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A comparison of epithelial-to-mesenchymal transition and re-epithelialization

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Abstract

Wound healing and cancer metastasis share a common starting point, namely, a change in the phenotype of some cells from stationary to motile. The term, epithelial-to-mesenchymal transition (EMT) describes the changes in molecular biology and cellular physiology that allow a cell to transition from a sedentary cell to a motile cell, a process that is relevant not only for cancer and regeneration, but also for normal development of multicellular organisms. The present review compares the similarities and differences in cellular response at the molecular level as tumor cells enter EMT or as keratinocytes begin the process of re-epithelialization of a wound. Looking toward clinical interventions that might modulate these processes, the mechanisms and outcomes of current and potential therapies are reviewed for both anti-cancer and pro-wound healing treatments related to the pathways that are central to EMT. Taken together, the comparison of re-epithelialization and tumor EMT serves as a starting point for the development of therapies that can selectively modulate different forms of EMT.

Keywords

Epithelial-to-mesenchymal transition; Keratinocyte; Dermal wound healing; Metastasis; Metastasis

1. Introduction

Epithelial-to-mesenchymal transition, or EMT, describes a series of cascades that lead to a change in cell phenotype from a stationary, differentiated phenotype characteristic of healthy epithelial tissue to a migratory, de-differentiated phenotype characteristic of a fibroblast or metastasizing tumor cell [1,2]. The idea of comparing EMT to normal physiological processes such as re-epithelialization and cell migration in development is not a new idea. Grunert et al. [3] compared EMT to a number of different types of changes in cells resulting from normal physiology, pathophysiology, and transformation in an attempt to define EMT as a process rather than any one observation. More recently, three distinct manifestations of EMT have been proposed [4,5] based on stages of development and associated biomarkers such that the EMT commonly associated with cancer metastasis (Type III) can be clearly differentiated from the involvement of EMT in either

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embryogenesis (Type I) or regeneration/fibrosis in mature tissue (Type II). The use of only three categories of EMT may ultimately fail to reflect the complexity of cell plasticity of cells as they respond to changing environments. For example, Acloque et al. [6] have differentiated three stages of Type I EMT during embryogenesis. Despite the focus on the differentiators of various manifestations of EMT, it is most useful to identify the similarities and common mechanisms that give remarkable plasticity to our cells, both tumor and non-tumor. This approach is especially valuable in light of the potential for cross-fertilization in understanding the mechanisms of both EMT and its converse process, mesenchymal-to-epithelial transition (MET) that accompanies both physiological and pathological forms of EMT.

This review seeks to identify and update similarities and differences between traditional EMT mechanisms as they are currently understood in tumor progression and the specific case of re-epithelialization which represents, perhaps, the most minimal and reversible form of regenerative EMT in normal tissues [7]. With respect to re-epithelialization, keratinocytes are taken as model for comparison with tumor EMT although it is clear that similar re-epithelialization occurs in epithelial cells of the airway, digestive tract, kidney, and cornea, just to name a few sites. Furthermore, the focus in this review will be on early events that transform a mature, differentiated keratinocyte into a migrating keratinocyte and how these events compare to the initial transformation of a primary tumor cell into a metastatic tumor cell. In addition to interesting comparisons and contrasts in the biology of these processes, there is a compelling clinical need to establish a functional differentiation between tumor EMT and normal tissue regeneration due to the fact that normal wound healing must continue, even in the context of anti-metastatic therapies. Therefore, anti-metastatic therapies should be developed with an understanding of potential impacts on wound healing just as wound healing therapies must avoid induction of metastasis in the event that a malignancy is present.

2. A comparison of re-epithelialization and epithelial-to-mesenchymal transition

The epithelial layer of keratinocytes is maintained in mature skin by differentiation of progenitor cells that occupy the basal layer of the skin [8]. Under normal conditions, keratinocytes go through a process of terminal differentiation during which the cells convert from a cuboidal epithelium to a squamous epithelium with concomitant cell death such that the outer layer of the epidermis is composed of the keratin cytoskeleton and associated lipids providing a mechanical and hydration barrier to protect the underlying tissue. The barrier function of keratinocytes is enhanced by multiple cell–cell and cell–substrate interactions including cadherin-associated desmosomes and adherens junctions, integrin-associated hemi-desmosomes, focal adhesions, and tight junctions [9–13]. Keratinocytes also maintain connexin-associated gap junctions that facilitate intercellular communication among keratinocytes [14]. Upon wounding, the cells of the skin proceed through a characteristic response leading to re-establishment of the mechanical and hydration barrier. Mechanical strength is provided by the extracellular matrix of the dermis while the hydration barrier is re-established through re-epithelialization. Upon experiencing a cutaneous wound, four phases of response occur. These include an inflammatory response, a granulation phase during which connective tissue and extracellular matrix components are rebuilt, epithelialization to cover the wound and re-establish the important barrier functions of the skin, and finally scar formation [15]. All too often, necrosis accompanies wound healing, and debridement of the necrotic tissue is required to enable keratinocyte access to the dermis so that re-epithelialization can occur [16].

The process of EMT describes the conversion of cells from sedentary, proliferative cells into migratory cells, a process that is essential to accomplish re-epithelialization during wound healing. In both wounded skin and tumors, cells undergoing EMT lose contact with each other, change their mode of association with the extracellular matrix, and become motile. In both cases, the cells must be able to re-model the extracellular matrix around them and, thus, secrete proteases to assist in the process. The changes that accompany wound healing are desirable and the triggers that initiate the change in phenotype are clearly definable. In contrast, the changes that occur in a tumor as it transitions from quiescent to metastatic are deleterious and the triggers are a conundrum. With an eye toward understanding the similarities and differences between tumor EMT and reepithelialization of a wound, the principal growth factors, signaling pathways, transcriptions controls, and target genes are compared in Table 1.

2.1. Growth factors

Rapid responses and ongoing development of the wound healing response is coordinated by a series of growth factors [15,17]. Upon wounding of epidermal cells, blood clot formation induces the release of a host of growth factors from platelets. These growth factors play an important role in attracting macrophages and leucocytes. Together, the four cells types, keratinocytes, platelets, macrophages and leucocytes, release a host of additional growth factors including epidermal growth factor (EGF), transforming growth factor α (TGF α), and transforming growth factor β 1 and 2 (TGF β 1, TGF β 2) [18–22]. Later in wound healing, other growth factors act on keratinocytes including TGF β 3 from macrophages, insulin-like growth factor (IGF) from fibroblasts and epidermal cells, and hepatocyte growth factor (HGF) and keratinocyte growth factor (KGF) from fibroblasts [23–27]. These growth factors play complementary roles in inducing keratinocyte proliferation and migration (see targets of signaling pathways discussed below). In addition, several other growth factors are actively involved in wound healing. For example, platelet derived growth factor (PDGF) is initially released from platelets at the site of the blood clot, later participates in an autocrine signaling loop in epithelial cells [27,28]. TNF α can be released from macrophages or directly from epithelial cells, and leads to synthesis and secretion of a host of pro-inflammatory cytokines [18]. Finally, a new layer of regulation recently came to light through our understanding of an exciting new group of molecules designated as the “CCN” family (based on the names of the first three members: Cysteine-rich Angiogenic Inducer 61; Connective Tissue Growth Factor; Nephroblastoma Overexpressed) [29,30]. The CCN protein family regulates many aspects of growth, development, and regeneration by interacting with integrins, triggering release of growth factors, cytokines, and matrix metalloproteinases, specific binding interactions with multiple extracellular matrix proteins, and by affecting bioavailability of growth-promoting molecules. CCN2 and CCN4 are specifically up-regulated during wound healing while CCN3 and CCN5 are down-regulated [29–31].

The process of EMT for cancer cells aligns well with wound healing in terms of the growth factors that drive the process. Like wound healing, EMT is induced by increased levels of EGF, TGF β 1 [32–36], and PDGF [37–42]. In addition, hepatocyte growth factor (HGF) activation of the c-MET pathway is often part of the EMT milieu [43]. IGF1 and its receptor, IGFR have been implicated in EMT in breast cancer [44–47]. TNF α is also a major signaling molecule involved in EMT in a variety of carcinomas [48–50] and likely plays a key role in linking inflammation and EMT [51,52]. KGF has not been identified as a major player in EMT, but at least one study noted its contribution to producing an EMT phenotype in cultured carcinoma cells under specified growth conditions [53]. HGF (also known as scatter factor) was one of the key growth factors that led to the identification of paracrine regulation of EMT [43]. In summary, EGF, TGF β 1, PDGF, IGF, TNF α , and HGF

show similar regulation in both re-epithelialization and EMT. Although KGF expression and signaling are consistent with proliferation of tumor cells, relatively little is known about KGF in EMT compared to the significant role played by KGF during re-epithelialization.

In both wound healing and tumor EMT, CCN3 and CCN5 are down-regulated while CCN4 is upregulated [54–57]. CCN1 and CCN6 have also been characterized to have tumor promoting activity [55,57,58]. CCN2 expression is more complex. Although CCN2 expression occurs during wound healing, it is associated with fibrotic rather than epidermal healing [31] while CCN2 expression is low in many different tumors [29]. The precise spectrum of CCN proteins that show evidence of up- or down-regulation may be a critical point of distinction between wound healing and EMT.

2.2. Intracellular signaling

During wound healing, the growth factors that act on keratinocytes stimulate a distinct subset of the intracellular signaling pathways within these epidermal cells. The pathways include increased signaling through p21Ras, extracellular signal-regulated kinase (ERK) isoforms 1, 2, and 5, c-Jun NH₂ terminal kinase (JNK), and p38 mitogen activated protein kinase (MAPK) pathways [7,59,60]. In addition, the IGF1-stimulated phosphoinositol-3-kinase/protein kinase B/mammalian target of rapamycin pathway, better known as the PI3K/Akt/mTOR axis, is also activated [61]. GSK3 β plays an important role in integrating signals downstream of the EGF-stimulated MAPK pathway during keratinocyte migration in wound healing [62,63], and GSK3 β must be suppressed to permit migration [63]. RhoGTPases are a group of Ras-family enzymes that act downstream of IGF receptor activation, and the increase in Rho activity serves as an intermediary in re-organization of the cytoskeleton during early responses to wound healing [64–66].

EMT utilizes the same signaling pathways as wound healing by increasing the activity of both the Ras/ERK/MAPK pathway [67,68] and the PI3K/Akt/mTOR axis [69,70] during EMT. Even ERK5, which is not directly involved in the classical ERK/JNK/MAPK pathway, shows elevated activity in both wound healing and EMT [71–73]. Likewise, RhoA activity is elevated in both settings [74], and GSK3 β activity is reduced during EMT just as it is during wound healing [75–78]. The similarity between the intracellular signaling pathways used by wound healing and EMT pathways is most likely a consequence of the similarity of the growth factors and receptors used to stimulate the process.

2.3. Transcription factors and post-transcriptional control

β -Catenin is part of the TGF β signaling pathway and has a unique biology in that it resides at cell junctions in quiescent cells, but translocates to the nucleus to activate the Tcf–Lef-1 transcription factors upon activation [79]. β -Catenin is instrumental in the wound healing response [80] and migrates to the nucleus during the wounding response of keratinocytes [81]. β -Catenin translocation to the nucleus has long been a hallmark of EMT [82,83] and is often used as a diagnostic test to determine whether typical EMT changes are occurring [6].

Snail family transcription factors including Snail1 (Snail) and Snail2 (Slug) mediate gene expression changes downstream of the TGF β and EGF receptors [84,85]. As transcription factors, Snail family members repress the expression of cell junction proteins (see below), another hallmark of EMT. While Slug activity is upregulated in both wounded epithelium and in tumor cells undergoing EMT [7,84,86–89], Snail is only involved in EMT and has not been shown to be a major player in keratinocytes during wound healing [85,90–94].

The Smad family of transcription factors has also been implicated in both wound healing and EMT. Smads, in a similar manner to Snail and Slug, act downstream of TGF β signaling [95,96]. Smad3 and Smad4 expression are both required for normal wound healing, although

Smad4 appears to have its primary activity through a paracrine mechanism while loss of Smad3 changes keratinocyte properties directly [21,97,98]. Smad-mediated signaling is fundamental to TGF β -induced EMT [32,99,100], and Smad3 and 4 form complexes with Snail as part of TGF β -induced EMT [94].

A host of other transcription factors have been implicated in EMT. Some prominent ones include Twist, Lef-1, Zeb-1, Ets-1, and FoxC2 [82,91,102–107]. Among these factors, Twist and Lef-1 have demonstrated roles in keratinocyte wound healing [46,108], but Zeb-1, Ets-1, and FoxC2 remain to be characterized in an epidermal wound healing setting. The expression levels of the transcription factors themselves can be modified during epithelial wound response. For example, the c-Fos gene is among the earliest genes to show elevated expression in epithelial cells following a wound [59,109,110]. Induced nuclear localization of c-Fos and induced expression of c-Fos have both been used as models of EMT [82,111].

Post-transcriptional regulation has become an active area of research, and characterization of microRNA involvement in both wound healing and EMT is advancing rapidly. This topic has been the subject of several recent comprehensive reviews for both epidermal wound healing [112,113] and for EMT [114–116]. There is significant, but not complete, overlap in the groups of microRNA that have been implicated in the two processes. MicroRNAs miR-21, -29a, -31, -34, -125b, -155, and -203 are involved in both processes. Of interest, a prominent feedback loop involving the miR-200 family and Zeb-1 has not yet been reported in epidermal wound healing [157].

2.4. Cell junctions

The change from a sedentary cell to a motile cell must ultimately involve a change in the way that cells interact with their environment. Strong, stable interactions such as most cell–cell junctions cannot be maintained during motility. At the same time, a new, strong but flexible interaction with the extracellular matrix is required to accomplish movement. As a result, up and down-regulation of the proteins involved in these junctions, quite naturally, represents the end target for many of the ligand/receptor/signal/transcription factor cascades described above. Gap junctions allow communication between adjacent cells, but such junctions become dispensable in both keratinocytes and tumor cells undergoing EMT, so connexin proteins, including Cx26 and Cx43, are downregulated [117,118].

Hemidesmosomes and desmosomes provide tissue integrity through the strength of the intercellular protein–protein interactions. Although there is a dearth of quantitative data on the subject, desmosome components (e.g., desmoglein and desmocollin) in keratinocytes appear to have a complex reaction to wounding during which the levels of different family members may be elevated or reduced [119]. In contrast, the desmosome disruption and resulting re-distribution of components has been clearly documented in EMT tumor cells [86,120,121]. The principal protein in hemidesmosomes, $\alpha 6\beta 4$ integrin, releases from hemidesmosomes as they disassemble, but goes on to play an important role in fibronectin binding during cell migration. While $\alpha 6\beta 4$ integrin persists in wounded keratinocytes [122,123], its expression level is reduced in EMT tumor cells [124]. E-cadherin presence at junctions is clearly reduced in both wounded keratinocytes [119] as well as in EMT tumor cells [74,82,83,101,104,125–128] where loss of E-cadherin from adherens and tight junctions is a common feature of EMT. Interestingly, while E-cadherin expression is reduced, a non-epithelial cadherin, N-cadherin, often shows elevated expression in migrating tumor cells and is also a hallmark of EMT [129,130,158]. Tight junction proteins including zonula occludens 1, occludin, claudin 1, and coxsackie-adenovirus receptor show a differential response comparing wound healing to EMT. During wound healing, these proteins maintain their expression levels [131,132] while they are uniformly reduced in EMT cells [94,126,133–135].

The cell matrix interactions of both wounded keratinocytes and EMT tumors require expression of integrins capable of binding fibronectin, laminin 5, and collagen I, all of which are observed in both cell types [124,136–138]. Both migrating keratinocytes and EMT tumor cells continuously re-model the extracellular matrix around them. The two types of cells make copious use of matrix metalloproteinase (MMP) enzymes with elevated expression of MMP-2 (gelatinase A), MMP-9 (gelatinase B), MMP-13 (collagenase 3), and MMP-14 (MT1-MMP) in a consistent manner in skin [139–144] and tumors [92,104,145–150]. MMP-1 and -3 are also involved in wound healing [151–153] and, to a lesser extent, in EMT [104,147,154].

Finally, Scribble is an actin-associated protein that helps to confer polarity in epithelial cell monolayers and has been identified as a component of the basolateral epithelial junction in *Drosophila* [155]. Scribble maintains its expression and function in migrating keratinocytes during wound healing where it confers polarity to the migration of keratinocytes in a wound [156]. It will be interesting to see what happens to Scribble in tumor cells and whether there is a polarized migration of tumor cells during EMT.

3. Clinical implications of the comparison of EMT and re-epithelialization

A number of anti-cancer drugs have been developed based on the receptors and/or signaling pathways that give rise to EMT. Given the prevalence of shared signaling and mechanisms between EMT and re-epithelialization, it stands to reason that inhibition of EMT may also result in the inhibition of wound healing at the level of epithelialization. It is not surprising to find a conflict between cancer therapy and wound healing when discussing anticancer drugs that target angiogenesis such as the anti-vascular endothelial growth factor (VEGF) monoclonal antibody, Bevacizumab (Avastin™) [159,160]. However, the focus here remains on mechanisms directly related to the transition of cell phenotypes at the onset of metastasis or wound healing. Table 2 lists data on adverse events of current anti-EMT and pro-wound healing therapies as well as potential therapeutic targets.

3.1. Effect of anti-metastasis drugs on wound healing

To review the potential for adverse events relating to wound healing in the context of anti-EMT therapies, several EMT-directed therapies were evaluated with regard to adverse effects on wound healing. This topic has already been the subject of significant concern [161–163]. Four therapies that target the EGF receptor were examined including Gefitinib (Iressa™), Erlotinib (Tarceva™), the monoclonal antibody, Cetuximab (Erbix™ antibody), and Lapatinib. All four therapies target EGF receptor 1 (Her-1/Erb1) while Lapatinib also inhibits Her-2 (Erb2). All four therapies are associated with significant rash formation as described in reviews of the clinical literature as well as case reports. In the cases of Gefitinib and Erlotinib, experimental models suggest that the therapies can cause direct inhibition of re-epithelialization [164–167].

Several multikinase drugs have been developed with Imatinib (Gleevec™) being the most prominent. Imatinib acts on the PDGF receptor as well as the tyrosine kinases such as c-KIT and the *Bcr-Abl* gene product [168]. Sorafenib and Sunitinib are two other multikinase inhibitors that, along with Imatinib, cause rashes [162,169]. Imatinib, as a PDGF inhibitor, has been reported to inhibit fibrosis, but PDGF also has a role in epithelialization and a careful examination of the data from Rajkumar [170] shows that epithelial cell proliferation in healing skin is diminished by imatinib treatment.

Some therapies may have less dermal involvement. TGFβ receptor 1 and TGFβ receptor 2 have also been used as targets for anti-EMT therapies. LY2109761 and SM16 directly against these targets have not been examined in depth with respect to their effects on re-

epithelialization. However, should the experience with EGF receptors hold, cutaneous side effects can be anticipated. Two other classes of drugs targeted at the endothelin receptor (ABT-627 or ZD4054) and the HGF receptor (Tivantinib) show anti-EMT activity [171–173]. Detrimental effects on wound healing have not been reported in the case of these drugs, and there was a distinct lack of skin reactions in a phase I trial of Tivantinib [174]. These results either indicate that certain pathways for blocking EMT are inherently less toxic to the process of cutaneous wound healing or that dose-limiting toxicity was not yet reached and that further investigation is warranted.

3.2. Effect of wound-healing drugs on metastasis

While there is a wealth of data on the effects of chemotherapy drugs on wound healing, there are relatively few drugs that have been approved to enhance wound epithelialization, and thus less opportunity to evaluate a connection between drugs that enhance epithelialization and cancer metastasis.

Becaplermin (Regranex™), a form of recombinant human PDGF based on a homodimer of the PDGF-B isoform, is an FDA-approved growth factor for wound care. Although extensive experience in clinical trials has not suggested problems related to the advancement of cancer [175–181], laboratory experiments have demonstrated the concept that PDGF can induce the EMT phenotype [38,42,182]. A phase IV post-marketing study of Becaplermin noted an apparent dose-dependent increase in mortality due to cancer although no overall increased incidence of cancer was noted, leading to a modified label of the product [183]. This finding was particularly concerning since exactly this type of accelerated cancer as a by-product of growth factor therapy is a common concern with growth-promoting biologics. Later, a larger study failed to indicate a higher cancer incidence or mortality rate in a treated population [184].

Another potential wound healing biologic that has direct effects on keratinocytes is the cathelicidin-derived peptide, LL-37. Although originally identified for anti-microbial activities, LL-37 can interact directly with keratinocytes causing epidermal cell migration [185]. The surprising biological activity of LL-37 was later traced to its ability to induce cell signaling via binding to the EGF receptor and insulin-like growth factor receptor type I [186–188]. The potential for cross-talk between re-epithelialization and EMT is particularly clear with LL-37 due to its ability to promote metastatic phenotypes in breast and ovarian cancer models [189,190]. Not surprisingly, high levels of LL-37 have been found in breast tumors [191].

Other FDA approved treatments for wound healing include therapeutics based on fibrin and non-physiological polymers. Fibrin glues have also been approved by the FDA for wound healing (Evicel™, Tisseel™, Artiss™), but these products are not examined in detail herein due to the fact that keratinocytes do not bind to fibrin due to a lack of $\alpha V\beta 3$ integrin expression [192,193]. However, the use of fibrin does echo the issue of biologics and EMT since melanoma cells, upon a shift toward a more aggressive phenotype begin expressing $\alpha V\beta 3$ integrin [194]. Likewise, cyanoacrylate polymers have long been used in wound healing. However, due to their chemical rather than biologic nature, a discussion of cyanoacrylates is beyond the scope of this review. Fortunately, the use of cyanoacrylates, including 2-octylcyanoacrylate (Dermabond™), has not been associated with EMT or metastasis [195].

3.3. Potential for identifying new targets for wound healing or anti-EMT therapies

The value in identifying similarities and differences between wound healing therapeutics and EMT therapeutics lies in the comparison of drug targets and the potential development

of new strategies for intervention. A review of the literature suggests several potential targets for anti-EMT drugs/pro-wound healing drugs based on patterns of effects regarding EMT and epithelialization that are similar to several of the drugs under development or approved for use as described in Sections 3.1 and 3.2 (Table 2).

Potential anti-EMT/pro-wound healing targets have consistent actions when comparing their activities in epithelial wound healing and EMT. Transglutaminase 2, also known as tissue transglutaminase, is a widely expressed enzyme involved in formation of covalent crosslinks between the primary amine on glutamine and a primary amino group on another molecule, e.g., a lysine on another protein [196]. The modifications that transglutaminases carry out are typically considered to be important for stabilization of proteins for the purpose of increased mechanical strength and resistance to degradation, e.g., as needed in hair and skin. While skin and hair follicle keratinocytes express a unique form transglutaminase as part of their normal function [197,198], tissue transglutaminase activity is upregulated during epithelial wound healing in skin as well as cornea [199,200]. Mehta, Verma and colleagues have made an argument that tissue transglutaminase should be good target for inhibition of cancer progression [201–203] based on the fact that tissue transglutaminase activity is elevated in metastatic cancers (reviewed by [203]) and that inhibition of transglutaminase activity reduced cancer progression [204,205].

While tissue transglutaminase has been long recognized for its importance in the skin and in wound healing and only recently was suggested as an anti-cancer target, the converse is true for β -1,6-N-acetylglucosaminyltransferase V (Mgat5). Mgat5, an enzyme that controls crosslinking of carbohydrate groups at the cell surface, can crosslink growth factor receptors including the EGF receptor and TGF β receptor, thus delaying their removal from the cell surface [206]. In addition, Mgat5 is involved with positive feedback in the EMT pathway since it is also upregulated by TGF β signaling [206]. Only recently was there a suggestion that the inherent growth potentiation observed with Mgat5 might also contribute to re-epithelialization [108]. Certainly, transient upregulation of Mgat5 might be very helpful in wound healing in contrast to constitutive upregulation that promotes metastasis.

Sphingosine-1-PO₄ (S1P), like tissue transglutaminase and Mgat5, induces epithelial migration, but does so without increasing proliferation [207–209]. Thus, S1P would appear to be an anti-EMT candidate molecule. An earlier characterization of S1P as inducing differentiation stood out as contrary to the complementary effects that S1P shares with TGF β ; however, these finding can now be reconciled since the elevated transglutaminase levels observed by Vogler et al. were likely an increase in tissue transglutaminase as opposed to keratinocyte transglutaminase, and thus could be understood to be a marker of EMT [203,207]. Along these same lines of reasoning, S1P has been linked to both positive and negative regulation of metastasis in melanoma cells [210] and elevated expression levels in colon carcinoma [211]. It also explains why inhibitors of this pathway are of interest in anti-cancer drug development [212,213]. In summary, sphingosine-1-phosphate and its receptor play context-dependent roles in wound healing and EMT.

Some interventions that appear to have simple, straightforward effects suffer from multiple, complex interactions in in vivo systems due to the presence of multiple target cells and competing pathways. Prostaglandin E2, like LL-37 discussed above, has multiple targets and, thus, defies a simple relationship to cancer progression and wound healing. Prostaglandins are well known for their antiinflammatory effects and, thus, would be expected to limit both wound healing and EMT which depend on inflammatory signaling. A report that prostaglandin E2 inhibited EMT was consistent with our understanding of the mechanism of EMT [214]. Similarly, prostaglandin E2 failed to show significant effects on wound healing [215,216]. However, using alternative experimental systems, Tanaka et al.

showed that prostaglandin E2 favored EMT-like changes in Caco-2 cells, with the notable exception that ZO-1 was not removed from tight junctions [217]. In fact, ZO-1 retention is recognized as one of the differentiating factors between wound healing and tumor EMT as highlighted in Table 1. Interestingly, a separate report shows that prostaglandin E2 accelerates tumor growth of intestinal tumors via a novel mechanism involving DNA methylation [218] and highlights the difficulty in accomplishing manipulation of cell physiology with surgical precision in vivo. The hypoxia response, like that of prostaglandins, is complex, touching on angiogenic growth factors produced in response to low tissue oxygenation, changes in levels of reactive oxygen species, and changes in metabolism. As a result, hypoxia and responses to hyperbaric oxygen do not follow a simple formula when comparing in vitro and in vivo data [219–224].

The elevated levels of MMPs characterized during epidermal wound healing suggest that the extracellular milieu of a wound is highly proteolytic. This environment might have wound healing significance over and above the need for re-modeling of the extracellular matrix. Prior work on inflammatory responses has demonstrated that neutrophil proteases including elastase and cathepsin G cause proteolysis of extracellular matrix proteins, as expected, but also cleave insulin-like growth factor 1 as well as its binding proteins [225]. Extrapolating to a wound, the highly proteolytic environment might be changing signaling pathways in addition to structure. MT1-MMP has been recognized to cause changes in the migration of prostate cancer cells by a mechanism involving cleavage of the extracellular matrix protein, laminin-5 [226]. Upstream of MMPs and signaling molecules, there exists a complex protease-based activation system that modulates both cancer progression and wound healing through the use of enzyme-activating convertases [227,228]. Therefore, one might imagine that wholesale intervention at the level of proteolysis might have a beneficial effect on wound healing. Various enzymatic combinations have been used for debridement of wounds [229]. A preparation of enzymes from North Atlantic krill has been effective at debridement, but has also shown promise in improving epithelialization [230,231].

The final potential target to be addressed here is the cellular metabolism, particularly as controlled by glucose levels. The drug, metformin, is known to inhibit hepatic gluconeogenesis and to lower blood glucose levels in vivo. Recently, metformin was reported to reverse cellular changes associated with EMT [232,233] using in vitro models. As a result, one would expect metformin to inhibit wound healing. However, metformin sped overall wound healing and epithelialization, in particular, in ulcers [234]. The apparently disparate results may reflect an underlying complexity in how metabolism affects tumors vs. normal tissue. Sparvchikov et al. [235] reported that high glucose inhibited proliferation of keratinocytes and, instead, favored keratinocyte differentiation. In contrast, Li et al. [236], studying hyperglycemia, found that hyperglycemia elevated metastatic risk, at least for pancreatic cancer.

4. Conclusions

As noted above, EMT is now broadly recognized as a normal physiological process that occurs in development (Type I EMT) and in tissue regeneration (Type II EMT) as well as in pathological conditions such as metastasis (Type III EMT). Therefore, it is not surprising that these processes share so many biochemical mechanisms. Future development of therapies that enhance wound healing without promoting tumor growth and fight metastasis without compromising wound healing will require precision targeting of pathways that are differentially utilized by these processes. This review has only started the process of a full accounting of shared and distinct pathways between tumor EMT and wound healing. Even in the cross section of mechanisms discussed here, there appear to be opportunities for differential treatment including potential targets such as CCN2, Snail transcription, and,

possibly tight junction proteins that play roles in cytosolic sequestration of transcription factors. Other potential targets may require further research for validation, but Ets-1, Zeb-1, FoxC2, and miR200 are likely candidates for selective manipulation of Type III EMT. In addition to the value in identifying differences between the Type II and III pathways, there is also potential value in understanding the similarities. Insofar as some drug targets are likely to be shared between the two pathways, validation of a target in one pathway may serve as a starting point for drug development in the other pathway. Control of drug delivery may be the key to the use of therapies that have potential to stimulate or inhibit both healing and metastasis.

In part, because of all of the individual relationships that are coming to light through wound healing and cancer research, the most significant challenge going forward appears to be one of bioinformatics. Our understanding of the individual molecular events is excellent and growing by the day. However, our ability to integrate all of the molecular controls and feedback into a meaningful picture of wound healing or metastasis is limiting. At this point, understanding how entire families of chemokines, receptors, signal transducers, transcription factors, micro RNAs, and target proteins are coordinately controlled is not a trivial problem. Improved computational models that can incorporate all of the knowledge about the pathways in a quantitative manner will likely represent the next major step toward developing therapies in this arena.

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Table 1Keratinocyte responses during re-epithelialization vs. markers of EMT.^a

Hallmarks of keratinocytes in wound healing	Refs.	Hallmarks of tumor cells in EMT	Refs.
Growth factor responses			
EGF/TGF- α $\uparrow$	[18–20]	EGF $\uparrow$	[32–34]
TGF- β $\uparrow$	[21, 22]	TGF- β $\uparrow$	[35, 36]
KGF $\uparrow$	[26]	KGF $\uparrow$	[53]
IGF1 $\uparrow$	[23]	IGF1 $\uparrow$	[44–47]
HGF $\uparrow$	[24, 25]	HGF $\uparrow$	[43]
PDGF $\uparrow$	[27, 28]	PDGF $\uparrow$	[37–42]
TNF α $\uparrow$	[18]	TNF α $\uparrow$	[48–52]
CCN2, 4 $\uparrow$; CCN 3, 5 $\downarrow$	[30, 31]	CCN1, 4, 6 $\uparrow$; CCN 2, 3, 5 $\downarrow$	[54–58]
Signaling pathways			
ERK1,2/JNK/p38 MAPK $\uparrow$	[59]	ERK1,2/JNK/p38 MAPK $\uparrow$	[67, 68]
ERK5 $\uparrow$	[7]	ERK5 $\uparrow$	[71–73]
PI3K/Akt/mTOR $\uparrow$	[61]	PI3K/Akt/mTOR $\uparrow$	[69, 70]
RhoA $\uparrow$	[64–66]	RhoA $\uparrow$	[74]
GSK3 β $\downarrow$	[63]	GSK3 β $\downarrow$	[75, 76, 78]
Transcriptional/post-transcriptional regulation			
c-Fos $\uparrow$	[59, 109, 110]	c-Fos $\uparrow$	[82, 111]
β -catenin $\uparrow$	[80, 81]	β -catenin $\uparrow$	[82, 83]
Snail (Snail1) $\leftrightarrow$	[85]	Snail (Snail1) $\uparrow$	[90–94]
Slug (Snail2) $\uparrow$	[7, 84, 87–89]	Slug (Snail2) $\uparrow$	[86]
Smad3/4 $\uparrow$	[21, 97, 98]	Smad 3/4	[32, 94, 99, 100]
Twist $\uparrow$	[108]	Twist $\uparrow$	[101, 102]
Lef-1 $\uparrow$	[19]	Lef-1 $\uparrow$	[82, 103]
Not reported		Ets-1 $\uparrow$	[104, 105]
Not reported		Zeb-1 $\uparrow$	[91, 106]
Not reported		FOXC2 $\uparrow$	[107]
MicroRNA	[112, 113]	MicroRNA	[114–116]
Not reported		miR-200/Zeb-1 feedback loop	[157]
Cellular/extracellular matrix interactions			
Gap junctions			
Connexins (Cx26, Cx43) $\downarrow$	[117]	Connexins (Cx26, Cx43) $\downarrow$	[118]
Desmosomes			

Hallmarks of keratinocytes in wound healing	Refs.	Hallmarks of tumor cells in EMT	Refs.
Desmoglein 1 ↓	[119]	Desmoplakin ↓	[86, 120, 121]
Desmoglein 2 ↑		Desmoglein ↓	
Desmoglein 1 ↑		Plakoglobin ↓	
Desmoglein 3 ↓			
Hemidesmosomes			
α6β4 integrin ↔	[122, 123]	α6β4 integrin ↓	[124]
Adherens junctions			
E-cadherin ↓	[119]	E-cadherin ↓	[74, 82, 83, 101]
Tight junction			
ZO-1 ↔	[131]	ZO-1 ↓	[126]
Occludins ↔		Occludins	[133]
Claudin 1 ↔		Claudin 1 ↓	[134, 135]
Coxsackie-adenovirus receptor ↔ or ↑	[132]	Coxsackie-adenovirus receptor ↓	[94]
Enhanced focal adhesions (increased interaction with fibronectin and vitron ectin)			
Integrin ↑: αVβ6, α2β1, α3β1, α5β1	[136, 137]	Integrin ↑: αVβ6, α5β1, β4	[124, 138]
Integrin ↓: αVβ5	[136]		
Other			
Not expressed		N-cadherin ↑	[129, 130, 158]
Scribble ↔	[156]	Not reported	
Matrix metalloproteinases			
MMP-1 (collagenase 1), -3 (stromelysin 1) ↑	[151–153]	MMP-1 (collagenase 1), -3 (stromelysin 1) ↔/ ↑	[104, 147, 154]
MMP-2 (gelatinase A), -9 (gelatinase B), -13 (collagenase 3), -14 (MT1-MMP) ↑	[139–144]	MMP-2 (gelatinase A), -9 (gelatinase B), -13 (collagenase 3), -14 (MT1-MMP) ↑	[92, 104, 145–150]

^aLight gray shading indicates actual of potential differential responses between keratinocyte wound healing and tumor EMT.

Table 2

Therapeutic implications of EMT/re-epithelialization comparison.

Target	Anti-EMT therapy	Effect on re-epithelialization
EGF receptor (Her-1)	Gefintinib (Iressa™) [238–245]	Rash in 53% of patients [246]; also, inhibition of corneal epithelialization [164]; case reports differ in opinion on potential significance for patients [247–249]
EGF receptor (Her-1)	Erlotinib (Tarceva™) [239–241,243,250–257]	Rash in 79% of patients [246]; also delays tympanic membrane healing [165–167]; case reports of epithelialization defect in the cornea [258] and scarring alopecia [259]
EGF receptor (Her-1)	Cetuximab (Erbix™ antibody) [240,260–262]	Acneiform skin rash in 90% of patients [162]; high incidence of skin toxicity during combined radiotherapy [263]; a related monoclonal antibody against EGFR has similar outcomes [162]
EGF receptor (Her-1) and Her-2	Lapatinib [264]	Extensive cutaneous effects [265]
TGFβ-receptor 1, TGFβ-receptor 2	LY2109761 [266–271]	No reports, but Flechsig [272] report that LY2109761 has anti-fibrotic activity in lung suggesting a potential effect on wound healing
TGFβ-receptor 1	SM16 [273,274]	No reports on epithelialization
PDGF receptor (also targets c-KIT and <i>BCR-ABL</i> tyrosine kinases)	Imatinib mesylate (Gleevec™) [275,276]	30–45% of patients experience skin eruptions [169]; in an experimental study, imatinib delayed wound healing; direct effect on epithelialization implied by Figure 2 although direct effect on epithelialization vs. indirect effect through impaired fibrosis was not clear [170]; other multikinase inhibitors including sorafenib and sunitinib have similar problems [162]
Endothelin A receptor	ABT-627 or ZD4054 [170–172]	No reports of effects on epithelialization
Hepatocyte growth factor receptor (c-MET)	Tivantinib (ARQ 147) [173]	No cutaneous adverse events in a phase I dose escalation study [174]
Target	Pro-epithelialization therapy	Effect on EMT
PDGF receptor	Becaplermin (Regranex™, rhPDGF-BB) [277–280]	Becaplermin produces EMT in tumor cells [38,42,182]; although there was no report of increased incidence of cancer in several clinical trials with topical application [175–181], a post-marketing study concluded that there was a dose-dependent increased risk of death from cancer that has now been incorporated into the product label [183]; more recently, a follow up study concluded that there was no statistically significant link between Becaplermin therapy and either cancer incidence or severity [184]
EGF receptor/insulin-like growth factor receptor I	Cathelicidin/LL-37 [185–190]	Induces metastatic phenotype in breast cancer [189]; causes ovarian tumor progression [190]

Target	Anti-EMT therapy	Effect on re-epithelialization
Potential targets	Re-epithelialization/EMT relationship	
Tissue transglutaminase	Activated during corneal re-epithelialization [200]; proposed target for anti-EMT drug [203]	
β -1,6-N-acetylglucosaminyltransferase V (Mgat5)	Upregulated in carcinomas [206]; increased expression enhances wound healing [108]	
Sphingosine-1-PO ₄ receptor	Anti-proliferative, anti-motility effects in keratinocytes that express Smad3 [207–209]; proposed target for EMT drugs [212,213,237]	
Complex protease mixtures	Proteases have been used to debride wounds [229,231]; however, proteases also modulate the wound healing response at many levels [228] and may have a synergistic ability to improve epithelialization [230,231]	
Prostaglandin E2	Inhibits EMT in transformed kidney epithelial (MDCK) cells [214]; little or no effect on wound healing [215,216]; however, enhances EMT in colorectal cancer (Caco2) cells [217] and favors intestinal tumor growth [218]	
Hypoxia inducible factors (HIFs)	Mixed data on effects of anti-HIF treatments and hyperbaric oxygen on tumor growth and re-epithelialization [219–224]	
AMP-activated protein kinase/Glut1 glucose transporter	Metformin (hepatic gluconeogenesis inhibitor) reverses EMT-like characteristics of transformed cells [232,233]; curiously, metformin was also reported to speed healing of ulcerations including epithelialization [234]; these findings must be considered within the context of the conflicting reports that high glucose inhibits proliferation and induces differentiation of keratinocytes [235] while Li et al. [236] provide evidence that hyperglycemia elevates metastatic risk in the pancreas	
EGF receptor via the P2Y receptor	ATP, UTP, and diadenosine polyphosphates have been reported to have enhancing and inhibitory properties with respect to keratinocyte spreading and migration, in part due to use of multiple receptor and G proteins [281–290]; P2Y receptors are elevated in some cancers [291], enhance interaction of tumor cells with lymphatic endothelium [292], and, most recently, have been implicated in Ca ²⁺ signaling during EGF-induced EMT [293]	