Comparative animal mucomics: Inspiration for functional materials from ubiquitous and understudied biopolymers

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ABSTRACT

The functions of secreted animal mucuses are remarkably diverse, and include lubricants, wet adhesives, protective barriers, and mineralizing agents. Although present in all animals, many open questions related to the hierarchical architectures, material properties, and genetics of mucus remain. Here we summarize what is known about secreted mucus structure, describe the work of research groups throughout the world who are investigating various animal mucuses, and relate how these studies are revealing new mucus properties and the relationships between mucus hierarchical structure and hydrogel function. Finally, we call for a more systematic approach to studying animal mucuses so that datasets can be compared, in an omics-style approach, to address unanswered questions in the emerging field of mucomics. One major result that we anticipate from these efforts is design rules for creating new materials that are inspired by the structures and functions of animal mucuses.

Keywords: mucus, mucins, omics, functional materials, bioinspired materials, biomimetics

INTRODUCTION

Secreted mucuses are heterogeneous hydrogels containing a large fraction of high molecular weight, highly glycosylated proteins called mucins.[1-10] Mucuses are ubiquitous in animals and appeared roughly 600 million years ago in metazoans.[11] Their physiological roles and material properties are remarkably diverse. Most higher animals express at least five individual mucin genes but in some cases can contain as many as 25,[11] suggesting their function as a fast-evolving and modular scaffold.[11, 12] While all of these animals produce internal gels that line respiratory and digestive tracts, and frequently many more,[13, 14] here we focus on mucuses secreted outside of the body that have unique biological functions. For example, mucus acts in some animals as a lubricant[15, 16] and in others as an adhesive;[17] it can direct hydration[18] or mineralization;[19] mucus has a prominent role in marine ecosystem energy cycling;[20, 21] or can mediate predator-prey dynamics[22] and immune responses[23, 24] where it additionally acts as a semi-permeable barrier.[25, 26] As such, the systematic evaluation of these abundant biopolymers could lead to the development of technical and biomedical applications. These advances include new, bioinspired glues for surgical implants,[27] coatings to mediate organic-inorganic interfaces in medical implants,[28] biocompatible lubricants,[29] composites for 3D bioprinting,[30] sustainable alternatives to industrial plastics,[31] antimicrobial and immune agents,[32] additives for wound healing,[33] environmental remediation systems,[34] and many other useful ecologically derived materials and biomedically relevant compounds.

Despite their prevalence and utility, mucuses have not been studied to the same extent as other biological materials, such as cellulose,[35-37] nucleic acids,[38, 39] and silk.[40-42] This is partly because of the complexity of their structure and uncertainty as to what seems to be the requirement for a sophisticated network of genes and proteins working together to make a functional hydrogel. Mucus is a hierarchical material in that interactions and structures at the Ångstrom, nanometer, and micrometer length scales contribute to its desirable macroscopic properties (Figure 1).[43, 44] In addition, it is a heterogeneous material that encases other proteins, salts, and small molecules;[45] these additives affect mechanical properties and physiological function.[46] While individual mucin glycoproteins vary in their specific viscoelastic properties, mucins are known in general to provide boundary lubrication to biological surfaces, reducing friction in a manner similar to hydrophilic polymer brushes.[15, 47-50] Additionally, the substances' adhesive and cohesive properties can vary with concentration,[51] and the rheological interactions of materials with mucus (mucoadhesion) is highly dependent on the nature of the substrate.[52, 53] These multifaceted features make investigating structure at all length scales necessary to understand the origin and design principles that direct mucus functional properties and account for their diversity.

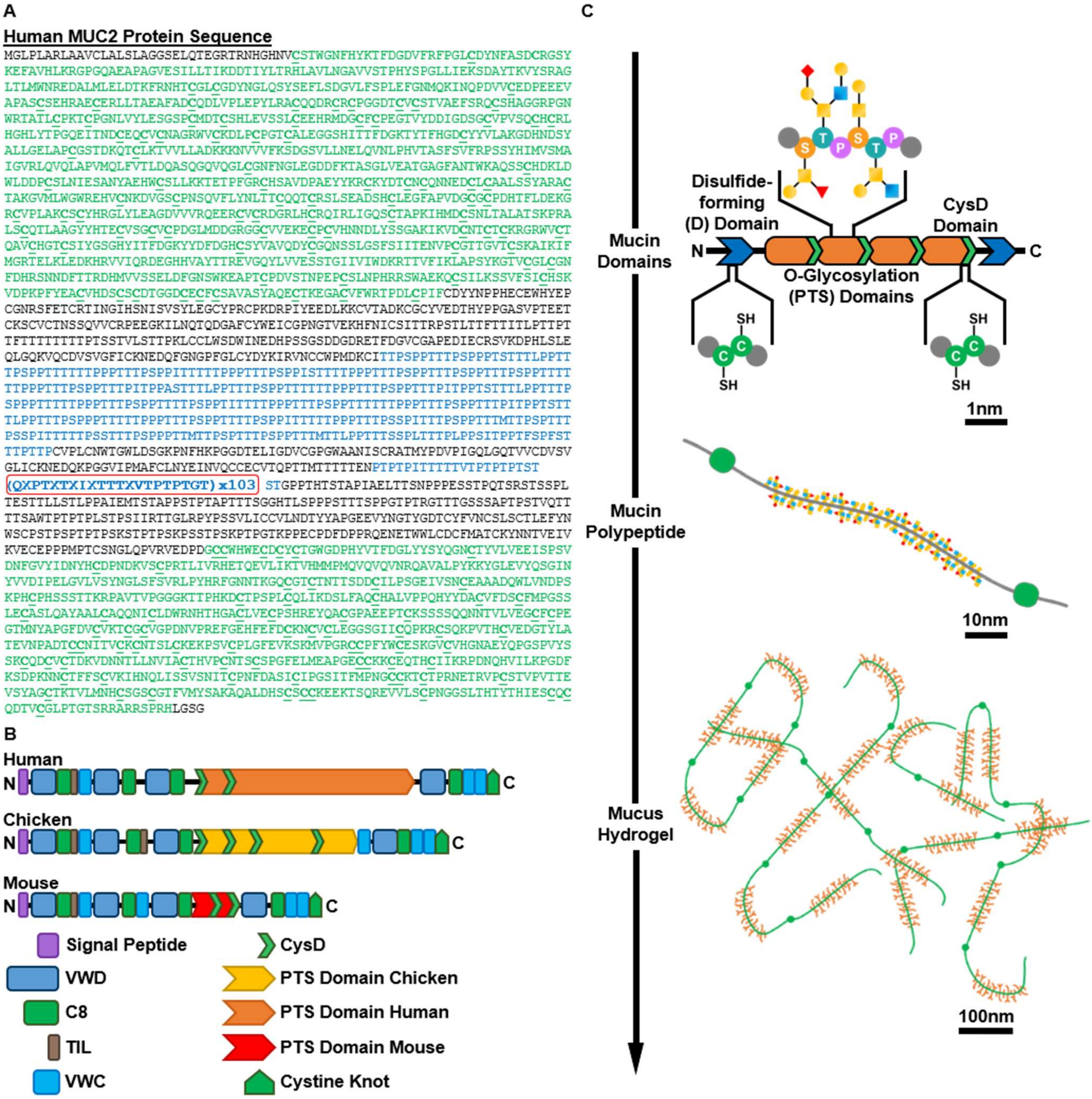

Figure 1. A) Sequence of human MUC2 protein. O-glycosylated PTS and VNTR domains (composed of 95.8% and 80.9% serine, threonine, and proline, respectively) are labelled in blue. N- and C-terminal D domains (composed of 8.6% and 10.5% cysteine, respectively) are labelled in green. Cysteines within the D domains are underlined. Region outlined in red indicates the sequence repeated 103 times within the tandem repeat domain,

QXPTXTXIXTTTTVTPTPTGT, where X is a mutational hotspot. B) MUC2 protein domain architectures from human, chicken, and mouse models. Image adapted from Jiang *et al.,* 2013.[54] C) Mucus structural hierarchy. Mucins are organized into glycosylated serine-, threonine-, and proline-rich domains (orange), CysD domains (green), and D domains (blue). Mucin glycoproteins form gel networks as a result of disulfide bridges and H-bonding networks.

Although mucus has widely varying physical properties, all mucins have certain conserved features. Their molecular weights range typically from 5–10 MDa and can have individual chain lengths of nearly 14,000 amino acids.[43, 55, 56] Their sequences generally incorporate two major domains: 1) disulfide-forming cysteine-rich (D) domains at the termini which participate in the establishment of mucus gel networks,[1, 10, 57] and 2) the proline-, threonine-, and serine-rich "mucin domain," whose dense O-glycosylation accounts for upwards of 80% of mucin molecular weight (Figure 1A).[9, 58, 59] To date, 22 human mucin genes have been identified,[60] each with a unique set of glycoforms and expression profiles.[61-64] The majority of the mucin proteins encoded by these genes could be categorized as gel-forming secreted mucins (MUC2, 5AC, 5B, 6, 19), non-gel-forming secreted mucins (MUC7, 8, 9), or transmembrane mucins (MUC1, 3A, 3B, 4, 12, 13, 14, 15, 16, 17, 18, 20, 21, 22) based on their cellular localizations.[65] At the C-terminus of the protein, all gel-forming mucins contain a "cystine-knot domain" (CK domain), whose cystines are critical for end-to-end dimerization of mucin proteins via intermolecular disulfide-bond formation (Figure 1B).[56, 66] In addition, all but MUC6 proteins also contain a von Willebrand Factor like C-domain (VWC) at the C-terminus, which is known to participate in protein complex formation.[67-69] In general, the N-terminal portions of gel-forming mucin proteins contain domains with high homology to von Willebrand Factor like D-domains (VWD). MUC2, 5AC, and 5B also contain a VWD domain at the C-terminal end. The N-terminal VWD domains, and in particular, the one referred to as the third VWD domain, play an important role in mediating trimerization of dimeric mucin molecules, inducing matrix formation and contributing to hydrogel formation.[70] Another unique feature of MUC2, MUC5AC, and MUC5B mucin proteins is the presence of hydrophobic cysteine-containing domains (CysD) between adjacent mucin domains. Each CysD domain contains multiple cysteines that form intramolecular disulfide bonds. Although at least one of the CysD domains in each mucin was predicted to be C-mannosylated, tissue culture experiments suggest that the mucin CysD domains are not C-mannosylated.[71] It has been suggested that the CysD domains also participate in multimerization of mucin proteins and stiffening of mucus gels (Figure 1C).[71, 72]

The central portion of secreted mucins constitutes the majority of the protein mass and is the site of heavy O-linked glycosylation. This region is typically comprised of two types of repeats – one that is rich in proline, threonine, and serine (PTS domain), and another having a variable number of tandem repeats (VNTR domain). The former has a high abundance of these three amino acids while the latter contains these as well as glutamine, glycine, isoleucine, and valine in numerous short repeating sequences. (Figure 1A). The number of repeats could range from tens to hundreds of repeating units. Regarding glycosylation, there is a high proportion of GalNAc residues directly O-linked to the peptide chain, and the average number of monosaccharides per glycan, n, is typically smaller ($n \sim 3$) than cell-surface mucins, where $n \sim 8$.[73-75] In fact, these repeated domains are so heavily glycosylated that mucins are typically fixed in a linear conformation.[76] While the sequences of these repeats do not show strict conservation within and between individual mucin types, both PTS and tandem repeat domains are enriched in PTS amino acid residues. Both MUC2 and MUC5AC proteins also contain an autocatalytic proteolytic cleavage site near the C-terminus with the sequence of GDPH (glycine-aspartate-proline-histidine). The presence of this proteolytic cleavage site in the less glycosylated region of the protein suggests that the mucin gel matrix is destabilized by proteases.

Non-gel-forming secreted mucins, MUC7, MUC8, and MUC9, do not appear to contain CK domains at the C-terminus. Based on available sequences, the non-gel-forming mucins are smaller proteins of less than 1,000 amino acids. MUC7 is the most studied of these three mucins.[77-83] Similar to the gel-forming secreted mucins, the majority of the protein is comprised of tandem repeats – sites of heavily O-linked glycosylation. The N-terminal region of MUC7 also contains two cysteine residues. Two histatin-like domains are found at the N-terminal portion of the protein. Histatins are histidine-rich peptides frequently found in human saliva,[84] and, given that the N-terminal peptides of MUC7 exhibit antimicrobial and anti-fungal activities, possibly play a biological role as part of the immune response.[81, 85]

Detailed knowledge of the mucin gene family in other metazoans is currently unavailable partly because of the lack of complete genome sequences from key animal lineages. Lang and coworkers reported that the genome of the amphibian, *Xenopus tropicalis* (western clawed frog), contains 26 gel-forming mucin genes corresponding to MUC2, MUC5, and MUC19 orthologs.[86] While one of the major features of the human MUC2 and MUC5 proteins is the presence of CysD domains interspersed in the mucin domain, 15 *X. tropicalis* mucin proteins do not contain CysD domain. Furthermore, some of the MUC5 orthologs do not have the fourth VWD domain at the C-terminus, which is present in all mammalian and sauropsid MUC2 and MUC5 proteins. Based on limited genome sequence of *Danio rerio* (zebrafish), 11 gel-forming mucin genes were identified that are considered to be human MUC2, MUC5, and MU19 orthologs. Using available genome and protein sequences, Lang and colleagues also identified putative gel-forming mucin genes in invertebrates, including members of Lophotrochozoa and Arthropoda clades, and even in lower metazoans such as the comb jelly *Pleurobrachia bachei* (sea gooseberry).[86] Many of these mucins contain the characteristic VWD and PTS domains,[86] including the well-characterized pig proteins MUC5AC and MUC5B. MUC5AC and MUC5B have very similar domain features. The major differences between the two proteins are the arrangement of PTS domains and tandem repeat, as well as intermixture of the CysD repeats in the mucin domain. Differential presentation of these domains in mucin proteins could influence the macrostructure of mucuses. Immunohistochemical and lectin staining of airway epithelium in *Sus scrofa domesticus* (pig) revealed that MUC5AC mucins are secreted from the epithelial goblet cells, while MUC5B mucins are produced by the mucous cells in the submucosal glands. Nonetheless, mucus formed by these mucin proteins exhibited different structures, where MUC5AC forms mucus sheets and threads of 1 to 4 µm in diameter, while MUC5B constitutes thick mucus strands of 5 to 50 µm in diameter.[87] Although both MUC5AC and MUC5B are gel-forming mucins, the *in vivo* structural differences suggest that these proteins might play a role in influencing the final assembly and, potentially, composition of mucus. For example, the altered expression of MUC5AC and MUC5B in humans are implicated in asthma pathology.[88]

Many open questions remain regarding the evolutionary history of animal mucuses. Mucins appeared early in multicellular organisms and are present in virtually all metazoans (Figure 2), leading to many theories on their origins. For example, some argue that mucin diversity arose as a result of gene duplication,[11] while others suggest mucins evolved from domain shuffling.[89] Both events quite possibly occurred to arrive at current genetic diversity, however it is difficult to determine the precise trajectory of mucin evolution, and to what extent gene duplication and domain shuffling may have played a role. In addition, mucin-like proteins have been found in *Saccharomyces cerevisiae* (yeast) cell adhesion proteins, further complicating mucin evolutionary history.[90] Finally, studies into *Salmo salar* (Atlantic salmon) O-glycomes revealed structural variation in skin mucin glycans between populations from different geographical regions, indicating differential glycosylation within a single species.[91]

Testing these hypotheses requires genetic analysis at multiple levels. Integrated investigation of mucus genomics, transcriptomics, proteomics, and glycomics could allow researchers to better understand the timing and nature of events that generated each mucin gene. Further, these analyses may reveal that synergistic interactions of peptide sequence and glycan composition are the driving forces behind mucus behavior, so methods are emerging to determine mucus structures at all levels. For example, quantifying the amount of mucin glycan and protein components is an instrumental first step. Experimentally, this comes from gel permeation chromatographic (molecular weight),[92] mass spectroscopic (glycan identification),[93, 94] and transcriptomic/proteomic (sequencing)[95] analyses. In addition, rheology of natural mucins characterizes the viscoelastic material properties of mucus hydrogels.[8] However, even in concert, these methods are limited in that sequences of the repeat domains, glycan structures, and absolute configurations remain difficult to determine. As a result, the data reported on animal mucin structures vary widely and are difficult to compare. This lack of standardization makes structure-activity relationships elusive, thus obscuring our understanding of how different structural motifs lead to different properties.

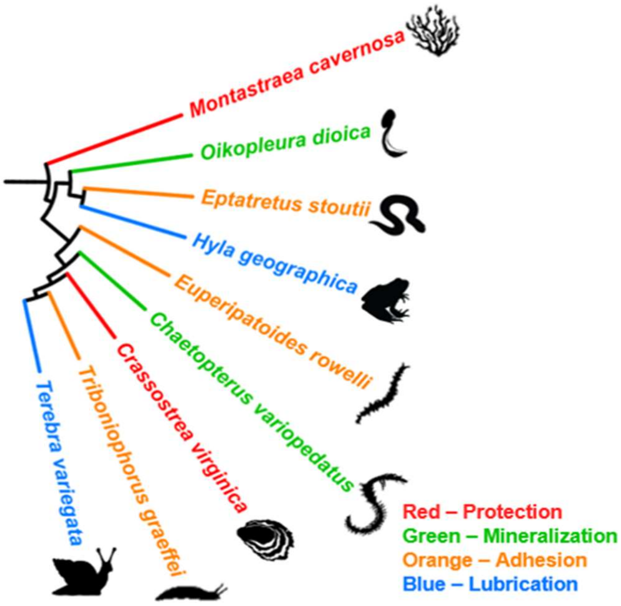

Figure 2. Phylogenetic tree of the species described in this paper. Clades are colored according to the species' mucus function that is discussed herein, although it should be noted that each of these animals produce multiple mucuses with diverse functions and properties.

Research into animal mucus and the questions being asked are as diverse as the mucus itself, and by understanding key factors contributing to mucin functional diversity, the versatility of mucus could be exploited in highly tunable advanced materials. Examples of secretions actively studied and the properties investigated include tissue-dependent proteomic immunology in oysters,[96] biomechanics and biochemistry of slime in velvet worms,[97] venom transport in marine snails,[98] predator traps in slugs,[99] wet adhesion in tree frogs,[100] particle capturing networks in tunicates,[21] UV protection in corals,[101] bioluminescence[102] and tube construction[103] in marine worms, and fibrous network formation in hagfish slime.[104] Our goal here is to highlight recent advances by the groups who study these animal mucuses, and in doing so, illustrate the wide diversity of approaches used to investigate these fascinating matrices. We thereby bring attention to the small, but growing research field of Comparative Animal Mucomics – the comparative study of mucus molecular structures, physical properties, and functions of mucuses across metazoans. The following sections are ordered by grouping the discussed organisms according to both evolutionary, ecological, and mucus material similarities.

Cnidaria: Coral Mucus

The Medina laboratory at Pennsylvania State University, USA, applies multi-omics approaches to investigate the interactions between corals and their microbiomes. Reef-building corals are sessile animals that secrete vast amounts of mucus that perform many roles in coral biology, including UV protection, calcification creating a physical barrier to prevent desiccation, and as a means to overcome sediment load (Figure 3).[20, 105, 106] Additionally, mucus is a key component of a coral's innate immune system,[107] where a symbiotic microbial community linked to the release of antimicrobial compounds assists as a first barrier of defense against predation.[108] Coral mucus often traps organic matter that, once released into the water column, acts as a conduit of nutrient recycling and is therefore essential in marine biogeochemical cycles.[20, 109, 110] The microbial actors supporting the movement of nutrients across the benthos are currently poorly characterized and deserve further study.[110, 111] Some of the recent interest in coral mucus microbiomes stems from the increased incidence of microbe-induced diseases.[111] Ecological factors, such as shifts in herbivore communities, increased nutrient pollution, and bleaching, affect coral mucus microbial communities, rendering them more vulnerable to pathogens.[112-114] Coral mucus microbiomes show specificity to some level of coevolution with particular hosts.[115] Additionally, coral mucus carbohydrate composition has been found to vary across species.[116] Understanding coral mucus has therefore important implications for ensuring the survival of tropical reef ecosystems for which corals are foundational species.

Mucins are critical components of coral mucus, and these proteins serve multiple functions.[117] Coral mucins and mucin-like proteins have been reported to have differential expression along a colony in *Acropora* species[118, 119] hinting that these glycoproteins may have a role in skeletal organization.[120] Studies into *A. digitifera* (staghorn coral) revealed that Mucin4-like protein, which is involved in skeletal matrix formation, shares multiple functional domains with human MUC4 and an *Aiptasia* (sea anemone) protein, as well as high sequence identity with *A. millepora* (staghorn coral) mucin-like protein.[89, 121] In the Caribbean species *A. palmata* (elkhorn coral) and *A. cervicornis* (staghorn coral), MUC5AC was found to span three divergent genomic intervals, which could underlie differences in colony mucus composition.[120] Co-option and domain shuffling of mucins may have allowed this dual role in both protection (against desiccation, predators, and pathogens) and biomineralization.[89] Recent findings also suggest that some proteins, such as the transcription factor NF-κB, may regulate mucin expression in corals as part of their innate immune response.[120]

During a multi-day heat stress experiment with the Caribbean corals *Pseudodiploria clivosa* and *Orbicella faveolata*, a mucin-like protein shows opposite differential gene expression in these two species. *P. clivosa* is a heat-sensitive species that shows downregulation of this protein in response to increasing temperature, while *O. faveolata*, a thermally tolerant species, upregulates the protein.[122] Also observed in these experiments is that another putative mucin, MUC3A, is upregulated in both species.[122] After acute thermal stress, *P. clivosa* shuts down many functions, including the expression of genes involved in the early immune response such as those which code for mucins. However, upregulation of MUC3A suggests again multiple possible roles for these glycoproteins. A search for these putative mucins in the genomes of three species encompassing the genus *Orbicella* complex (*O. faveolata, O. annularis* and *O. franksi*), revealed multiple MUC3A paralogs in each lineage (M. Medina, unpublished). Mucins have also been recently reported as having a role in tissue regeneration after lesion in the Caribbean coral *Montastraea cavernosa*.[123] While the integumentary mucin-like protein increased in abundance 2–4 weeks after the lesion, mucin-5B showed a decrease in abundance, illustrating how poorly understood the role of mucins is in coral physiology. Coral mucus production is threatened as a result of decreasing coral cover worldwide. Given the critical role in nutrient cycling and host defense, better understanding of the makeup, structure, and function of coral mucus is paramount.

The establishment of related model organisms such as the jellyfish, *Cassiopea xamachana* (upside-down jellyfish), facilitates controlled experimentation to study cnidarian biology.[124] The recent discovery of motile stinging cell structures called cassiosomes that are released into the water column within *C. xamachana* mucus seem to play an important role in prey capture.[125] Cassiosomes are also found in other related jellyfish belonging to the taxon Rhizostomeae.[125] Characterizing the mucus microbiome of *C. xamachana* and its cassiosomes will enable further investigation of cnidarian mucus and its role in tropical marine environments. Characterization of the varied properties of coral and jellyfish mucin will lead to inspiration of similarly functioning materials, as these organisms naturally create hydrating agents, UV barriers, and microbe-regulating gels that function in tandem to allow corals to thrive in ever-changing conditions.

Figure 3. White, viscous mucus is found over the surface of entire coral colonies. Examples of the *Goniastrea aspera* (left) and *Montastraea cavernosa* (right) corals. The *M. cavernosa* colony has been cored for mucus microbiome-processing of the corals.

Annelida: Tube Worm Mucus

The Deheyn lab at the Scripps Institution of Oceanography at the University of California, San Diego, USA, specializes in the biochemistry of light production in marine organisms, particularly polychaete marine worms that secrete a glowing mucus. Such organisms have long been reported by explorers and scientists alike,[126] yet with few rigorous studies detailing the biochemistry of light production.[127] This is a consequence of the difficulty in acquiring sufficient quantities of the precious secretion in water.[128] The Deheyn group studies two types of luminous mucus: the secretion of *Odontosyllis* worms in open water during reproduction, and one secreted by the seafloor-dwelling tube worm belonging to *Chaetopterus*. *Odontosyllis* species are also referred to as “fireworms” (not to be confused with the evolutionarily unrelated venomous “bearded fireworm”)[129] because these organisms launch an underwater “firework” display of glowing mucus as part of their mating ritual.[127, 129-131] Fireworms produce bursts of this glowing mucus in the water column at very specific times of the solar and lunar cycles.[132, 133] These flares are made of fireworm-secreted mucus that the female emitters release together with egg gametes, so that males waiting on the seafloor can easily locate potential fertilization sites. The males then quickly swim to these glowing puffs of light to release sperm within them.[134] In addition to being highly visible to mates, the mucus is more viscous than the surrounding seawater and therefore concentrates the gametes by limiting diffusion, increasing the chance of fertilization. The luminous mucus also provides a protective environment that persists long enough to enable the critical first steps of reproduction.

The *Chaetopterus* worm (Figure 4), in contrast, is sedentary and benthic, meaning that it lives on the seafloor where it makes a tube likely composed of a solidified mucus.[103] The tube consists of smooth concentric sheets of a woven, fiber-like material, leading to the organism’s nickname: the “parchment tube worm.”[103, 135-137] The tube itself has fascinating material properties, including rubber-like flexibility in water, and glass-like behavior when dehydrated.[137] Furthermore, the mechanical properties are unaffected by temperature changes from –50˚C to 200˚C, and each layer of the tube is constructed from a parallel array of fibers that is oriented 45˚ from the main angular direction of the juxtaposing layer.[103, 137] Being built in such an organized fashion provides the tube some anisotropy, increasing angular resistance to pulling or pressure forces, a trait found in well-engineered pipes.[138]

Intriguingly, this same organism also produces an adhesive luminescent mucus that glows bright blue (Figure 4).[102, 139, 140] This adhesive mucus is spat by the animal and adheres to attacking predators, suggesting that this mucus may have evolved for anti-predatory functions. The stickiness of this mucus is clearly related to its chemical composition, which is made of various glycoproteins.[141] The mucus shows ferning patterns when drying, suggesting it contains mucins, however there are no reported peptide sequences of *Chaetopterus* mucus proteins currently available.[142] We also know that this mucus presents rheological and micro-rheological properties similar to other mucuses,[140, 143] but with unique properties related to the content of ferritin/flavin complex, iron, and an unknown secreted chromophore. With regards to mucus function, any assailant of the worm is tagged with a visible glowing mark, likely making hunters more vulnerable to their own predators for extended periods of time.[141, 144] This mucus results in a remote and prolonged defense using a unique light-producing system fueled by a highly performant ferritin, which is exceptional amongst luminous marine organisms. The Deheyn group has identified that the ferritin can build redox potential by coupling oxidoreduction reactions of iron with flavins,[102, 141] which releases electrons to power the unidentified luminescent chromophore. Tube worm ferritin shares high sequence identity with human ferritin, but exhibits redox properties with nearly an order of magnitude increase in catalytic efficiency.[142]

Future efforts to understand the structures and properties of these tube worm mucuses will require interdisciplinary efforts that bring together researchers from ecology, biochemistry, and material science. Active studies into these substances focus on the hierarchical nature of the mucuses, which exhibit distinct functionality dependent on the scale in question of the material.[135, 136, 143, 145, 146] Further investigation into the genomics of these organisms' secretions will provide understanding of mucin evolutionary history, providing insight as to if mucus, like bioluminescence, is a convergent phenomenon.[147] Comparative studies of secretions produced by other annelids will shed light on the underlying molecular basis of the material properties of marine worm mucus.[148] Questions currently being addressed in these studies include: How do structures of varying mucuses fluctuate to change properties so dramatically? And, do the structures of their mucins fundamentally differ? Or do intermolecular interactions between the various components of the mucuses drive function in these animals? Investigation into the molecular nature of the solidifying and luminescent tube worm mucuses will be the next step in answering these questions, with the aim of leading scientists toward leveraging these systems to develop novel materials that can act as both environmentally responsive sensors and biological cements. Tube worm-inspired materials can be used as self-patching surfaces, glues in marine environments, and contact-reporting dyes.

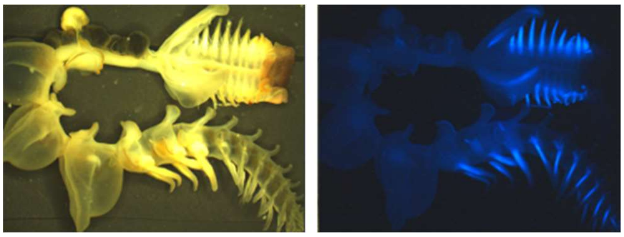

Figure 4. Tube worm *Chaetopterus* sp. shown in white light (left panel) and exhibiting bioluminescence in the dark (right panel).

Mollusca: Bivalve Mollusk Mucus

Faculty at the Marine Animal Disease Laboratory (MADL) at Stony Brook University (Allam and Pales Espinosa), USA, investigate bivalve immunology, with a particular emphasis on how these organisms use differential protein expression to regulate interactions with environmental particulates and microbes. With about 200,000 described (and likely many more undescribed) extant species, the Mollusca is the second largest major bilaterian group after the arthropods.[149] Gastropods and bivalves represent the largest two subtaxa, encompassing 98 percent of the known living molluscan species.[150] Mollusks, and suspension-feeding bivalves in particular (e.g. clams, oysters and mussels), also represent an important source of food and valuable goods (shells, pearls) around the world, with over 17 million tons captured or produced from seas or inland waters worldwide, accounting for over 20 billion USD in economic activity annually.[151] In addition to their economic value, suspension-feeding bivalves are among the most important foundation species in coastal waters as they build habitats for other species, remove phytoplankton, and transfer energy to the benthos.[152] The biology, ecology, and economic importance of bivalve mollusks makes them ideal candidates for investigations targeting critical basic and applied research questions, including those pertaining to health and industry.[153] The soft tissue of these animals is covered with copious mucus secretions that have a role in multiple functions, including protection from biological and environmental stressors, as well as mediation of interactions with waterborne microbes.[154-157] The importance of mucus in molluscan biology is well reflected in the energy allocated to mucus production, sometimes exceeding 15% of energy gained from food.[158] Their mucosal tissues are also readily accessible both for *in vivo* observation[159] and sampling,[160] making them ideal candidates for the investigation of mucosal processes.

These animals have the intriguing ability to sort their food from a complex mix of particles suspended in water by using the mucus as a semi-permeable filter. To do so, they pump and circulate water in the shell (pallial) cavity, then use mucus covering their feeding organs (gills, labial palps) to capture and selectively transport food particles to be ingested or rejected using a "conveyor belt" made with mucus (Figure 5).[161-164] Particles rejected before reaching the mouth are embedded in mucus and expelled back to the environment as masses of mucoid substances entangling live unwanted cells, debris, and abiotic material of low nutritional value. Those directed to the mouth are ingested in a cohesive mucus string. How these animals discriminate and sort food particles has been the subject of dozens of studies since the early 1900s, although the underlying mechanisms remained elusive until recently, as the last decade revealed the critical role of mucus in all these processes.[164-167]

Recent joint investigations between Pales Espinosa and Allam combining proteomics, transcriptomics and reverse genetics showed that mucus covering the feeding organs is not a mere carrier for particles, but that specific interactions take place between mucus and food particles. The researchers demonstrated that mucus covering the feeding organs of oysters and mussels contain sugar-binding proteins (i.e. lectins) that differentially bind microalga cell surface carbohydrates, triggering selection with a preference for glucose and mannose residues.[165-168] Pales Espinosa and coworkers also demonstrated that mucosal lectins are necessary for food particle selection in the oyster, *Crassostrea virginica*.[164] Some of the most important open research questions regarding these processes include: Do mucosal lectins mediate an efficient particle-sorting mechanism that is common across all suspension feeders? What is the nature of the interactions between bivalve lectins and mucins? And how do these animals control mucus characteristics to regulate food uptake?

The primary role of mucosal immunity in maintaining animal health is now well recognized in vertebrates.[169] The net created by cross-linked glycoproteins contained in mucus traps microorganisms before reaching the soft tissues. In addition to representing an efficient physical barrier, mucus matrices contain various cells and bioactive molecules and have gained prominence in the last few decades as an essential component of the innate and acquired immune system. Suspension-feeding bivalves are excellent model organisms for investigating host-microbe interactions at mucosal interfaces, in part, given the extraordinarily large number of microbes (~25 million microbes/second) they encounter via their water filtering activities.[170] In these animals, the mucus layer covering soft molluscan tissues is the first host factor encountered by waterborne, soft tissue-attaching microbes regardless of whether it leads to predation, mutualism, commensalism or parasitism.[171-175] Therefore, the outcome of interactions between waterborne microbes and pallial mucus can determine the success or failure of these associations.

In this context, MADL researchers investigate the role of mucosal interfaces in bivalve innate immunity and defense against pathogens. Investigations on *C. virginica* (Atlantic oyster) showed significant regulation of the proliferation and virulence of the alveolate parasite *Perkinsus marinus* following exposure to host mucus.[96, 175, 176] While mucus collected from oyster pallial organs enhanced the proliferation of the parasite, mucus collected from the digestive gland was inhibitory. Interestingly, pallial mucus of the non-compatible host *C. gigas* (Pacific oyster) was strongly inhibitory suggesting that host specificity of *P. marinus* may begin in the mucus.[176] The exact regulatory nature of the mucosal molecules and how these factors are regulated in response to environmental or pathologic stress remain to be determined. Additionally, comparative investigations into each species' mucus could provide insights into the structure-property relationships in microbiome-regulating materials.

Bivalves are an excellent system for understanding the role of mucosal microbial communities in animal health given the interplay between mutualistic, commensal, and pathogenic microbes at mucosal interfaces. A growing body of evidence highlights the role of mucosal microbiomes in regulating host resistance to infection either directly through microbe-microbe interactions (e.g. "non-host-derived immunity")[177] or indirectly via immune stimulation and maturation.[178] One such example is the presence of IgGFc-binding proteins in *C. virginica* mucus;[179] a human IgGFc-binding protein found mucosal surfaces (FcγBP) contains a mucin-like cysteine-rich domain as well as an amino acid motif conserved in MUC2.[180] How mucus interacts with microbes (whether beneficial, commensal or harmful) and how changes in mucus physicochemical characteristics (either caused by disease, by other microbes or by natural cycles) affect microbial homeostasis at mucosal surfaces are among the many questions that still need to be addressed, and doing so could lead to better disease management strategies and improvements in state-of-the-art biomimetic materials. These studies raise fascinating questions around host-microbe crosstalk and feedback controls, and studies into the molecular nature of bivalve mucus may lead to powerful insights in the development of barrier technologies. Advances in this area can bring about new technologies in terms of bacteria- or particle-selecting filters for commercial and research applications as well as microfluidics mobility agents.

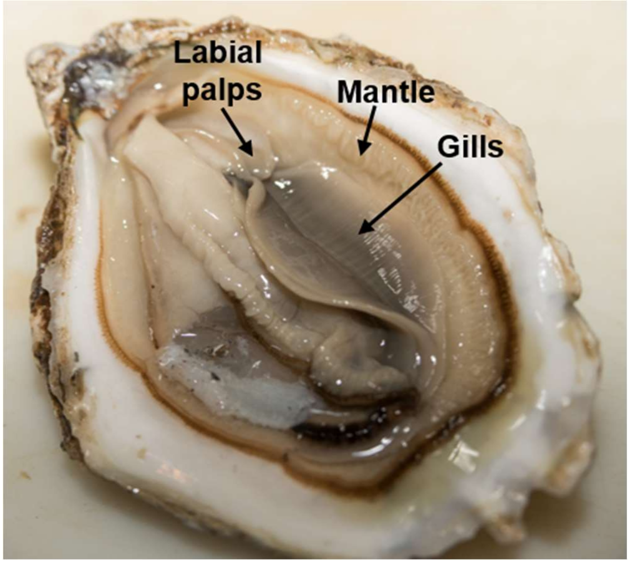

Figure 5. The American oyster *Crassostrea virginica* with the right shell removed. Major mucus-producing tissues are noted. Viscous mucus covers all tissues inside the oyster.

Mollusca, Gastropoda: Marine and Terrestrial Snail Mucus

The Holford laboratory at Hunter College, City University of New York, USA, examines the evolution and the potential therapeutic applications of marine snail mucus and venom peptides from Conoideans, while the Barrientos group at Universidad Estatal a Distancia, Costa Rica, specializes in the ecology of tropical land snails. Snails secrete a variety of mucuses for strong adhesion to both dry and wet surfaces, as a potent lubricating and hydrating agent, and also as a protective barrier.[181] Snail mucus protects their skin against cuts, bacteria, and UV radiation through a potent combination of antimicrobial peptides and glycoproteins.[181] Most of the mucins found in gastropods exhibit excellent antimicrobial activity against various microorganisms.[98] Snail mucus is an attractive area of study because of the increased focus on developing alternative treatments for antibiotic-resistant bacteria.[98] Additionally, the development of new technologies allows these mucins to be examined at the level of detail required to use their designs in future functional materials.[181]

Conoidea, made up of Conidae, Terebridae, and Turridae snails, includes species that produce and secrete very complex venoms, with thousands of unique toxin and mucin peptides (Figure 6A).[182, 183] The venom peptide toxins found in conoideans have evolved over millions of years to rapidly and effectively disrupt macromolecular functions in their prey by manipulating important physiologically relevant drug targets such as G-protein coupled receptors, ion channels, enzymes, receptors and transporters.[182, 184, 185] The first conoidean commercially available therapeutic, ziconotide (Prialt®), is a non-addictive, nonopioid analgesic peptide, isolated from the venom of *Conus magus* (magical cone snail) that is used to treat chronic pain in cancer patients.[186] Ziconotide opened the floodgates for the therapeutic development of snail venom peptides, however, an equally promising, but less explored avenue is the potential application of conoidean snail mucins. The Holford lab has leveraged omics technologies (genomics, transcriptomics, and proteomics) to advance the discovery of venom peptides from previously neglected venomous animals such as terebrids.[182, 185] The group currently seeks to apply this general omics approach to identify conoidean mucus and investigate if there is an evolutionary pattern that can be used to determine mucin molecular function.

The Barrientos laboratory specializes in the ecology of tropical land snails and is currently focused on investigating *Tikoconus costarricanus,* a tiny snail that lives in Costa Rica's forests (Figure 6B).[187] This recently described snail species has a "caudal gland" on the dorsal side of the foot, and the snail uses mucus secreted from this gland to hang upside down during aestivation to avoid dehydration under leaf cover (Figure 6C). When abandoning the inverted position, a thread of mucus is formed between the caudal gland and the leaf surface (Figure 6D). In some cases, the thread becomes so tough that the snail cannot break it through tensile force alone, and it must use its mouth to break the tether. It is possible that this land snail, like many others, produces several types of mucus that function in surface adhesion, locomotion, lubrication, and hydration.[181] The lab's efforts aim to answer questions related to the molecular composition of and differences between the snail's multiple mucuses, the ability of the caudal mucus to be drawn into tensile fibers, and the reversibility of the mucus's phase transitions.

As mentioned above, mucuses from snails are relatively unexplored. There are several areas in which discovery-driven research targeted on identifying genetic phenotypes that elucidate functional activity of mucins would lead to transdisciplinary breakthroughs. For example, the increase of antibiotic-resistant bacteria is a growing threat that requires the use of new therapeutics and mucins are a resource for finding potentially new antimicrobial compounds.[98] Additionally, a recent study of several Giant African snail genomes (genus *Achatina*) identified 99 mucin genes in *A. immaculata* and 71 in *A. fulica* that may have roles in immunity, water retention, and wound healing, underscoring the need to investigate gastropod mucus further.[188] By applying a systems-wide omics approach to the discovery and characterization of mucins across the tree of life, we can establish a repository of information for how genes have evolved over time and how functionalization and novelty arise. This information is at the heart of scientific questions ranging from evolutionary biology to cellular physiology. The Holford and Barrientos labs have only scratched the surface of snail mucin and peptide discovery, and it is astonishing to consider that in the secretions of a marine or terrestrial snail we can find answers to how and why venoms and mucuses evolved; treatments for infections,[189, 190] cancer,[191, 192] pain,[193, 194] and a host of other human diseases and disorders; and inspiration for adhesive, lubricating, and tensile materials.

Figure 6. Terrestrial snails. A) Assortment of shells from terebrid snails. Image credit Robert Clark, National Geographic. B) *Tikoconus costarricanus* sliding on mucus. C) Same species aestivating in a bat-like position, hanging from the underside of a leaf with the assistance of adhesive mucus. White arrow points to mucus strand. D) Snail using the radular teeth to cut the mucus thread between the caudal gland and the leaf.

Mollusca, Gastropoda: Red Triangle Slug Mucus

The team of Gould at the University of Newcastle, Australia investigates the behavior, evolution, and natural history of Australia's diverse and unique wildlife.[195, 196] The red triangle slug, *Triboniophorus graeffei*,[197] is Australia's largest and arguably most striking terrestrial slug [198, 199]. While the body of the slug is ghostly white, the base (or foot) is skirted by a thin band of intense vermillion, with a triangular mantle that is also skirted by the same intense pigmentation which gives this species its name. Like many of the Australian terrestrial mollusks, most aspects of *T. graeffei*'s ecology remain poorly described, which is surprising given that it can be found in forest systems up and down the east coast of the continent. This could perhaps be attributed to its elusive nature, as it is often only observed during rainy periods, when it comes out of hiding to feed on algae growing on the exterior of smooth-barked eucalypts. Gould's team has discovered that *T. graeffei* produces an adhesive mucus when disturbed.[99]

The discovery of *T. graeffei*'s extraordinary secretory ability was made by chance while conducting fieldwork in the Watagan Mountain Range in New South Wales. On one particular night of fieldwork, an adult red-eyed green tree frog, *Litoria chloris*, was found immobile on the side of a fallen eucalyptus branch in close proximity to a large *T. graeffei* specimen (Figure 7). On closer inspection, the ventral skin surfaces of the frog were found to be adhered to the branch and surrounded by mucus, with the toe pads and webbing of the front and back legs adhered to each other and to the branch as well. Given the close proximity of the frog to the slug, the Gould team speculated that it had become ensnared in the slug's mucus secretions. They subsequently tested this hypothesis by examining the secretions of multiple *T. graeffei* specimens under laboratory conditions and found that an adhesive was secreted in regions of dorsum that were mechanically stimulated, providing evidence that the frog was indeed trapped in *T. graeffei* mucus.

Mechanical stimulation of the *T. graeffei* dorsum results in contractions in the immediate area and the rapid development of mucus droplets, which then coalesce and spread out over the surrounding surface. Upon secretion, this mucus is initially wet and translucent, but rapidly forms a thick, sticky, and opaque mass. It has been proposed that this adhesive mucus is a defense against predation, causing predators to stick to themselves or their immediate surroundings and thereby preventing them from successfully finalizing an attack. This adaptive function of the mucus has been observed in the field under natural conditions (as stated above), with a potential predator being found adhered to surrounding vegetation upon contact with the mucus, and for an extended period of time. Given these findings, it is likely that this adhesive serves to incapacitate predators, possibly to allow the slug to make its getaway. However, the aforementioned data is the first reporting of the red triangle slug's adhesive mucus,[99] and thus investigations into the underlying molecular composition are still needed.

The production of defense adhesives has been recorded for at least two unrelated species of terrestrial slugs.[200-202] However, it has not been recorded among Australian forms. While the natural predators of *T. graeffei* remain unknown, amphibians have been reported to predate on slugs,[203, 204] suggesting that the aforementioned observations in the wild are the first showing the anti-predatory function of this mucus for slugs. What continues to remain a mystery is the mechanism that allows individual slugs to remain un-adhered to their own secretions upon their release, as opposed to predators which appear to become quickly trapped and possibly for days. A strong bioadhesive is a valuable form of defense, particularly for slugs which are slow moving and lacking any protective shell. Interestingly, this study by Gould and coworkers[99] indicates that the adhesive property of *T. graeffei* defense mucus is reactivated upon hydration, making it potentially useful in the development of biological glues. A precedent for the economic value of these properties of slug mucus has been set by the recent development of a biological adhesive based on studies of the secretions in a different species, *Arion subfuscus.*[205] Interestingly, it has been suggested this model organism produces glues based on double network hydrogels,[202, 206-208] consisting of distinct stiff and deformable polymer networks linked by sulfated polysaccharides and divalent metal ions.[209] Since the biochemical makeup of mucus varies between species, [210, 211] there is an exciting opportunity to exploit the specific adhesive and water-activated properties of *T. graeffei*'s defense mucus to create new bio-inspired materials.

Figure 7. Adult *Litoria chloris* frog adhered to a eucalyptus branch in close proximity to a *Triboniophorus graeffei* slug (light grey mass, lower right). Reprinted in part with permission from ref. 87. Copyright 2019 Ethology.

Onychophora: Velvet Worm Slime

The Mayer (University of Kassel, Germany), Schmidt (Heinrich Heine University Düsseldorf, Germany), Harrington (McGill University, Canada), and Monge-Nájera (Universidad de Costa Rica, Costa Rica) groups study the biochemical and biomechanical properties of the adhesive slime launched from onychophorans, or velvet worms (Figure 8, top). Onychophorans comprise a phylogenetically ancient group of soft-bodied, terrestrial invertebrates that originated 600–540 million years ago.[212, 213] Approximately 200 extant species of both major velvet worm subgroups, the Peripatidae and the Peripatopsidae, have been described, and they mainly live in temperate and tropical forests of the southern hemisphere.[214, 215] Within their humid micro-habitats—mostly decaying wood and leaf litter—they implement a fascinating strategy for capturing prey and defending themselves against predation. The velvet worms shoot out a mucus-like slime (Figure 8, top) onto their prey to entrap it before consuming it.[22, 216-225] This projectile glue is strong enough to immobilize even the powerful legs of a cricket.[22] To achieve this feat, velvet worm slime exhibits several remarkable qualities. When the fluid slime is mechanically stimulated (e.g. via compression, agitation, or shearing), it converts immediately into a gel, which is adhesive even in humid environments and underwater. In this activated state, the slime can be rapidly drawn into load-bearing fibers. These stiff fibers are presumably adapted to resist escape attempts of trapped insects. Remarkably, this mechanoresponsive transformation process is fully reversible as the drawn material reverts to the original fluid state when dissolved in water, from which new fibers can be generated through drawing (Figure 8, bottom).[97, 215, 222, 226-233] Onychophoran slime proteins exhibit some structural distinctions from mucin, as protein secondary structure and divalent ions are more prominent in this slime.

The Monge-Nájera group has studied this exotic creature for nearly 40 years, and has made significant contributions to understanding of onychophoran natural history, behavior, and biomechanics, having discovered many species of velvet worm.[234-236] Recently, his group elucidated the mechanics of the velvet worm's oscillatory slime ballistics,[217] and also found that the adhesive slime is used as a food source for young worms.[237] Working collaboratively the groups of Mayer, Schmidt and Harrington have investigated the slime of the Australian velvet worm *Euperipatoides rowelli* to reveal the physical and biochemical principles behind its reversible fiber formation. An initial multiscale, structural and compositional investigation provided the first clear evidence of the molecular and nanoscale origins of fibers assembly.[215] The slime is comprised of nearly monodisperse protein-based nanodroplets (diameter ~100 nm), which appear to be stabilized by noncovalent electrostatic interactions between charged domains of the dominant protein building blocks that likely possess β-crystalline structure,[228] and positively charged divalent cations in the slime (e.g. Ca^{2+} and Mg^{2+}).[227] Electrostatic repulsion between the nanodroplets, which carry a weak positive surface charge, prevents the premature aggregation of proteins into a gel-like network and keeps the slime in the fluid storage state. However, when agitated, nanodroplets are forced into contact and the nanodroplets aggregate, forming an activated gel phase, which can then be further transformed into stiff fibers when drawn and dried. Unlike many other natural fibers, velvet worm fiber proteins do not exhibit a preferred orientation along the fiber axis and are linked only by noncovalent interactions. This accounts for the reversibility of the fiber formation process – fibers can be dissolved in water and regenerated by drawing.[215, 228]

Biomechanical and physico-chemical analyses of the last 20 years have provided wide-ranging insights into the properties and complex functionalities of velvet worm prey capture slime.[215, 226-230] However, there are a number of open questions, which must be answered to understand the molecular principles in this material required for transferring the lessons of velvet worm slime into synthetic systems. For example, only a small fraction of the total number of slime proteins has been identified and characterized. To understand the function of the proteins and their potential role in fiber formation, complete sequences and post-translational modifications of the key proteins implicated in the process are required. Additionally, the potential functions of lipid, carbohydrate, and ion components of the slime need to be further assessed. Thus far, deep structure-function analyses were primarily performed only on a single velvet worm species – the peripatopsid, *E. rowelli*. A comparison between representatives from both major onychophoran subgroups, the

Peripatidae and the Peripatopsidae, will be highly relevant to discover the entire range of fiber formation strategies of the velvet worms. These efforts will allow us to mimic the material in a simplified synthetic model that could be used as reversible surgical adhesives and structural materials in ionic environments. In addition, the analysis of slime ejection[217] could be used as inspiration for oscillatory microfluidics systems.

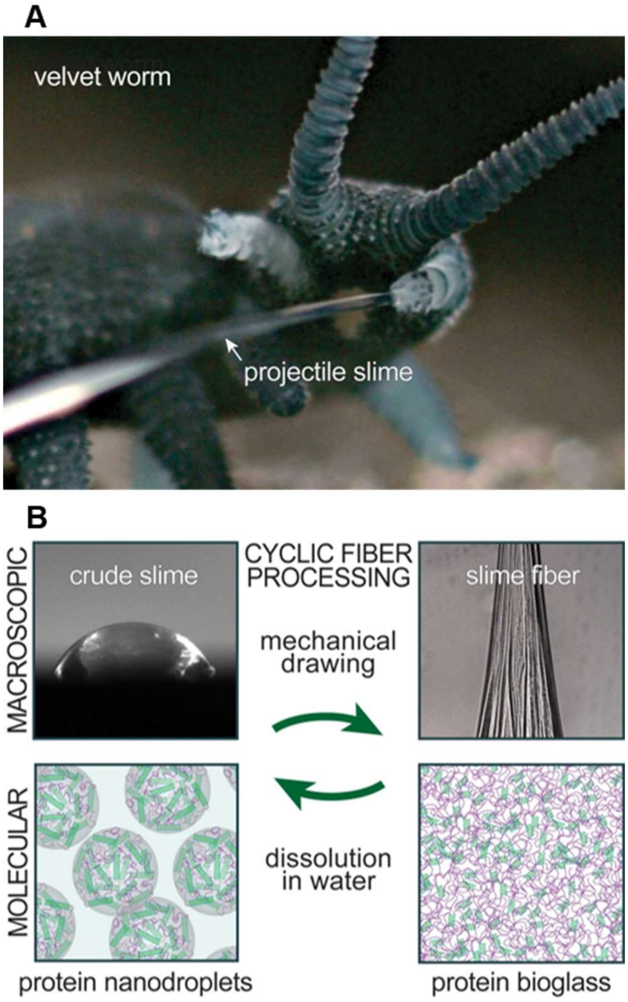

Figure 8. A) *Euperipatoides rowelli* during slime ejection. B) Fiber formation in velvet worm prey capture slime. Cyclic fiber processing is triggered by mechanical impact at macroscopic and molecular levels. At the macroscale, the crude slime instantly forms a

stiff fiber via compressing and drawing. In water, the fiber returns back into the fluid slime state. At the molecular level, β-sheet containing proteins self-assemble into nanodroplets which aggregate into a gel-like state by shear forces. When further stressed, the nanodroplets disrupt and the stored proteins unfold and cross-link into the stiff and glassy fiber. Fibrillated proteins dissolve in water and reassemble back into the storage nanodroplets (via coacervation). Images adapted with permission from ref. 215. Copyright 2019 American Chemical Society.

Chordata, Tunicata: Appendicularian Mucus

The Thompson laboratory at the University of Bergen, Norway, studies the molecular ecology of tunicates (or urochordates), the marine organisms comprising the closest living relatives to vertebrates.[238] Tunicates (comprised of Ascidiacea, Appendicularia, and Thalicea) are animals partially or completely enclosed in either mucus "houses" (Appendicularians) or "tunics" (Ascidiaceans, Thaliceans). The filter-feeding house secreted by appendicularians (also called larvaceans) is among the most complex extracellular structures constructed by any organism.[239-241] These structures feature complexity in their architecture, consisting of physically and functionally distinct inner and outer layers, and can extend to lengths of over one meter, nearly 100 times the length of the animal itself (Figure 9). The resulting so-called house allows appendicularians to exploit a wide range of food particles, including nanoplankton and sub-micron colloids, establishing them as important, abundant components of marine zooplankton communities. The Thompson group focuses on *Oikopleura dioica* (Figure 9), a coastal marine appendicularian with a pan-global distribution. This species is noted for rapid expansion of population size in response to algal blooms and, to maintain sufficient filtration rates, it synthesizes an entirely new house (15% of its total body carbon) every 3–4 hours. These discarded filter-feeding houses are a major component of marine snow and have significant, sometimes dominant, roles in vertical carbon flux cycles.[242]

The oikopleurid house is built on a scaffold of cellulose microfibrils[243, 244] and associated house proteins (oikosins).[239] Oikosins generally lack identity with known proteins, but do share architectural similarities with mucins. Phylogenetic analyses indicate that a single lateral gene transfer event from a prokaryote at the base of the lineage conferred cellulose biosynthetic capacity in tunicates.[243] Despite the common tunicate strategy of extracellular mucus filter-feeding structures, the Thompson group has shown that the proteome of the *Oikopleura* house has little in common with the proteome of the sister group, the ascidian, *Ciona* tunics. Of the now 80 identified oikosins, about half lack domain modules or similarity to known proteins, suggesting *de novo* appearance in appendicularians.

The oikoplastic epithelium, a monolayer of cells covering the trunk of the animal, is responsible for secretion of the house. Expression patterns revealed that individual oikosins are produced from specific fields of cells within the oikoplastic epithelium, but in some cases migrate up to at least 20 cell diameters in extracellular space to combine in defined house structures. Among the oikosins, Oikosin1 has 13 repeats of a Cys-domain, a subunit of repeating sequences, also present in some vertebrate mucins. One such repeat of this Cys-domain is also found in human cartilage intermediate layer protein (CILP), but no evidence of this domain in any other invertebrate species has been found. Oikosin1 is produced in an intermediate zone between the anterior and posterior mesh zones of the food-concentrating filter. In this respect, the weak sequence homology with human CILP is intriguing, as CILP is found only in cartilage in an intermediate layer between collagen mats.[245] The high concentration of CILP in rib cartilage compared to low levels in tracheal cartilage has been interpreted to suggest that compressive load is a factor in controlling the tissue distribution of this protein. The fact that CILP is restricted to an interterritorial zone indicates that this protein has a structural rather than regulatory role, and it is known that the expression of CILP is increased during the early stages of osteoarthritis.[246] In this context, Oikosin1 may be an interesting example of recruitment of the Cys-domain found in mucins for related structural purposes in very different functional settings. Further characterization of the mucin-homologous region of Oikosin1 will bolster mucin structure-function analysis, strengthening the design rules generated for biomimetic materials.

Though all tunicates employ extracellular matrices founded on a cellulose scaffold, they have evolved quite different protein compositions that build large multiplexed structures. Though tunicates employ a common cellulose building block, they have been innovative in incorporating various structural domains into original extracellular proteins for specific architectural solutions in the three main urochordate lineages. The *Oikopleura* house offers a tractable model to investigate how proteins evolved in different eras. In this system, roughly 100 distinct proteins have combined and diversified to create a complex extracellular structure essential to filter feeding. Studying these proteins will help to better understand the architecture in similar mineralized biosystems, such as those in corals and jellyfish. Additionally, the *de novo* appearance of the numerous oikosins provides a large unexplored space to investigate the structural basis of these unique mucus proteins. Greater understanding of tunicate houses can lead to underwater filtration systems to improve the longevity of aquatic vehicles and machinery.

Figure 9. The tunicate *Oikopleura dioica* (in yellow at center) in its mucus-coated filter-feeding house. The house captures floating organic matter, and filter sets concentrate particles toward the animal's mouth in the center of the image.

Chordata, Cyclostomata: Hagfish Mucus

The Fudge Laboratory at Chapman University, USA, studies hagfishes in contexts ranging from their ecology and evolution, to their cellular and organismal behavior, to the biochemical properties of their natural defenses. Hagfishes are marine, bottom-dwelling animals known for their burrowing behavior,[247] their recycling of organic matter in the world's oceans,[248] and, most strikingly, their ability to secrete enormous amounts of slime when they are provoked (Figure 10).[104, 249, 250] There are currently 82 hagfish species known worldwide of which 48 species fall within the taxon *Eptatretus*.[251] One of the most widely studied species, the Pacific hagfish (*E. stoutii*), is found at depths of 15–800 meters and is distributed in Pacific waters stretching from Mexico to southern Alaska (Figure 10, left).

Hagfish slime is secreted as a defense mechanism to discourage attacks from gill-breathing predators, such as other fishes.[252, 253] When a hagfish is attacked, approximately 100 mg of white, viscous exudate is ejected from several of its numerous slime glands.[104] This amount of exudate, after mixing with seawater, is capable of forming about one liter of slime in 100–400 milliseconds (Figure 10, right).[104] This exudate contains two main components — skeins and mucous vesicles.[254, 255] Each skein is an intricately coiled bundle of a silk-like thread consisting of intermediate filament family cytoskeletal proteins.[256, 257] When deployed in seawater, skein unraveling occurs alongside mucous vesicles. These vesicles contain mucous glycoproteins, which, working synergistically with the unraveled threads, provide remarkable strength to the slime network.[258] Vesicle deployment involves swelling of condensed glycoproteins and their transformation into a vast mucous network that interpenetrates the network of slime threads from the skeins.[259]

One way of understanding the large volumes of slime that hagfishes can produce is by recognizing that the slime is remarkably dilute, with the dry weight of mucus and thread components being only 15 and 20 mg mL^{-1}, respectively.[104] The dilute nature of hagfish slime can be further understood as a consequence of the fact that the slime does not bind seawater as much as it *traps* it, which is supported by the fact that substantial volumes of seawater drain out of the slime when it is subjected to a pressure gradient, e.g. when it is pulled out of water into air.[104]

The glycoproteins that make up the mucous component of the slime remain mostly uncharacterized. Salo *et al*. showed that the mucous fraction of *E. stoutii* slime contains 77% protein, 12% carbohydrate, 6% sulfate and 5% lipid on a dry weight basis.[258] The amino acid composition revealed some resemblance to mucin glycoproteins but also differed in many aspects such as proline, sulfate, and carbohydrate content in addition to the ratio of neutral to amino sugars. Characterizing the glycoproteins (i.e. the protein backbone and the attached glycans) that make up the mucous component of hagfish slime will shed further light on the biophysics of mucus vesicle deployment, the interactions between slime threads and mucus, and the rules that govern mucus glycoprotein properties in other organisms.

The Fudge Laboratory continues to investigate hagfish slime, with recent work focusing on the biophysics of slime deployment, molecular mechanisms of slime production, and biomimetic applications. Hagfish slime differs from other mucus secretions in that it is reinforced with high-aspect ratio silk-like fibers, which imbue the slime with unique biomechanical properties and make it fiendishly effective at clogging the gills of would-be fish predators. In the last few years, the group has begun producing materials possessing physical properties that resemble hagfish slime. They anticipate that hagfish slime mimics, once produced, could have uses in a diverse array of consumer and industrial products and applications, including fast-acting hull puncture repair in ships and water-responsive sensors.

Figure 10. Pacific hagfish, *Eptatretus stoutii* (left panel), and hagfish defensive slime (right panel).

Tetrapoda, Lissamphibia: Tree Frog Mucus

The Barnes group at the University of Glasgow, Scotland, studies the physicochemical basis of tree frog adhesion and uses their discoveries to guide the design of biomimetic materials. Tree frogs are mainly found in the tropics and are well adapted to living in trees.[260] Their main adaptation for climbing is their possession of adhesive toe pads at the end of each digit, and pad-like structures (sub-articular tubercles) located more proximally on the ventral surface of the digits. Like all frogs they respire through their skin despite possessing lungs. This means that their skin must be kept moist to allow gaseous exchange, something that is achieved by mucus secreted by subdermal mucus glands.[261] Mucus also plays an important role in adhesion, in that there is a mucus-filled joint between the toe pad and the structure (leaf, branch) to which the frog is adhering. Here, capillary forces, generated by the meniscus surrounding each toe pad (and sub-articular tubercle), are thought to play an important role in the tree frog's adhesive mechanism, allowing them to climb inclined and vertical surfaces (Figure 11).[262] Additionally, the Barnes Lab's experiments show that such a mechanism (known as "wet adhesion") allows frogs to hang onto rotating surfaces, but they tend to slip when attempting to climb when the newly-inverted surfaces are not moving.[263] In a recent paper, Langowski and coworkers show that the ventral digital mucus glands, whose ducts end in the toe pads, form distinct clusters that differ in their morphology from regular anuran mucus glands.[264] A chemical analysis, based mainly on cryo-histochemical techniques, failed to identify clear-cut differences between ventral and other mucus glands and between the chemistry of the mucus from climbing and non-climbing species. Interestingly, recent work on the chemistry of the mucus has shown that tree frogs can, for instance, exert capillary forces that allow adhesion to the surfaces of hydrophobic leaves. This is because their mucus contains molecules such as carboxylic acids that act as surfactants, lowering contact angles to levels where capillarity can occur (<90°).[265]

Adhesion in climbing animals is dynamic. It must be reversible but strong enough to support the weight of the animal[266] and effective climbing requires friction as well as adhesion.[267] There must also be mechanisms for self-cleaning and adhering only when required.[268] To understand this adhesion, the Barnes lab also measures adhesion forces on toe pads, with millinewton precision.[269] Studies of toe pad structure and physical properties involving both electron microscopy techniques and microindentation are also essential.[100, 270] Tree frog adhesion is complicated, and many questions remain unresolved. These include a better understanding of how toe pads actually adhere. In addition to capillary forces, there is good evidence for involvement of viscosity-dependent hydrodynamic forces and possibly van der Waals forces to explain this adhesion. Barnes's recent research shows that contact between the tips of the nanopillars that cover each epithelial cell becomes extremely close as tree frogs, tilted on a microscope stage, adjust their pads to prevent sliding or falling.

Since frogs stick to wet surfaces and can repeatedly stick and detach their sticky pads every time they take a step, there is potential for using tree frog adhesion as inspiration for new adhesives that can stick reversibly to wet surfaces and possess the ability to self-clean, so that they do not degrade with use. Improved wet weather tires, non-slip footwear, plasters for surgery that are able to adhere to tissue, holding devices for neurosurgery, and MEMS devices are other obvious examples of the many uses to which these toe pad analogues might be applied.

Figure 11. The Australian green tree frog, *Litoria caerulea,* adhering to a vertical glass rod. Images adapted with permission from ref 259. Copyright 2018 Journal of Experimental Biology.

Conclusions and Outlook

In highlighting this selection of animal mucus research, we find that many unresolved questions and challenges persist that must be addressed so that the full potential of mucus can be mimicked in bioinspired materials. Specific unresolved questions are: (i) Do mucins with similar functions have similar structures and shared phylogenetic histories, or are they the result of convergent evolution? (ii) What are the differences between vertebrate and invertebrate mucins? (iii) How do the mucin peptide and glycan components each contribute to the material behavior of the mucus? (iv) When animals produce multiple mucuses with distinct functions, do these mucuses contain similar mucin proteins? And (v) how do non-mucin additives of the hydrogels contribute to their properties?

Studying mucus by conventional molecular biological techniques faces many challenges. For example, recombinant expression of synthetic mucin proteins that retain natural function has been difficult as a result of several factors inherent to the mucins, including the size of the mucin protein backbone, the lack of understanding in the function of different mucin protein domains, the complexity of the polysaccharide structures, and the challenge of introducing glycan domains into the recombinant protein.[271-288] Furthermore, many mucins have variable mucin domain lengths arising from alternative splice variants, adding the difficulty of characterizing each isoform.[289-292] Considering the factors above, the number of mucin genes present in typical animal genomes, and the complex tissue expression patterns of mucin proteins, it is challenging to decipher the roles of different domain features in mucin function from typical genomics and proteomics analyses alone. To address these unresolved issues, the researchers in the newly established

Comparative Animal Mucomics Project (CAMP) have adopted a collaborative approach that combines field work with experimental and computational methods. The various research groups will make the best effort to ensure that datasets are compatible and collect similar information, so that the salient properties of the mucuses can be more easily compared.

To address issues of data-consistency, an omics-style approach that compares different mucus samples at multiple hierarchical levels across both the central dogma of biology and length scales is needed. Data-driven genomics, transcriptomics, proteomics, and metabolomics methods are highly effective strategies to quantitatively organize and analyze large, multi-dimensional datasets to answer the complex biological questions listed above. Models like the Consortium for Functional Glycomics,[290] National Center for Biotechnology Information,[293] the Protein Data Bank,[294] and the Omics Database Generator[295] set rigorous standards for data collection, organization, and analysis to be universally accessible and practical. Therefore, we suggest that adopting a similar "mucomics" approach is essential to answering the aforementioned questions about mucus structure-function relationships. This mucomics approach will compile gene and protein sequences, transcriptomic data, glycomic profiles, molecular weights of the mucins, the additives that exist in a mucus sample, and the material properties of the hydrogel. These data and integrative analyses, information on our mucus sample library, a list of CAMP members, publications, and means of being involved are available on our CAMP website, reachable at [WEBSITE URL].

Our aim in establishing CAMP is to understand the roles of diverse mucins in nature and tease apart structure-activity relationships that can guide the design of synthetic mucus mimics. These bio-inspired analogues could be used to replace current materials that serve as adhesives, lubricants, structural materials, barriers, and semi-permeable membranes. Although several important papers have shown that the advantageous properties of mucuses can be emulated with synthetics[27, 296-310], the field of synthetic mucus is currently in its infancy. We hope that the efforts of CAMP and others already working to understand the structures and properties of mucuses[18, 311-317] will support efforts to design biomimetic materials that seek to emulate the remarkable properties of these secretions found throughout the animal kingdom.

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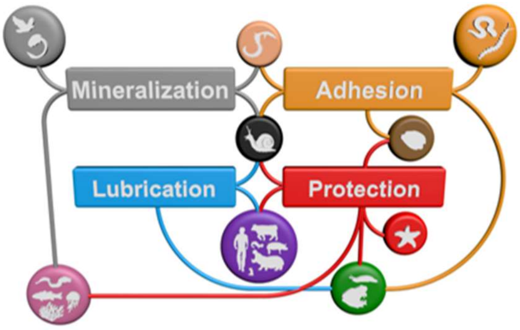

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