRSRVFSQLTSLQE
LDLSKNSLVRLETNCLVGLGSLQILDLSSNTINALPRGVFMSLGSLTSLDLSANNINFINATGKDAFAAMPSLSTLDL
SNNAIRSFNPSLFHGMKNLKTLLLMHNHLGLSFSDQLQDYTGFLSRLPRLMVVNMSSNGITVLPKQMISNTSALEV
LDLGMNHIYSWDSQQTFQGAVGLKKLLLNTNRLALFNETSFSDLKNLTVLDLGNNPFACTCDMRWFRDWLKTTK
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SPATVVMLCQHYKEDRQCELELAASLQEEDRRIILVVLDDIVQSRPKLVPVALRVMLNRNEAIEWHRNEQQARLD
MLKGKLAEVWTFAGPADTAQNGYGALED*
>Mme-TLRβ2
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ISETLFQNFPALETLDLGWCRFNNIATGAFKGLNLLDLSLNMNQLGSREFWPFGPDNQNLTSTVKRLDISHCGIVA
LHYYAFFIAKTFPNLEFLDLSNNMLQYLPNFHQKDKITPISEIRRLHLERNSIRELSGDHMNNICNIMPKLQSLSAYN
NHISNLSDLCISLRYLSLDHNLLWKNADSNFKAISLLRNLEYLDLDTNNLTFIRNHTFDHMPNLNTLILSANNLKHIDD
QAFIHNYNLATLLLQANKFSVFNVTLLEGPKNLRKLCISTNLITHFDSSFVKFMDDRQDNGTLQTVKIANNPFDCSC
GRKFFSDWLNRTKLVHESVGLECTTPENMAQKKVYNYQEDLFECTIKVPLIWSAVVLCLIIVTIMIAVPCYRYRWYI
SHMVIVMQAVKDRAMDIKHSDECKYDAMILSDNDSEADMKFVKTLLLHLEGGVFPALDSMSEADESERSNRLYHS
LRDAIPGTYRFESLCEVMRQSRKIIIVISNSYLNSSECMSEAAFAGEELFGTKVYKPEKIVVLVLEDLNEDLMQSPSI
AGLLTETVIDLPESKRQSKKTMAPVWDRLKKFVENKPNSYIFRKRNISRNASRNGYESI*
>Mme-TLRβ1

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LTVKHYSGPPVKMSPAMFKRYRNLTDIIISGNFIGIEPETFAGLTLKYVSITYTNISSLPDDAFGVKTNIRELFLHNNKF
TVIPLSLFNSFTRISKLDFSYNPIDICNSNVTSIGEEFAQLKTLMHLFLSGIGTDVRNCTNIGDDFFKPIAHLSYLLNISE
SCFFTGSTAVLSGLRKIQVLDMSSVYPFTECPGRAGDFLLNLPANAALQKLIAHNWRSQVKEVESDCTIVPKTLQG
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TAGRESYIETLSLSNIGIRSDGKMIYNLFMFISKLPNLSVLDLSDNVIATLPCFTHFPSTSSQFSIHDCISIENRTTSIES
LDISGNLLTSLNMQRMETACRSMPELQTFRAESNQLRDVSGLCTTIKNLYLSNNFIGFHPATDFYPQLKLMTQLQK
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NQFTSFAPSVISVVDNDLKALKTLSLLGNPFDCDCNIGRLQDWLSETEKVIDVINITCGGPEHAADTISIFEYSPPPF
RCKFLLPLIIGCAVVGFVLLILLVCLPCICSRWYISHRKIVLPELKGILKNIRYGYKCDYDAVVCYNTGSDIDQQWVGG
RLVPALEGDDHQSRKGKARLYIYERDSTIGAEKTVQIRDAMERSRNVIIVLSKSYLASEAFLPEVDIVADVMRQNEL
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>Goc-TLRγ23
MKYGSMFLRSLELICVICMFMTVTPMANVTKQTDNGYKRSCVDCLNTSVSEQNVSKNNSSIRDYSVNMHGSGDE
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TFLDMENVQYINISNNKLTSLDIKLTSTKNLTLNISSNLLDHLSNKMTQLLDQMEMKGQNIILDLSYNPIMCGCPQIDF
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EIHNVDIGDINQENNASRETDETDSIIDQIVEIHKIDIDEDMNLIV*
>Goc-TLRγ17
MITSWWVGSSHFYNIHNRIMRFCLDLNFKMESTLYSVMIFVIFVLNDAAVETTMKERMERLLRVQVRGLINGKIMD
NLAILIHAQTTNDTLNFNTSLNTLCDGKIANSMKKIFATYQRFGLPDRQIKMCASPECSCIGTNRNCSFVHLGSMLS
FDENITDFTWRFSEILDQTSTGMLFIWYPKLTYLDIRGACIPALYQDEMNVPLETLMVGNFDGHCDIIRPMQFTYFK
QLRVFHLEHVISSYNAYAREGFYFLDIMRGLHASPIERVSFNEIFMDTDNYTLGWVTLSYLQHAPLRKLTLDGAGIK
HVDFNILYESMDRESSFSIGYLTKTFIFPSKEISQSKLCTDGIDMKWDYLWMAHYIPEVIKFCQEAMVNYNTANTPM
NTTQFNFWINHLNVTNVTISPADTIDIMVLKMATGLEDWIKTKPEMFHSYLKYICRLRHWTDQSYCTGPTVLKHLD
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HLNLSGNLFANLEISHEVTQLTKLQVLDLSYNRFQAIPESWRHTIQLLGARTKSFKLYISGNPFMCSCDTVDHLIWL
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INRILHAPQIPDYTYDAFISYSSLDIEYMLTLYQKLEQEHNYELCIDMRNFRPGNPIDDEITNGIMDSHKIILVISQNFL
RSGWCLYEMQLAHGELAVRGGDGLLLILKEPREMLPQELITDKLQGLLDSRIYLEWSEEGDRQQVFWQRLRDAL
GMPLQQRPRPLDPDHRHLVDPHAVNIEL*
>Goc-TLRβ11
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>Goc-TLRγ16
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>Goc-TLRα2
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>Goc-TLRγ10
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>Goc-TLRγ9
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>Goc-TLRγ3
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>Goc-TLRγ1
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>Goc-TLRγ5
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>Goc-TLRβ10
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>Goc-TLRγ20
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>Goc-TLRβ9
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>Goc-TLRβ8
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>Goc-TLRα5
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VKLE*
>Goc-TLRβ6
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>Goc-TLRγ15
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>Goc-TLRγ19
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>Goc-TLRα4
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>Goc-TLRγ4
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PKRDTGILADTDDGDDEHAPLLGSNLMHH*
>Goc-TLRγ6
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>Ttr-TLRγ4
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>Ttr-TLRα5
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>Ttr-TLRβ3
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>Ttr-TLRδ
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>Ttr-TLRα2
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>Ttr-TLRα3
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>Ttr-TLRγ3
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>Ttr-TLRα1
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>Ttr-TLRγ2
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>Ttr-TLRγ1

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>Ttr-TLRβ5
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>Ttr-TLRα4
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>Ttr-TLRβ4
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>Ttr-TLRβ1
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>Hps-TLRγ4
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>Hps-TLRγ3
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>Hps-TLRα
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>Hps-TLRγ1
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>Hps-TLRγ2
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NNTGLRVVRPKQFSTWKCAAPMAIKDKPMLSVCEDQFIYKRDLSNCPKECTCYVRSAQATLTVDCKEKHLVAMP
RSVPDGQTQLLLQSNNIREIPSYGYLENVTQLYLSHNNIERLDEKTIDRLKRIEKLFIDSNKLTTLPRNIENVSFTKIAL
QHNLFRCDCKTKWIKHWLSRQEDHIEHIDNILCHSDHVKDKVISNLPDEEFVCLEEESDKSGNQAESPAFKITACTL
GGLLFMFLLAFAVGYKFRSEGKVFMYTHFNWHPFDRTNDSNPNKTYDAFISFSGNDYAWISNTLCARLENHDPPY
NLCLHHRDFLVGAPIQQNIFNAIEKSKRMIMILSKNFVKSEWCLLEFRAAHQKVLEDRINYLIIILFDDVDMAEVDDEI
KLYMRTNTYLSVKNKWFWEKLFYALPQNSNRETKANDCHRGAHVNSTADEDNDLSNVCMNDSHNEARQLLMQF
AKEDLEPVTARSKVRYSELVDEHLRLNSDN
>Ad_TLR4
MEVLHVENNQITTIDEEAFPIDSTSLREIHLQNNKITRVPRSLLLLSHARHIDLSFNRLTFQDLDKTIAELDVAKFIYQH
HESASSPQLRLPESVNQMNFAYNNFTTIDIAGMNQSGRSMFEYFLRVYEIDMTGNPLLCDGKILDFIRWLKQWMQ
NNTGLRVVRPKQFSTWKCAAPMAIKDKPILSVREDQFISKRDLRNCPKECTCYVRSAQGTVIVDCKEKHLVTMPR
SVPDGQTELFLQSNDIQEIPSYRYLENVTSLYLSHNQIERLDEKTIDRLKRIQVLFIDSNKLTTLPRNIENVSFTKISM
QHNFFRCDCKTKWMKQWLLREEAHVDNIENILCHSNHVQGKAISRLPDEKFVCLEGENDTSQNPAEPPAFKITAY
TLGCLFLVFLVAFAVGYKFRSEAKVFMYTHFNWHPFDRIKDSDPNKIYDAFVSFSGNDYEWISNTLCVRLENHDPP
YKLCLHHRDFLVGAPIQQNIFNGIEKSKRMIMILSKNFVRSEWCLLEFRAAHQKVLEDRINYLIIILFDDVDMAEVDDE
IKLYMRTNTYLSVKNKWFWEKLFYALPQNSNRETEAKDCHRSAYVNSTANEDYDLSSEGAKV
>Am_TLR
QIPIFESKNHTVQMQAIQCNIQMNQTGSKCVVDINAVLTAVQTSQDTMLYFMATCLTPVNITFHNSQNATKKNVISY
LDLRGHCSISTSDMSKWGNATDFRVFRIMNNDVLVNDNSVQLSNKSIPGLENISTLTLYKAQTKKIPEIFKKYSWPS
MAEIAFVDLQLTSIPTELKTTMPFLQSIDLSHNNLTKPPDFPWYNDTLNLPRGLRRKTTYGFYYEVRKIVSPTIYPRF
FDLSFNMIEDLWAHEFRGRLNVLNLKGNRLKSIGRNCFRSLKGVQMIDLSHNNLQHLPSQLFRQLNDLLLLRLNFN
QISNIPKELFKSQKQVKRIDLDHNKVTSIPKGLFSELNKMEVLHLENNHITAIDDEAFATDSSSLSEIHLQNNKFTRAP
ISLLLLRQARHIDLSFNRLTFQDLDKTIAELDVSTFAYQHQETASSPQFRLPESVNQMNFAHNHFTTIDIAGMTQSR
RKMFELFLRVYEIDMTGNPLLCDGKILDFIRWLKGWMKNNTGLRVVRPQQFSTWKCAAPVEIKDKPILSVAENQFI
SNINLSNCPKECTCYVRSMDETVIVDCKEKDFVAMPRSLPDGQTELFLQSNNIREIPSYGYLENVTSLYLSHNQIER
LDEKTIDRLKRIQVLFIDSNKLTTLPRNIENVSFTKISLQHNFFRCDCKTKWMKQWLLREEAHVDNIENILCHSDHVQ
GKAISRLPDEEFVCLDTVTSRPQAESPAFKITAYTLGGLLLVFLVAFAVGYKFRGEVKVFMYTHFNWHPFDRINDL
DPNKPYDAFISFSGIDYEWISNTLCVRLENHDPPYKLCLHHRDFLVGAPIQQNIFDGIERSKRMIMILSKHFVKSEW
CLLEFRAAHQKVLEDRINYLIIILFDDVDMAEVDDEIKLYMRTNTYLSVKNKWFWEKLFYALPQNSNRETDAKDCQR
SAHVNSTADGDNNLSSERAQV
>Of_TLR
MFVKSQTALIQSNLHILVLDQRHTVLLATSLVFDTKGSLIIFSCLVLFAIEATGQQRRRFLHCGASFCLLKRSMSSFF
ETGNGTLIKEQAVICVLKSDKVRDRCVVDISLILKTITTPQDVVLHFAAVCLTPMEIAFYNSLNATKKNAIFYLQIKGH
CSFSADGISHWGKATDFRVFYLMENSTLLEGNKTLANNSRRALENIGTLMIDKSKLRTLPKMFSSTKVWPRMAEV
VFSKLQLTSIPPELNTTMPFLQSLELANNKLTTPPPFPWCKATLKLPRGLQRTPTGNHHYQFGTNVRPNIYRRFLD
LSYNNIEDLSTHNFRGFLNKLTLEGNGLKVIGTSCFRNLKGIHVISLSKNKLKSLPSELFQGQDSLLELRLDHNNISII
PNDLFKTVTQIKRIDLHSNKLSCIPQELFSKLKNIKILHLEDNHITQVHDKAFSIDSSSLQNIYLQKNKISRIPLTLLLQR
HAVKIDLSFNQLTFQDFNRLIQELDLETFLYHHRHTASSSQMRLQESLKSISFAHNKFTTINIEAFNRTEELTFEYLLR
VYEIDMSGNLLLCDCKILLLSRWLRALVQRHTRIRNEQFQTWKCAAPTELKGKPILSVDENRFKCQRNLENCPHGC
LCLVRALDGTVVIDCKGRNLTAIPPKVPSGRIELKLEDNNIREIPPYPYMENVTALYLTHNKIQVLNKSTVRRFTRIKV
LFIDSNKLTYLPKNIENLNFTSLALHHNFFKCDCTTLWIKHWLQRKQSKILHIKNVLCNSEGSTQGKAIYTLPNEEFV
CKKNKKDIPTTQSITKDKTFKIIALTLGGALVLTFIAFIVAYKYRGEMKVLMYTHFNWHPFDRVDDSDPRKIYDAFVS
YSGSDHQWVVNTLQERLEHHDPPYKLCIHHRDFVVGAPIQENILNSVDQSKRMLMVLSRNFLKSEWCLLEFRAAH
RKVLEDRMNYLIIILFDGINMDELDDEMKLYMRTNTYLSVSYKWFWEKLYYAMPQSTDRQFRARDLSSISSNAGM
QYSTETVFKNEAYLKVTDILE
>Mm_MyD88
MSAGDPRVGSGSLDSFMFSIPLVALNVGVRRRLSLFLNPRTPVAADWTLLAEEMGFEYLEIRELETRPDPTRSLLD
AWQGRSGASVGRLLELLALLDREDILKELKSRIEEDCQKYLGKQQNQESEKPLQVARVESSVPQTKELGGITTLD
DPLGQTPELFDAFICYCPNDIEFVQEMIRQLEQTDYRLKLCVSDRDVLPGTCVWSIASELIEKRCRRMVVVVSDDY
LQSKECDFQTKFALSLSPGVQQKRLIPIKYKAMKKDFPSILRFITICDYTNPCTKSWFWTRLAKALSLP
>Dm_MyD88
MRPRFVCHQQHSVAHSHYQPHSHFHHHTHRHPNPPHHHHIYGATDVSYRRYRTAGMVVAEGVMDSGSGSGTG
TGLGHFNETPLSALGIETRTQLSRMLNRKKVLRSEEGYQRDWRGISELAKQKGFVDENANNPMDLVLISWSQRSP
QTAKVGHLEHFLGIIDRWDVCDDIQENLAKDTQRFIMKQEQRQTALVEACPPPPSDCFETNNNYSSSNNITVGQS
VQILSDEDQRCVQMGQPLPRYNACVLYAEADIDHATEIMNNLESERYNLRLFLRHRDMLMGVPFEHVQLSHFMAT

RCNHLIVVLTEEFLRSPENTYLVNFTQKIQIENHTRKIIPILYKTDMHIPQTLGIYTHIKYAGDSKLFNFWDKLARSLHD
LDAFSIYSTRQVQTPSPVEESAPRVTTPSIRIQINDKDVTDMPNYNSCKVPEAETTIVSVSGDTGSPLPEHKPKKKD
RFLRRITHSFGKTARSDGASGKTLRHAHSVSTINVTERERTLSASSSNISTTSESKKSFIKWQPNILKKALFSRSSSK
LQTPG
>Bg_MyD88
MMAACMPEESWQTFLESSLYDVPLHALRNSVCHRLALYLDIEDVVMHNGYIPNYGGLAELIGFSGLEIMEFERAKS
PTQALLLEWKSRPDLKPKIGKLVEFLFQLDRIDVLTDCHQAINDEAKLFIDKESKALLKPIQDETVTPGPGSETPPYIT
RQDVLTGKKTYYDAYICYNPIGESSKDLEFVRELISRFESDKYRFTLFVPFRDDLPGMNEHAINAKIISERCRHMIVV
LSKNFLQSEACEFQSTFAQSLSPGARNKRIVPIKIEDCVIPNILRIMACCDFTKKDLWDWSWDRLARSITAQLATED
FQSYQSSSESTSGFSRGYSSMSSLQQSNSPRSSSPDSGISVIQNHTVPIATASGSTPSMSPFKKITEKLSKNKSRD
KSKMATAQF
>La_MyD88
MASGMDVAGPPWYSEYREVPVRALNRSVRNILARLLNPPSVVLTDSGFSKDWKGLAELMGFMNDDISNFESMR
DSYTLLILKDWEKQKDSMIATLFDYIQQLERYDILEDPTIKTQVENNVKSYLQRQSKEMEIEKPLQDCEVSSAMEYD
DMKEDQYKYMTTQDVQTGKAMYYDAFVSYAEEDIGFVKKLISELEKPEYGLKLCVQARDLIPGASTNTVCAKLIEE
RCTRMVIILSPKFLNSAQCDFQIKFAQSLSPGSRGKKLVPIMYKCCDIPSILRHIAICDYTKQDLQEWFWNRLAMSL
KAPGAQLSSQDKTSELDNLFLSMSSSSSSEFSWTQSSSPPTSSDVFPPIYPTTSSASSCAPPAPATSGEVPTAEA
GARGVLSLNDIGQIDSDESEPTSDPPKHKKKEKKKKGKPSIFSKFKHSSQSSRSTHC
>Aq_MyD88
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LQHRNGSASTNSSDCEHVQKQLSSLSLDHQNGDYNKKEGIGDDGGGIEVMIRDRSLSDLDRSLLIDGSDFDIFLSF
APADAEFADEMRLRLINRAGISVYIASEGLMPGQSFIDEVADKIKRGCRKTIIILSPDYNQCSWCNYEARLAHHKNP
DPKRHTLIPIVYRKCEVPDFMSHLFYLDFSRYKDDHRQCEKYFWDRLYKSVRHQQPGHT
>Lp_MyD88
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WTDSQPSNTVGKLFDLLEEIERTDVIDDVKQYAEIDAHNYLERKQKWCDKESPLQDPNVSSCTRSAFPADHPNHL
TVDDVTNSEYKGQEVSLYDAYVCYTDEDIECVHILSRQLESEGIRLFIRDRDLLLGQMEYEAFARLIDERCNRVLIVL
SPEFLKSVECEFQTRYATSLAVEQQQRKLIPIIYRSCDVPHLLRYLSKIDFTKLHIHDWVWHRLIHSIKGENGREFTS
SVSEQSSISCSIPPTYVTSVPFSAKNNPPYVQSQNDRESCCDDKEEVSPVPGTSSVSSLHTSGKWAFHTGLKFFK
PRKMKHKRSSNTSVATSGYCSYSQISDTSASDINSNLT
>Spi_MyD88
MEQTKAKHRCKRIKVVVKKFFTRGRQSDEKRSKSKVSGEAGPTVGFSVLDIGVLPERGDDVSSDGDTMLNSSNG
LPSDIPLSGTVALPLDGDHEGGDVSPPASEEKLLKDLCTQGHEKLIILLRPACALGNDYRLLAAKMGYTNEEIKYLE
SLREPVKELMTRYDKEGRTIAELLSLLQQIDRPDVVQDLQPYIDSTPFPREVKEREQRTNNNVVQRTVRKSYHAFV
CFAEEDKAFVDNLVKKMENKNRNLHLCLPVRDFLPVGSHLETTALAIEQRCKKFIVILSKNYDSSQGAIYQAQIATS
LAPGAKEKRIIPVLIDEEYRCSIPRTLSHITYLDYLRQDEKHFWNLLCDTLTRNI
>Spu_MyD88
MAAEIPEKEPKDENINKIERSMPATGIGWRTTNILSQYLRPPRPGSCDWRDMAEEMGFSYQLHIQNFALESDPVA
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FLQSPSCDFQTKFAVSLEPGAMKRRIIPILVKPCDLPLIIRHITLCDFTKQDLRPWFWGRLRKAMSIR
>Cg_MyD88
MSITSEQLIVEGKNVPLHALNMSVRSKLGTYLDPEGFVTGDYSNDYQGLAEVIGFTFQDITNFQRQSKPTQEMLYQ
WGTRPELSPTVDNLIKHLQPIGRSDDVITECAHLIKKDVDRYKQCHKDITGSKDMIQDPSVSQGPNRPSCDYVPES
DKLGLVTIDDVKEKGDTLYYDAFVIYNPVGKDLEFVKELAGKMEAPPYNLKFCIPWRDDLPGGSRYEVSAHMIATR
CRRTLVILSSDFLKSAAADFQLKFAHCLSPGARSKKVVPVFSAPCKMPGILRAVSFVDFTNPGLRDWNWPRLNAV
LRCPLNPDPRDYMSEAELEELKLNAGVITKRMWYSTGVLTMNFPEESEDNTPYNG

**Supplementary Table 1. Species included in our study.** See supplementary Table 2 for the accession number of individual sequences.

| | Species | TLR Source | Publication | Genome/transcriptome NCBI Accession number | Transcriptome BUSCO values |
|---|---|---|---|---|---|
| **Cnidaria** | *N. vectensis* | Literature | (Brennan *et al.*, 2017) | - | - |
| | *A. digitifera* | Literature | (Poole and Weis, 2014) | - | - |
| | *A. millepora* | Literature | (Poole and Weis, 2014) | - | - |
| | *O. faveolata* | Literature | (Williams *et al.*, 2018) | - | - |
| **Xenacoelomorpha** | *X. profunda* | This study: Genome | Unpublished | | - |
| | *H. miamia* | This study: Genome | - | GCA004352715 | - |
| | *P. naikaiensis* | This study: Genome | - | PRJDB7329 | - |
| | *I. pulchra* | This study: Genome | Unpublished | | - |
| | *M. stichopi* | This study: Genome | Unpublished | | - |
| | *C. macropyga* | This study: Transcriptome | (Cannon *et al.*, 2016) | SRX1343815 | 89.2% |
| **Bryozoa** | *M. membranacea* | This study: Transcriptome | - | SRX1121923 | 96.9% |
| | *B. neritina* | This study: Transcriptome | (Wong *et al.*, 2015) | | 96.6% |
| **Cycliophora** | *S. pandora* | This study: Transcriptome | (Neves *et al.*, 2017) | SRX1531719 | 87.4 |
| **Annelida** | *G. oculata* | This study: Transcriptome. | Unpublished | | 99% |
| | *E. fetida* | This study: Transcriptome | - | SRX3108745 | 96.2% |
| | *H. robusta* | This study: Genome | (Simakov *et al.*, 2013) | AMQM00000000.1 | - |
| | *P. prolifica* | Literature | (Halanych and Kocot, 2014) | - | - |
| **Mollusca** | *C. gigas* | This study: Genome | (Zhang *et al.*, 2012) | AFTI00000000 | - |
| | *O. bimaculoides* | This study: Genome | (Albertin *et al.*, 2015) | PRJNA270931 | - |
| | *C. sinensis* | Literature | (Ren *et al.*, 2016) | - | - |
| | *L. rugatus* | Literature | (Halanych and Kocot, 2014) | - | - |

| | | | | | |
|---|---|---|---|---|---|
| | *B. glabrata* | This study: Genome | (Adema *et al.*, 2017) | APKA00000000.1 | - |
| | *B. glabrata* | Individual sequence(s) downloaded from NCBI | - | - | - |
| **Brachiopoda** | *T. transversa* | This study: Transcriptome. | (Cannon *et al.*, 2016) | SRX1307070 | 95.7% |
| | *H. psittacea* | This study: Transcriptome. | (Halanych and Kocot, 2014) | SRX731469 | 94.5% |
| | *L. anatina* | This study: Genome | (Luo *et al.*, 2015) | LFEI00000000 | - |
| **Micrognathozoa** | *L. maerski* | This study: Transcriptome. | | SRX1121929 | 93.8% |
| **Gastrotricha** | *L. squamata* | This study: Transcriptome. | (Laumer *et al.*, 2015) | SRX1000997 | 89.6%. |
| | *Macrodasys sp* | This study: Transcriptome. | (Struck *et al.*, 2014) | SRX534826 | 75.9% |
| | *Megadasys sp* | This study: Transcriptome. | (Struck *et al.*, 2014) | SRX534835 | 70% |
| | *D. aspetos* | This study: Transcriptome. | | SRX1121926 | 90% |
| | *M. laticaudatus* | This study: Transcriptome. | | SRX872416 | 82.5% |
| **Nemertea** | *Lineus longissimus* | This study: Transcriptome. | (Cannon *et al.*, 2016) | SRX1343823 | 95.2% |
| | *Lineus ruber* | This study: Transcriptome. | Unpublished | | 95% |
| | *N. geniculatus* | This study: Genome | (Luo *et al.*, 2018) | NMRB00000000 | - |
| | *P. peregrina* | Literature | (Halanych and Kocot, 2014) | - | - |
| **Phoronida** | *P. harmeri* | This study: Transcriptome. | | SRX1121914 | 90.4% |
| | *P. australis* | This study: Genome | (Luo *et al.*, 2018) | NMRA00000000 | - |
| | *P. psammophila* | Literature | (Halanych and Kocot, 2014) | - | - |
| | *P. vancouverensis* | Literature | (Halanych and Kocot, 2014) | - | - |
| **Platyhelminthes** | *M. lignano* | This study: Genome | (Wasik *et al.*, 2015) | SRP059553 | - |
| | *E. multilocularis* | This study: Genome | (Tsai *et al.*, 2013) | PRJEB122 | - |

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|---|---|---|---|---|---|
| | *H. microstoma* | This study: Genome | (Tsai *et al.*, 2013) | PRJEB124 | - |
| | *S. mansoni* | Literature | (Zheng *et al.*, 2005) | - | - |
| | *S. mediterranea* | Literature | (Peiris *et al.*, 2014) | - | - |
| **Rotifera** | *E. senta* | This study: Transcriptome. | Unpublished | | 95.2% |
| | *R. tardigrada* | This study: Transcriptome. | (Eyres *et al.*, 2015) | SRX1253177 | 91.1% |
| | *E. gadi* | This study: Transcriptome. | | SRX1121912 | 74.9% |
| | *M. hirudinaceus* | This study: Transcriptome. | (Struck *et al.*, 2014) | PRJEB5803 | 84.5%. |
| | *A. vaga* | Literature | (Flot *et al.*, 2013) | - | - |
| **Priapulida** | *P. caudatus* | This study: Transcriptome. | (Cannon *et al.*, 2016) | SRX507009 | 93.9% |
| | *H. spinulosus* | This study: Transcriptome | (Cannon *et al.*, 2016) | SRX1343820 | 96.4% |
| **Tardigrada** | *H. exemplaris* | This study: Genome | (Yoshida *et al.*, 2017) | SRX2495681 | - |
| | *R. varieornatus* | This study: Genome | (Hashimoto *et al.*, 2016) | DRX012456 | - |
| **Onychophora** | *P. capensis* | This study: Transcriptome. | (Sharma *et al.*, 2014) | SRX451023 | 62% |
| **Nematoda** | *L. loa* | This study: Genome | (Desjardins *et al.*, 2013) | ADBU00000000.2 | - |
| | *O. volvulus* | This study. Genome | (Cotton *et al.*, 2017) | CBVM000000000 | - |
| | *C. elegans* | Individual sequence(s) downloaded from NCBI | - | - | - |
| **Loricifera** | *A. elegans* | This study: Transcriptome. | | SRX1120677 | 36.2% |
| **Arthropoda** | *D. pulex* | This study: Genome | (Colbourne *et al.*, 2011) | ACJG00000000 | - |
| | *D. melanogaster* | Individual sequence(s) downloaded from NCBI | - | - | - |
| | *I. scapularis* | Literature | (Gulia-Nuss *et al.*, 2016) | - | - |
| **Tunicata** | *C. intestinalis* | Literature | (Sasaki *et al.*, 2009) | - | - |

| | | | | | |
|---|---|---|---|---|---|
| | *O. dioika* | Literature | (Denoeud *et al.*, 2010) | - | - |
| **Echinodermata** | *S. purpuratus* | Literature | (Hibino *et al.*, 2006) | - | - |
| **Craniata** | *H. sapiens* | Individual sequence(s) downloaded from NCBI | - | - | - |

**Supplementary Table 2. LRR finder analyses and TLR classification**

| GENOMIC/TRANSCRIPTOMIC SURVEYS | | | | | |
|---|---|---|---|---|---|
| **Species** | **Seq_name** | **LRR finder analysis** | **Complete sequence?** | **TLR classification** | |
| *M. membranacea* | >Mme-TLRβ3 | 12LRR-LRRCT | YES | V-type | |
| *M. membranacea* | >Mme-TLRβ4 | 9LRR-LRRCT | NO | Not classified | |
| *M. membranacea* | >Mme-TLRα | 3LRR-LRRCT-2LRR-LRRCT | NO | P-type | |
| *M. membranacea* | >Mme-TLRβ5 | 18LRR-LRRCT | YES | V-type | |
| *M. membranacea* | >Mme-TLRβ2 | 11LRR-LRRCT | YES | V-type | |
| *M. membranacea* | >Mme-TLRβ1 | 14LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRγ23 | 3LRR-LRRCT-LRR-LRRCT | YES | P-type | |
| *G. oculata* | >Goc-TLRγ17 | LRR-LRRCT-4LRR-LRRCT | YES | P-type | |
| *G. oculata* | >Goc-TLRβ11 | 4LRR-LRRCT | NO | Not classified | |
| *G. oculata* | >Goc-TLRγ16 | LRR-LRRCT-3LRR-LRRCT | YES | P-type | |
| *G. oculata* | >Goc-TLRα2 | 8LRR-LRRCT-5LRR-LRRCT | NO | P-type | |
| *G. oculata* | >Goc-TLRγ10 | 7LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRγ9 | 6LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRγ3 | LRRCT-3LRR-LRRCT-5LRR-LRRCT | YES | P-type | |
| *G. oculata* | >Goc-TLRγ1 | LRRCT-6LRR-LRRCT | YES | P-type | |
| *G. oculata* | >Goc-TLRγ5 | LRRCT-6LRR-LRRCT | YES | P-type | |
| *G. oculata* | >Goc-TLRβ10 | 2LRR-LRRCT-2LRR-LRRCT | NO | P-type | |
| *G. oculata* | >Goc-TLRγ20 | 6LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRβ9 | 4LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRβ8 | 3LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRα5 | 4LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *G. oculata* | >Goc-TLRβ6 | 4LRR-LRRCT | NO | Not classified | |
| *G. oculata* | >Goc-TLRγ15 | 4LRR-LRRCT | NO | Not classified | |
| *G. oculata* | >Goc-TLRγ19 | 6LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRα4 | 2LRR-LRRCT | NO | Not classified | |
| *G. oculata* | >Goc-TLRγ4 | 4LRR-LRRCT | NO | Not classified | |
| *G. oculata* | >Goc-TLRγ6 | 3LRR-LRRCT | NO | Not classified | |
| *G. oculata* | >Goc-TLRβ7 | LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRβ4 | 9LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRγ22 | 7LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRβ5 | 6LRR-LRRCT | NO | Not classified | |
| *G. oculata* | >Goc-TLRγ14 | 3LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRβ3 | 11LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRβ2 | 9LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRβ1 | 9LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRγ12 | 9LRR-LRRCT | YES | Not classified | |

| | | | | | |
|---|---|---|---|---|---|
| *G. oculata* | >Goc-TLRγ2 | 7LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRγ8 | 4LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRγ21 | 5LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRα3 | 3LRR-2LRRCT | YES | P-type | |
| *G. oculata* | >Goc-TLRγ13 | 3LRR-LRRCT | NO | Not classified | |
| *G. oculata* | >Goc-TLRα1 | 3LRR-LRRCT-3LRR-LRRCT | YES | P-type | |
| *G. oculata* | >Goc-TLRγ7 | 3LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *G. oculata* | >Goc-TLRγ11 | 3LRR-LRRCT | YES | V-type | |
| *G. oculata* | >Goc-TLRγ18 | 11LRR-LRRCT | YES | V-type | |
| *E. fetida* | >Efe-TLRα | 12LRR-LRRCT-4LRR-LRRCT | NO | P-type | |
| *E. fetida* | >Efe-TLRβ1 | 18LRR-LRRCT | NO | Not classified | |
| *E. fetida* | >Efe-TLRβ8 | 10LRR-LRRCT | NO | Not classified | |
| *E. fetida* | >Efe-TLRβ7 | 6LRR-LRRCT | NO | Not classified | |
| *E. fetida* | >Efe-TLRβ2 | 7LRR-LRRCT | NO | Not classified | |
| *E. fetida* | >Efe-TLRγ2 | LRR-LRRCT | NO | Not classified | |
| *E. fetida* | >Efe-TLRγ1 | LRR-LRRCT | NO | Not classified | |
| *E. fetida* | >Efe-TLRβ6 | 6LRR-LRRCT | NO | Not classified | |
| *E. fetida* | >Efe-TLRβ5 | 8LRR-LRRCT | NO | Not classified | |
| *E. fetida* | >Efe-TLRβ4 | 8LRR-LRRCT | NO | Not classified | |
| *E. fetida* | >Efe-TLRβ3 | 13LRR-LRRCT | NO | Not classified | |
| *H. robusta* | >Hro-TLRα3 | 2LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *H. robusta* | >Hro-TLRα1 | 2LRR-2LRRCT | YES | P-type | |
| *H. robusta* | >Hro-TLRα2 | 3LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *H. robusta* | >Hro-TLRγ1 | 9LRR-LRRCT | YES | V-type | |
| *C. gigas* | >Cgi-TLRγ2 | 4LRR-LRRCT | YES | V-type | |
| *C. gigas* | >Cgi-TLRα4 | 5LRR-LRRCT | YES | V-type | |
| *C. gigas* | >Cgi-TLRα3 | LRRCT-LRR-LRRCT | YES | P-type | |
| *C. gigas* | >Cgi-TLRα1 | 2LRR-LRRCT | YES | V-type | |
| *C. gigas* | >Cgi-TLRα2 | 2LRR-LRRCT | YES | V-type | |
| *C. gigas* | >Cgi-TLRδ2 | 8LRR-LRRCT | YES | V-type | |
| *C. gigas* | >Cgi-TLRδ1 | 7LRR-LRRCT | YES | V-type | |
| *C. gigas* | >Cgi-TLRβ4 | 3LRR-LRRCT | YES | V-type | |
| *C. gigas* | >Cgi-TLRβ3 | 8LRR-LRRCT | YES | V-type | |
| *C. gigas* | >Cgi-TLRβ1 | 14LRR-LRRCT | YES | V-type | |
| *C. gigas* | >Cgi-TLRβ2 | 8LRR-LRRCT | YES | V-type | |
| *C. gigas* | >Cgi-TLRγ1 | 4LRR-LRRCT-4LRR-LRRCT | YES | P-type | |
| *O. bimaculoides* | >Obi-TLRβ5 | 2LRRCT | YES | P-type | |
| *O. bimaculoides* | >Obi-TLRα2 | 12LRR-LRRCT-4LRR-LRRCT | YES | P-type | |
| *O. bimaculoides* | >Obi-TLRβ4 | 2LRRCT | YES | P-type | |
| *O. bimaculoides* | >Obi-TLRβ2 | 3LRR-LRRCT | YES | V-type | |
| *O. bimaculoides* | >Obi-TLRγ | 6LRR-LRRCT | NO | Not classified | |

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|---|---|---|---|---|---|
| *O. bimaculoides* | >Obi-TLRβ1 | 4LRR-LRRCT | NO | Not classified | |
| *O. bimaculoides* | >Obi-TLRβ3 | 2LRR-2LRRCT | YES | P-type | |
| *O. bimaculoides* | >Obi-TLRα3 | 9LRR-LRRCT-LRR-LRRCT | YES | P-type | |
| *O. bimaculoides* | >Obi-TLRα1 | 14LRR-LRRCT-4LRR-2LRRCT | YES | P-type | |
| *B. glabrata* | >Bgl-TLRγ10 | 3LRR | YES | Not classified | |
| *B. glabrata* | >Bgl-TLRγ3 | 5LRR-2LRRCT | YES | P-type | |
| *T. traversa* | >Ttr-TLRγ4 | 3LRR-LRRCT-3LRR-LRRCT | NO | P-type | |
| *T. traversa* | >Ttr-TLRα5 | 4LRR-LRRCT-LRR-LRRCT | NO | P-type | |
| *T. traversa* | >Ttr-TLRβ3 | 9LRR-LRRCT | YES | V-type | |
| *T. traversa* | >Ttr-TLRδ | 7LRR-LRRCT | YES | V-type | |
| *T. traversa* | >Ttr-TLRα2 | 5LRR-LRRCT | NO | Not classified | |
| *T. traversa* | >Ttr-TLRα3 | 2LRR-LRRCT-LRR | NO | Not classified | |
| *T. traversa* | >Ttr-TLRγ3 | 3LRR-LRRCT | NO | Not classified | |
| *T. traversa* | >Ttr-TLRα1 | LRR-LRRCT | NO | Not classified | |
| *T. traversa* | >Ttr-TLRγ2 | LRR-LRRCT | NO | Not classified | |
| *T. traversa* | >Ttr-TLRγ1 | LRR-LRRCT | NO | Not classified | |
| *T. traversa* | >Ttr-TLRβ5 | LRR-LRRCT | NO | Not classified | |
| *T. traversa* | >Ttr-TLRα4 | 5LRR-LRRCT-2LRR-LRRCT | NO | P-type | |
| *T. traversa* | >Ttr-TLRβ2 | 15LRR-LRRCT | YES | V-type | |
| *T. traversa* | >Ttr-TLRβ4 | 3LRR-2LRRCT | YES | P-type | |
| *T. traversa* | >Ttr-TLRβ1 | 16LRR-LRRCT | YES | V-type | |
| *H. psittacea* | >Hps-TLRγ4 | 3LRR-LRRCT-3LRR-LRRCT | NO | P-type | |
| *H. psittacea* | >Hps-TLRγ3 | 4LRR-LRRCT | YES | V-type | |
| *H. psittacea* | >Hps-TLRδ | 5LRR-LRRCT | YES | V-type | |
| *H. psittacea* | >Hps-TLRα | 3LRR-LRRCT | NO | Not classified | |
| *H. psittacea* | >Hps-TLRγ1 | 4LRR-LRRCT | NO | Not classified | |
| *H. psittacea* | >Hps-TLRγ2 | 3LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRδ7 | LRRCT-8LRR-LRRCT | NO | P-type | |
| *L. anatina* | >Lan-TLRα2 | 6LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *L. anatina* | >Lan-TLRδ1 | 2LRR-LRRCT | NO | Not classified | |
| *L. anatina* | >Lan-TLRα7 | 4LRR-LRRCT-LRR-LRRCT | YES | P-type | |
| *L. anatina* | >Lan-TLRβ6 | 3LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRβ9 | 14LRR-LRRCT | NO | Not classified | |
| *L. anatina* | >Lan-TLRβ8 | 3LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRα4 | 6LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *L. anatina* | >Lan-TLRα3 | 10LRR-LRRCT-8LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *L. anatina* | >Lan-TLRα8 | LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRβ5 | 11LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRα1 | 3LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRα6 | 4LRR-LRRCT-LRR-LRRCT | YES | P-type | |

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| *L. anatina* | >Lan-TLRβ7 | 15LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRδ3 | 7LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRδ4 | 3LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRδ2 | 5LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRβ1 | 16LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRβ10 | 5LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRδ5 | 6LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRβ4 | 11LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRα5 | 16LRR-LRRCT-5LRR-LRRCT | YES | P-type | |
| *L. anatina* | >Lan-TLRβ2 | 11LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRδ6 | 7LRR-LRRCT | YES | V-type | |
| *L. anatina* | >Lan-TLRβ3 | 9LRR-LRRCT | NO | Not classified | |
| *L. longissimus* | >Llon-TLRα2 | 7LRR-2LRRCT | NO | P-type | |
| *L. longissimus* | >Llon-TLRβ8 | 9LRR-LRRCT | YES | V-type | |
| *L. longissimus* | >Llon-TLRβ4 | 11LRR-LRRCT | YES | V-type | |
| *L. longissimus* | >Llon-TLRβ7 | 3LRR-LRRCT | YES | V-type | |
| *L. longissimus* | >Llon-TLRβ6 | 3LRR-LRRCT | YES | V-type | |
| *L. longissimus* | >Llon-TLRα1 | 8LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *L. longissimus* | >Llon-TLRβ5 | 6LRR-LRRCT | YES | V-type | |
| *L. longissimus* | >Llon-TLRβ2 | 15LRR-LRRCT | YES | V-type | |
| *L. longissimus* | >Llon-TLRβ1 | 18LRR-LRRCT | YES | V-type | |
| *L. longissimus* | >Llon-TLRβ3 | 5LRR-LRRCT | NO | Not classified | |
| *L. ruber* | >Lrub-TLRβ2 | 11LRR-LRRCT | YES | V-type | |
| *L. ruber* | >Lrub-TLRα1 | 9LRR-LRRCT-LRR-LRRCT | NO | P-type | |
| *L. ruber* | >Lrub-TLRβ1 | 15LRR-LRRCT | YES | V-type | |
| *L. ruber* | >Lrub-TLRα3 | 1LRR-LRRCT-3LRR-LRRCT | NO | P-type | |
| *L. ruber* | >Lrub-TLRα4 | 13LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *L. ruber* | >Lrub-TLRα2 | LRRCT | NO | Not classified | |
| *N. geniculatus* | >Nge-TLRβ6 | 8LRR-LRRCT | YES | V-type | |
| *N. geniculatus* | >Nge-TLRβ5 | 10LRR-LRRCT | YES | V-type | |
| *N. geniculatus* | >Nge-TLRα | 6LRR-LRRCT | YES | V-type | |
| *N. geniculatus* | >Nge-TLRβ2 | 5LRR-LRRCT | NO | Not classified | |
| *N. geniculatus* | >Nge-TLRβ4 | LRRCT-LRR-LRRCT | YES | P-type | |
| *N. geniculatus* | >Nge-TLRβ1 | 16LRR-LRRCT | YES | V-type | |
| *N. geniculatus* | >Nge-TLRβ3 | LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRγ14 | 4LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRγ6 | 3LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRγ5 | 5LRR-LRRCT-3LRR-LRRCT | YES | P-type | |
| *P.australis* | >Pau-TLRγ2 | 5LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRγ13 | 10LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRα2 | 15LRR-LRRCT-3LRR-LRRCT | YES | P-type | |

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| *P.australis* | >Pau-TLRα1 | 16LRR-LRRCT-4LRR-LRRCT | YES | P-type | |
| *P.australis* | >Pau-TLRβ3 | 16LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRβ2 | 4LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRγ10 | LRR-LRRCT | NO | Not classified | |
| *P.australis* | >Pau-TLRγ7 | 5LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRγ15 | 11LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRα6 | 6LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *P.australis* | >Pau-TLRα4 | LRRCT-2LRR-LRRCT-LRR-LRRCT | YES | P-type | |
| *P.australis* | >Pau-TLRα3 | 4LRR-LRRCT-LRR-LRRCT | YES | P-type | |
| *P.australis* | >Pau-TLRγ4 | 10LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRα5 | 2LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRγ1 | 10LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRγ12 | 10LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRγ11 | 7LRR-LRRCT | NO | Not classified | |
| *P.australis* | >Pau-TLRγ9 | 8LRR-LRRCT-2LRR-LRRCT | NO | P-type | |
| *P.australis* | >Pau-TLRγ8 | LRR-LRRCT-7LRR-LRRCT-LRRCT | YES | P-type | |
| *P.australis* | >Pau-TLRγ3 | 9LRR-LRRCT | YES | V-type | |
| *P.australis* | >Pau-TLRβ1 | 2LRR-LRRCT | YES | V-type | |
| *P. hermeri* | >Phe-TLRα | 17LRR-LRRCT-3LRR-LRRCT | YES | P-type | |
| *P. hermeri* | >Phe-TLRβ | LRR-LRRCT | NO | Not classified | |
| *E. senta* | >Ese-TLRα | 5LRR-LRRCT | YES | V-type | |
| *P. caudatus* | >Pcau-TLRα2 | 13LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *P. caudatus* | >Pcau-TLRα1 | LRR-LRRCT-5LRR-LRRCT-LRRCT | YES | P-type | |
| *P. caudatus* | >Pcau-TLRα3 | 5LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *H. spinulosus* | >Hsp-TLRα3 | 16LRR-LRRCT-3LRR-LRRCT | YES | P-type | |
| *H. spinulosus* | >Hsp-TLRα4 | 6LRR-LRRCT-LRR-LRRCT-LRR | YES | P-type | |
| *H. spinulosus* | >Hsp-TLRα1 | 12LRR-LRRCT | YES | V-type | |
| *H. spinulosus* | >Hsp-TLRα2 | 16LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *R. varieornatus* | >Rva-TLRα | 17LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *H. exemplaris* | >Hex-TLRα | 17LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *P. capensis* | >Pcap-TLRβ | 5LRR-LRRCT | NO | Not classified | |
| *L. loa* | >Lloa-TLRα | 5LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *O. volvulus* | >Ovo-TLRα | 17LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *A. elegans* | >Ael-TLRα1 | 8LRR-LRRCT-2LRR-LRRCT | YES | P-type | |
| *A. elegans* | >Ael-TLRα2 | 7LRR-LRRCT | YES | V-type | |
| *D. pulex* | >Dpu-TLRβ | 18LRR-LRRCT | YES | V-type | |
| *D. pulex* | >Dpu-TLRα3 | 15LRR-LRRCT-LRR-LRRCT | YES | P-type | |
| *D. pulex* | >Dpu-TLRα2 | 20LRR-LRRCT-4LRR-LRRCT | YES | P-type | |

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| *D. pulex* | >Dpu-TLRα1 | 4LRR-LRRCT | YES | V-type | |
| *D. pulex* | >Dpu-TLRα4 | 21LRR-LRRCT-3LRR-LRRCT | YES | P-type | |
| **LITERATURE AND NCBI DATABASE** | | | | | |
| **Species** | **Seq_name** | **LRR domains** | **Complete sequence?** | **type** | **NCBI accession number/ reference** |
| *P. prolifica* | >Ppr-TLR1 | LRRCT | NO | Not classified | (Halanych and Kocot, 2014) |
| *P. prolifica* | >Ppr-TLR2 | 10LRR-LRRCT | YES | V-type | (Halanych and Kocot, 2014) |
| *P. prolifica* | >Ppr-TLR3 | 3LRR-LRRCT | NO | Not classified | (Halanych and Kocot, 2014) |
| *P. prolifica* | >Ppr-TLR4 | 20LRR-LRRCT | YES | V-type | (Halanych and Kocot, 2014) |
| *C. sinensis* | >Cs_Toll4 | 3LRR-LRRCT-8LRR-LRRCT | YES | P-type | (Ren *et al.*, 2016) |
| *C. sinensis* | >Cs_Toll13 | 8LRR-LRRCT | YES | V-type | (Ren *et al.*, 2016) |
| *L. rugatus* | >Lrug-TLR2 | 2LRR-LRRCT | NO | Not classified | (Halanych and Kocot, 2014) |
| *B. glabrata* | >Bgl-TLRα2 | 19LRR-LRRCT-LRR-LRRCT | YES | P-type | XP_013084818 |
| *B. glabrata* | >Bgl-TLRγ23 | 13LRR-LRRCT | YES | V-type | XP_013065900 |
| *B. glabrata* | >Bgl-TLRγ20 | 12LRR-LRRCT | YES | V-type | XP_013089343 |
| *B. glabrata* | >Bgl-TLRγ19 | 11LRR-LRRCT | YES | V-type | XP_013082305 |
| *B. glabrata* | >Bgl-TLRα3 | 13LRR-LRRCT-2LRR-LRRCT | YES | P-type | XP_013092995 |
| *B. glabrata* | >Bgl-TLRγ22 | 13LRR-LRRCT | YES | V-type | XP_013089347 |
| *B. glabrata* | >Bgl-TLRγ21 | LRRCT-11LRR-LRRCT | YES | P-type | XP_013089346 |
| *B. glabrata* | >Bgl-TLRγ18 | 13LRR-LRRCT | YES | V-type | XP_013086494 |
| *B. glabrata* | >Bgl-TLRα4 | 5LRR-LRRCT | YES | V-type | XP_013083420 |
| *B. glabrata* | >Bgl-TLRα1 | LRR-LRRCT | YES | V-type | XP_013081976 |
| *B. glabrata* | >Bgl-TLRγ16 | LRRCT-12LRR-LRRCT | YES | P-type | XP_013076041 |
| *B. glabrata* | >Bgl-TLRγ14 | 3LRR-LRRCT | YES | V-type | XP_013075799 |
| *B. glabrata* | >Bgl-TLRγ8 | 9LRR-LRRCT | YES | V-type | XP_013077467 |
| *B. glabrata* | >Bgl-TLRγ7 | 7LRR-2LRRCT | NO | P-type | XP_013095644 |
| *B. glabrata* | >Bgl-TLRγ6 | 3LRR-2LRRCT | YES | P-type | XP_013087194 |
| *B. glabrata* | >Bgl-TLRγ1 | 2LRR-LRRCT | YES | V-type | XP_013086922 |
| *B. glabrata* | >Bgl-TLRγ5 | 5LRR-LRRCT | YES | V-type | XP_013085514 |
| *B. glabrata* | >Bgl-TLRγ13 | LRRCT-8LRR-LRRCT-2LRR-LRRCT | YES | P-type | XP_013084288 |
| *B. glabrata* | >Bgl-TLRγ2 | 8LRR-LRRCT | YES | V-type | XP_013077006 |
| *B. glabrata* | >Bgl-TLRγ9 | LRRCT-4LRR-LRRCT | YES | P-type | XP_013074023 |
| *B. glabrata* | >Bgl-TLRγ15 | 11LRR-LRRCT | YES | V-type | XP_013069695 |
| *B. glabrata* | >Bgl-TLRγ17 | 12LRR-LRRCT | YES | V-type | XP_013067575 |
| *B. glabrata* | >Bgl-TLRγ11 | LRRCT-7LRR-LRRCT | YES | P-type | XP_013062263 |
| *B. glabrata* | >Bgl-TLRγ12 | 9LRR-LRRCT | YES | V-type | XP_013062262 |
| *B. glabrata* | >Bgl-TLRγ4 | 4LRR-LRRCT | YES | V-type | XP_013061949 |
| *P. peregrina* | >Ppe-TLR1 | 16LRR-LRRCT | YES | V-type | (Halanych and Kocot, 2014) |
| *P. peregrina* | >Ppe-TLR3 | 6LRR-LRRCT | NO | Not classified | (Halanych and Kocot, 2014) |
| *P. psammophila* | >Pps-TLR2 | 5LRR-LRRCT | NO | Not classified | (Halanych and Kocot, 2014) |

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| *P. psammophila* | >Pps-TLR3 | 15LRR-LRRCT | YES | V-type | (Halanych and Kocot, 2014) |
| *P. psammophila* | >Pps-TLR4 | 2LRR-LRRCT-2LRR-LRRCT | NO | P-type | (Halanych and Kocot, 2014) |
| *P. vancouverensis* | >Pva-TLR1 | LRRCT | NO | Not classified | (Halanych and Kocot, 2014) |
| *P. vancouverensis* | >Pva-TLR2 | 13LRR-LRRCT | YES | V-type | (Halanych and Kocot, 2014) |
| *P. vancouverensis* | >Pva-TLR3 | 12LRR-LRRCT | YES | V-type | (Halanych and Kocot, 2014) |
| *P. vancouverensis* | >Pva-TLR4 | 14LRR-LRRCT | YES | V-type | (Halanych and Kocot, 2014) |
| *P. vancouverensis* | >Pva-TLR5 | 8LRR-LRRCT | YES | V-type | (Halanych and Kocot, 2014) |
| *P. vancouverensis* | >Pva-TLR6 | 16LRR-LRRCT | YES | V-type | (Halanych and Kocot, 2014) |
| *C. elegans* | >Ce_Toll1 | 24LRR-LRRCT-4LRR-LRRCT | YES | P-type | NP_001020983.1 |
| *D. melanogaster* | >Dm_Toll1 | 16LRR-LRRCT-4LRR-LRRCT | YES | P-type | NP_524518.1 |
| *D. melanogaster* | >Dm_Toll2 | 18LRR-LRRCT-5LRR-LRRCT | YES | P-type | NP_476814.1 |
| *D. melanogaster* | >Dm_Toll3 | 1LRR-LRRCT-1LRR-2LRRCT | YES | P-type | NP_649719.2 |
| *D. melanogaster* | >Dm_Toll4 | 1LRR-LRRCT-2LRR-LRRCT-LRR-LRRCT | YES | P-type | NP_523519.2 |
| *D. melanogaster* | >Dm_Toll5 | 2LRR-LRRCT-2LRR-LRRCT | YES | P-type | NP_001285901.1 |
| *D. melanogaster* | >Dm_Toll6 | 20LRR-LRRCT-3LRR-LRRCT | YES | P-type | NP_001246766.1 |
| *D. melanogaster* | >Dm_Toll7 | 21LRR-LRRCT-3LRR-LRRCT | YES | P-type | NP_523797.1 |
| *D. melanogaster* | >Dm_Toll8 | 21LRR-LRRCT-3LRR-LRRCT | YES | P-type | NP_524757.1 |
| *D. melanogaster* | >Dm_Toll9 | 11LRR-LRRCT | YES | V-type | NP_649214.1 |
| *I. scapularis* | >Isc-TLR3 | 3LRR-LRRCT | YES | V-type | (Gulia-Nuss *et al.*, 2016) |
| *I. scapularis* | >Isc-TLR2 | 9LRR-LRRCT | NO | Not classified | (Gulia-Nuss *et al.*, 2016) |
| *I. scapularis* | >Isc-TLR1 | 15LRR-LRRCT-4LRR-LRRCT | YES | P-type | (Gulia-Nuss *et al.*, 2016) |
| *I. scapularis* | >Isc-TLR5 | 23LRR-LRRCT-5LRR-LRRCT | YES | P-type | (Gulia-Nuss *et al.*, 2016) |
| *I. scapularis* | >Isc-TLR4 | 23LRR-LRRCT-5LRR-LRRCT | YES | P-type | (Gulia-Nuss *et al.*, 2016) |
| *C. intestinalis* | >Ci_TLR1 | 16LRR-LRRCT | YES | V-type | (Sasaki *et al.*, 2009) |
| *C. intestinalis* | >Ci_TLR2 | 12LRR-LRRCT-2LRR-LRRCT | YES | P-type | (Sasaki *et al.*, 2009) |
| *O. dioica* | >Od_TLR | 11LRR-LRRCT | YES | V-type | (Denoeud *et al.*, 2010) |
| *S. purpuratus* | >Sp_TLR020 | 14LRR-LRRCT | YES | V-type | (Hibino *et al.*, 2006) |
| *S. purpuratus* | >Sp_TLR007 | 20LRR-LRRCT-5LRR-LRRCT | YES | P-type | (Hibino *et al.*, 2006) |
| *S. purpuratus* | >Sp_TLR053 | 16LRR-LRRCT | YES | V-type | (Hibino *et al.*, 2006) |
| *S. purpuratus* | >Sp_TLR039 | 12LRR-LRRCT | YES | V-type | (Hibino *et al.*, 2006) |
| *S. purpuratus* | >Sp_TLR056 | 16LRR-LRRCT | YES | V-type | (Hibino *et al.*, 2006) |
| *S. purpuratus* | >Sp_TLR044 | 20LRR-LRRCT | YES | V-type | (Hibino *et al.*, 2006) |
| *S. purpuratus* | >Sp_TLR016 | 19LRR-LRRCT | YES | V-type | (Hibino *et al.*, 2006) |
| *S. purpuratus* | >Sp_TLR100 | 21LRR-LRRCT | YES | V-type | (Hibino *et al.*, 2006) |
| *H. sapiens* | >Hs_TLR1 | 19LRR-LRRCT | YES | V-type | NP_003254.2 |
| *H. sapiens* | >Hs_TLR2 | 19LRR-LRRCT | YES | V-type | NP_001305716.1 |
| *H. sapiens* | >Hs_TLR3 | 23LRR-LRRCT | YES | V-type | NP_003256.1 |
| *H. sapiens* | >Hs_TLR4 | 21LRR-LRRCT | YES | V-type | NP_003257.1 |
| *H. sapiens* | >Hs_TLR5 | 21LRR-LRRCT | YES | V-type | NP_003259.2 |
| *H. sapiens* | >Hs_TLR6 | 19LRR-LRRCT | YES | V-type | NP_006059.2 |

| | | | | | |
|---|---|---|---|---|---|
| *H. sapiens* | >Hs_TLR7 | 1LRR-LRRCT-23LRR-LRRCT | YES | V-type | NP_057646.1 |
| *H. sapiens* | >Hs_TLR8 | 25LRR-LRRCT | YES | V-type | NP_057694.2 |
| *H. sapiens* | >Hs_TLR9 | 25LRR-LRRCT | YES | V-type | NP_059138.1 |
| *H. sapiens* | >Hs_TLR10 | 19LRR-LRRCT | YES | V-type | NP_001017388.1 |
| *N. vectensis* | >Nv_TLR | 8LRR-LRRCT-LRR-LRRCT | YES | P-type | (Brennan *et al.*, 2017) |
| *A. digitifera* | >Ad_TLR1 | 8LRR-LRRCT-LRR-LRRCT | YES | P-type | (Poole and Weis, 2014) |
| *A. digitifera* | >Ad_TLR2 | LRR-LRRCT | YES | V-type | (Poole and Weis, 2014) |
| *A. digitifera* | >Ad_TLR3 | 2LRR-LRRCT-LRR-LRRCT | YES | P-type | (Poole and Weis, 2014) |
| *A. digitifera* | >Ad_TLR4 | 3LRR-LRRCT-LRR-LRRCT | YES | P-type | (Poole and Weis, 2014) |
| *A. millepora* | >Am_TLR | 8LRR-LRRCT-LRR-LRRCT | NO | P-type | (Poole and Weis, 2014) |
| *O. faveolata* | >Of_TLR | 10LRR-LRRCT-2LRR-LRRCT | YES | P-type | (Williams *et al.*, 2018) |

**Supplementary Table 3 - *Hypsibius exemplaris* stage specific transcriptome analyses (RSEM and Kallisto methods)**

*HYPSIBIUS EXEMPLARIS*

**Values inicate Transcripts per Milion (TEM)**

| RSEM | Zigot | Morula1 | Morula2 | Morula3 | Early gastrula | Gastrula 1 | Gastrula 2 | Elongation | Segmentation 1 | Segmentation 2 | Limb bud formation | Differentiation 1 | Differentiation 2 | Differentiation 3 | Differentiation 4 | Differentiation 5 | Differentiation 6 | Differentiation 7 | Differentiation 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hexe-TLRα | 3,165 | 0,000 | 0,000 | 8,589 | 8,071 | 8,335 | 1,421 | 9,685 | 25,103 | 0,000 | 0,000 | 0,000 | 27,095 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |

| kallisto | Zigot | Morula1 | Morula2 | Morula3 | Early gastrula | Gastrula 1 | Gastrula 2 | Elongation | Segmentation 1 | Segmentation 2 | Limb bud formation | Differentiation 1 | Differentiation 2 | Differentiation 3 | Differentiation 4 | Differentiation 5 | Differentiation 6 | Differentiation 7 | Differentiation 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hexe-TLRα | 0,000 | 0,000 | 0,000 | 27,214 | 0,000 | 9,697 | 0,000 | 0,000 | 33,087 | 0,000 | 0,000 | 0,000 | 77,060 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |

TEM ≥0,150
TEM <0,150

**Supplementary Table 4 - Priapulus caudatus stage specific transcriptome analyses.** Analyses for the different methods (RSEM and Kallisto) and replicates (Rep 1_and Rep_2). For each method, average and standard error (SE) of the two replicates is provided.

***PRIAPULUS CAUDATUS***

**Values inicate Transcripts per Milion (TEM)**

| **Rep_1_RSEM** | **0d** | **1d** | **3d** | **5d** | **9d** |
|---|---|---|---|---|---|
| Pcau-TLRα1 | 2,551 | 2,294 | 1,509 | 1,016 | 1,512 |
| Pcau-TLRα2 | 1,471 | 2,427 | 1,822 | 1,983 | 2,988 |
| Pcau-TLRα3 | 0,000 | 0,000 | 0,822 | 2,371 | 5,496 |

| **Rep_1_kallisto** | **0d** | **1d** | **3d** | **5d** | **9d** |
|---|---|---|---|---|---|
| Pcau-TLRα1 | 2,433 | 2,059 | 1,487 | 0,940 | 1,589 |
| Pcau-TLRα2 | 1,440 | 2,093 | 1,767 | 1,890 | 3,089 |
| Pcau-TLRα3 | 0,000 | 0,000 | 0,825 | 2,156 | 4,627 |

| **Rep_2_RSEM** | **0d** | **1d** | **3d** | **5d** | **9d** |
|---|---|---|---|---|---|
| Pcau-TLRα1 | 7,824 | 6,555 | 3,418 | 2,230 | 3,617 |
| Pcau-TLRα2 | 0,680 | 2,285 | 1,477 | 2,630 | 5,675 |
| Pcau-TLRα3 | 0,000 | 0,000 | 0,167 | 1,159 | 3,396 |

| **Rep_2_kallisto** | **0d** | **1d** | **3d** | **5d** | **9d** |
|---|---|---|---|---|---|
| Pcau-TLRα1 | 7,609 | 6,107 | 3,311 | 1,985 | 3,445 |
| Pcau-TLRα2 | 0,724 | 2,432 | 1,475 | 2,469 | 6,272 |
| Pcau-TLRα3 | 0,000 | 0,000 | 0,189 | 0,667 | 3,275 |

| **RSEM_average** | **0d** | **1d** | **3d** | **5d** | **9d** |
|---|---|---|---|---|---|
| Pcau-TLRα1 | 5,188 | 4,425 | 2,464 | 1,623 | 2,565 |
| Pcau-TLRα2 | 1,076 | 2,356 | 1,650 | 2,307 | 4,332 |
| Pcau-TLRα3 | 0,000 | 0,000 | 0,495 | 1,765 | 4,446 |

| **Kallisto_average** | **0d** | **1d** | **3d** | **5d** | **9d** |
|---|---|---|---|---|---|
| Pcau-TLRα1 | 5,021 | 4,083 | 2,399 | 1,463 | 2,517 |
| Pcau-TLRα2 | 1,082 | 2,263 | 1,621 | 2,180 | 4,681 |
| Pcau-TLRα3 | 0,000 | 0,000 | 0,507 | 1,412 | 3,951 |

**Values indicate Standard Error (SE)**

| **RSEM_SE** | **0d** | **1d** | **3d** | **5d** | **9d** |
|---|---|---|---|---|---|
| Pcau-TLRα1 | 2,637 | 2,131 | 0,955 | 0,607 | 1,053 |
| Pcau-TLRα2 | 0,396 | 0,071 | 0,172 | 0,324 | 1,344 |
| Pcau-TLRα3 | 0,000 | 0,000 | 0,328 | 0,606 | 1,050 |

| **Kallisto_SE** | **0d** | **1d** | **3d** | **5d** | **9d** |
|---|---|---|---|---|---|
| Pcau-TLRα1 | 2,588 | 2,024 | 0,912 | 0,523 | 0,928 |
| Pcau-TLRα2 | 0,358 | 0,170 | 0,146 | 0,289 | 1,592 |
| Pcau-TLRα3 | 0,000 | 0,000 | 0,318 | 0,745 | 0,676 |

TEM ≥0,150

TEM <0,150

**Supplementary Table 5 - Crassostrea gigas stage specific transcriptome analyses (RSEM and Kallisto methods)**

| | *CRASSOSTREA GIGAS* | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **RSEM** | **Early morula** | **Morula** | **Blastula** | **Rotary movement** | **Free swimming** | **Early gastrula** | **Gastrula** | **Trochophore 1** | **Trochophore 2** | **Trochophore 3** | **Trochophore 4** | **Trochophore 5** | **early Dshaped larva 1** | **early Dshaped larva 2** | **Dshaped larva 1** | **Dshaped larva 2** | **Dshaped larva 3** | **Dshaped larva 4** | **Dshaped larva 5** |
| Cgi-TLRα1 | 0,000 | 0,000 | 0,163 | 0,507 | 0,446 | 0,136 | 0,279 | 0,132 | 0,758 | 0,331 | 0,249 | 0,646 | 0,586 | 0,666 | 0,371 | 0,315 | 0,265 | 0,279 | 0,287 |
| Cgi-TLRα2 | 0,048 | 0,121 | 0,154 | 0,119 | 0,085 | 0,027 | 0,058 | 0,042 | 0,000 | 0,052 | 0,065 | 0,055 | 0,053 | 0,047 | 0,000 | 0,000 | 0,000 | 0,052 | 0,000 |
| Cgi-TLRα3 | 0,000 | 0,028 | 0,029 | 0,000 | 0,000 | 0,000 | 0,058 | 0,000 | 0,124 | 0,114 | 0,195 | 0,109 | 0,120 | 0,257 | 0,379 | 0,420 | 0,054 | 0,279 | 0,231 |
| Cgi-TLRα4 | 0,000 | 0,000 | 0,000 | 0,075 | 0,276 | 0,345 | 0,221 | 0,118 | 0,310 | 0,362 | 0,498 | 0,777 | 0,918 | 0,947 | 1,190 | 0,954 | 1,183 | 1,311 | 2,648 |
| Cgi-TLRβ1 | 0,000 | 0,000 | 0,000 | 0,000 | 0,032 | 0,045 | 0,000 | 0,000 | 0,108 | 0,052 | 0,000 | 0,044 | 0,000 | 0,047 | 0,098 | 0,097 | 0,048 | 0,052 | 0,311 |
| Cgi-TLRβ2 | 0,019 | 0,028 | 0,000 | 0,000 | 0,021 | 0,000 | 0,000 | 0,000 | 0,000 | 0,052 | 0,000 | 0,000 | 0,000 | 0,000 | 0,091 | 0,000 | 0,048 | 0,000 | 0,191 |
| Cgi-TLRβ3 | 0,000 | 0,121 | 0,029 | 0,104 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,065 | 0,000 | 0,000 | 0,000 | 0,053 | 0,000 | 0,054 | 0,000 | 0,072 |
| Cgi-TLRβ4 | 0,381 | 1,021 | 0,807 | 0,343 | 0,266 | 0,209 | 0,581 | 0,439 | 0,511 | 0,671 | 0,217 | 0,361 | 0,373 | 0,175 | 0,280 | 0,291 | 0,088 | 0,093 | 0,255 |
| Cgi-TLRγ1 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,300 | 0,054 | 0,000 | 0,093 | 0,117 | 0,083 | 0,040 | 0,041 | 0,083 | 0,000 |
| Cgi-TLRγ2 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,063 | 0,093 | 0,000 | 0,000 | 0,077 | 0,000 | 0,082 | 0,159 | 0,154 | 0,000 | 0,083 | 0,000 |
| Cgi-TLRδ1 | 0,029 | 0,000 | 0,000 | 0,000 | 0,000 | 0,027 | 0,163 | 0,042 | 0,402 | 0,331 | 0,260 | 0,537 | 0,399 | 0,666 | 0,636 | 0,259 | 0,734 | 0,382 | 0,686 |
| Cgi-TLRδ2 | 0,877 | 0,798 | 0,499 | 0,418 | 0,223 | 0,254 | 0,221 | 0,272 | 0,170 | 0,186 | 0,249 | 0,088 | 0,333 | 0,257 | 0,152 | 0,267 | 0,326 | 0,217 | 0,295 |
| **Kallisto** | | | | | | | | | | | | | | | | | | | |
| Cgi-TLRα1 | 0,000 | 0,000 | 0,141 | 1,011 | 0,890 | 0,187 | 0,671 | 0,100 | 1,331 | 0,772 | 0,302 | 1,031 | 0,821 | 1,193 | 0,820 | 0,457 | 0,472 | 0,512 | 0,384 |
| Cgi-TLRα2 | 0,058 | 0,137 | 0,279 | 0,143 | 0,068 | 0,062 | 0,133 | 0,099 | 0,000 | 0,127 | 0,149 | 0,127 | 0,135 | 0,000 | 0,000 | 0,000 | 0,000 | 0,127 | |
| Cgi-TLRα3 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,136 | 0,262 | 0,461 | 0,131 | 0,139 | 0,608 | 0,596 | 0,816 | 0,120 | 0,653 | 0,392 |
| Cgi-TLRα4 | 0,000 | 0,000 | 0,000 | 0,190 | 0,541 | 0,737 | 0,353 | 0,262 | 0,701 | 0,508 | 0,794 | 1,017 | 1,441 | 1,413 | 1,694 | 0,752 | 1,709 | 2,865 | 4,888 |
| Cgi-TLRβ1 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,119 | 0,115 | 0,000 | 0,000 | 0,000 | 0,107 | 0,000 | 0,205 | 0,000 | 0,115 | 0,344 |
| Cgi-TLRβ2 | 0,049 | 0,000 | 0,000 | 0,000 | 0,058 | 0,000 | 0,000 | 0,000 | 0,000 | 0,109 | 0,000 | 0,000 | 0,000 | 0,000 | 0,199 | 0,000 | 0,100 | 0,000 | 0,326 |
| Cgi-TLRβ3 | 0,000 | 0,209 | 0,068 | 0,270 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,147 | 0,000 | 0,000 | 0,000 | 0,114 | 0,000 | 0,115 | 0,000 | 0,124 |
| Cgi-TLRβ4 | 2,735 | 2,132 | 2,365 | 2,237 | 1,301 | 1,388 | 2,383 | 1,783 | 1,924 | 2,013 | 1,517 | 1,440 | 0,865 | 1,734 | 0,615 | 1,150 | 0,924 | 1,002 | 1,002 |
| Cgi-TLRγ1 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,502 | 0,118 | 0,000 | 0,214 | 0,186 | 0,091 | 0,089 | 0,092 | 0,100 | 0,000 |
| Cgi-TLRγ2 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,150 | 0,200 | 0,000 | 0,000 | 0,193 | 0,000 | 0,179 | 0,352 | 0,343 | 0,000 | 0,192 | 0,000 |
| Cgi-TLRδ1 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,267 | 0,000 | 0,794 | 0,768 | 0,300 | 1,025 | 0,545 | 1,424 | 1,048 | 0,455 | 1,527 | 0,765 | 1,402 |
| Cgi-TLRδ2 | 1,543 | 1,722 | 0,993 | 0,977 | 0,618 | 0,491 | 0,227 | 0,506 | 0,300 | 0,290 | 0,595 | 0,363 | 0,540 | 0,538 | 0,264 | 0,451 | 0,532 | 0,433 | 0,650 |

TEM ≥0,150
TEM <0,150

**Supplementary Table 6 - Terebratalia transversa stage specific transcriptome analyses.** Analyses for the different methods (RSEM and Kallisto) and replicates (Rep 1_and Rep_2). For each method, average and standard error (SE) of the two replicates is provided.

*TEREBRATALIA TRANSVERSA*

**Values inicate Transcripts per Milion (TEM)**

| **Rep_1_RSEM** | **oocyte** | **8 hr mid blastula** | **19 hr late blastula** | **24 hr moving blastula** | **26 hr early gastrula** | **37 hr mid gastrula** | **51 hr late gastrula** | **59 hr bilobed gastrula** | **68 hr trilobed gastrula** | **82 hr early larva** | **98 hr late larva** | **competent larva (131h)** | **1 day juvenile** | **2 day juvenile** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ttr-TLRα1** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| **Ttr-TLRα2** | 0,290 | 0,216 | 0,189 | 0,104 | 0,058 | 0,028 | 0,028 | 0,064 | 0,116 | 0,139 | 0,062 | 1,570 | 0,359 | 0,600 |
| **Ttr-TLRα3** | 0,000 | 0,000 | 0,000 | 0,088 | 0,099 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 2,302 | 1,983 | 2,589 |
| **Ttr-TLRα4** | 0,807 | 0,059 | 0,074 | 0,249 | 0,214 | 0,047 | 0,000 | 0,000 | 0,412 | 0,492 | 1,123 | 2,691 | 4,488 | 2,578 |
| **Ttr-TLRα5** | 0,105 | 0,137 | 0,041 | 0,064 | 0,074 | 0,056 | 0,120 | 0,100 | 0,245 | 0,177 | 0,072 | 0,071 | 0,098 | 0,235 |
| **Ttr-TLRβ1** | 0,129 | 0,000 | 0,000 | 0,096 | 0,222 | 0,150 | 0,000 | 0,000 | 0,039 | 0,253 | 0,577 | 0,708 | 0,153 | 0,000 |
| **Ttr-TLRβ2** | 0,524 | 0,634 | 0,287 | 0,329 | 0,330 | 0,122 | 0,240 | 0,237 | 0,155 | 0,164 | 0,546 | 0,342 | 0,065 | 0,071 |
| **Ttr-TLRβ3** | 0,331 | 0,471 | 0,771 | 0,553 | 0,577 | 0,207 | 0,065 | 0,428 | 0,142 | 0,076 | 0,330 | 0,224 | 0,458 | 0,271 |
| **Ttr-TLRβ4** | 0,000 | 0,000 | 0,090 | 0,048 | 0,346 | 0,197 | 0,037 | 0,391 | 0,567 | 0,076 | 0,824 | 0,602 | 0,381 | 0,294 |
| **Ttr-TLRβ5** | 0,000 | 0,039 | 0,066 | 0,160 | 0,058 | 0,066 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,059 | 0,000 | 0,000 |
| **Ttr-TLRγ1** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,092 | 0,064 | 0,000 | 0,000 | 0,000 | 0,000 | 0,501 | 0,094 |
| **Ttr-TLRγ2** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,106 | 0,000 | 0,282 |
| **Ttr-TLRγ3** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| **Ttr-TLRγ4** | 0,226 | 0,275 | 0,082 | 0,192 | 0,568 | 0,442 | 0,406 | 0,309 | 0,142 | 0,088 | 0,227 | 0,236 | 0,458 | 0,294 |
| **Ttr-TLRδ** | 0,024 | 0,020 | 0,057 | 0,152 | 0,148 | 0,160 | 0,000 | 0,064 | 0,052 | 0,126 | 0,165 | 0,224 | 0,033 | 0,000 |

| Rep_2_RSEM | oocyte | 8 hr mid blastula | 19 hr late blastula | 24 hr moving blastula | 26 hr early gastrula | 37 hr mid gastrula | 51 hr late gastrula | 59 hr bilobed gastrula | 68 hr trilobed gastrula | 82 hr early larva | 98 hr late larva | competent larva (131h) | 1 day juvenile | 2 day juvenile |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ttr-TLRα1 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| Ttr-TLRα2 | 0,121 | 0,161 | 0,207 | 0,222 | 0,080 | 0,116 | 0,034 | 0,035 | 0,157 | 0,343 | 0,229 | 0,668 | 0,639 | 0,403 |
| Ttr-TLRα3 | 0,000 | 0,000 | 0,057 | 0,000 | 0,000 | 0,045 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,196 | 1,943 | 1,327 |
| Ttr-TLRα4 | 0,664 | 0,484 | 0,607 | 0,625 | 1,045 | 0,695 | 0,051 | 0,129 | 0,868 | 0,520 | 0,774 | 0,701 | 3,791 | 5,293 |
| Ttr-TLRα5 | 0,121 | 0,101 | 0,136 | 0,277 | 0,195 | 0,196 | 0,488 | 0,493 | 1,129 | 0,213 | 0,229 | 0,163 | 0,326 | 0,522 |
| Ttr-TLRβ1 | 0,113 | 0,000 | 0,064 | 0,000 | 0,000 | 0,062 | 0,000 | 0,000 | 0,220 | 0,106 | 0,264 | 0,342 | 0,163 | 0,030 |
| Ttr-TLRβ2 | 0,089 | 0,040 | 0,236 | 0,087 | 0,062 | 0,018 | 0,069 | 0,082 | 0,366 | 0,095 | 0,035 | 0,065 | 0,122 | 0,000 |
| Ttr-TLRβ3 | 0,810 | 0,471 | 0,743 | 0,688 | 0,789 | 0,740 | 0,950 | 0,258 | 1,098 | 0,118 | 0,211 | 0,261 | 0,353 | 0,268 |
| Ttr-TLRβ4 | 0,000 | 0,000 | 0,043 | 0,111 | 0,000 | 0,000 | 0,000 | 0,000 | 0,063 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| Ttr-TLRβ5 | 0,000 | 0,000 | 0,036 | 0,222 | 0,000 | 0,000 | 0,077 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,119 |
| Ttr-TLRγ1 | 0,000 | 0,034 | 0,000 | 0,000 | 0,000 | 0,053 | 0,103 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| Ttr-TLRγ2 | 0,000 | 0,000 | 0,036 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,209 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| Ttr-TLRγ3 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,027 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| Ttr-TLRγ4 | 0,121 | 0,195 | 0,129 | 0,182 | 0,106 | 0,134 | 0,325 | 0,317 | 0,324 | 0,154 | 0,457 | 0,326 | 0,476 | 0,656 |
| Ttr-TLRδ | 0,000 | 0,040 | 0,279 | 0,649 | 0,230 | 0,160 | 0,394 | 0,047 | 0,178 | 0,035 | 0,070 | 0,065 | 0,190 | 0,313 |

| RSEM_average | oocyte | 8 hr mid blastula | 19 hr late blastula | 24 hr moving blastula | 26 hr early gastrula | 37 hr mid gastrula | 51 hr late gastrula | 59 hr bilobed gastrula | 68 hr trilobed gastrula | 82 hr early larva | 98 hr late larva | competent larva (131h) | 1 day juvenile | 2 day juvenile |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ttr-TLRα1 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| Ttr-TLRα2 | 0,206 | 0,189 | 0,198 | 0,163 | 0,069 | 0,072 | 0,031 | 0,050 | 0,137 | 0,241 | 0,146 | 1,119 | 0,499 | 0,502 |
| Ttr-TLRα3 | 0,000 | 0,000 | 0,029 | 0,044 | 0,050 | 0,023 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 1,249 | 1,963 | 1,958 |
| Ttr-TLRα4 | 0,736 | 0,272 | 0,341 | 0,437 | 0,630 | 0,371 | 0,026 | 0,065 | 0,640 | 0,506 | 0,949 | 1,696 | 4,140 | 3,936 |
| Ttr-TLRα5 | 0,113 | 0,119 | 0,089 | 0,171 | 0,135 | 0,126 | 0,304 | 0,297 | 0,687 | 0,195 | 0,151 | 0,117 | 0,212 | 0,379 |
| Ttr-TLRβ1 | 0,121 | 0,000 | 0,032 | 0,048 | 0,111 | 0,106 | 0,000 | 0,000 | 0,130 | 0,180 | 0,421 | 0,525 | 0,158 | 0,015 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ttr-TLRβ2 | 0,307 | 0,337 | 0,262 | 0,208 | 0,196 | 0,070 | 0,155 | 0,160 | 0,261 | 0,130 | 0,291 | 0,204 | 0,094 | 0,036 |
| Ttr-TLRβ3 | 0,571 | 0,471 | 0,757 | 0,621 | 0,683 | 0,474 | 0,508 | 0,343 | 0,620 | 0,097 | 0,271 | 0,243 | 0,406 | 0,270 |
| Ttr-TLRβ4 | 0,000 | 0,000 | 0,067 | 0,080 | 0,173 | 0,099 | 0,019 | 0,196 | 0,315 | 0,038 | 0,412 | 0,301 | 0,191 | 0,147 |
| Ttr-TLRβ5 | 0,000 | 0,020 | 0,051 | 0,191 | 0,029 | 0,033 | 0,039 | 0,000 | 0,000 | 0,000 | 0,000 | 0,030 | 0,000 | 0,060 |
| Ttr-TLRγ1 | 0,000 | 0,017 | 0,000 | 0,000 | 0,000 | 0,027 | 0,098 | 0,032 | 0,000 | 0,000 | 0,000 | 0,000 | 0,251 | 0,047 |
| Ttr-TLRγ2 | 0,000 | 0,000 | 0,018 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,105 | 0,000 | 0,000 | 0,053 | 0,000 | 0,141 |
| Ttr-TLRγ3 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,014 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| Ttr-TLRγ4 | 0,174 | 0,235 | 0,106 | 0,187 | 0,337 | 0,288 | 0,366 | 0,313 | 0,233 | 0,121 | 0,342 | 0,281 | 0,467 | 0,475 |
| Ttr-TLRδ | 0,012 | 0,030 | 0,168 | 0,401 | 0,189 | 0,160 | 0,197 | 0,056 | 0,115 | 0,081 | 0,118 | 0,145 | 0,112 | 0,157 |

TEM ≥0,150

TEM <0,150

**Values indicate Standard Error (SE)**

| RSEM_SE | oocyte | 8 hr mid blastula | 19 hr late blastula | 24 hr moving blastula | 26 hr early gastrula | 37 hr mid gastrula | 51 hr late gastrula | 59 hr bilobed gastrula | 68 hr trilobed gastrula | 82 hr early larva | 98 hr late larva | competent larva (131h) | 1 day juvenile | 2 day juvenile |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ttr-TLRα1 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| Ttr-TLRα2 | 0,085 | 0,028 | 0,009 | 0,059 | 0,011 | 0,044 | 0,003 | 0,015 | 0,020 | 0,102 | 0,084 | 0,451 | 0,140 | 0,098 |
| Ttr-TLRα3 | 0,000 | 0,000 | 0,029 | 0,044 | 0,050 | 0,023 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 1,053 | 0,020 | 0,631 |
| Ttr-TLRα4 | 0,072 | 0,213 | 0,267 | 0,188 | 0,416 | 0,324 | 0,026 | 0,065 | 0,228 | 0,014 | 0,175 | 0,995 | 0,349 | 1,358 |
| Ttr-TLRα5 | 0,008 | 0,018 | 0,048 | 0,107 | 0,061 | 0,070 | 0,184 | 0,197 | 0,442 | 0,018 | 0,079 | 0,046 | 0,114 | 0,144 |
| Ttr-TLRβ1 | 0,008 | 0,000 | 0,032 | 0,048 | 0,111 | 0,044 | 0,000 | 0,000 | 0,091 | 0,074 | 0,157 | 0,183 | 0,005 | 0,015 |
| Ttr-TLRβ2 | 0,218 | 0,297 | 0,026 | 0,121 | 0,134 | 0,052 | 0,086 | 0,078 | 0,106 | 0,035 | 0,256 | 0,139 | 0,029 | 0,036 |
| Ttr-TLRβ3 | 0,240 | 0,000 | 0,014 | 0,067 | 0,106 | 0,267 | 0,443 | 0,085 | 0,478 | 0,021 | 0,059 | 0,019 | 0,053 | 0,002 |
| Ttr-TLRβ4 | 0,000 | 0,000 | 0,024 | 0,032 | 0,173 | 0,099 | 0,019 | 0,196 | 0,252 | 0,038 | 0,412 | 0,301 | 0,191 | 0,147 |
| Ttr-TLRβ5 | 0,000 | 0,020 | 0,015 | 0,031 | 0,029 | 0,033 | 0,039 | 0,000 | 0,000 | 0,000 | 0,000 | 0,030 | 0,000 | 0,060 |
| Ttr-TLRγ1 | 0,000 | 0,017 | 0,000 | 0,000 | 0,000 | 0,027 | 0,006 | 0,032 | 0,000 | 0,000 | 0,000 | 0,000 | 0,251 | 0,047 |
| Ttr-TLRγ2 | 0,000 | 0,000 | 0,018 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,105 | 0,000 | 0,000 | 0,053 | 0,000 | 0,141 |
| Ttr-TLRγ3 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,014 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| Ttr-TLRγ4 | 0,053 | 0,040 | 0,023 | 0,005 | 0,231 | 0,154 | 0,040 | 0,004 | 0,091 | 0,033 | 0,115 | 0,045 | 0,009 | 0,181 |
| Ttr-TLRδ | 0,012 | 0,010 | 0,111 | 0,249 | 0,041 | 0,000 | 0,197 | 0,008 | 0,063 | 0,046 | 0,048 | 0,080 | 0,079 | 0,157 |

| Rep_1_kallisto | oocyte | 8 hr mid blastula | 19 hr late blastula | 24 hr moving blastula | 26 hr early gastrula | 37 hr mid gastrula | 51 hr late gastrula | 59 hr bilobed gastrula | 68 hr trilobed gastrula | 82 hr early larva | 98 hr late larva | competent larva (131h) | 1 day juvenile | 2 day juvenile |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ttr-TLRα1** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,006 | 0,000 | 0,000 | 0,000 |
| **Ttr-TLRα2** | 0,300 | 0,139 | 0,162 | 0,084 | 0,059 | 0,034 | 0,032 | 0,063 | 0,127 | 0,114 | 0,031 | 1,694 | 0,342 | 0,638 |
| **Ttr-TLRα3** | 0,000 | 0,000 | 0,000 | 0,000 | 0,068 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,042 | 2,292 | 1,974 | 2,754 |
| **Ttr-TLRα4** | 0,726 | 0,074 | 0,125 | 0,249 | 0,224 | 0,043 | 0,000 | 0,000 | 0,335 | 0,481 | 0,913 | 2,408 | 3,993 | 2,758 |
| **Ttr-TLRα5** | 0,076 | 0,109 | 0,020 | 0,064 | 0,054 | 0,061 | 0,119 | 0,096 | 0,194 | 0,186 | 0,056 | 0,107 | 0,057 | 0,225 |
| **Ttr-TLRβ1** | 0,099 | 0,101 | 0,001 | 0,095 | 0,004 | 0,000 | 0,000 | 0,000 | 0,000 | 0,237 | 0,000 | 0,628 | 0,004 | 0,008 |
| **Ttr-TLRβ2** | 0,490 | 0,517 | 0,228 | 0,301 | 0,248 | 0,071 | 0,137 | 0,172 | 0,089 | 0,133 | 0,560 | 0,312 | 0,065 | 0,064 |
| **Ttr-TLRβ3** | 0,313 | 0,398 | 0,737 | 0,463 | 0,360 | 0,185 | 0,089 | 0,408 | 0,145 | 0,000 | 0,252 | 0,252 | 0,517 | 0,225 |
| **Ttr-TLRβ4** | 0,000 | 0,038 | 0,000 | 0,062 | 0,371 | 0,460 | 0,063 | 0,624 | 0,630 | 0,408 | 0,767 | 0,568 | 0,285 | 0,309 |
| **Ttr-TLRβ5** | 0,000 | 0,045 | 0,000 | 0,140 | 0,066 | 0,075 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,065 | 0,000 | 0,000 |
| **Ttr-TLRγ1** | 0,000 | 0,000 | 0,127 | 0,041 | 0,249 | 0,144 | 0,316 | 0,061 | 0,000 | 0,000 | 0,000 | 0,057 | 0,071 | 0,136 |
| **Ttr-TLRγ2** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,188 |
| **Ttr-TLRγ3** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| **Ttr-TLRγ4** | 0,211 | 0,228 | 0,039 | 0,176 | 0,551 | 0,404 | 0,371 | 0,283 | 0,115 | 0,092 | 0,204 | 0,176 | 0,393 | 0,304 |
| **Ttr-TLRδ** | 0,000 | 0,020 | 0,038 | 0,135 | 0,200 | 0,192 | 0,000 | 0,042 | 0,079 | 0,209 | 0,183 | 0,281 | 0,000 | 0,000 |

| Rep_2_kallisto | oocyte | 8 hr mid blastula | 19 hr late blastula | 24 hr moving blastula | 26 hr early gastrula | 37 hr mid gastrula | 51 hr late gastrula | 59 hr bilobed gastrula | 68 hr trilobed gastrula | 82 hr early larva | 98 hr late larva | competent larva (131h) | 1 day juvenile | 2 day juvenile |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ttr-TLRα1** | 0,000 | 0,000 | 0,000 | 0,019 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,021 | 0,027 | 0,000 | 0,000 |
| **Ttr-TLRα2** | 0,143 | 0,165 | 0,184 | 0,150 | 0,083 | 0,120 | 0,037 | 0,037 | 0,157 | 0,364 | 0,194 | 0,578 | 0,690 | 0,443 |
| **Ttr-TLRα3** | 0,000 | 0,000 | 0,058 | 0,000 | 0,000 | 0,000 | 0,105 | 0,000 | 0,000 | 0,000 | 0,000 | 0,167 | 2,062 | 1,534 |
| **Ttr-TLRα4** | 0,466 | 0,403 | 0,583 | 0,849 | 0,905 | 0,667 | 0,129 | 0,214 | 0,865 | 0,347 | 0,730 | 0,630 | 3,468 | 5,164 |
| **Ttr-TLRα5** | 0,116 | 0,090 | 0,133 | 0,252 | 0,186 | 0,159 | 0,430 | 0,401 | 1,017 | 0,222 | 0,207 | 0,147 | 0,312 | 0,618 |
| **Ttr-TLRβ1** | 0,094 | 0,001 | 0,047 | 0,003 | 0,001 | 0,045 | 0,000 | 0,000 | 0,226 | 0,001 | 0,192 | 0,354 | 0,130 | 0,000 |
| **Ttr-TLRβ2** | 0,082 | 0,025 | 0,235 | 0,079 | 0,058 | 0,014 | 0,065 | 0,076 | 0,314 | 0,116 | 0,034 | 0,069 | 0,140 | 0,086 |
| **Ttr-TLRβ3** | 0,626 | 0,416 | 0,633 | 0,515 | 0,671 | 0,562 | 0,778 | 0,221 | 0,927 | 0,086 | 0,076 | 0,183 | 0,199 | 0,000 |
| **Ttr-TLRβ4** | 0,000 | 0,000 | 0,060 | 0,000 | 0,000 | 0,119 | 0,000 | 0,000 | 0,172 | 0,071 | 0,000 | 0,170 | 0,080 | 0,000 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ttr-TLRβ5** | 0,000 | 0,000 | 0,038 | 0,253 | 0,000 | 0,000 | 0,042 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| **Ttr-TLRγ1** | 0,000 | 0,000 | 0,033 | 0,000 | 0,000 | 0,088 | 0,145 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,123 |
| **Ttr-TLRγ2** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,174 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| **Ttr-TLRγ3** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| **Ttr-TLRγ4** | 0,100 | 0,166 | 0,131 | 0,113 | 0,100 | 0,109 | 0,279 | 0,264 | 0,256 | 0,159 | 0,321 | 0,348 | 0,477 | 0,572 |
| **Ttr-TLRδ** | 0,000 | 0,026 | 0,255 | 0,657 | 0,327 | 0,120 | 0,512 | 0,091 | 0,460 | 0,000 | 0,054 | 0,216 | 0,201 | 0,287 |

| **Kallisto_average** | **oocyte** | **8 hr mid blastula** | **19 hr late blastula** | **24 hr moving blastula** | **26 hr early gastrula** | **37 hr mid gastrula** | **51 hr late gastrula** | **59 hr bilobed gastrula** | **68 hr trilobed gastrula** | **82 hr early larva** | **98 hr late larva** | **competent larva (131h)** | **1 day juvenile** | **2 day juvenile** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ttr-TLRα1** | 0,000 | 0,000 | 0,000 | 0,010 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,014 | 0,014 | 0,000 | 0,000 |
| **Ttr-TLRα2** | 0,222 | 0,152 | 0,173 | 0,117 | 0,071 | 0,077 | 0,035 | 0,050 | 0,142 | 0,239 | 0,113 | 1,136 | 0,516 | 0,541 |
| **Ttr-TLRα3** | 0,000 | 0,000 | 0,029 | 0,000 | 0,034 | 0,000 | 0,053 | 0,000 | 0,000 | 0,000 | 0,021 | 1,230 | 2,018 | 2,144 |
| **Ttr-TLRα4** | 0,596 | 0,239 | 0,354 | 0,549 | 0,565 | 0,355 | 0,065 | 0,107 | 0,600 | 0,414 | 0,822 | 1,519 | 3,731 | 3,961 |
| **Ttr-TLRα5** | 0,096 | 0,100 | 0,077 | 0,158 | 0,120 | 0,110 | 0,275 | 0,249 | 0,606 | 0,204 | 0,132 | 0,127 | 0,185 | 0,422 |
| **Ttr-TLRβ1** | 0,097 | 0,051 | 0,024 | 0,049 | 0,003 | 0,023 | 0,000 | 0,000 | 0,113 | 0,119 | 0,096 | 0,491 | 0,067 | 0,004 |
| **Ttr-TLRβ2** | 0,286 | 0,271 | 0,232 | 0,190 | 0,153 | 0,043 | 0,101 | 0,124 | 0,202 | 0,125 | 0,297 | 0,191 | 0,103 | 0,075 |
| **Ttr-TLRβ3** | 0,470 | 0,407 | 0,685 | 0,489 | 0,516 | 0,374 | 0,434 | 0,315 | 0,536 | 0,043 | 0,164 | 0,218 | 0,358 | 0,113 |
| **Ttr-TLRβ4** | 0,000 | 0,019 | 0,030 | 0,031 | 0,186 | 0,290 | 0,032 | 0,312 | 0,401 | 0,240 | 0,384 | 0,369 | 0,183 | 0,155 |
| **Ttr-TLRβ5** | 0,000 | 0,023 | 0,019 | 0,197 | 0,033 | 0,038 | 0,021 | 0,000 | 0,000 | 0,000 | 0,000 | 0,033 | 0,000 | 0,000 |
| **Ttr-TLRγ1** | 0,000 | 0,000 | 0,080 | 0,021 | 0,125 | 0,116 | 0,231 | 0,031 | 0,000 | 0,000 | 0,000 | 0,029 | 0,036 | 0,130 |
| **Ttr-TLRγ2** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,087 | 0,000 | 0,000 | 0,000 | 0,000 | 0,094 |
| **Ttr-TLRγ3** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| **Ttr-TLRγ4** | 0,156 | 0,197 | 0,085 | 0,145 | 0,326 | 0,257 | 0,325 | 0,274 | 0,186 | 0,126 | 0,263 | 0,262 | 0,435 | 0,438 |
| **Ttr-TLRδ** | 0,000 | 0,023 | 0,147 | 0,396 | 0,264 | 0,156 | 0,256 | 0,067 | 0,270 | 0,105 | 0,119 | 0,249 | 0,101 | 0,144 |

TEM ≥0,150
TEM <0,150

| RSEM_Standard error | oocyte | 8 hr mid blastula | 19 hr late blastula | 24 hr moving blastula | 26 hr early gastrula | 37 hr mid gastrula | 51 hr late gastrula | 59 hr bilobed gastrula | 68 hr trilobed gastrula | 82 hr early larva | 98 hr late larva | competent larva (131h) | 1 day juvenile | 2 day juvenile |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ttr-TLRα1** | 0,000 | 0,000 | 0,000 | 0,010 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,008 | 0,014 | 0,000 | 0,000 |
| **Ttr-TLRα2** | 0,079 | 0,013 | 0,011 | 0,033 | 0,012 | 0,043 | 0,003 | 0,013 | 0,015 | 0,125 | 0,082 | 0,558 | 0,174 | 0,098 |
| **Ttr-TLRα3** | 0,000 | 0,000 | 0,029 | 0,000 | 0,034 | 0,000 | 0,053 | 0,000 | 0,000 | 0,000 | 0,021 | 1,063 | 0,044 | 0,610 |
| **Ttr-TLRα4** | 0,130 | 0,165 | 0,229 | 0,300 | 0,341 | 0,312 | 0,065 | 0,107 | 0,265 | 0,067 | 0,091 | 0,889 | 0,263 | 1,203 |
| **Ttr-TLRα5** | 0,020 | 0,010 | 0,057 | 0,094 | 0,066 | 0,049 | 0,156 | 0,153 | 0,412 | 0,018 | 0,076 | 0,020 | 0,128 | 0,197 |
| **Ttr-TLRβ1** | 0,003 | 0,050 | 0,023 | 0,046 | 0,002 | 0,023 | 0,000 | 0,000 | 0,113 | 0,118 | 0,096 | 0,137 | 0,063 | 0,004 |
| **Ttr-TLRβ2** | 0,204 | 0,246 | 0,003 | 0,111 | 0,095 | 0,029 | 0,036 | 0,048 | 0,113 | 0,009 | 0,263 | 0,122 | 0,038 | 0,011 |
| **Ttr-TLRβ3** | 0,157 | 0,009 | 0,052 | 0,026 | 0,156 | 0,189 | 0,345 | 0,093 | 0,391 | 0,043 | 0,088 | 0,035 | 0,159 | 0,113 |
| **Ttr-TLRβ4** | 0,000 | 0,019 | 0,030 | 0,031 | 0,186 | 0,171 | 0,032 | 0,312 | 0,229 | 0,169 | 0,384 | 0,199 | 0,103 | 0,155 |
| **Ttr-TLRβ5** | 0,000 | 0,023 | 0,019 | 0,057 | 0,033 | 0,038 | 0,021 | 0,000 | 0,000 | 0,000 | 0,000 | 0,033 | 0,000 | 0,000 |
| **Ttr-TLRγ1** | 0,000 | 0,000 | 0,047 | 0,021 | 0,125 | 0,028 | 0,086 | 0,031 | 0,000 | 0,000 | 0,000 | 0,029 | 0,036 | 0,007 |
| **Ttr-TLRγ2** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,087 | 0,000 | 0,000 | 0,000 | 0,000 | 0,094 |
| **Ttr-TLRγ3** | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 | 0,000 |
| **Ttr-TLRγ4** | 0,056 | 0,031 | 0,046 | 0,032 | 0,226 | 0,148 | 0,046 | 0,009 | 0,071 | 0,034 | 0,059 | 0,086 | 0,042 | 0,134 |
| **Ttr-TLRδ** | 0,000 | 0,003 | 0,109 | 0,261 | 0,064 | 0,036 | 0,256 | 0,025 | 0,191 | 0,105 | 0,065 | 0,033 | 0,101 | 0,144 |

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## 7.3 ADDITIONAL PAPER - PAPER III: GENE EXPRESSION IN THE DEVELOPING NEMERTEAN BRAIN INDICATES CONVERGENT EVOLUTION OF COMPLEX BRAINS. IN SPIRALIA.

Paper III

# Gene expression in the developing nemertean brain indicates convergent evolution of complex brains in Spiralia

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## Abstract

**Background:** Nemertea is a clade of worm-like animals, which belongs to a larger animal group called Spiralia (together with e.g. annelids, flatworms and mollusks). Many of the nemertean species possess a complex central nervous system (CNS) with a prominent brain, and elaborated chemosensory and neuroglandular cerebral organs, which have been suggested as homologues to the annelid mushroom bodies. In order to understand the developmental and evolutionary origins of complex nemertean brain, we investigated details of neuroanatomy and gene expression in the brain and cerebral organs of the juveniles of nemertean *Lineus ruber*.

**Results:** In the hatched juveniles the CNS is already composed of all major elements present in the adults, including the brain (with dorsal and ventral lobes), paired longitudinal lateral nerve cords and an unpaired dorsal nerve cord. The TEM investigation of the juvenile cerebral organ revealed that the structure is already composed of several distinct cell types present also in the adults. We further investigated the expression of twelve transcription factors commonly used as brain and cell type markers in bilaterian brains, including genes specific for annelid mushroom bodies. The expression of the investigated genes in the brain is region-specific and divides the entire organ into several molecularly distinct areas, partially overlapping with the morphological compartments. Additionally, we detected expression of mushroom body specific genes in the developing cerebral organs.

**Conclusions:** At the moment of hatching, the juveniles of *L. ruber* already have a similar neuroarchitecture as adult worms, which suggests that further neural development is mostly related with increase in the size but not in complexity. Comparison in the gene expression between *L. ruber* and the annelid *Platynereis dumerilii* and other spiralians, indicates that the complex brains present in those two species evolved convergently by independent expansion of non-homologues regions of the simpler brain present in their common ancestor. The similarities in gene expression in mushroom bodies and cerebral organs might be a result of the convergent recruitment of the same genes into patterning of non-homologues organs or the results of more complicated evolutionary processes, in which conserved and novel cell types contribute to the non-homologues structures.

## Key words:

CNS, brain patterning, neuroanatomy

## Background

Nemertea is a clade of ca. 1300 described species of unsegmented worms, which predominantly occur in marine environments [1-3]. Phylogenetically, they belong to the large animal group called Spiralia (together with e.g. annelids, mollusks and flatforms) [4-12], however, despite recent progress in molecular phylogenetics, their exact position on the spiralian tree of life remains controversial [6-8, 10, 13].

Most nemerteans are active predators, which hunt for their invertebrate prey using a specialized eversible proboscis, a morphological apomorphy of the clade [1, 14-18]. This active lifestyle is accompanied by a relatively complex nervous system, composed of a large, multilobed brain (with two ventral and two dorsal lobes), a pair of lateral medullary nerve cords, extensive peripheral network and multiple specialized sensory organs [17-29]. Among the latter, the most conspicuous are the so-called cerebral (or cephalic) organs – paired structures of neurosecretory and either chemo- or mechanosensory function, located on the lateral sides of the head [17-23, 28, 30-33]. The exact arrangement of the cerebral organs varies between nemertean clades from relatively simple ciliated pits present in some Tubulaniformes, to the complex neuroglandular structures connected both directly to the brain and, through the convoluted ciliated canal, to the external environment in lineid heteronemerteans [17-23, 27, 28, 32, 33]. The phylogenetic analysis of morphological traits in nemerteans indicated that cerebral organs were already present in the last common nemertean ancestor [20]. However, it remains unclear, whether the cerebral organs represent an autapomorphy of nemerteans or homologs to some organs present in other spiralians such as ciliated pits of flatworms [30, 34] or mushroom bodies of annelids [19, 35, 36].

In the present study, we describe the detailed morphology of the nervous system and gene expression in the brain and cerebral organs of the juveniles of *Lineus ruber* (Müller, 1774), a directly developing lineid heteronemertean. *L. ruber* has been studied in past for both adult morphology [20, 22-26, 29-31] and some aspects of its development [29, 37, 38], including the molecular patterning of anterior-posterior axis, germ layers and lateral nerve cords [39, 40]. Comparison of our data with the existing morphological descriptions of the adult nervous system in *L. ruber* [20, 22-26, 29-31] and other closely related species, allows a better understanding of the ontogeny of the complex nemertean nervous system. Additionally, juxtaposition of gene expression profiles in the developing brain of *L. ruber* with that of other Spiralia [39, 41-48] can pinpoint similarities and differences in the molecular patterning of the spiralian brains in general, which in turn can inform evolution of the complex nemertean brain. Moreover, by comparing gene expression in cerebral organs of *L. ruber* and mushroom bodies of a comprehensively studied annelid *P. dumerilii* [49], we can provide new data to test the homology hypothesis of the cerebral organs of nemerteans and mushroom bodies of annelids.

## Results

*Morphology of the nervous system in the juvenile* L. ruber

The investigated juveniles of *L. ruber* were freshly hatched from the egg mass, 42 days after oviposition [40]. We visualized the nervous system of the juveniles by applying antibody staining against tyrosinated tubulin, FMRF-amide and serotonin (5-HT), as well as Sytox green nuclear staining and fluorescent *in situ* mRNA hybridization of the choline acetyltransferase (*ChAT*), a genetic marker of the cholinergic neurons [50].

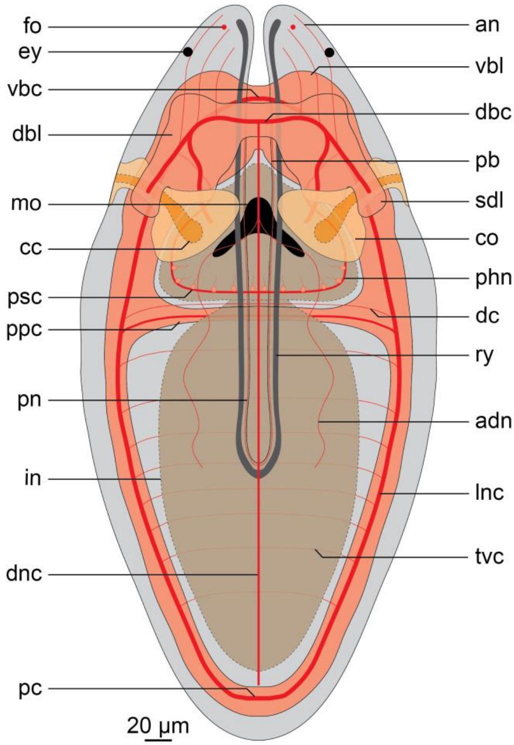


**Fig. 1.** Schematic drawing of the nervous system in 42 days old juveniles of *Lineus ruber*. Anterior is to the top. Abbreviations: *adn* accessory dorsal nerve, *an* anterior nerve, *cc* ciliated canal, *co* cerebral organ, *dbc* dorsal brain commissure, *dbl* dorsal brain lobe, *dc* dorsal commissure, *dnc* dorsal nerve cord, *ey* eye, *fo* frontal organ, *in* intestine, *lnc* lateral nerve cord, *mo* mouth opening, *pb* proboscis, *pc* posterior commissure, *phn* pharyngeal nerve, *pn* proboscis nerve, *ppc* postpharyngeal commissure, *psc* pharyngeal sensory cell, *ry* rhynchocoel, *sdl* superior branch of the dorsal lobe, *tvc* transverse ventral commissure, *vbc* ventral brain commissure, *vbl* ventral brain lobe.

42 days old juveniles have already all major components of the nervous system (Figs. 1 and 2), which is composed of: 1) central nervous system (CNS) with brain, two lateral nerve cords (LNCs) connected by a postpharyngeal and posterior commissures and a single dorsal nerve cord (DNC); 2) stomatogastric nervous system (SNS), especially well developed in the pharyngeal region; 3) innervation of the proboscis; 4) network of fine peripheral nerves; 5) a pair of large cerebral organs; and 6) other sensory structures such as frontal organs and frontal sensory nerves.

The brain is located anteriorly and is divided into four lobes: two ventral (*vbl*, Figs. 1 and 2B, F, H, I) and two dorsal ones (*dbl*, Figs. 1 and 2A, E). Each lobe is composed of the internal neuropile and the external layer of perikarya (Fig. 2C–F, J). Anteriorly both dorsal and ventral lobes are connected by dorsal (*dbc* Figs. 1 and 2A, C, E, G, I) and ventral (*vbc* Figs. 1 and 2B, D, F, H–J) brain commissures, respectively. Thus, the brain neuropile forms a ring around rhynchocoel and proboscis (Fig. 1). Posteriorly, each dorsal brain lobe is further divided into an inferior and a superior branch. The former connects directly to the cerebral organ (see below), while the latter ends blindly on the dorsal side of the animal (Figs. 1 and 2E). The neuropiles of the ventral lobes posteriorly give rise to the LNCs (Fig. 2D, H, J). FMRF-amide-like immunoreactive (FLIR) perikarya and *ChAT*$^+$ cells have been observed in both dorsal and ventral brain lobes (Fig. 2A – F), while serotonin-like immunoreactive (SLIR) perikarya are present only in the ventral lobes (Fig. 2H–J). Both dorsal and ventral commissures and neuropiles of all brain lobes are composed of FLIR, SLIR and tyrosinated tubulin-like immunoreactive (TLIR) neurites (Fig. 2 A–D, G–J).

Three longitudinal nerve cords originate from the brain: a pair of thick LNCs (*lnc*, Figs. 1 and 2A, B, D, F, H–J) and a finer, unpaired DNC (*dnc*, Figs. 1, 2A, G, I). The LNCs are composed of an external layer of perikarya and an internal neuropile (and hence represent medullary nerve cords [51]). The neuropiles are densely packed with TLIR, SLIR and FLIR neurites (*lnc*, Fig. 2 A, B, D, H–J), while numerous *ChAT*$^+$ neuronal cell bodies as well as more sparsely distributed FLIR and SLIR perikarya are mostly present in the anterior section of each LNC (Fig. 2B, D, F, I, J). The LNCs are connected behind the pharynx by a medullary postpharyngeal commissure (*ppc*, Figs. 2B, F, H, J), which is composed of TLIR and SLIR neurites as well as few SLIR and numerous *ChAT*$^+$ perikarya (Fig. 2F and J). At the end of the animal body, both LNCs converge in a posterior commissure (*pc*, Figs. 1, 2B, H), which shows the same immunoreactivity patterns as neuropiles of LNCs. The DNC originates from the dorsal brain commissure. Compared to the LNCs, it is much finer and does not seem to be associated with any perikarya (Figs. 2A, G, I). It is composed of only a few TLIR and SLIR neurites, while anteriorly, a pair of fine FLIR dorsal accessory nerves branch out from it (*adn*, Figs. 1 and 2A). At the level of the pharynx, a fine, SLIR and TLIR dorsal commissure connects dorsal and lateral nerve cords (*dc*, Figs. 1 and 2I).

The SNS is composed of thick TLIR, FLIR and SLIR pharyngeal nerves, which originate from the ventral brain lobes and meander around the pharynx (*phn*, Figs. 1, 2C, D, J). Numerous sensory FLIR and SLIR cells are located along the pharyngeal nerves (*psc*, Fig. 1; *double arrowheads* Fig. 2D, J). Each of those cells has a basal connection to the pharyngeal nerve and an apical process pointing towards the pharyngeal lumen.

Some neural structures are also associated with the proboscis. Two longitudinal TLIR and FLIR nerves extend along the proboscis (*pn*, Figs. 1 and 2C), however their exact origin in the brain remains unclear. Scattered *ChAT*$^+$ cells, of probably sensory function, are present in the epidermis of the proboscis (*yellow arrowheads*, inset in Fig. 2E).

The extensive network of peripheral nerves was detected, especially evident on the ventral side of the animal. It is composed of regular transverse ventral TLIR commissures (*tvc*, Fig. 1; arrowheads, Fig. 2B), some of which are additionally SLIR (*arrowheads*, Fig. 2H–J). A less regular network of SLIR intraepidermal neurites is present on both dorsal and ventral sides of the juvenile (Fig. 2 G–J).

A pair of conspicuous cerebral organs is located on the lateral sides of the head, just behind the brain (*co*, Figs. 1, 2C and E). More details of their morphology can be found in the following section. Other sensory structures, detected in addition to the cerebral organs, includes FLIR and *ChAT*$^+$ anterior sensory cells (*asc*, Figs. 1 and 2 C, E), which likely contribute to the so-called frontal organs [19, 22, 23, 25], and numerous SLIR cephalic nerves extending anteriorly from the brain (*an*, Figs. 1 and 2H). Although 42 days old juveniles already possess rudiments of eyespots [40], we were not able to conclusively detect them in our investigation.

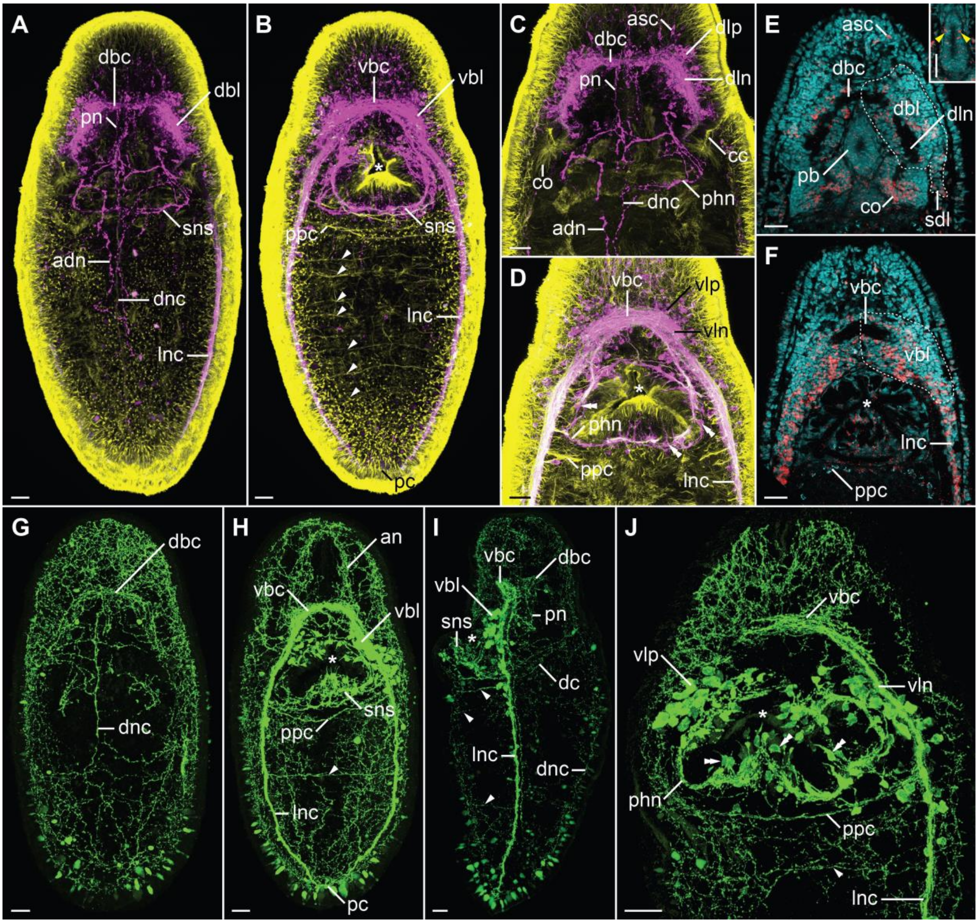


**Fig. 2.** Morphology of the nervous system in 42 days old juveniles of *L. ruber* visualized with CLSM and antibody staining against tyrosinated tubulin (*yellow*, panels **A**–**D**), FMRF-amide (*magenta*, panels **A**–**D**) and serotonin (*green*, panels **G**–**J**) as well as Sytox green nuclear staining (*cyan*, panels **E**, **F**) and *in situ* hybridization with probe against choline acetyltransferase (*red*, panels **E**, **F**). Entire animal in dorso-ventral projection with a focus on dorsal (**A**, **G**) and ventral (**B**, **H**) structures; anterior part of the animal in dorso-ventral projection with a focus on dorsal (**C**, **E**) and ventral (**D**, **F**, **J**) structures, *inset* in panel **E** shows *ChAT* expression in the proboscis (*yellow arrowheads*); **I** lateral projection of the entire animal. Anterior is to the top on all panels. Scale bars 20 µm. Abbreviations: *adn* accessory dorsal nerve, *an* anterior nerve, *asc* anterior sensory cell, *cc* ciliated canal, *co* cerebral organ, *dbc* dorsal brain commissure, *dbl* dorsal brain lobe, *dc* dorsal commissure, *dln* dorsal lobe neuropile, *dlp* dorsal lobe perikaryon, *dnc* dorsal nerve cord, *lnc* lateral nerve cord, *pb* proboscis, *pc* posterior commissure, *phn* pharyngeal nerve, *pn* proboscis nerve, *ppc* postpharyngeal commissure, *sdl* superior branch of the dorsal lobe, *sns* stomatogastric nervous system, *vbc* ventral brain commissure, *vbl* ventral brain lobe, *vln* ventral lobe neuropile, *vlp* vetral lobe perikaryon. *White arrowheads* indicate transverse ventral commissures, *double white arrowheads* pharyngeal sensory cells and *asterisks* the mouth opening.

EdU staining in 60 days old juveniles showed that most of the brain cells at this later developmental stage are not mitotically active in contrast to the cells in other organs, such as proboscis, rhynchocoel or cerebral organs (Fig. 3A and B).

*Detailed morphology of the cerebral organs*

Each cerebral organ is composed of two parts: a distal ciliated canal (*cc*, Figs. 1, 2C, 4B, C), which opens to the exterior on the side of the head (in the posterior part of the so called lateral cephalic slit), and a proximal neuroglandular portion (*co*, Figs. 1, 2C). The lumen of the ciliated canal is slightly curved in 42 days old juveniles, but the characteristic triple right-angle bends, present in the adult lineids [30-32] are not yet evident (*cc*, Fig. 2C). The ciliated canal connects the external environment with the neuroglandular part, which itself is firmly attached to the superior branch of the dorsal brain lobe (Fig. 1, 2E, and 4B, C). A thick TLIR and FLIR nerve of cerebral organ extends from the most posterior part of the dorsal lobe neuropile and penetrates the neuroglandular portion of the cerebral organ (*con*, Fig. 4C). We detected a few FLIR and much more numerous *ChAT*$^{+}$ cells in the neuroglandular portion of the organ (*arrowhead*, Fig. 4C and *arrow*, Fig. 4B, respectively), while serotonin-like immunoreactivity was not detected (data not shown).

To gain further insight into the morphology of the cerebral organs, we supplemented the afore-mentioned confocal laser scanning microscopy (CLSM) based methods with ultrathin sectioning of resin-embedded specimens (60 days old juveniles) and TEM examination of the organ. That allowed us to describe the fine structure of the cerebral organ and ultrastructure of the particular cell types contributing to it. Since all detected cell types correspond directly to the ones described previously by Ling in his investigation of adult *L. ruber* [30], we adopted the terminology used therein.

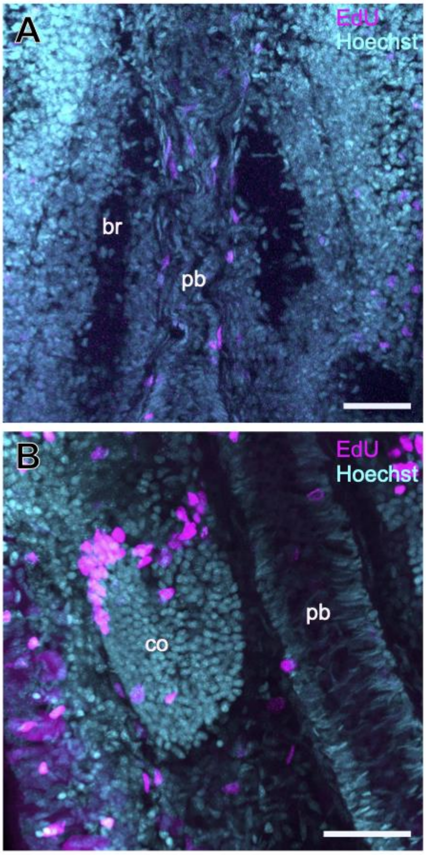


**Fig. 3.** Proliferating cells in the head of 60 days old juveniles of *L. ruber* visualized by incorporation of EdU (*magenta*), counterstained with nuclear marker Hoechst (*cyan*). Dorso-ventral Z-projections of brain region (**A**) and cerebral organ (**B**), with anterior to the top. Scale bars 25 µm. Abbreviations: *br* brain, *co* cerebral organ, *pb* proboscis.

We investigated cross-sections through the neuroglandular portion of the cephalic organ. The mass of the organ is located between the proboscis and the lateral nerve cords (Fig. 4A) and it is penetrated by both the cerebral organ nerve (*con*) and the ciliated canal (*cc*). The ciliated canal is divided into two parallel parts: a larger major ciliated canal (*mjc*) and a smaller minor ciliated canal (*mnc*) (Fig. 4G). Based on the ultrastructure, six distinct cell types can be distinguished in the sectioned area of the cerebral organ. The most numerous are type 1 bipolar cells (*bc1*), which constitute the majority of the cells in the neuroglandular mass (Fig. 4D, E). Their relatively small nuclei are roughly polygonal in cross-section and have dark nucleoplasm with the irregularly distributed chromatin (Fig. 4D). The very similar type 2 bipolar cells (*bc2*) are much less frequent (Fig. 4E). They have the same nuclear size and shape as well as chromatin arrangement as *bc1*, but their nucleoplasm is electron-translucent (Fig.

4E). A relatively few ganglion cells (*gc*) are present in the vicinity of the nerve of cerebral organ (Fig. 4D, E). Those cells have large nucleus that is almost circular in section and displays an electron-translucent nucleoplasm with nucleolus and irregularly distributed chromatin (Fig. 4D). On the dorsolateral side of the cerebral organ a single, large, irregularly shaped cell has been identified as neuroglandular cell (*ngc*, Fig. 4D–F). Its branching, spacious cytoplasm is filled with numerous electron-dense inclusions. Additionally, the Golgi apparatus was observed in the cytoplasm (*ga*; inset, Fig. 4F). A single neuroglial cell (*ng*) was observed on the opposite, ventro-median side of the organ (Fig. 4E). It is less voluminous than the neuroglandular cell, has a darker cytoplasm and more densely packed inclusions. A structure interpreted as a neuroglial axon is visible ca. 3 μm from the neuroglial cell body (*ax*; inset, Fig. 4E). The cells of the ciliated canal (*ccc*) represent the last cell type visible on the examined cross section (Fig. 4D, E). The apical surface of those cells is densely packed with cilia, which are equipped with asymmetrically bifurcating ciliary rootlets (*cr*; inset, Fig. 4G). Numerous mitochondria are present just below the ciliary rootlets, while the lateral sides of the cells are connected apically by desmosomes (*mt* and *ds*, respectively; inset, Fig. 4G). The cilia on the border of the major and the minor canals (*lcc*) are characteristically dilated and form a septum that divides both canals (inset, Fig. 4G). Those cilia indicate the presence of the seventh cell type, lappet cells, although the cells themselves could not be told apart from the other cells of the ciliated canal.

EdU staining of mitotically active cells in the 60 days old juveniles indicted intensive proliferation in cerebral organs, especially in its anterior region (Fig. 3B).

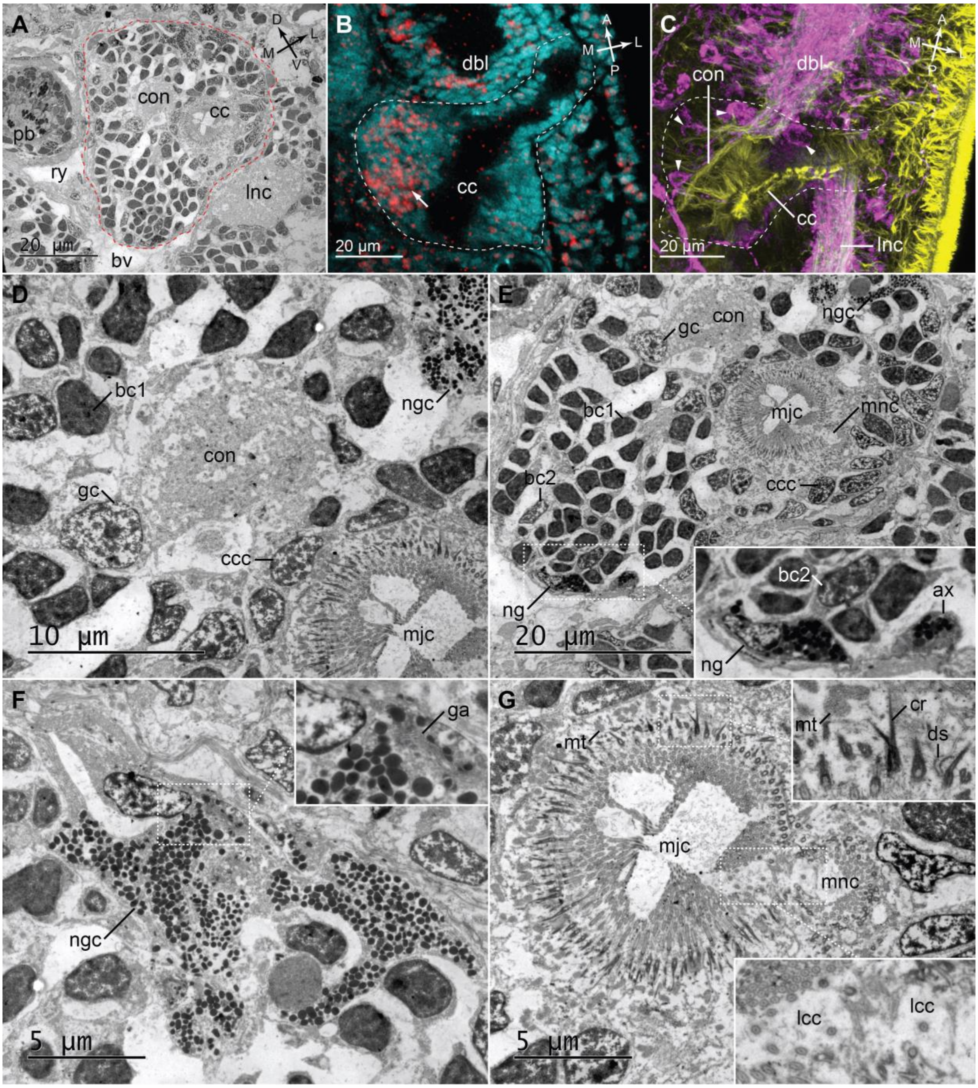


**Fig. 4.** Detailed morphology of cerebral organs in juveniles of *L. ruber*. TEM micrographs of cerebral organs in 60 days old juvenile, showing cross section (**A**) and details of particular regions of the organ (**D**–**G**). Z-projections of cerebral organs in 42-days old juveniles visualized with Sytox green nuclear staining and *in situ* hybridization with probe against *ChAT* (*cyan* and *red*, respectively; **B**) and antibodies against FMRF-amide and tyrosinated tubulin (*magenta* and *yellow*, respectively; **C**). Cerebral organs are outlined in *red* (**A**) and *white* (**B**, **C**). Orientation inside the animal is indicated in the top-right corners in panels **A**–**C** (A, anterior; P, posterior; D, dorsal; V, ventral; M, median; L, lateral). Micrographs in panels **D**–**G**, show magnified areas of panel **A**. White outlined boxes on panels **E**, **F**, **G** indicates areas magnified in corresponding insets. Abbreviations: *ax* neuroglia axon, *bc1* bipolar cell type1, *bc2* bipolar cell type 2, *bv* blood vessel, *cc* ciliated canal, *ccc* ciliated canal cell, *con* nerve of cerebral organ, *cr*

ciliary rootlet, *dbl* dorsal brain lobe, *ds* desmosome, *ga* Golgi apparatus, *gc* ganglion cell, *lcc* dilated cilia of lappet cell, *lnc* longitudinal nerve cord, *mjc* major ciliated canal, *mnc* minor ciliated canal, *mt* mitochondrium, *ng* neuroglia, *ngc* neuroglandular cell, *pb* proboscis, *ry* rhynchocoel. *White arrow* indicates $ChAT^+$ cells in cerebral organ, *white arrowhead* FMRF-amide-like immunoreactivity in cerebral organ.

*Gene expression in the head*

We investigated expression of 12 transcription factors (TFs), which have a role in CNS development of many bilaterians. Those genes include the conserved general brain markers (*otx*, *bf1*), genes involved in brain regional specification (*pax6*, *nk2.1*, *nk2.2*, *rx*, *otp*) and other neural genes, which are co-expressed in the annelid mushroom bodies (*dach*, *emx*, *arx*, *svp*, *tll*).

Expression of *otx* has been previously described for earlier developmental stages of *L. ruber*, in which the gene has a general anterior expression in the head [40]. In the 42 days old juveniles, which we investigated, the gene *otx* is predominantly expressed in the brain (Fig. 5A and B) and cerebral organs (Figs. 5A, 6B). In the brain, *otx* is broadly and uniformly expressed both in dorsal and ventral lobes (Fig. 5A and B). In the cerebral organs it is also widely expressed, both in the ciliated canal and neuroglandular part (Fig. 6B). A similar expression pattern of *otx* in the brain and cerebral organs has been also reported from developing juveniles of closely related *Lineus viridis* [52].

*bf1* is expressed in the brain, cerebral organs, scattered cells in the anterior epidermis and in the rhynchocoel (Figs. 5C and D, 6C). In the brain *bf1* is broadly expressed in the dorsal lobe (Fig. 5C), but in the ventral one it is only detectable in the lateral clusters of cells (Fig. 5D). The detected expression of *bf1* in the cerebral organ is very strong in the neuroglandular part, whereas we did not detect a signal in the ciliated canal (Fig. 6C).

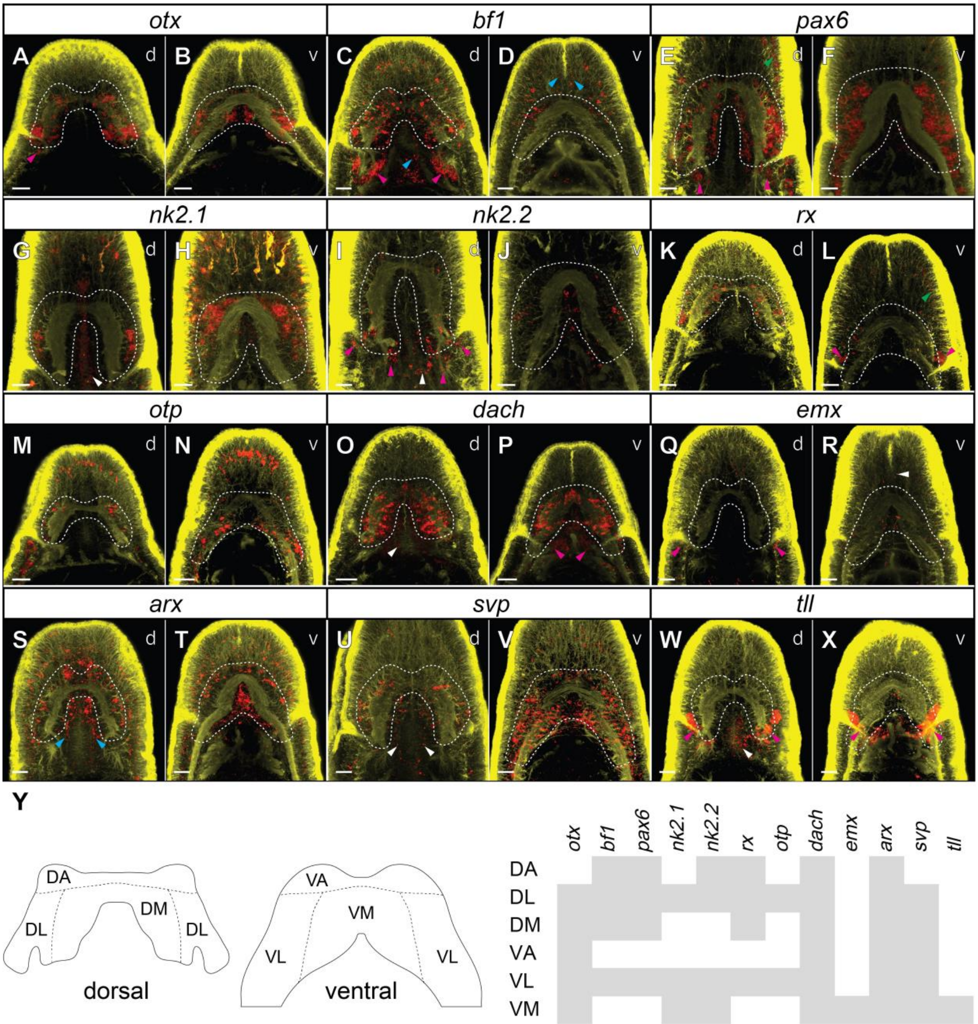


**Fig. 5.** Expression of investigated transcription factors in the heads of 42 days old juveniles of *L. ruber*. **A**–**X** fluorescent *in situ* RNA hybridization, for each panel the name of the hybridized gene is shown in the white box above the micrographs. Fluorescent signal from RNA probes is in *red*, from antibody staining against tyrosinated tubulin in *yellow* and brain lobes are outlined in *white*. All animals are shown in dorso-ventral projection with anterior to the top; the letter in the top-right corner of each panel indicates whether focus is on dorsal (*d*) or ventral (*v*) structures. Detailed expression patterns are described in the text. *Magenta* arrowheads indicate expression in the cerebral organs, *blue* in the rhynchocoel, *green* in the lateral cephalic slits, *white* in the proboscis. Scale bars 20 µm. **Y** map of gene expression in the *L. ruber* brain. Grey bars indicate that gene is expressed in a particular brain region. Abbreviations: *DA* dorso-anterior brain domain, *DL* dorso-lateral brain domain, *DM* dorso-median brain domain, *VA* ventro-anterior brain domain, *VL* ventro-lateral brain domain, *VM* ventro-median brain domain.

Expression of *pax6*, *nk2.1* and *nk2.2* has been previously investigated in the juveniles *of L. ruber* in relation to the nerve cord patterning [39], however, the expression of those three genes in the brain was not described in the details that we provide here. In the head region, *pax6* is expressed in the brain, the epidermal cells of the lateral cephalic slits and in the cerebral organs (Figs. 5E and F, 6D). The gene is broadly expressed in the dorsal lobes (Fig. 5E), while in the ventral ones its expression is restricted to the lateral portions of the brain (Fig. 5F). In the cerebral organs the gene is expressed in the stripe of cells on the lateral side of the neuroglandular portion (Fig. 6D).

In the head region, *nk2.1* is expressed in the brain and proboscis (Fig. 5G and H). In the dorsal lobes the gene is expressed only in the small lateral clusters of cells (Fig. 5G), while on the ventral side the gene is broadly expressed both in the median and lateral domains (Fig. 5H). *nk2.1* is not expressed in the cerebral organs.

*nk2.2* is expressed in the brain, proboscis and cerebral organs (Fig. 5I and J). In the dorsal brain lobes, the gene is expressed in large clusters of posterior cells and in scattered anterior domains (Fig. 5I), whereas ventrally, it is expressed in median and lateral cell clusters (Fig 5J). Expression in the cerebral organs is detected in isolated domains of both ciliated canal and neuroglandular portion (Fig. 5I).

The gene *rx* is expressed in the brain, anterior sensory organs, epidermal cells of lateral cephalic slits and in the cerebral organs (Figs. 5K and L, 6E). Dorsally, the gene is expressed in isolated cells distributed relatively uniformly throughout the brain lobes (Fig. 5K). In the ventral lobes, *rx* is expressed only in a pair of postero-lateral cell clusters (Fig. 5L). In the cerebral organs, the gene is specifically expressed in the cluster of epidermal cells at the anterior side of the ciliated canal opening (Fig. 6E).

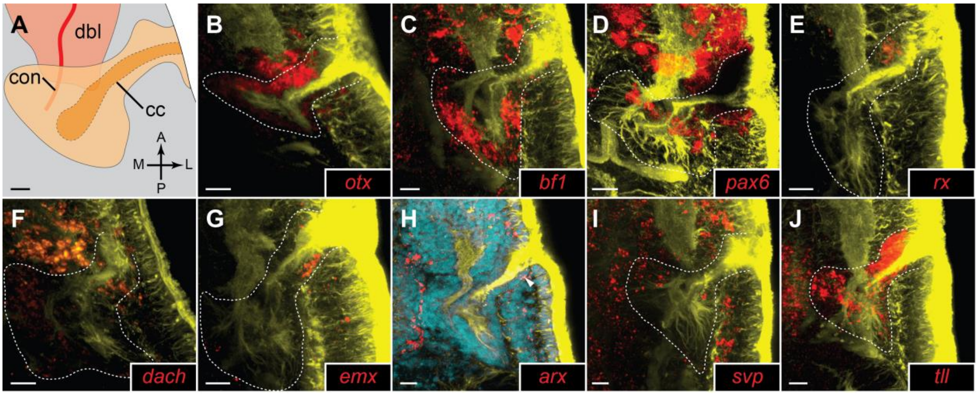


**Fig. 6.** Details of gene expression in the cerebral organs of 42 days old juveniles of *L. ruber*. **A** schematic drawing of the cerebral organ and accompanying neural structures, orientation in the animal is indicated in bottom-right corner (A, anterior; P, posterior; M, median; L, lateral). Abbreviations: *cc* ciliated canal, *con* nerve of cerebral organ, *dbl* dorsal brain lobe. **B**–**J** fluorescent *in situ* RNA hybridization, for each panel the name of hybridized gene is provided in the bottom-right corner. Fluorescent signal from RNA probes is in *red*, from antibody staining against tyrosinated tubulin in *yellow* and from Sytox green nuclear staining in *cyan*; cerebral organs are outlined in *white*. The detailed expression patterns are described in the text. White arrowhead indicates *arx*⁺ cell at the posterior side of the ciliated canal opening. Scale bars 10 μm.

Expression of *otp* is detectable in the brain, LNCs, and numerous anterior sensory cells (Fig. 5M and N). In the dorsal lobes, the gene is expressed only in a relatively few lateral cells (Fig. 5M), while ventrally it is also predominantly expressed in the lateral cells of the brain lobes, but its expression was also detected in the more median cells contributing to the mouth innervation and anterior part of the LNC (Fig. 5N).

In the head region, the gene *dach* is expressed in the brain, cerebral organs, proboscis and few isolated anterior cells (Figs. 5O and P, 6F). The expression in the brain is rather uniform and transcripts of the gene were detected in all regions of both dorsal and ventral lobes (Fig. 5O and P). In the cerebral organs, the gene was detected in some of the cells of both the ciliated canals and the neuroglandular portion (Fig. 6F).

Expression of the gene *emx* was detected in the brain, cerebral organs, proboscis, and cells along anterior cephalic nerves (Figs. 5Q and R, 6G). In the brain the gene is expressed only in a few cells in the ventro-median domain (Fig. 5R). In the cerebral organs the gene transcripts were detected in the cells at the posterior side of the ciliated canal opening and in a single median cell in the neuroglandular part of the organ (Fig. 6G).

The TF *arx* has a broad expression in the anterior body of the juvenile *L. ruber*. It is expressed in the brain, rhynchocoel, epidermal cells, anterior sensory cells and in the cerebral organs (Figs. 5S and T, 6H). In both dorsal and ventral brain lobes, its expression was detected in numerous anterior, lateral and median cells (Figs. 5S and T). In contrast, the expression in the cerebral organs was restricted to a single cell at the posterior side of the ciliated canal opening (Fig. 6H).

The gene *svp* is also broadly expressed in anterior structures; its expression was detected in the brain, cerebral organs, LNCs, anterior sensory cells and proboscis (Figs. 5U and V, 6I). In the dorsal brain lobes, it is expressed in cells distributed through the lateral and median regions (Fig. 5U), while ventrally it is expressed uniformly in the entire ventral lobes (Fig. 5V). In the cerebral organs, expression of *svp* was detected in some anterior and lateral cells of the neuroglandular part (Fig. 6I).

Transcripts of the gene *tll* were detected in the brain, cerebral organs and proboscis (Figs. 5W and X, 6J). Expression in the brain was restricted just to a few cells posteriorly to the ventral commissure (Fig. 5X). Signal from the probes against *tll* was extremely strong in the cerebral organs (Fig. 5W and X) and was observed throughout the entire structure in cells of both the ciliated canal and the neuroglandular portion (Fig. 6J).

The brain of the juvenile *L. ruber* is divided by commissures and lobe neuropiles into eight regions: unpaired dorso-anterior, dorso-median, ventro-anterior and ventro-median regions as well as paired dorso-lateral and ventro-lateral areas (Fig. 5Y). Mapping of the above-described gene expression patterns onto those brain domains reveled that most of the regions express unique combination of the TFs (Fig. 5Y). The only brain regions which seem to express the same sets of TFs are dorsal and ventral lateral domains (Fig. 5Y).

*Gene co-expression during brain development*

To further explore co-expression of some of the TFs in the brain, we performed double *in situ* hybridization of the selected brain patterning genes (*nk2.1*, *nk2.2*, *pax6* and *rx*). In addition to the investigation of 42 days old juveniles, we also examined co-expression of those genes in the earlier developmental stage, 25 days old early juveniles, in order to test whether the observed co-expression patterns are conserved throughout ontogenesis.

The CNS of 25 days old juveniles shows much simpler morphology when compared to the hatched juveniles (Fig. 7A). It is composed of LNCs, which merge anteriorly in the brain with two commissures – a thicker ventral and thinner dorsal – that form a ring shaped neuropile around the developing proboscis rudiment. At this developmental stage, the brain is not yet divided into the dorsal and ventral lobes and the cerebral organs are not fully formed, being mainly composed by the ciliated canal, that is not directly connected with the brain [40].

In the brain of 25 days old juvenile, *nk2.1* is expressed along the ventral commissure and in the lateral parts of the brain (Fig. 7B, C, E, G). In its lateral domains the gene is co-expressed with *pax6* (blue arrowheads, Fig. 7B and C) and *rx* (blue arrowheads, Fig. 7G). Additionally, some of the lateral *nk2.1*$^+$ cells also express *nk2.2* (blue arrowheads, Fig. 7E). The more median *nk2.1*$^+$ cells that are associated with the ventral commissure are devoid of *pax6*, *nk2.2* and *rx* expression (white arrowheads, Fig. 7C, E, G). In addition to the expression in lateral domains, *pax6*, *nk2.2* and *rx* are also expressed in cells associated with the dorsal commissure, which do not co-express *nk2.1* (white arrowheads, Fig. 7B, D, F).

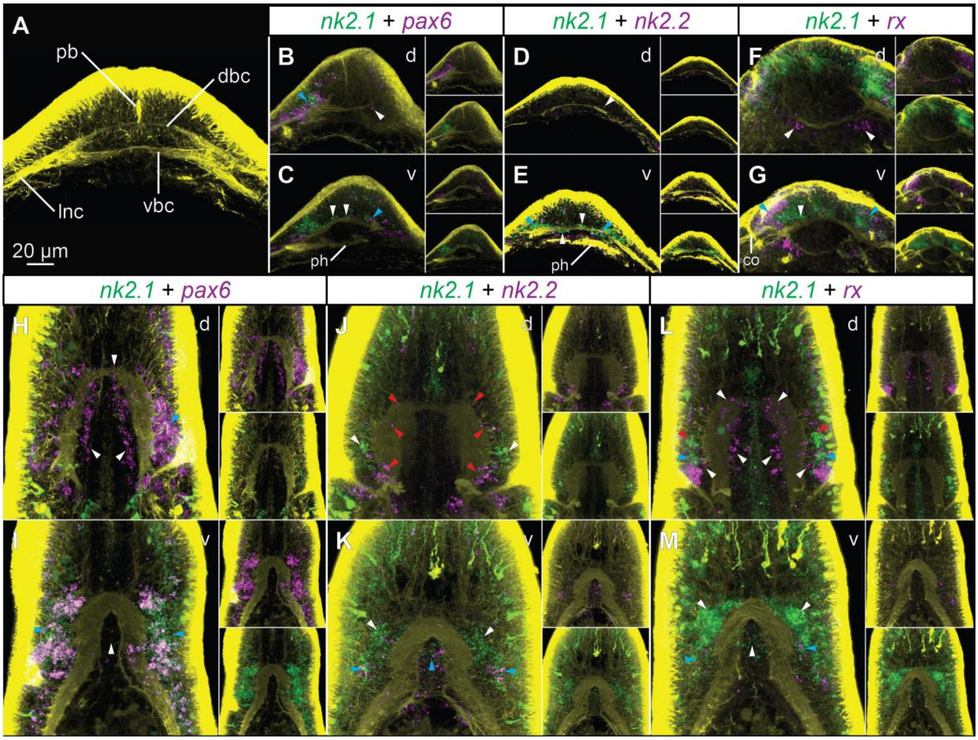


**Fig. 7.** Co-expression of brain patterning genes in the developing brain of *L. ruber*. **A** morphology of the brain in 25 days old juveniles. **B**–**G** co-expression in the brain of 25-days old juveniles. **H**–**M** co-expression in the brain of 42-days old juveniles. For each panel the color-coded names of hybridized genes are shown in the white box above the micrographs. *White* and *red* arrowheads indicate exclusive expression of one of the hybridized genes, *blue* arrowheads indicate co-expression. All animals are shown in dorso-ventral projection with anterior to the top; the letter in the top-right corner of each panel indicates whether the focus is on dorsal (*d*) or ventral (*v*) structures. Micrographs on panels **B**–**M** are not to the scale. Abbreviations: *co* cerebral organ, *dbc* dorsal brain commissure, *lnc* lateral nerve cord, *pb* proboscis rudiment, *ph* pharynx.

The analysis of gene co-expression in the 42 days old juveniles generally corroborates the expression map based on single gene hybridization, however it allows more detailed description of the brain molecular regionalization. In the dorsal brain *pax6* is broadly expressed in the lateral and median domains (white arrowheads, Fig. 7H) and only small clusters of lateral cells co-express *pax6* and *nk2.1* (blue arrowhead, Fig. 7H). In the ventral lobes, the lateral cells co-express *pax6* and *nk2.1* (blue arrowheads, Fig. 7I), while cells in the median domain express only *nk2.1* (white arrowhead, Fig. 7I). *nk2.1* and *nk2.2* are not co-expressed in the dorsal brain (Fig. 7J). *nk2.1* is expressed in the most lateral cells of the dorsal brain (white arrowheads, Fig. 7J), while *nk2.2* is expressed in the large, more posterior domains and in scattered cells in the anterior brain region (red arrowheads, Fig. 7J). In the ventral brain, both genes are co-expressed in the postero-lateral and median domains (blue arrowheads, Fig. 7K), however *nk2.1* has much broader ventral expression with many *nk2.1*$^+$ cells devoid of *nk2.2* expression (white arrowheads, Fig. 7K). *rx* is expressed in scattered anterior, median and lateral cells in the dorsal brain, which do not co-express *nk2.1* (white arrowheads, Fig. 7L). In the lateral parts of the brain some cells co-express *rx* and *nk2.1* (blue arrowheads, Fig. 7L), while some *nk2.1*$^+$ cells do not express *rx* (red arrowheads, Fig. 7L). In the ventral brain the antero-lateral and median *nk2.1*$^+$ cells do not express *rx* (white arrowheads, Fig. 7M), while small clusters of postero-lateral cells co-express both genes (blue arrowheads, Fig. 7M).

On the whole, comparison of gene co-expression between 25- and 42-days old juveniles shows that the general molecular patterning of the developing brain is retained throughout development. The ventro-median region expresses *nk2.1* but not *pax6* nor *rx*. The lateral brain includes cells co-expressing *nk2.1* with *pax6*, *nk2.2* and *rx*, while dorsal brain is mainly composed of *pax6*, *nk2.2* and *rx* positive cells which do not co-express *nk2.1*. The differences between both life stages are primarily associated with the more complex architecture of the brain in 42 days old juveniles, which requires a more intricate developmental control, nevertheless the most general gene expression patterns are conserved.

**Discussion**

*Comparison of juvenile and adult morphology*

Nervous system has been investigated in great detail in adult *Lineus ruber* [20, 22-26, 29-31] and *Lineus viridis* [19, 20, 24, 25], a morphologically similar species that belongs to the same species complex [53, 54]. Comparison between the juvenile and adult worms reveals that all major nervous structures described in the adults are already present in the 42 days old juveniles, indicating that at this stage the general neuroarchitecture is already fully formed and that further development is mostly related with increase in the size but not morphological complexity. The same pattern is observed in number and diversity of cell types contributing to the cerebral organs. There are, however, some minor differences in immunoreactivity patterns between both life stages. For instance, SLIR perikarya have been reported in the dorsal brain ganglia of adult *L. ruber* [23], while we observed immunoreactivity against serotonin only in the ventral brain ganglia of the juveniles (Fig. 2I). This indicates, that even though the general morphology of the brain is already established at the moment of hatching, the following growth of the brain is not purely quantitative, but also new cell types are added in some brain regions during further development. Moreover, staining of mitotically active cells showed that in 60 days old juveniles cell proliferation in the brain is lower than in the other organs, while the cells of the cerebral organs are still intensively dividing (Fig. 3), indicating allometric growth of the CNS.

The major postpharyngeal commissure, which ventrally connects the lateral nerve cords, is the only juvenile neural structure which does not correspond directly to any of the elements of the adult nervous system of *L. ruber* [20, 22, 29] or, to our best knowledge, of any other nemertean, which nervous system has been studied thus far [e.g. 17-19, 20, 21, 28, 55-58]. In adult nemerteans, the lateral nerve cords are connected by numerous delicate ventral commissures, that are composed just of bundles of neurites and are considered as part of the peripheral nervous system. Conversely, the postpharyngeal commissure described in this study is associated with few SLIR and numerous *ChAT*+ perikarya and has typical medullary arrangement, markedly different from the remaining ventral commissures (Figs. 1 and 2). There are two possibilities to explain this discrepancy in morphology of both stages: either the commissure degenerates during ontogeny or, due to the allometric growth, becomes much less prominent in later developmental stages and was overlooked in previous investigations.

Nevertheless, the observation of the postpharyngeal ventral commissure in a nemertean is interesting since similar structures are present in numerous annelids (e.g. the first commissure connecting ventral nerve cords [59-64]), as well as in all major clades of gastrotrichs [65-67] and gnathiferans [68-71]. Therefore, the distribution of this character on the phylogenetic tree raises the possibility that the ventral postpharyngeal commissure connecting the major nerve cords might represent a plesiomorphic spiralian trait retained in some form in numerous clades.

*Expression of brain patterning genes in Spiralia*

Molecular patterning of the brain has been investigated in relatively many spiralians, representing diverse clades with broad spectrum of morphological complexity of their brains (Tab. 1). Among those species, the best studied is the annelid *Platynereis dumerilii*, which possesses a relatively complex brain with multiple morphologically, functionally and developmentally distinct regions [42, 49, 72-74]. One of the important characteristics of gene expression patterns during the development of the *P. dumerilii* brain is regional restriction of *nk2.1* expression to the ventro-median region and *pax6* expression in the lateral domains (including eyes and mushroom bodies), with only the minimal overlap of expression of both genes (Fig. 8A; [42, 49]). This expression pattern resembles the one observed in vertebrates [75, 76] and has been proposed as an ancestral bilaterian trait [42]. Although a comparable expression of those two genes is also witnessed in some Spiralia (Tab. 1), including other annelids [43, 47, 48], rotifers [39] and brachiopods [39, 46, 77-79], we did not retrieve a similar pattern in neither 25- nor 42-days old juveniles of *L. ruber* (Figs. 7B, C, H, I and 8B). *nk2.1* is indeed mostly expressed in the ventral domain (Figs. 5H, 8B), however, it is broadly co-expressed with *pax6* in the ventral lobes and in the small dorso-lateral domains (Figs. 7H, J, 8B); while *pax6* shows expression not only in the lateral domains but is generally broadly expressed throughout the entire brain (including the dorso-median domain), with the only exception of the small ventro-median region (Figs. 5E, F, 8B). A very similar expression of *nk2.1* and *pax6* has been observed in planarians, where *nk2.1* is expressed mostly in the ventral portion of the brain [44, 45], while one of the *pax6* paralogs, *pax6A*, is broadly expressed in the brain tissue [44, 80]. A further parallel between planarians and *Lineus* is associated with a seemingly diminished role of *pax6* in eye formation: *pax6* is not expressed during eye development neither in *L. ruber* (this study) nor in *L. viridis* [81] (although it seems to have a role in eye regeneration in *L. sanguisues* [81]), while in flatworms eye regeneration has been demonstrated to be *pax6* independent [80]. The role of *pax6* in eye patterning is otherwise highly conserved among bilaterians [e.g. 82, 83, 84]. Due to the unstable position of Nemertea on the spiralian phylogeny [e.g. 6-8, 10], it is currently impossible to determine whether those similarities between platyhelminths and nemerteans are due to the convergent evolution, a common evolutionary innovation or retention of ancestral plesiomorphic conditions in both lineages.

**Table 1.** Expression of the selected genes in the spiralian brains.

| **Species** | **Clade** | **Brain type** | **Gene expression in the brain** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ***pax6*** | **ref** | ***nk2.1*** | **ref** | ***nk2.2*** | **ref** | ***rx*** | **ref** |
| *Lineus ruber* | Nemertea | complex | broadly expressed with the exception of ventro-median domain | this study | ventral brain, dorso-lateral domains | this study | scattered expression in ventral, dorso-lateral and dorso-posterior domains | this study | dorsal brain, ventro-lateral domains | this study |
| *Platynereis dumerilii* | Annelida | complex | paired lateral domains | [42, 49] | ventro-median domain | [42, 49] | no expression in the brain | [41] | anterior brain | [42] |
| *Dimorphilus gyrociliatus* | Annelida | compact | paired lateral domains | [43] | ventro-median and medio-lateral domains | [43] | no expression in the brain | [43] | N/A | |
| *Capitella teleta* | Annelida | compact | paired lateral domains | [48] | *nk2.1a*: paired medio-lateral domains<br>*nk2.1b*: paired medio-later domains | [47] | N/A | | N/A | |
| *Terebratalia transversa* | Brachiopoda | larval apical organ | paired dorso-lateral domains | [77, 79] | ventral domain | [46, 78] | no expression in the apical organ | [39] | N/A | |
| *Novocrania anomala* | Brachiopoda | larval apical organ | dorso-lateral domain | [79] | ventral domain | [78] | no expression in the apical organ | [39] | N/A | |
| *Phoronopsis harmeri* | Phoronida | larval apical organ | no expression in the apical organ | [85] | no expression in the apical organ | [86] | N/A | | N/A | |
| *Schmidtea mediterranea* | Platyhelminthes | compact | *pax6A*: broadly expressed throughout the brain<br>*pax6B*: lateral brain | [44] | ventral brain, dorso-median domains | [45] | no expression in the brain | [87] | N/A | |
| *Epiphanes senta* | Rotifera | compact | paired lateral domains | [39] | *nk2.1a*: dorso-median domain<br>*nk2.1b*: median domain<br>*nk2.1c*: vento-median domain | [39] | paired lateral domains | [39] | N/A | |

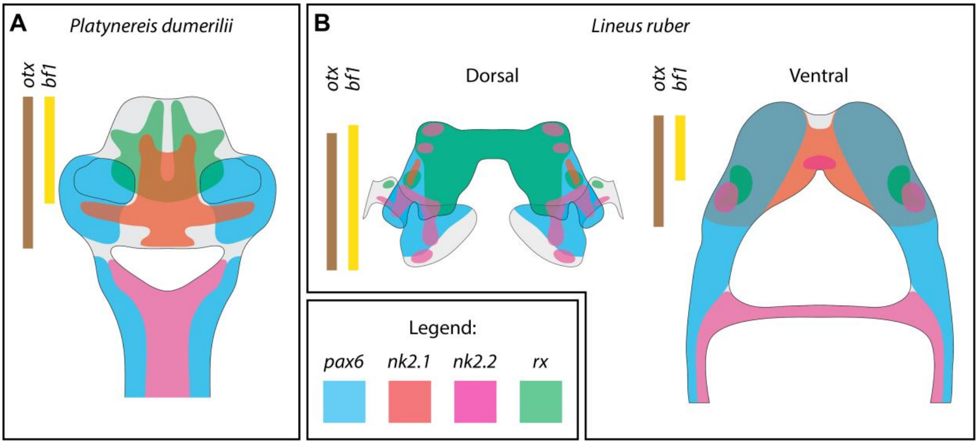


**Fig. 8.** Comparison of gene expression in the CNS of (**A**) annelid *Platynereis dumerilii* (based on results from [41, 42, 49]) and (**B**) nemertean *Lineus ruber* (based on current study and [39]).

Another important differences in expression of brain patterning genes between *L. ruber* and other Spiralia includes the expression of *nk2.2* within numerous brain domains of *L. ruber* (while the gene lacks brain expression not only in annelids [41, 43], but also in brachiopods [39] and flatworms [87]) as well as broad expression of *rx* in the dorsal lobes of the nemertean brain (*versus* their more rostral expression in *P. dumerilii* [42, 49]). Altogether this comparison shows that complex brains of nemerteans, and especially their dorsal lobes, show little resemblance in the molecular patterning to the complex brains of *P. dumerilii* (Fig. 8), which in turns seem to share more molecular similarities with simpler brains of other annelids and apical organs of brachiopod larvae (Tab. 1). This observation, in concert with morphological data [21, 64, 88], indicates that complex brains of nemerteans and errant annelids evolved convergently, due to e.g. similar selective pressure associated with predatory/active life style [89]. We propose that the increase in the brain size and complexity in those two lineages was achieved by independent expansions of non-homologous regions of simpler brains present in their respective ancestors.

Some of the investigated nemertean brain patterning genes are also expressed in the proboscis (*nk2.1*, nk2.2, *dach*, *svp*, *tll*) and rhynchocoel (*bf1*, *arx*), two morphological apomorphies of Nemertea [15, 16]. Taking into account that the proboscis is a highly innervated structure [this study; also 15-20, 22, 23, 25, 26, 29, 57, 58, 90], the neuronal genes in the proboscis might be expressed in the developing neuronal network of the organ. Comparable results were obtained by body region-specific transcriptomics of the nemertean *Notospermus geniculatus*, in which expression of some of the neuronal markers (e.g. *elav*, *syt12*) was also detected in the proboscis [91]. Expression of *arx* and *bf1* in the rhynchocoel, a coelom derived structure [16, 92], seems more peculiar, since those genes have a generally conserved neuroectodermal expression in Bilateria [46, 93-97]. However, *arx* is also expressed in clade-specific morphological structures of brachiopods (in chaetal sacs and protegulum forming epithelium [98, 99]), annelids (in chaetal sacs [100]) and mollusks (in radula formative tissue [101]). Therefore, our data just further expand the list of potential co-options of *arx* into patterning of spiralian evolutionary novelties.

*Are mushroom bodies and cerebral organs derived from the same ancestral organs?*

In numerous annelid brains, morphologically distinct structures, referred to as mushroom bodies, are present, which have allegedly chemosensory and cognitive functions [35, 36, 49, 73, 102-107]. There is an ongoing discussion on whether those structures are part of the ancestral annelid body plan or whether they evolved more recently in one of the annelid subclades [35, 73, 108]. However, their phylogenetic distribution (especially the lack of comparable structures in Palaeoannelida and Sedentaria [64, 88, 109]) favors the latter option [64, 88, 108, 110].

Nevertheless, morphologically similar structures are also present in Panarthropoda [36, 105, 111-114], which lead some authors to the idea that mushroom bodies-like structures were already present in the common protostome ancestor [36, 49, 73, 105]. Although similarities in molecular patterning of annelid mushroom bodies and vertebrate pallium led to the assumption that both structures originated from the same sensory and associative brain center of hypothetical ancestral bilaterians [49], such homology statements, based on observation of only two phylogenetically distant clades, are always at the best case highly tentative [89, 115].

Cerebral organs of nemerteans, in contrast to the annelid mushroom bodies, can be unequivocally reconstructed as present in the last common nemertean ancestor [20, 22, 28]. However, it remains unresolved whether they are nemertean evolutionary novelty or rather homologs of the mushroom bodies of annelids [19, 35, 36] or the lateral ciliated pits present in catenulids and macrostomids [30, 34, 116, 117], the two earliest sequentially branching platyhelminth clades [118]. Similarities between the mushroom bodies of annelids and the cerebral organs of nemerteans are rather superficial: the former are integral parts of the brain and are not connected to the external realm, while the latter are always contacting ambient environment and, especially in Hoplonemertea, might be spatially separated from the CNS [17, 28, 32, 33]. On the other hand, the function, general morphology, connectivity and fine structure of cerebral organs of nemerteans and ciliated pits of flatworms bear a strong resemblance [30, 34, 116, 117], making their homology much more likely. Taking into account the arrangement of the cerebral organs in various nemertean clades, the "ciliated pit" organization seems to represent an ancestral character state also in nemerteans [19-21]. If one accepts that the cerebral organs of nemerteans and ciliated pits of catenulids and macrostomids are homologues [34], then, depending on the phylogenetic position of nemerteans, there are two possible scenarios of their evolution: 1) If nemerteans are sister group to platyhelminths (Parenchymia hypothesis [7, 119]), then the ciliated pits-like structures represent a synapomorphy of Parenchymia. 2) On the other hand, if nemerteans are closer to annelids than flatworms [5, 6, 8, 10], then the presence of ciliated pits might represent a plesiomorphic condition, present also in the annelid ancestor.

In the face of the above-discussed concerns about the homology of mushroom bodies and cerebral organs, we were surprised to find that cells constituting the cerebral organs express the same set of transcription factors as mushroom bodies of annelids (with both structures being additionally free of *nk2*.1 expression). Although all nine of the annelid mushroom body markers, which expression we tested, were expressed in the cerebral organs of *L. ruber*, they were not co-expressed uniformly throughout the entire structure. Some genes (*otx*, *bf1*, *dach* and *tll*) were expressed in all regions of the organ, while others were restricted only to some cells in the neuroglandular portion (*pax6*, *emx*, *svp*) or the ciliated canal (*rx*, *emx*, *arx*). The complicated landscape of TFs expression in *L. ruber* correlates well with the fact, that the cerebral organs of 60 days old juveniles are already composed of numerous diverse cell types, including neurons, glia cells, glandular cells and ciliated epidermal cells (Fig. 4) as well as still dividing, possibly not fully differentiated, cells (Fig. 3). Unfortunately, with the resolution of our data, we were not able to pinpoint co-expression of particular TFs with specific cell types contributing to the organ. In *P. dumerilii* these TFs are also not expressed uniformly in the entire mushroom body and show regionalized expression [49], however, their regionalization does not simply correspond to the one observed in the cerebral organs of *L. ruber*. For example, *otx* and *tll* are expressed only in the subset of neurons constituting mushroom body, while expression of *pax6*, *arx* and *svp* is detected in most of the cells forming the organ [49]. Therefore, even though the same set of genes is expressed in both types of organs, their exact co-expression in particular cell types is probably divergent and the apparent similarities in gene expression profiles between both organs might be more superficial than they appear on the first sight.

A further problem with the interpretation of the gene expression patterns in the cerebral organs is related to the fact that, both in annelid and in nemertean, it remains unknown whether those TFs interact in the same gene regulatory network (GRN) or whether they are independently expressed in different, unrelated cell types. If they are part of the same GRN, then co-option of the ancestral regulatory program into patterning of non-homologues structures might explain the observed similarities. If indeed the ciliated pits-like structures, homologues to the cerebral organs of nemerteans, were present in the annelid ancestor (see above) it is possible to envision a recruitment of the established genetic control of those organs into the patterning of chemoreceptive portion of the brain in the ancestral errant annelid. On the other hand, if the genes are not part of the same GRN and instead act independently in particular cell types (which is supported by non-corresponding, region-specific expression of particular TFs in mushroom bodies and cerebral organs) a more complicated mechanism might account for the observed similarities. For instance, some of the cell types present in both organs might be homologues and derived from the common ancestor, but the organs containing those cell types are convergent and include other, unrelated and lineage-specific cell types. This could happen due to the reduction of the ciliated duct and the secretory cells and further integration of the neural part of the ancestral ciliated pits with the CNS in annelids. A solid phylogenetic position of Nemertea, analysis of function and interactions of the studied TFs as well as additional gene expression data from catenulids, macrostomids and Palaeoannelida are needed to ascertain on any of those evolutionary scenarios.

## Conclusions

In this study, we investigated the morphology and gene expression in the developing CNS of the nemertean *Lineus ruber*. At the moment of hatching, juveniles of *L. ruber* have already all major components of the adult nervous system, which indicates that further development is mostly related with increase in the size but not morphological complexity. This likeness corelates well with a similar predatory lifestyle of both juveniles and adults [40]. Comparison of gene expression in the brain of *L. ruber* and the annelid *P. dumerilii* [41, 42, 49] indicates that complex brains, observed in those two animal species, evolved convergently by independent expansion of non-homologues regions of simpler ancestral brains. Such scenario corresponds with the similar conclusions drawn by comparative morphology [21, 64, 88]. In contrast to the discrepancies in gene expression in the brains, we observed that the same set of transcription factors, which is expressed in the mushroom bodies of *P. dumerilii* [49] is also expressed in the cerebral organs of *L. ruber*. These similarities might be a result of convergent recruitment of the same GRN into patterning of non-homologue organs or indicators of the homology of some cell types contributing to mushroom bodies and cerebral organs that could evolve from the cell type present in the lateral chemosensory ciliated pits of the hypothetical spiralian ancestor. Further studies on the cell-type level and functional interactions of the studied TFs are needed to fully resolve the level of homology, or convergence, between mushroom bodies and cerebral organs.

## Methods

*Animal collection and morphological investigation*

Adult specimens of *Lineus ruber* were collected near Bergen, Norway (Fanafjord; GPS coordinates: 60.251845N, 5.320947E). The animals had dark red coloration with wide pigment-free areas in the terminal part of the head. Animals were kept in the laboratory in filtered seawater at 14°C with a daytime cycle: 13 hours of sunshine and 11 hours of darkness. Collection of egg masses and desired developmental stages, animal fixation as well as antibody, nuclear and EdU stainings followed the already established protocols [40].

Specimens for TEM investigation were fixed in 4% PFA in PBS, rinsed in the same buffer, postfixed in 1% $OsO_4$ diluted in PBS for 120 min at 4˚C, rinsed again and dehydrated in graded ethanol/acetone series. The samples were embedded in Epon 812 resin (Sigma Aldrich) and cut to semi- and ultrathin sections with a diamond knife (Diatome Histo Jumbo) using ultramicrotome Leica EM UC6. The ultrathin cross sections of cerebral organ were placed on formvar-covered (Fluka) single slot copper grids and stained with 1% uranyl acetate and lead citrate.

*Gene expression analysis*

Coding sequences for analyzed genes were identified in the transcriptome of *L. ruber* with the reciprocal TBLASTN search using orthologous protein sequences from *P. dumerilii*. Sequence of all of the newly identified genes were translated into protein sequences and aligned with reference sequences from other animals (Table S1). The alignments were trimmed either manually or with TrimAl software [120] and analyzed with FastTree v2.1 [121] in order to assess orthology of the analyzed genes (Figs. S1–5). All newly obtained sequences were submitted to GenBank (Accession numbers MW720144–MW720151).

Fragments of genes were amplified from cDNA library using specific primer pairs, cloned into pGEM-T Easy vectors (Promega, USA) and then transformed into competent *Escherichia coli* cells for amplification. Plasmid DNA was isolated and sequenced in both forward and reverse directions using T7 and SP6 primers to assure that the desirable genes were cloned. The antisense probes were transcribed from linearized DNA and labeled either with digoxigenin (for hybridization of single mRNA) or with dinitrophenol (for detection of second gene in double *in situ* hybridization). Whole mount *in situ* hybridization followed the same procedure as described for *L. ruber* juveniles in other studies [39, 40].

*Imaging and image processing*

Samples for confocal laser scanning microscopy (antibody staining and *in situ* hybridization) were mounted in Murray's clear and scanned in either Leica SP5 or Olympus FV3000 CLSM. Z-stacks of confocal scans were projected into 2D images in IMARIS 9.1.2. TEM microphotographs were obtained with Gatan ES500W camera mounted on transmission electron microscope Jeol JEM-1011. Both CLSM images and TEM micrographs were assembled in Adobe Illustrator CS6 into final figures. All the schematic drawings were done with Adobe Illustrator CS6.

## Declarations

*Ethics approval and consent to participate*

Studies of nemerteans do not require ethics approval or consent to participate.

*Consent for publication*

Not applicable.

*Availability of data and material*

Sequences generated and analyzed in this study have been deposited in NCBI's GenBank database under accession numbers MW720144–MW720151. All remaining data generated or analyzed during this study are included in this article or its supplementary materials.

*Competing interests*

The authors declare that they have no competing interests.

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*Authors' contributions*

LG conducted gene search and orthology assessments, cloned genes, performed *in situ* hybridization, arranged figures and drafted the manuscript. AB performed antibody staining, searched and cloned genes and performed *in situ* hybridization. IAC prepared, examined and photographed samples for TEM. AOA searched and cloned genes, performed antibody and EdU stainings. AH designed and coordinated the study and contributed to the writing. All authors read, accepted and approved the final version of the manuscript.

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## Supplementary material Paper III

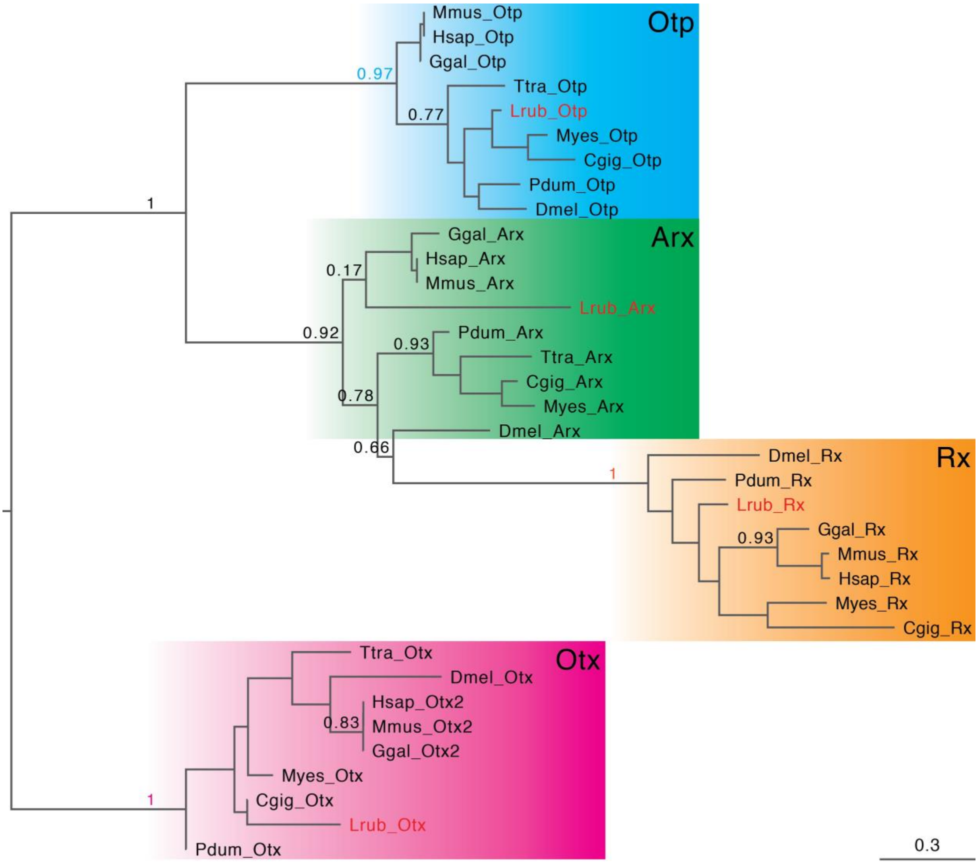


**Fig. S1.** Phylogenetic analysis of PRD-class homeobox transcription factors. SH-like support values are shown for the important nodes. Scale bar on the lower right corner shows amino acid substitution rate per site. Sequences from *L. ruber* are marked in red. For abbreviation and source of other sequences see table S1.

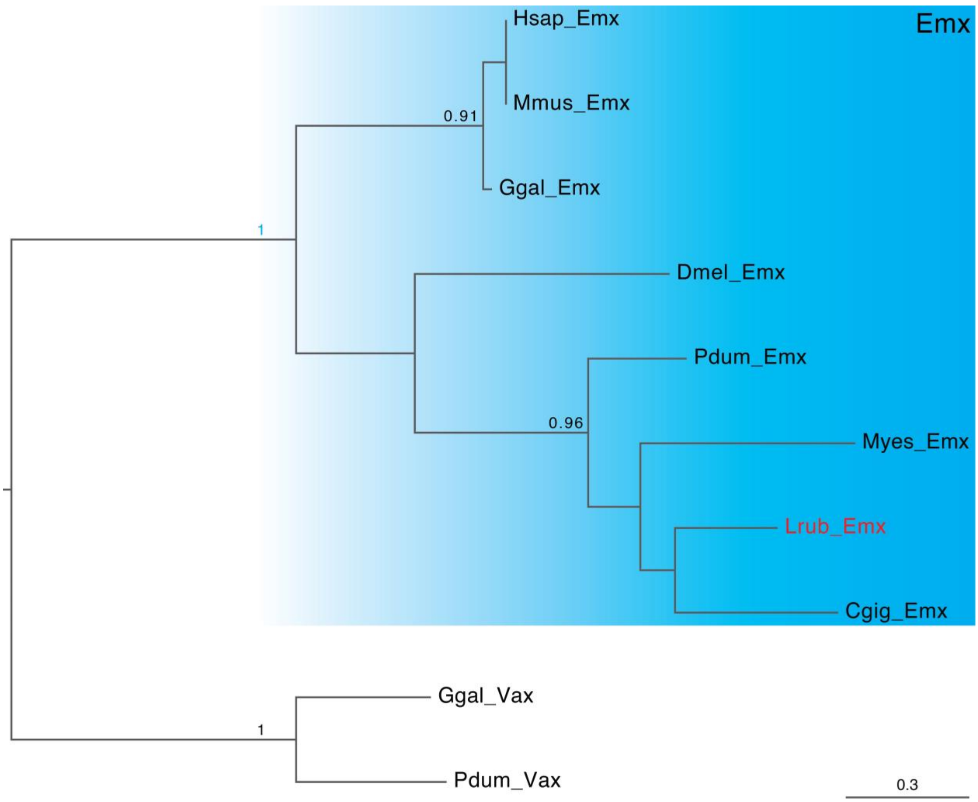


**Fig. S2.** Phylogenetic analysis of Emx sequences. SH-like support values are shown for the important nodes. Scale bar on the lower right corner shows amino acid substitution rate per site. Sequence from *L. ruber* is marked in red. For abbreviation and source of other sequences see table S1.

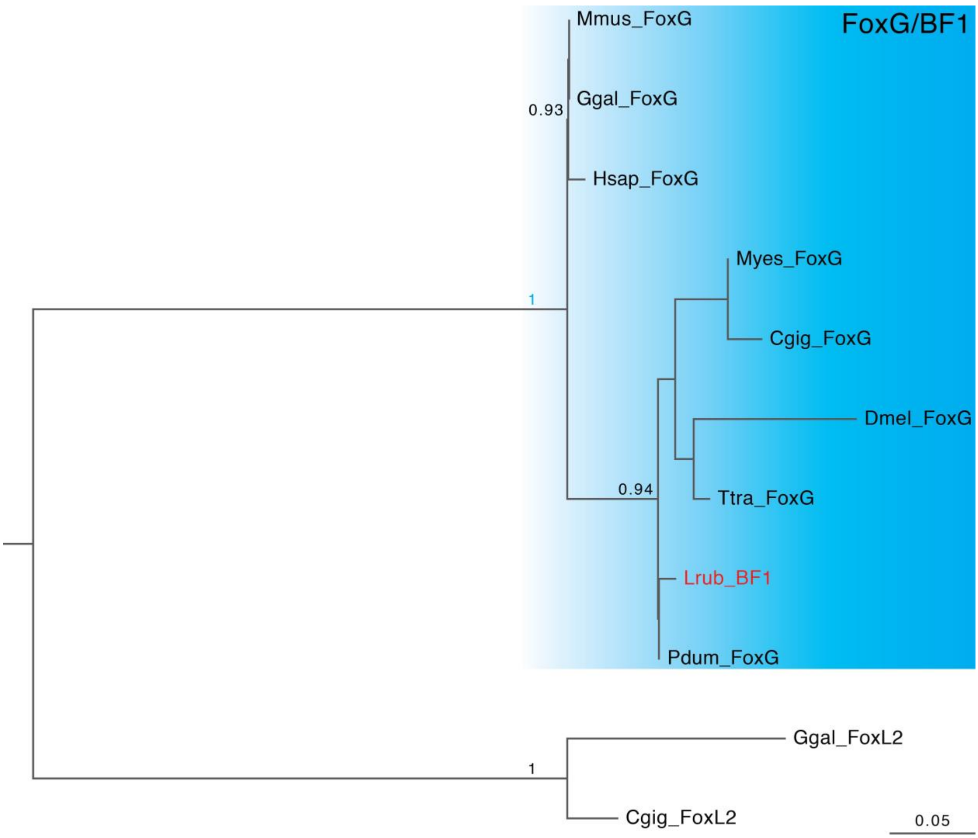


**Fig. S3.** Phylogenetic analysis of Fox sequences. SH-like support values are shown for the important nodes. Scale bar on the lower right corner shows amino acid substitution rate per site. Sequence from *L. ruber* is marked in red. For abbreviation and source of other sequences see table S1.

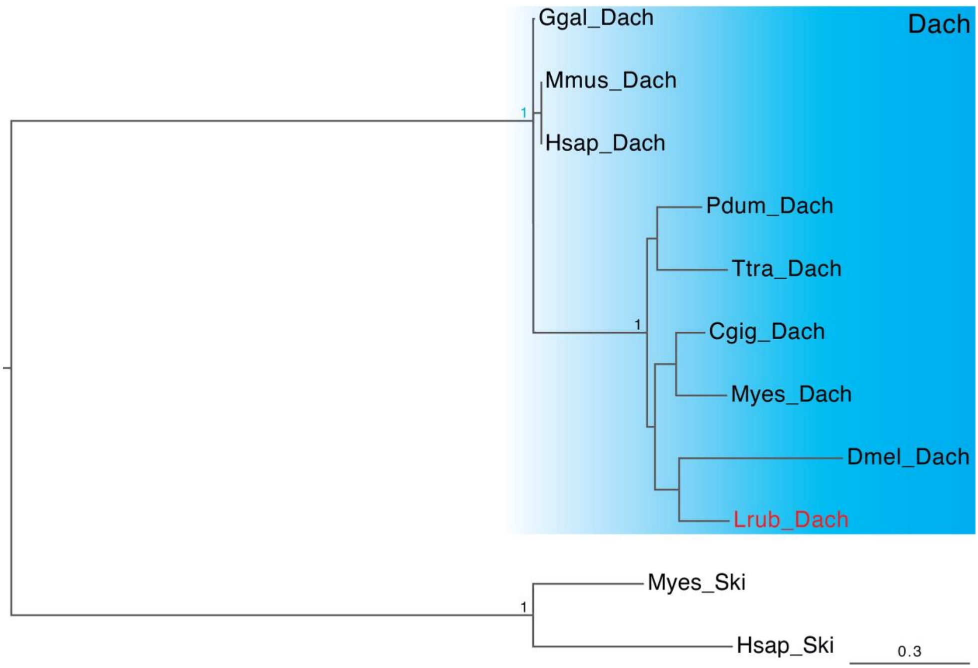


**Fig. S4.** Phylogenetic analysis of Dach sequences. SH-like support values are shown for the important nodes. Scale bar on the lower right corner shows amino acid substitution rate per site. Sequence from *L. ruber* is marked in red. For abbreviation and source of other sequences see table S1.

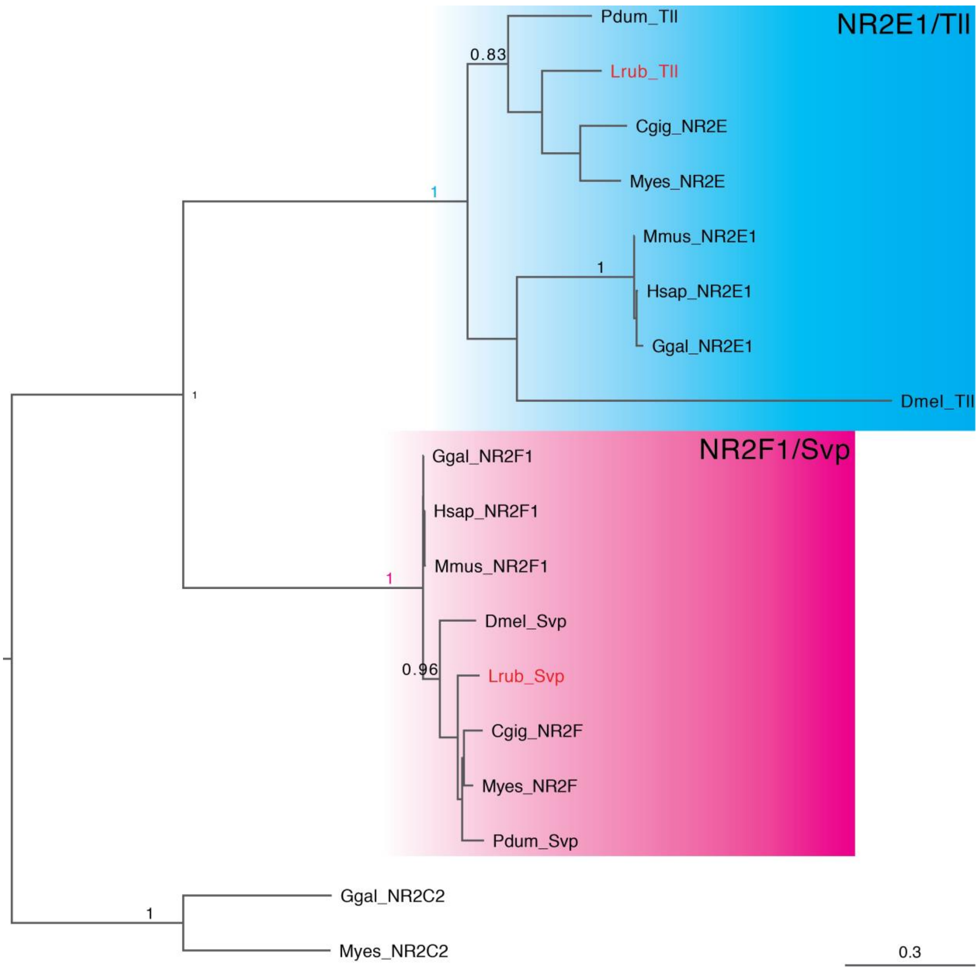


**Fig. S5.** Phylogenetic analysis of nuclear receptor subfamily 2. SH-like support values are shown for the important nodes. Scale bar on the lower right corner shows amino acid substitution rate per site. Sequences from *L. ruber* are marked in red. For abbreviation and source of other sequences see table S1.

**Table S1.** Sequences used in phylogenetic analyses

| **label** | **gene** | **clade** | **species** | **accession no** |
|---|---|---|---|---|
| Pdum_Rx | Rx | Annelida | *Platynereis dumerilii* | AAU20320.1 |
| Myes_Rx | Rx | Mollusca | *Mizuhopecten yessoensis* | XP_021372253.1 |
| Cgig_Rx | Rx | Mollusca | *Crassostrea gigas* | XP_011427710.2 |
| Dmel_Rx | Rx | Arthropoda | *Drosophila melanogaster* | NP_726006.3 |
| Ggal_Rx | Rx | Chordata | *Gallus gallus* | NP_989435.2 |
| Mmus_Rx | Rx | Chordata | *Mus musculus* | NP_038861.2 |
| Hsap_Rx | Rx | Chordata | *Homo sapiens* | NP_038463.2 |
| Pdum_Arx | Arx | Annelida | *Platynereis dumerilii* | ADG26723.1 |
| Ttra_Arx | Arx | Brachiopoda | *Terebratalia transversa* | AQU64617.1 |
| Cgig_Arx | Arx | Mollusca | *Crassostrea gigas* | XP_011423594.2 |
| Myes_Arx | Arx | Mollusca | *Mizuhopecten yessoensis* | XP_021346595.1 |
| Dmel_Arx | Arx | Arthropoda | *Drosophila melanogaster* | NP_722629.1 |
| Mmus_Arx | Arx | Chordata | *Mus musculus* | EDL29739.1 |
| Ggal_Arx | Arx | Chordata | *Gallus gallus* | XP_025002251.1 |
| Hsap_Arx | Arx | Chordata | *Homo sapiens* | NP_620689.1 |
| Lrub_Otx | Otx | Nemertea | *Lineus ruber* | AMR72028.1 |
| Pdum_Otx | Otx | Annelida | *Platynereis dumerilii* | CAC19028.1 |
| Ttra_Otx | Otx | Brachiopoda | *Terebratalia transversa* | ADZ24785.1 |
| Cgig_Otx | Otx | Mollusca | *Crassostrea gigas* | XP_011415946.1 |
| Myes_Otx | Otx | Mollusca | *Mizuhopecten yessoensis* | XP_021353640.1 |
| Dmel_Otx | Otx | Arthropoda | *Drosophila melanogaster* | NP_511091.4 |
| Hsap_Otx2 | Otx2 | Chordata | *Homo sapiens* | NP_001257454.1 |
| Mmus_Otx2 | Otx2 | Chordata | *Mus musculus* | NP_001273410.1 |
| Ggal_Otx2 | Otx2 | Chordata | *Gallus gallus* | NP_989851.2 |
| Myes_Otp | Otp | Mollusca | *Mizuhopecten yessoensis* | XP_021340833.1 |
| Cgig_Otp | Otp | Mollusca | *Crassostrea gigas* | XP_011436433.1 |
| Ttra_Otp | Otp | Brachiopoda | *Terebratalia transversa* | AEZ03829.1 |
| Pdum_Otp | Otp | Annelida | *Platynereis dumerilii* | ABR68849.1 |
| Dmel_Otp | Otp | Arthropoda | *Drosophila melanogaster* | NP_001097388.2 |
| Mmus_Otp | Otp | Chordata | *Mus musculus* | XP_006517630.1 |
| Ggal_Otp | Otp | Chordata | *Gallus gallus* | XP_003643004.1 |
| Hsap_Otp | Otp | Chordata | *Homo sapiens* | NP_115485.1 |
| Pdum_Emx | Emx | Annelida | *Platynereis dumerilii* | ADG26729.1 |
| Myes_Emx | Emx | Mollusca | *Mizuhopecten yessoensis* | XP_021359646.1 |
| Cgig_Emx | Emx | Mollusca | *Crassostrea gigas* | XP_011414574.2 |
| Dmel_Emx | Emx | Arthropoda | *Drosophila melanogaster* | CAA35965.1 |
| Ggal_Emx | Emx | Chordata | *Gallus gallus* | XP_001232151.3 |
| Hsap_Emx | Emx | Chordata | *Homo sapiens* | NP_004088.2 |
| Mmus_Emx | Emx | Chordata | *Mus musculus* | NP_034261.1 |

**Table S1.** Continued.

| label | gene | clade | species | accession no |
|---|---|---|---|---|
| Ggal_Vax | Vax | Chordata | *Gallus gallus* | AAF20017.1 |
| Pdum_Vax | Vax | Annelida | *Platynereis dumerilii* | ABR68848.1 |
| Pdum_FoxG | FoxG | Annelida | *Platynereis dumerilii* | ADG26725.1 |
| Myes_FoxG | FoxG | Mollusca | *Mizuhopecten yessoensis* | XP_021363790.1 |
| Cgig_FoxG | FoxG | Mollusca | *Crassostrea gigas* | XP_011427689.2 |
| Ttra_FoxG | FoxG | Brachiopoda | *Terebratalia transversa* | AEZ03828.1 |
| Dmel_FoxG | FoxG | Arthropoda | *Drosophila melanogaster* | NP_476834.1 |
| Ggal_Foxg | FoxG | Chordata | *Gallus gallus* | NP_990524.1 |
| Mmus_FoxG | FoxG | Chordata | *Mus musculus* | NP_001153584.1 |
| Hsap_FoxG | FoxG | Chordata | *Homo sapiens* | AAH50072.1 |
| Ggal_FoxL2 | FoxL2 | Chordata | *Gallus gallus* | AEE80502.1 |
| Cgig_FoxL2 | FoxL2 | Mollusca | *Crassostrea gigas* | NP_001295827.1 |
| Pdum_Dach | Dach | Annelida | *Platynereis dumerilii* | ADG26728.1 |
| Cgig_Dach | Dach | Mollusca | *Crassostrea gigas* | XP_011445430.2 |
| Myes_Dach | Dach | Mollusca | *Mizuhopecten yessoensis* | XP_021340456.1 |
| Ttra_Dach | Dach | Brachiopoda | *Terebratalia transversa* | AJV21306.1 |
| Dmel_Dach | Dach | Arthropoda | *Drosophila melanogaster* | NP_723968.1 |
| Hsap_Dach | Dach | Chordata | *Homo sapiens* | EAW80509.1 |
| Mmus_Dach | Dach | Chordata | *Mus musculus* | XP_036014326.1 |
| Ggal_Dach | Dach | Chordata | *Gallus gallus* | AAL76234.1 |
| Myes_Ski | Ski | Mollusca | *Mizuhopecten yessoensis* | XP_021339316.1 |
| Hsap_Ski | Ski | Chordata | *Homo sapiens* | NP_003027.1 |
| Pdum_Svp | NR2F | Annelida | *Platynereis dumerilii* | ADG26733.1 |
| Pdum_Tll | NR2E | Annelida | *Platynereis dumerilii* | ADG26734.1 |
| Myes_NR2F | NR2F | Mollusca | *Mizuhopecten yessoensis* | XP_021372361.1 |
| Cgig_NR2F | NR2F | Mollusca | *Crassostrea gigas* | XP_019917917.1 |
| Dmel_Svp | NR2F | Arthropoda | *Drosophila melanogaster* | NP_001369011.1 |
| Mmus_NR2F1 | NR2F1 | Chordata | *Mus musculus* | EDL37125.1 |
| Ggal_NR2F1 | NR2F1 | Chordata | *Gallus gallus* | XP_003643114.1 |
| Hsap_NR2F1 | NR2F1 | Chordata | *Homo sapiens* | NP_005645.1 |
| Cgig_NR2E | NR2E | Mollusca | *Crassostrea gigas* | XP_011438581.1 |
| Myes_NR2E | NR2E | Mollusca | *Mizuhopecten yessoensis* | XP_021369330.1 |
| Dmel_Tll | NR2E | Arthropoda | *Drosophila melanogaster* | NP_524596.1 |
| Ggal_NR2E1 | NR2E1 | Chordata | *Gallus gallus* | NP_990501.1 |
| Hsap_NR2E1 | NR2E1 | Chordata | *Homo sapiens* | NP_003260.1 |
| Mmus_NR2E1 | NR2E1 | Chordata | *Mus musculus* | NP_689415.1 |
| Ggal_NR2C2 | NR2C2 | Chordata | *Gallus gallus* | XP_414462.3 |
| Myes_NR2C2 | NR2C2 | Mollusca | *Mizuhopecten yessoensis* | XP_414462.3 |

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