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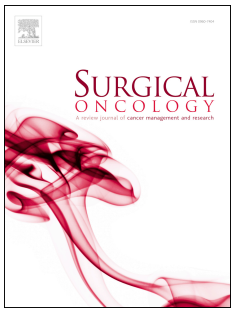

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Hanna Dillekås, Oddbjørn Straume

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The link between wound healing and escape from tumor dormancy

Hanna Dillekås[a*], Oddbjørn Straume[b,c]

[a]Department of Clinical Science, University of Bergen, N5020 Bergen, Norway. hanna.dillekas@uib.no

[b]Centre for Cancer Biomarkers CCBIO, Department of Clinical Medicine, University of Bergen, N5020 Bergen, Norway. oddbjorn.straume@helse-bergen.no

[c]Department of Oncology and Medical Physics, Haukeland University Hospital, N5021 Bergen, Norway

*Corresponding author:

Hanna Dillekås, MD

Department of Clinical Science

University of Bergen

N5020 Bergen, Norway

Tel: +4741209809

Email: hanna.dillekas@uib.no

ORCID, H. Dillekås: 0000-0002-4355-7197

ORCID, O. Straume: 0000-0001-8867-3645

ABSTRACT/ SUMMARY:

Tumor dormancy is considered one of the major unsolved questions in cancer biology. Understanding the mechanisms responsible for maintaining and interrupting dormancy would be a major step towards preventing overt metastatic disease. Increasing evidence points to tissue trauma and subsequent wound healing as contributing events in escape from dormancy. In this review, we outline relevant aspects of the wound healing process, and relate this to mechanisms of tumor dormancy and metastatic progression. In addition to important findings in epidemiological and experimental studies, more direct evidence of such a link has recently been presented. These results can have major implications for treatment and prevention of cancer.

Keywords: Tumor dormancy, metastasis, wound healing, inflammation

1. 1 Wound healing and cancer

The process of wound healing is a carefully orchestrated series of partly overlapping events, involving multiple local and systemic changes, all with the intent to restore tissue homeostasis, regain function and protect from infection. Whether the wound is caused by a traumatic event or deliberately inflicted by surgery, successful healing is crucial, as demonstrated by the major health issues caused by deficient wound healing capacity seen in diabetic patients amongst others. The similarities between the composition of the granulation tissue in healing wounds and the stroma of tumors led to the seminal publication by Harold Dvorak, stating that tumors are "wounds that do not heal" [1]. Clinical observations of increased susceptibility for cancer development at sites of chronic inflammation, such as ventricular cancer in *H. Pylori*-infected gastric mucosa, hepatocellular cancer in patients with chronic viral hepatitis and colorectal cancer in inflammatory bowel disease, demonstrate the interplay between cancer development and local inflammation[2]. The increased risk of breast and colorectal cancer in obesity, a condition of chronic elevation of inflammatory mediators, supports the existence of a systemic effect[3]. One of the first experimental evidences that infliction of wounds leads to tumor formation was the Fisher brothers' series of experimental factors influencing the formation of hepatic metastases, where both liver resection (local trauma effect) and laparotomy (systemic effect) caused an increase in liver metastasis formation[4, 5]. Later, in a model of tumor development after injection with Rous sarcoma virus, Bissel and coworkers demonstrated that tumors developed at a site distant from inoculation only if a wound was inflicted at that site. If the animal was treated with an anti-inflammatory drug, tumor development was prevented[6]. The stimulating effect on cancer cells by cells involved in wound healing has later been demonstrated in even more

sophisticated models, such as melanoma cells in wounded translucent zebrafish, where live imaging revealed rapid divergence of wound healing activated neutrophils to nearby pre-neoplastic cells causing increased proliferation and full malignant transformation[7]. Recently, outgrowth of dormant tumors at a distant anatomical site in response to surgery and wound healing was robustly demonstrated in a murine model system of immune-restricted tumor growth. Inflammatory monocytes were implicated as the functional mediators, and the effect was counteracted by perioperative administration of an NSAID.[8]

2.1 Tumor dormancy overview

The concept of tumor dormancy, where cancer cells from a primary tumor disseminate early and enter a state of dormancy with a potential to cause late relapses is recognized in many cancers[9]. Autopsy studies have revealed dormant tumors in a large number of people dying from other causes, reviewed in [10, 11]. When comparing the prevalence of microscopic tumors of the thyroid and breast in autopsy studies to overt thyroid and breast cancer it is clear that for most people, the cancer remains dormant throughout life [12, 13]. Most research in the field of tumor dormancy has been focused on breast cancer, notorious for late relapses even decades after apparently successful treatment of small primary tumors[14]. Studies of the relapse pattern of breast cancer in several large patient series have revealed a biphasic distribution of relapses, consistent with the existence of a dormant phase[15, 16]. The mechanisms causing and maintaining dormancy in the clinical setting are not definitely established. Models suggest multiple factors such as inability to recruit blood vessels[17], immune suppression[18], entrance into cell cycle arrest[19], microenvironmental growth restriction[20] and autophagy[21]. Likewise, the means by which cancer cells can escape from dormancy are not fully elucidated, but as wound healing has been demonstrated to accelerate cancer growth [22], and epidemiological studies have revealed a peak in relapses after surgical procedures[23, 24] the theory that some factors in wound healing can mediate escape from tumor dormancy is highly relevant. This is especially unsetteling when considering the fact that surgery, where cancer-stimulating wound healing may take place in the presence of occult, dormant micrometastases, remains primary treatment in many cancer forms. In addition to wound healing, cancer surgery also includes anesthesia and analgesia, as well as potentially perioperative hypothermia and hypovolemia, factors that may add to cancer growth stimulation. Details on the scientific evidence for such effects were recently comprehensively reviewed [25]. When studying the phases of wound healing, with inflammation, immune suppression, stimulation of proliferation and migration of cells [26], a stimulating effect on dormant cancer cells

makes biological sense. Each phase of wound healing is outlined below with corresponding evidence from studies linking the involved mechanisms to escape from tumor dormancy.

3.1 The phases of wound healing and their effects on tumor dormancy and metastasis

3.1.1 The immediate response

The immediate response, initiated by tissue and vessel trauma, rapidly leads to blood clotting to stop local hemorrhage. The blood clot, predominantly consisting of cross-linked fibrin and platelets, previously considered merely a temporary physical sealing of the wound, is now known to have several biological functions [27]. When endothelial integrity is disrupted, underlying collagen and von Willebrand factor are exposed and activate platelets in the blood stream. Activated platelets release alpha-granules, packed with over 300 growth factors and cytokines including platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor beta (TGF-β) and matrix metalloproteinases (MMPs) [28, 29]. This cocktail of factors is intended to attract inflammatory cells, stimulate cell proliferation, vessel formation and degradation of matrix. If a microscopic tumor is suspended in dormancy by insufficient blood supply, this release of VEGF may constitute an “angiogenic switch” allowing escape from dormancy by stimulated angiogenesis[17, 30] and VEGF levels have been correlated with disease progression[31]. *In vitro* and *in vivo* studies have demonstrated both improved wound healing and enhanced breast cancer cell colony formation by addition of platelet lysate [32, 33, 34]. The main effect of platelet activation on cancer seems to be to promote invasion and metastasis. TGF-β is one of the most potent drivers of epithelial to mesenchymal transition (EMT), a process where cells of epithelial origin gain a more mesenchymal phenotype by losing polarity and cell-to-cell adhesions, downregulating E-cadherin and upregulating vimentin, thus becoming more mobile[35]. This is needed for keratinocytes to re-epithelialize the wound surface, but when adopted by cancer cells, especially in combination with leakier capillaries due to VEGF and matrix degradation by MMPs, promotes invasion and metastasis. Fig. 1a.

3.1.2 Inflammation

Chemoattractants released from platelets, together with complement activation leads to the next phase: inflammation. First to arrive are the neutrophils[36], followed by macrophages[37] and lymphocytes. Neutrophils secrete prostaglandin E2 (PGE2), and reactive oxygen species (ROS), further fueling inflammation with the purpose of eradicating invading bacteria [38]. Macrophages also secrete PGE2 when stimulated by pro-

inflammatory cytokines such as IL-6, and bacterial lipopolysaccharides (LPS) [39]. PGE2 is prominent among the inflammatory mediators that also exert tumor-sustaining effects [40], and elevated levels have been associated with poor prognosis in various malignancies, including breast, lung and colon [41, 42, 43, 44]. Among the physiological functions of PGE2 in wound healing are stimulation of proliferation, migration and angiogenesis, cancer cells may utilize these effects to increase metastatic efficiency [40]. PGE2 is also a key mediator of cancer immune evasion by suppressing type I interferons and T-cell mediated tumor elimination and altering dendritic cell maturation and ability to secrete cytokines [45]. The cancer promoting role of PGE2 is further supported by the beneficial effect on recurrence free survival associated with cyclooxygenase (COX) - inhibitors such as aspirin [46, 47]. A central role for neutrophils in escape from dormancy was supported by an in vivo study of LPS-induced inflammation in mice with disseminated dormant carcinoma cells. By upregulation of EMT-factor Zeb1, dormancy was interrupted and macroscopic metastases developed. Neutrophil depletion abrogated this effect [48]. ROS and reactive nitrogen species can have tumorigenic effects by directly damaging DNA as well as by modifying proteins involved in critical steps of cell-cycle checkpoint control, DNA-repair and apoptosis [49]. In addition, ROS stimulates activation of COX-2 and thereby increases PGE2-production [38]. A large number of cells, including fibroblasts, keratinocytes, endothelial cells and macrophages, produce IL-6 in response to infection and tissue damage [50]. The classical effects of IL-6 includes induction of fever, hepatocyte stimulation to produce acute phase proteins such as C-reactive protein (CRP) and release of adrenocorticotropic hormone [51, 52], mainly mediated via signal transducer and activator of transcription 3 (STAT3). In cancer cells, IL-6 has been demonstrated to induce EMT [53, 54], promote proliferation and survival, and serum levels are a negative prognosticator of both relapse and response to therapy in breast and kidney cancer patients [55, 56, 57]. CRP and IL-6 levels have been demonstrated to be negative prognostic markers in most cancers [58, 59, 60, 61, 62].

Recent evidence suggests an important role of macrophages in early breast cancer dissemination; intra-epithelial macrophages were observed in early murine mammary lesions, corresponding to ductal carcinoma in situ in humans, depletion of macrophages at these early stages significantly reduced later metastatic development [63]. The macrophages in wound healing are predominantly of the M2, or alternately activated type [64], which is considered to be mainly pro-tumorigenic, as compared to the classically activated M1 macrophages, potent killers of microorganisms and cancer cells [65]. The M2 macrophages have a central role in promoting angiogenesis, tissue remodeling and repair by producing growth factors including VEGF, EGF, TGF-β and fibroblast growth factor (FGF) and enzymes and inhibitors to digest extracellular matrix, such as MMPs,

urokinase-type plasminogen activator (uPA) and its receptor uPAR [65]. In a model of carcinoma cell growth, high uPAR was demonstrated to induce escape from dormancy by upregulating the mitogenic extracellular regulated kinase (ERK) 1/2, and blocking the apoptotic and growth-arresting activity of p38 via regulation of fibronectin fibril assembly [66]. Production of PGE2 and accumulation of neutrophils and macrophages is partly counteracted by activation of the hypothalamic-pituitary-adrenal (HPA) axis, which takes place within minutes of wounding and results in release of cortisol and adrenaline [67]. However, this also results in release of T-regulatory cells (Tregs), and can thus aid in cancer immune evasion [68]. The physiological rationale for this immunomodulatory effect in wounding probably is to avoid excessive tissue damage and autoimmunity [69, 70]. VEGF, in addition to its angiogenic effects, also contributes to immunosuppression by inhibiting dendritic cell maturation of hematopoietic progenitor cells [71] allowing for accumulation of myeloid-derived suppressor cells [72]. Silencing VEGF *in vivo* has been shown to unleash an antitumor immune response leading to tumor eradication [73] and VEGF blockade to decrease the number of Tregs [74]. Fig. 1b.

3.1.3 Proliferation, migration and contraction

Proliferating, sprouting blood vessels are a key component to wound healing by supplying nutrients, cells and growth factors. While endothelial cells of stable blood vessels produce thrombospondin-1 (TSP-1), which induces breast cancer cell quiescence, sprouting vessels not only loses TSP-1, but are also rich in tumor-promoting factors such as periostin and TGF-β, thus sparking metastatic outgrowth as has been demonstrated both *in vitro* and *in vivo* [75]. Metastasis incompetent cancer cells have been demonstrated to create a metastasis refractory microenvironment by endocrine and paracrine secretion of prosaposin, a peptide that increases expression of TSP-1. Highly metastatic cells have significantly lower levels of this peptide [76]. Bone-marrow specific genetic deletion of TSP-1 increased metastasis formation in distant organs *in vivo*, an effect that was abrogated by bone marrow transplant from TSP-1^{+} donors. In the same study, pharmacological induction of TSP-1 dramatically suppressed metastasis [77]. Activated neutrophils have been shown to participate in degrading TSP-1 in the lungs, further facilitating escape from dormancy [78]. The bone marrow is considered a dormancy supportive niche; this may be mediated by TGF-β and dependent on the EMT associated receptor tyrosine kinase Axl [79]. Increased Axl activity has been associated with a differentiated and proliferating cellular phenotype which can switch to an invasive, non-proliferative, therapy resistant and dormant phenotype when the Axl activity is reduced[80, 81]. In prostate cancer cells, Axl has been demonstrated to be upregulated when binding to osteoblasts, and decreased in proliferating metastases [82]. Keratinocytes and fibroblasts from

the wound margins are stimulated to migrate into the wound and proliferate, mainly by TGF-β which is secreted from activated platelets in the early phase and later by several cell types [83]. In keratinocytes, migration is preceded by a partial epithelial-to-mesenchymal-transition, EMT, where the keratinocytes downregulate cell-to-cell contact and hemidesmosomes, rearrange the cytoskeleton, secrete proteases and extend lamellipodia to be able to degrade connective tissue and move into the granulation tissue of the wound [49]. These mechanisms, when applied to cancer cells, facilitate invasion and dissemination and thus metastatic seeding. In cancer, the EMT is more frequently complete, characterized by complete loss of cell-to-cell adhesions and expression of mesenchymal marker proteins like vimentin, resembling early embryogenesis, as opposed to the partial EMT in wound healing keratinocytes[84]. For cancer cells to regain their proliferative potential, mesenchymal to epithelial transition, MET, is also necessary as the decision between EMT/MET state determines if the cell should "go or grow" [85]. In physiological wound healing, the keratinocytes, by an as yet undetermined signal, reverts to the epithelial phenotype at completion of wound healing leading to the final phase, resolution and remodeling [86]. Parallel to these events, fibroblasts are recruited to the wound site and deposit extracellular matrix proteins. A few days after injury, fibroblasts differentiate to myofibroblasts with expression of α-smooth muscle actin, responsible for wound contraction [87]. Fibroblasts and myofibroblasts can be recruited by cancer cells to secrete growth factors, aid in invasion and in generating a cancer-supporting stroma which immune cells and cytotoxic agents have difficulties penetrating [88, 89, 90]. Fig. 1c.

3.1.4 Resolution and remodeling

In normal wound healing, the inflammation and proliferation, by not fully understood mechanisms, resolves when tissue regeneration is completed. The early collagen III-dominated matrix is gradually replaced by collagen I in dense bundles forming stiff scar tissue[91]. It has been demonstrated, *in vivo* and *in vitro*, that a collagen I-rich, fibrotic environment can be a determinant of cytoskeletal reorganization in dormant tumor cells, inducing proliferation and metastasis formation through β1-integrin downstream signaling, an effect that was repealed by blocking β1-integrin [92].

The resolution phase also includes regrowth of appendages, MMPs degrades and remodels the extracellular matrix to form organized collagen and proteoglycans, neutrophils and macrophages undergo apoptosis or return to the vasculature [27]. Failure of this resolution, with sustained inflammation, due to chronic infection, paracrine signaling from cancer cells, or other mechanisms, is a well-recognized hallmark of cancer [93]. Fig. 1d.

4.1 Conclusions and future perspectives

As outlined above, many of the signaling molecules and cells involved in wound healing have also been demonstrated to play a role in escape from tumor dormancy and development of metastases. Connecting the dots is a first step to being able to target this interplay in order to prevent overt, incurable, metastatic disease. An epidemiological study by our group identified a subgroup of breast cancer patients with early recurrences presenting with multiple, similar sized metastases, indicative of a synchronized onset of growth [94]. Post-surgery wound healing may constitute such a synchronizing signal. To study the effect of surgery on metastatic relapse, we proceeded to study the relapse pattern after delayed breast reconstruction. This revealed a peak in relapses 18 months after reconstruction[23], similar to what has been observed after primary breast cancer surgery[15]. The height of the peak correlated with the extent of surgery, thus demonstrating a dose-response relationship suggesting a causal connection[23]. The systemic impact of surgery on metastatic growth is also demonstrated in a study of patients presenting with stage IV disease, where locoregional surgical treatment of the breast tumor resulted in improved local control but also a significant reduction in distant progression-free survival [95].When considering targeting dormant cancer cells in the clinical setting one faces several obstacles. Treatment to maintain cancer cell dormancy throughout the patient's life might appear attractive. However, patients' adherence to therapy, which inevitably comes with side effects, to prevent an uncertain risk of recurrence is limited, as has been demonstrated for adjuvant hormonal therapy in early-stage breast cancer patients [96]. In this study, full adherence to prescribed treatment was 49%. Inducing escape from dormancy in order to make the cells sensitive to treatment is a risky method if we are not certain to be able to kill all cancer cells. At present, the most plausible approach would be to selectively prevent escape from dormancy at times when the risk is elevated, such as at surgery or during subsequent wound healing. Indeed, a short term burst of angiogenic factors has been demonstrated *in vivo* to be able to push a dormant tumor into progressive growth, after this, lower levels sufficed to maintain this phenotype [97]. Still, these findings remain to be confirmed. The peri-operative time as a window of opportunity to prevent escape from dormancy, is further supported by epidemiologic observations of improved disease-free survival and overall survival when non-steroidal anti-inflammatory drugs are used intraoperatively in conservative breast cancer surgery [98]. A randomized clinical trial investigating this is ongoing [99]. Identifying and targeting dormant tumor cells, to prevent metastatic relapse, is one of the great, unsolved questions in cancer research today, the answer to which could lead to entirely new treatment approaches and numerous lives saved.

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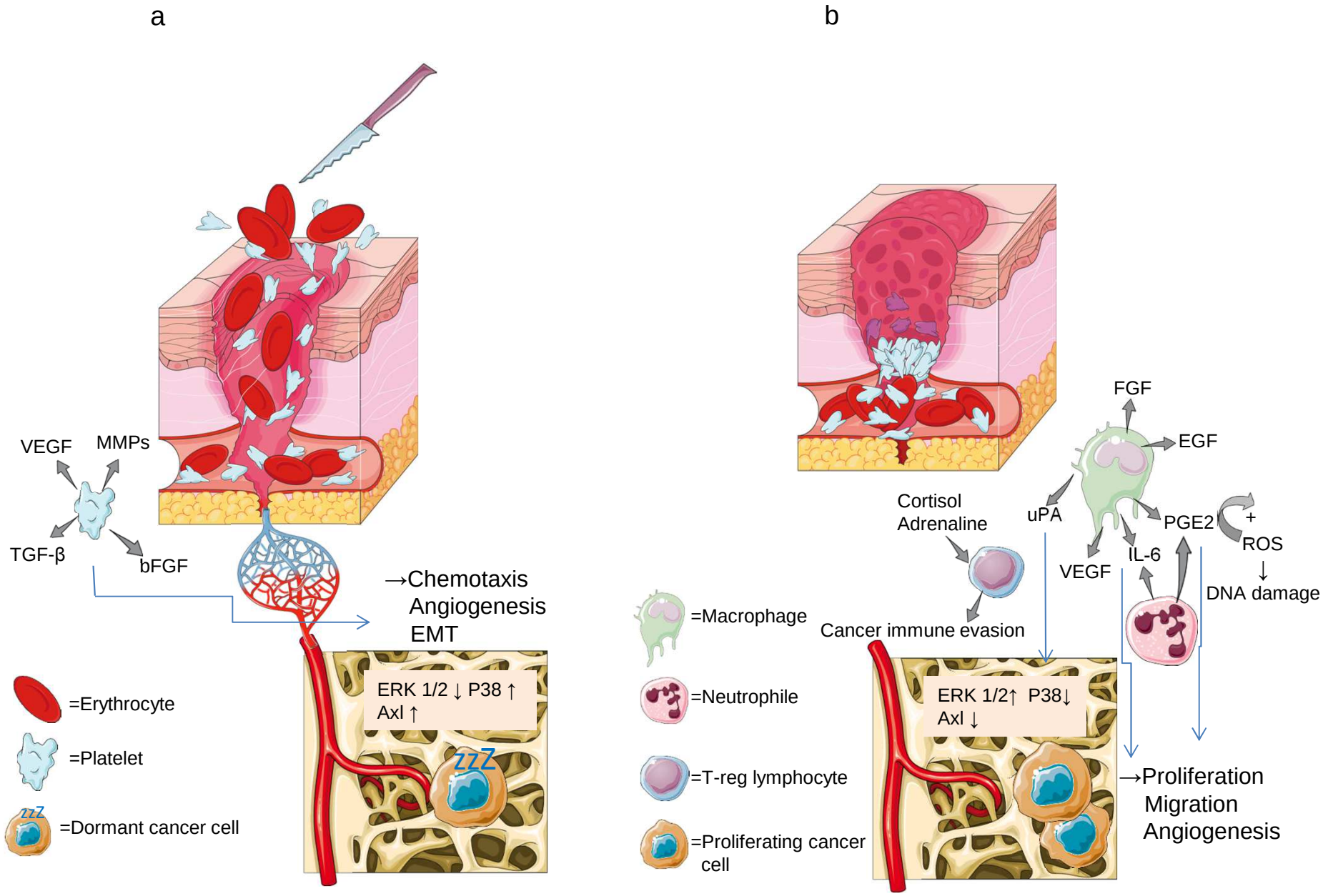
Legends

Fig. 1 a) The immediate response. Activated platelets release growth factors (vascular-endothelial growth factor (VEGF), transforming growth factor β (TGF-β), basic fibroblast growth factor (bFGF)), cytokines and and

matrix metalloproteinases (MMPs). These factors recruit inflammatory cells and stimulate vessel sprouting, re-epithelialization and degradation of matrix, but may also stimulate pre-existing dormant tumor cells at a distant site for proliferation and migration. EMT=epithelial to mesenchymal transition. b) Inflammation. Neutrophils and macrophages secrete growth factors, cytokines, reactive oxygen species (ROS) and prostaglandin E2 (PGE2), fueling an inflammatory response in the wound and surrounding tissues. Systemic levels increase, and these factors are also known to be able to stimulate proliferation and migration of tumor cells. Macrophage-derived uPA has been demonstrated to induce escape from dormancy by upregulating mitogenic extracellular regulated kinase (ERK) 1/2 and downregulating the growth arresting, pro-apoptotic p38. Systemic release of cortisol and adrenaline stimulates T-regulatory cells and can thus aid in cancer immune evasion. The receptor tyrosine kinase Axl is downregulated in proliferating metastases. c) Proliferation, migration and contraction. Sprouting vessels produce tumor-promoting factors such as TGF-β. In order to re-epithelialize the wound surface, keratinocytes undergo a partial EMT. Fibroblasts generate scar-tissue and can aid cancer cells in invasion and migration. d) Resolution and remodeling. In normal tissue, inflammation and proliferation resolves by unknown mechanisms when tissue is regenerated, inflammatory cells return to the vasculature. A stiff, fibrotic environment can determine cytoskeletal reorganization through β1-integrin downstream signaling, inducing proliferation and metastasis formation in cancer cells located in this environment.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ERK 1/2 ↓ P38 ↑
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Cortisol
Adrenaline
uPA
PGE2
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DNA damage
VEGF
IL-6
Cancer immune evasion
=Macrophage
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ERK 1/2↑ P38↓
Axl ↓
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Migration
Angiogenesis

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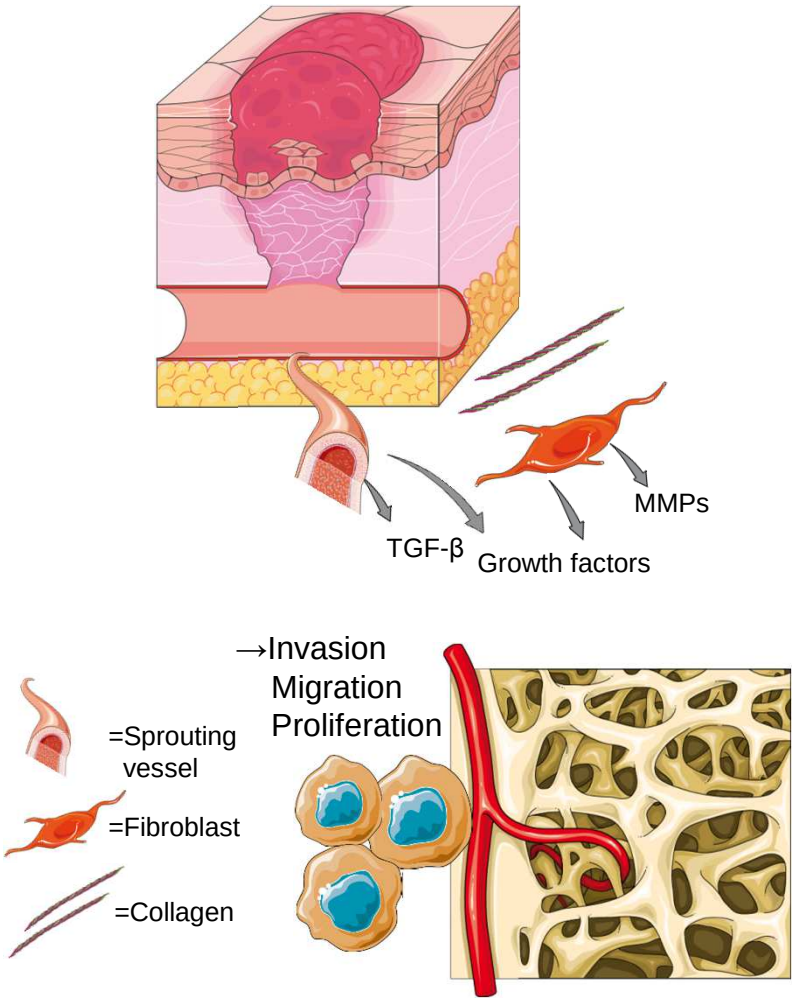

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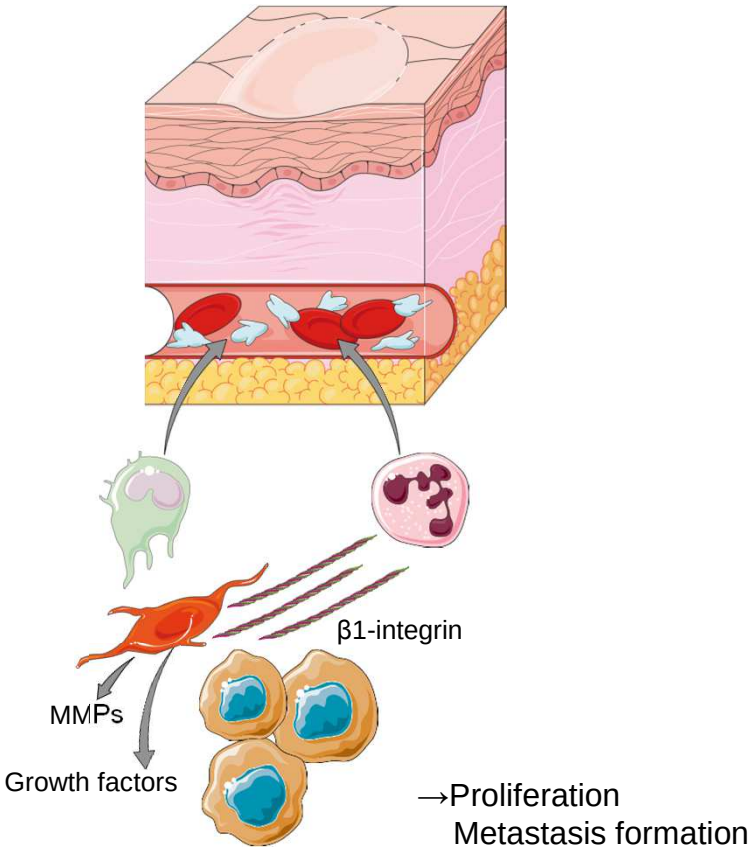

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