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Integrin-mediated regulation of epidermal wound functions

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Abstract

During cutaneous wound healing, keratinocyte proliferation and migration are critical for re-epithelialization. In addition, the epidermis secretes growth factors, cytokines, proteases, and matricellular proteins into the wound microenvironment that modify the extracellular matrix and stimulate other wound cells that control the inflammatory response, promote angiogenesis, and facilitate tissue contraction and remodeling. Wound keratinocytes express at least seven different integrins - the major cell adhesion receptors for the extracellular matrix - that collectively control essential cell-autonomous functions to ensure proper re-epithelialization, including migration, proliferation, survival, and basement membrane assembly (Fig. 1, arrow 1). Moreover, it has become evident in recent years that some integrins can regulate paracrine signals from wound epidermis that stimulate other wound cells involved in angiogenesis, contraction and inflammation (Fig. 1, arrows 2 and 3). Importantly, it is likely that abnormal integrin expression or function in the epidermis contributes to wound pathologies such as over-exuberant healing (e.g., hypertrophic scar formation) or diminished healing (e.g., chronic wounds). In this review, we discuss current knowledge of integrin function in the epidermis, which implicates them as attractive therapeutic targets to promote wound healing or treat wound pathologies. We also discuss challenges that arise from the complex roles that multiple integrins play in wound epidermis, which may be regulated through extracellular matrix remodeling that determines ligand availability. Indeed, understanding how different integrin functions are temporally coordinated in wound epidermis, and which integrin functions go awry in pathological wounds, will be important to determine how best to target them clinically to achieve maximum therapeutic benefit.

Graphical Abstract

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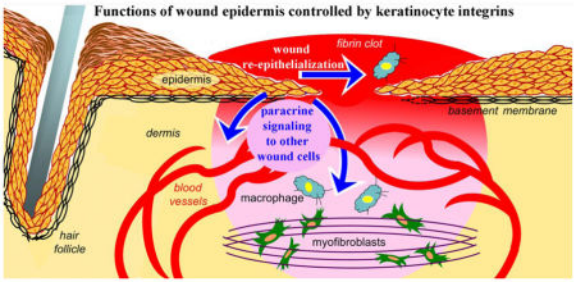

Keywords

Integrin; Wound healing; Epidermis; Keratinocyte; Extracellular matrix

Introduction

The skin consists of an underlying dermal layer that provides tissue strength and compliance, covered by the stratified epidermis that forms the outer barrier. When the skin is injured, the constituent cells undergo a highly coordinated wound healing response to repair the damaged tissue, close the wound, and restore barrier function (Gurtner et al., 2008). Wound healing is a tightly regulated process that can be divided into distinct, but overlapping stages of hemostasis/clotting, inflammation, re-epithelialization, and tissue remodeling (Gurtner et al., 2008; Martin, 1997). Throughout these stages, the extracellular matrix (ECM) undergoes continuous and temporally regulated changes in composition and structure that provide critical regulatory cues to a variety of wound cells to ensure proper healing. Importantly, abnormalities in mechanical and chemical properties of the ECM contribute to wound pathologies, such as chronic wounds or hypertrophic scars (Kenny and Connelly, 2015; Wong et al., 2013).

In addition to their well characterized roles in wound re-epithelialization, epidermal keratinocytes play a major role in modifying the wound microenvironment through secretion of extracellular factors (e.g., growth factors, extracellular proteases, ECM-associated proteins) that stimulate other cells to facilitate wound healing, including endothelial cells that drive angiogenesis, and fibroblasts/myofibroblasts that deposit a scar and promote contraction (Gurtner et al., 2008; Martin, 1997; Santoro and Gaudino, 2005). In non-wounded skin, basal keratinocytes of the stratified epidermis are adherent to a basement membrane (BM), which is a specialized, sheet-like ECM that consists mainly of laminins (LNs), type IV collagen, and type VII collagen and separates the epidermis from the sub-adjacent connective ECM of the dermis (Burgeson and Christiano, 1997). In addition to maintaining epidermal-dermal adhesion, the BM provides cues to keratinocytes that help control epidermal differentiation, stratification, and hair development. In wounded skin, keratinocytes that are proximal to the injury proliferate and migrate over the changing provisional ECM, which is initially composed of extravasated plasma proteins (e.g., fibrinogen, plasma fibronectin, vitronectin), and is gradually transformed by local expression of cellular fibronectin, type I collagen, and other matrix proteins. Eventual reassembly of an

intact BM during wound re-epithelialization is essential to restore barrier function and structural support to the neo-epidermis.

Integrins are the major cell surface receptors for epidermal adhesion to the both the BM in non-wounded skin and the provisional ECM in wounded skin (Hynes, 2002). As discussed in the following sections, integrins control a wide variety of keratinocyte functions during normal wound healing, including migration, proliferation, survival, BM regeneration, and paracrine induction of angiogenesis. Integrin-mediated interactions of keratinocytes with their adjacent ECM are dynamic and bidirectional throughout wound healing, and abnormal integrin expression or function in wound pathologies are likely to contribute to over-exuberant healing (e.g., hypertrophic scars) or diminished healing (e.g., chronic wounds) (reviewed in (Koivisto et al., 2014)). This review will focus on what we currently know about the regulatory roles that integrins play in wound keratinocytes, with regard to both cell-autonomous functions and epidermal functions that modify the wound microenvironment (illustrated in Fig. 1). As space limitations preclude a comprehensive review of the extensive literature in this field, we direct the reader to other reviews for additional coverage of relevant topics (Kenny and Connelly, 2015; Koivisto et al., 2014; Longmate and DiPersio, 2014; Margadant et al., 2010).

Overview of integrin function in cell adhesion and signal transduction

All integrins are heterodimeric glycoproteins consisting of an α and a β subunit. Eight different β subunits can each partner in limited combinations with 18 α subunits to form 24 distinct integrins with different, albeit often overlapping ligand-binding specificities (Hynes, 2002). Both α and β subunits consist of a large extracellular domain, a single-pass transmembrane domain, and a relatively short cytoplasmic domain of ~20–70 amino acids (the exception is the β4 subunit cytoplasmic domain of over 1000 amino acids). In addition to binding ECM ligands through their extracellular domains, many integrins are simultaneously linked to the actin cytoskeleton via scaffolding proteins (e.g., talin, vinculin) that bind to their cytoplasmic domains, thereby mediating a physical, transmembrane linkage between the ECM and the cytoskeleton that manifests as focal adhesions (Delon and Brown, 2007; Hynes, 2002; Iwamoto and Calderwood, 2015; Liu et al., 2000). Similarly, the epidermal integrin, α6β4, mediates a linkage between the ECM and the keratin cytoskeleton within hemidesmosomes, which are essential for stable adhesion of the basal keratinocyte layer (Litjens et al., 2006).

Integrins regulate bidirectional signal transduction across the plasma membrane through direct or indirect interactions of their cytoplasmic domains with a wide variety of intracellular signaling and adaptor proteins, such as talin, integrin-linked kinase (ILK), vinculin, kindlins, paxillin, focal adhesion kinase (FAK), and Src. The literature on integrin-mediated signal transduction has been reviewed extensively (Hynes, 2002; Iwamoto and Calderwood, 2015; Legate and Fassler, 2009; Schwartz and Ginsberg, 2002; Winograd-Katz et al., 2014), and it was recently estimated that the integrin “adhesome network” includes more than 180 potential signaling and adaptor proteins (Zaidel-Bar and Geiger, 2010). Here, we will discuss FAK activation as an instructive example of “outside-in” integrin signaling that feeds into a number of downstream pathways (Cary and Guan, 1999; Mitra and

Schlaepfer, 2006). Integrin-mediated cell adhesion can stimulate FAK auto-phosphorylation on Y397, which creates a high-affinity binding site for the Src-homology 2 (SH2) domain of Src (or another Src-family kinase). Upon binding to FAK, Src phosphorylates additional FAK tyrosines (e.g., Y861, Y925) to create binding sites for other kinases or adaptors, such as GRB2, phosphatidylinositol 3-kinase (PI3-K), and p130CAS, thereby linking the integrin/FAK/Src complex to downstream effectors such as mitogen-activated protein kinases (e.g., ERK, JNK, and p38), Rho family GTPases (e.g., CDC42, Rho, RAC1), or AKT (Cary and Guan, 1999; Mitra and Schlaepfer, 2006). Several keratinocyte integrins can activate FAK (e.g., α3β1, α5β1, αv integrins), and FAK signaling can regulate a number of keratinocyte functions in vitro, including migration, proliferation, survival, and ECM assembly/remodeling (Choma et al., 2007; Essayem et al., 2005; Kim et al., 2000; Manohar et al., 2004; McLean et al., 2004; Yurko et al., 2001). Surprisingly, wound studies performed in mice with keratinocyte-restricted deletion of FAK revealed no effect on wound re-epithelialization in vivo, although FAK function in the epidermis was linked to keratinocyte survival, stem cell proliferation, and tumorigenesis (Essayem et al., 2005; McLean et al., 2004). Further investigation is required to determine FAK involvement in other epidermal wound functions, such as ECM remodeling or paracrine signaling to other wound cells (see below).

Importantly, some integrins undergo lateral associations with other cell surface proteins, such as members of the tetraspanin family, growth factor receptors, caveolin, or urokinase receptor (uPAR) (Berditchevski, 2001; Chapman et al., 1999; Comoglio et al., 2003; Hemler, 2005; Porter and Hogg, 1998; Salanueva et al., 2007; Wei et al., 2001). Such interactions may regulate integrin activation or function by altering their affinity or avidity for ligands, turnover on the cell surface, subcellular localization to lipid rafts or other compartments, or ability to recruit signaling adaptors. Of particular relevance to wound healing, the epidermal integrins α3β1 and α6β4 can each bind to the CD151 tetraspanin protein (Kazarov et al., 2002; Yang et al., 2008; Yauch et al., 2000), and integrin/CD151 complexes have been linked to both intracellular signaling pathways (Yauch et al., 1998) and epithelial cell motility (Winterwood et al., 2006). In addition, coordinated interaction of CD151 with keratinocyte integrins α3β1 and α6β4 has been linked to hemidesmosome maturation (Sterk et al., 2000). Of note, CD151 is upregulated in wound epidermis and important for wound healing (Cowin et al., 2006). Further study is required to elucidate the mechanisms whereby integrin/CD151 complexes may contribute to wound healing.

Functions of epidermal integrins in wound healing

Integrin expression patterns within developing and adult epidermis have been documented in both humans and rodent models, and many aspects appear to have been conserved in evolution (Margadant et al., 2010; Watt, 2002). Within the stratified epidermis, integrin expression is restricted to the basal keratinocyte layer that is attached to the BM, and it is down-regulated as differentiating keratinocytes move upwards into the suprabasal layers (Watt, 2002). Studies using global or keratinocyte-specific knockout mice have revealed important roles for integrins in the epidermis (Margadant et al., 2010). Indeed, the general importance of β1 subfamily integrins was revealed through keratinocyte-restricted knockout of the *Itgb1* gene (encoding the β1 subunit), which leads to an array of skin defects that

includes reduced proliferation, loss of sebaceous glands and hair follicles, disorganized BM, and impaired wound re-epithelialization (Brakebusch et al., 2000; Grose et al., 2002; Raghavan et al., 2000). Of note, wound re-epithelialization defects were due mainly to severely impaired keratinocyte migration, whereas keratinocyte proliferation within the wound epidermis was not compromised and was even increased in later wounds (Grose et al., 2002). Importantly, however, subsequent studies showed that regeneration of wound epidermis in these mice most likely occurs through outgrowth of keratinocytes that have escaped Cre-mediated recombination, reflecting an essential role for β1 integrins in re-epithelialization (Piwko-Czuchra et al., 2009). Interestingly, knockout of any individual α subunit gene (i.e., deletion a specific αβ heterodimer) leads to only a subset of the defects seen in β1-null mice, indicating that different integrins have unique, albeit sometimes overlapping roles. Somewhat surprisingly, knockout mice with epidermis-specific deletion of either the β1 subunit (i.e., all β1 integrins) or individual integrins (α3β1, α6β4, α2β1, α9β1, or αvβ5) displayed mild or no defects in epidermal stratification or differentiation (Brakebusch et al., 2000; DiPersio et al., 1997; DiPersio et al., 2000b; Grenache et al., 2007; Huang et al., 2000; Raghavan et al., 2000; Singh et al., 2009; Zweers et al., 2007), indicating that epidermal development is not dependent on any particular integrin(s).

During wound healing, some integrins display persistent or enhanced expression (e.g., α3β1, α6β4, α2β1, α9β1, and αvβ5), while others are expressed de novo (e.g., α5β1 and αvβ6) (Thomas et al., 2006; Watt, 2002). As a group, these integrins can bind to a wide variety of ECM ligands that appear in the wound bed, including fibronectin (α5β1, α9β1, αvβ6), collagen (α2β1), vitronectin (αvβ5), tenascin (α9β1, αvβ6), and LN-332 that is deposited by migrating keratinocytes (α3β1, α6β4) (Margadant et al., 2010; Nguyen et al., 2001; Thomas et al., 2006; Watt, 2002). Many of these integrins have been shown to control keratinocyte motility in culture (Carter et al., 1990a; Carter et al., 1990b; Choma et al., 2004; Frank and Carter, 2004; Grose et al., 2002; Pilcher et al., 1997; Sehgal et al., 2006), and their potential to influence migration through traction generation and signaling is obvious (Ridley et al., 2003). Consistently, epidermal deletion of all β1 integrins together reduced wound re-epithelialization (Grose et al., 2002). Yet, the importance of individual integrins for wound re-epithelialization in vivo remains ambiguous, as wounds of adult mice with global or keratinocyte-specific deletion of individual integrins (e.g., αvβ6, αvβ5, α3β1, α2β1, or α9β1) showed surprisingly mild or no effects on epidermal migration (Grenache et al., 2007; Huang et al., 2000; Margadant et al., 2009; Singh et al., 2009; Zweers et al., 2007). In some cases, discordant results from in vitro and in vivo studies probably reflect the greater complexity of the wound ECM in vivo, where multiple integrin-ligand interactions might compensate for loss of a single interaction.

In the following sections, we will briefly discuss what is currently known about functions of individual integrins within the epidermis (summarized in Table 1). However, given the repertoire of integrins expressed in wound epidermis, it is important to keep in mind that different integrins may undergo complex interactions with potential for cumulative effects (either synergistic or opposing) on keratinocyte functions. Therefore, it is likely that coordinated regulation of different integrins during wound healing, perhaps achieved through the temporal and/or spatial regulation of their ECM ligands, is important to achieve proper wound outcome.

The laminin-binding integrins, α3β1 and α6β4

LN-332 is the main adhesive ligand in resting epidermis, and its effects on keratinocyte behavior are mediated through binding to integrins α3β1 and α6β4 (Carter et al., 1991; Longmate and DiPersio, 2014; Margadant et al., 2010; Nguyen et al., 2000). α6β4 is an essential component of the intermediate filament-associated hemidesmosomes that anchor the epidermis to the dermis (Litjens et al., 2006; Margadant et al., 2010). In contrast, α3β1 is associated with actin-based adhesions (i.e., focal adhesions) from within which it can initiate FAK/Src or other signaling pathways that promote keratinocyte motility and survival (Carter et al., 1990a; Choma et al., 2007; Choma et al., 2004; Litjens et al., 2006; Manohar et al., 2004). While α3β1 and α6β4 can both bind LN-332, these two integrins have distinct functions. For example, LN-332 proteolysis has differential effects on α3β1 or α6β4 binding (Goldfinger et al., 1998), and antagonistic roles of these two integrins in cell migration have been described (Russell et al., 2003). Further evidence of distinct roles for α3β1 and α6β4 comes from comparing variants of the human blistering skin disease, junctional epidermolysis bullosa (JEB), which have been linked to mutations in the α3, α6 or β4 integrin subunits, or in the individual chains of LN-332 itself (Has et al., 2012; Kiritsi et al., 2013; Ruzzi et al., 1997; Vidal et al., 1995). Indeed, differences between these JEB variants, and the corresponding knockout mice, reveal different mechanisms of blistering at the epidermal-dermal junction. For example, newborn mice with homozygous null mutations in the genes that encode either the α6 or β4 subunit (Dowling et al., 1996; Georges-Labouesse et al., 1996; van der Neut et al., 1996), or newborn human patients with loss-of-function mutations in α6β4 (Ruzzi et al., 1997; Vidal et al., 1995), show extensive epidermal blistering due to loss of hemidesmosomes and detachment from the BM. In contrast, absence of α3β1 due to null or loss-of-function mutation of the gene encoding the α3 subunit causes relatively minor skin blisters in newborn mice (DiPersio et al., 1997) or young patients (Has et al., 2012), which form due to BM rupture without loss of α6β4-mediated attachment to LN-332 (DiPersio et al., 1997; DiPersio et al., 2000b), revealing a distinct role for α3β1 in maintaining BM integrity.

Hemidesmosomes are dissassembled during wound re-epithelialization, then reassembled after wound closure to restore stable adhesion of the neo-epidermis (Litjens et al., 2006). Hemidesmosome disassembly may involve Src-mediated phosphorylation of the β4 cytoplasmic domain, possibly triggered by epidermal growth factor (EGF) or other signals from the wound microenvironment (Mariotti et al., 2001). While the role for α6β4 in stable epidermal adhesion has been long established, the extent to which this integrin may regulate intracellular signaling pathways in keratinocytes is less clear (Margadant et al., 2010). Moreover, while α6β4 can regulate motility of cultured keratinocytes (Russell et al., 2003; Sehgal et al., 2006), pro-migratory roles during wound re-epithelialization have not been described.

Integrin α3β1 can regulate a number of keratinocyte functions, including ECM organization (deHart et al., 2003; Hamelers et al., 2005), survival (Manohar et al., 2004), proliferation (Gonzales et al., 1999), and expression/secretion/activity of ECM proteases or pro-angiogenic factors (DiPersio et al., 2000a; Ghosh et al., 2000; Mitchell et al., 2009; Sugiura and Berditchevski, 1999). However, roles for α3β1 in keratinocyte migration have been

unclear, as some in vitro studies reported pro-migratory roles (Choma et al., 2007; Choma et al., 2004; Frank and Carter, 2004), while others reported that α3β1 dampens directional motility (deHart et al., 2003; Margadant et al., 2009). These discordant findings could be due to species-specific differences between rodent and human keratinocytes, and/or variation among models with regard to deposition of endogenous ECM ligands for other integrins (Hamill et al.; Nguyen et al., 2000). In any case, knockout studies revealed that α3β1 is not essential for epidermal closure in wounds of adult mice (Margadant et al., 2009; Mitchell et al., 2009); in fact, deletion of α3β1 from epidermis slightly enhanced re-epithelialization (Margadant et al., 2009). Interestingly, the rate of epidermal closure was reduced within transplanted skin grafts from neonatal mice with global deletion of α3 (Reynolds et al., 2008), possibly reflecting a role for α3β1 in wound re-epithelialization of sub-adult mice. Alternatively, α3β1 may have important roles in other cellular compartments of full-thickness skin grafts (Reynolds et al., 2008), illustrating the importance of investigating integrin functions from within specific cellular compartments of the wound microenvironment.

Although α3β1 is dispensable for wound re-epithelialization in adult mice, it is essential for the regeneration of a stable BM during wound healing. Indeed, mice lacking epidermal α3β1 display blisters in re-epithelialized wounds due to BM rupture, similar to skin blisters that of α3-null neonatal mice, indicating that the developmental role for α3β1 in maintaining BM integrity is recapitulated in adult wound healing (Longmate et al., 2014). Interestingly, blistering in both neonatal skin and adult wounds was linked to reduced expression of the matricellular protein, fibulin-2 (Longmate et al., 2014), which can bind to the LN-γ2 chain near the N-terminus (Utani et al., 1997) and has been implicated in stable incorporation of LN-332 into the developing BM (Gagnoux-Palacios et al., 2001). Of note, α3-null keratinocytes showed reduced fibulin-2 gene expression, providing a potential mechanism for loss of BM integrity (Longmate et al., 2014; Missan et al., 2014). Proteolytic processing of the LN-γ2 chain was also impaired in wounds of mice with α3-null epidermis, and in α3-null keratinocytes cultured in high calcium (Longmate et al., 2014), and proteolytic cleavage of γ2 within LN-332 may regulate interactions with fibulin-2 (Aumailley et al., 2003; Gagnoux-Palacios et al., 2001; Sasaki et al., 2001; Utani et al., 1997). Thus, α3β1-dependent processing of LN-332 may be important for regulating BM maturation through modulation of key ECM linkages. A role for α3β1 in ECM assembly/organization is supported further by studies showing that it regulates matrix metalloproteinases (MMPs) and other extracellular proteases (Ghosh et al., 2000; Iyer et al., 2005; Sugiura and Berditchevski, 1999), as well as LN-332 deposition/organization by keratinocytes (deHart et al., 2003). Finally, as we discuss later, recent studies have identified an important role for epidermal α3β1 in the paracrine induction of wound angiogenesis through secretion of soluble factors that stimulate endothelial cell function (Mitchell et al., 2009)(W. M. Longmate and C. M. DiPersio, unpublished).

Integrin α9β1

Integrin α9β1 is expressed constitutively in the epidermis and is upregulated during wound healing, although it remains relatively understudied compared with other epidermal integrins. A major ligand of α9β1 within the wound bed is the EDA/EIIIA segment of

cellular fibronectin, while other potential ligands found in the wound include tenascin-C, thrombospondin-1, EMILIN1, osteopontin, ADAMs proteins, and vascular endothelial growth factor (VEGF) -C and -D (Hoye et al., 2012; Margadant et al., 2010; Shinde et al., 2008; Singh et al., 2004). Studies in epidermis-specific α9 knockout mice revealed that α9β1 is important for proliferation of wound keratinocytes. Indeed, α9β1-deficient epidermis showed significantly impaired keratinocyte proliferation, while the rate of epidermal migration over the wound was not diminished, causing reduced thickness of the neo-epidermis and delayed differentiation (Singh et al., 2009). Interestingly, recent studies from our group indicate a complex interplay between integrins α9β1 and α3β1 during wound healing, wherein α9β1 exerts a transdominant-inhibitory effect over the pro-angiogenic functions of α3β1 (see below), possibly controlled through temporal regulation of α9β1 ligands within the wound bed (W. M. Longmate and C. M. DiPersio, unpublished).

Integrin α2β1

The collagen-binding integrin, α2β1, is expressed constitutively in epidermis and upregulated in wounds. Mice that are homozygous for a global α2-null mutation display normal skin development without overt defects in wound re-epithelialization or contraction, indicating that this integrin is not essential for wound closure per se (Chen et al., 2002; Zweers et al., 2007). However, α 2-null mice show enhanced wound angiogenesis, reduced mast cell infiltration into wounds, and reduced tensile strength of healed wounds, indicating complex roles for α2β1 in wound healing (Grenache et al., 2007; Zweers et al., 2007). It remains to be determined whether wound healing defects in α2-null mice are due to absence of α2β1 from the epidermis or from other wound cells, as this integrin has not been deleted specifically from the epidermis.

Integrin α5β1

Integrin α5β1 is expressed at very low levels in unwounded epidermis, but it is upregulated in healing wounds where it may promote keratinocyte migration over cellular fibronectin (via binding to the RGD site) that is deposited into the provisional wound ECM by wound macrophages and fibroblasts (Brown et al., 1993; Ffrench-Constant et al., 1989). However, it remains unknown whether epidermal α5β1 is required for in vivo wound healing, since the α5-null mutation is embryonic lethal (Yang et al., 1993), and wound studies in epidermis-specific α5 knockout mice have not been reported. Thus, it remains possible that defective epidermal migration reported in wounds of β1-deficient mice (Grose et al., 2002) is due largely to loss of α5β1, since to date no other α subunit knockout has produced the β1-null phenotype.

The αv integrins

Members of the αv integrin subfamily display dynamic expression patterns in the transition from unwounded to wounded skin (Koivisto et al., 2014). In unwounded epidermis, αvβ5 and αvβ8 are expressed at low levels, while αvβ6 is restricted to hair follicle stem cells (Breuss et al., 1995; Hamidi et al., 2000; Jones et al., 1997; Margadant et al., 2010). However, αvβ6 and αvβ5 are both upregulated in wound epidermis (Breuss et al., 1995; Hamidi et al., 2000; Jones et al., 1997; Margadant et al., 2010), where each may bind to RGD motifs within several ECM proteins (e.g., fibronectin, tenascin, vitronectin) (Hynes,

2002; Thomas et al., 2006). Interestingly, mice lacking αvβ6 (i.e., β6-null) displayed an age-dependent delay in wound healing (AlDahlawi et al., 2006). In addition to controlling cell migration over the provisional ECM, the de novo expression of αvβ6 may protect keratinocytes from undergoing anoikis (i.e., apoptosis triggered by altered adhesion during ECM remodeling), as this integrin can activate AKT survival pathways in epithelial cells (Janes and Watt, 2004). αvβ6 can also regulate extracellular proteases such as MMP-9 (Thomas et al., 2001a), MMP-3 (Ramos et al., 2002), and uPA (Ahmed et al., 2002), suggesting roles in ECM remodeling. Moreover, αvβ6 can bind and activate the ECM-bound reservoir of latent TGFβ, which is secreted as a complex of latency-associated protein (LAP) and latent TGFβ-binding protein (LTBP) that is covalently linked to fibronectin (Sheppard, 2005; Taipale et al., 1994). Indeed, αvβ6 (and perhaps to a lesser extent αvβ5) can bind the RGD motif within LAP to trigger a conformational change that activates latent TGFβ1 or TGFβ3 complex (Annes et al., 2004; Munger et al., 1999; Sheppard, 2005), suggesting that induction of αvβ6 during wound healing may provide a temporally controlled mechanism for local TGFβ activation.

Epidermal integrins regulate crosstalk to other cellular compartments of the wound

An extensive network of communication exists between the different cell types within the wound microenvironment, and mounting evidence supports the concept that integrins from within neutrophils, monocytes, fibroblasts, or endothelial cells can control crosstalk to keratinocytes that influences wound re-epithelialization (Koivisto et al., 2014). Importantly, the epidermis is also well known to send paracrine signals to other cellular compartments of the skin (Fig. 1), although mechanisms that regulate signaling in this direction remain unclear (Ghahary and Ghaffari, 2007; Nowinski et al., 2004; Werner et al., 2007; Zigrino et al., 2012). The following sections will focus on how keratinocyte integrins may regulate paracrine signals that emanate from the epidermis and influence functions of other wound cells. As we discuss below, such integrin-dependent intercellular crosstalk might be propagated through secretion of diffusable growth factors, altered physical properties of the ECM (e.g., matrix proteolysis or mechanical signaling), or proteolytic release of ECM-bound growth factors or bioactive fragments.

Paracrine signaling to the wound vasculature

The granulation phase of wound healing involves the growth of new vasculature through angiogenesis, which is important for delivering oxygen, nutrients and immune cells to the wound bed that are critical for the repair process. Later, during the tissue remodeling phase, the vasculature regresses to restore normal vessel density, thereby preventing tissue hyperoxia (Johnson and DiPietro, 2013). Control of blood vessel density involves the proliferation, migration, and apoptosis of endothelial cells, which can be regulated through accessibility of angiogenic growth factors such as basic fibroblast growth factor (FGF-2), EGF, platelet-derived growth factor (PDGF), and VEGF. Importantly, many pro-angiogenic growth factors are provided to endothelial cells by other wound cells, including neutrophils, platelets, and keratinocytes, representing pathways of intercellular communication that control wound angiogenesis. Moreover, defects in these pathways may contribute to vascular

abnormalities associated with chronic wounds (Eming et al., 2007; Eming et al., 2014; Johnson and Wilgus, 2014; Koh and DiPietro, 2011; Martinez et al., 2015; Nissen et al., 1998).

While it has long been known that the epidermis secretes factors that can influence wound angiogenesis (Santoro and Gaudino, 2005; Singer and Clark, 1999), recent studies from our group have linked keratinocyte integrins to the paracrine stimulation of endothelial cells. For example, keratinocyte α3β1 promotes the expression and secretion of mitogen-regulated protein 3 (MRP3), a pro-angiogenic factor that stimulates endothelial cell migration and wound angiogenesis (Mitchell et al., 2009). Moreover, keratinocyte α3β1 promotes expression of MMP-9 (Iyer et al., 2005; Lamar et al., 2008), which has pro-angiogenic functions in wound healing and other tissue remodeling processes (Bergers et al., 2000; Hattori et al., 2009; McCawley and Matrisian, 2001; Yu and Stamenkovic, 2000). In contrast, wound studies performed in α2-null mice indicate an anti-angiogenic role for α2β1, although the cellular compartment from within which this regulation occurs remains unclear due to the global nature of this knockout model (Zweers et al., 2007). Interestingly, integrin α6β4 has been shown to regulate the expression of both α3β1 and α2β1 in keratinocytes (Kligys et al., 2012), raising the possibility that complex interplay between different epidermal integrins may control wound angiogenesis. Along similar lines, our group recently determined that keratinocyte α9β1 suppresses the pro-angiogenic, paracrine functions of α3β1, suggesting that functional coordination of different keratinocyte integrins can regulate intercellular communication that controls vascular density (W. M. Longmate and C. M. DiPersio, unpublished). Since the appearance of ECM ligands for different epidermal integrins is dynamic throughout the stages of wound healing, we speculate that temporally coordinated integrin activation may control both angiogenic growth at early stages and vascular normalization at later stages.

Paracrine signaling to wound fibroblasts/myofibroblasts

There is considerable evidence that paracrine signaling from the epidermis to fibroblasts/myofibroblasts can influence wound contraction, and that loss of such intercellular crosstalk is associated with fibrosis and hypertrophic scar formation (Ghahary and Ghaffari, 2007; Werner et al., 2007). Indeed, studies in co-culture models have shown that keratinocyte-secreted factors (e.g., growth factors, cytokines, ECM components, MMPs) can have both positive and negative effects on fibroblast genes and functions (Nowinski et al., 2004; Shephard et al., 2004; Werner et al., 2007). For example, keratinocyte-derived TGFβ promoted α-smooth muscle actin (α-SMA) expression and myofibroblast differentiation (Hata et al., 2014), while secretion of interleukin-1 (IL-1) by keratinocytes at early time points in co-culture suppressed α-SMA expression (Shephard et al., 2004). In another example, the keratinocyte-derived anti-fibrogenic factor, stratifin, up-regulated MMP-1 expression in fibroblasts via a p38/MAPK pathway (Lam et al., 2005), possibly leading to less collagen deposition and reduced dermal fibrosis (Rahmani-Neishaboor et al., 2012). Keratinocytes also produce PDGF (Ansel et al., 1993), which has been shown to stimulate chemotaxis, proliferation, and gene expression in fibroblast in vitro, and enhance the influx of fibroblasts and extracellular matrix deposition during wound healing in vivo (Pierce et al., 1991). Moreover, it was shown recently that treatment of mouse corneal stromal fibroblasts

with PDGF, in combination with TGFβ, can stimulate differentiation to myofibroblasts in vitro (Singh et al., 2014). Other fibroblast responses to keratinocyte-released factors include down-regulation of type I collagen expression/synthesis in response to collagen-inhibitory factors (CIFs) (Ghaffari et al., 2009), and up- regulation of cyclooxygenase-2 (Cox-2) expression and prostaglandin E2 (PGE_2) production in response to IL-1α (Sato et al., 1997). Interestingly, the latter response may trigger a feedback loop, as fibroblast- derived PGE_2 has recently been shown to inhibit TGFβ-mediated myofibroblast differentiation in an autocrine manner (Penke et al., 2014).

Given the roles that keratinocyte integrins play in the paracrine induction of wound angiogenesis (see above), we speculate that they may also regulate paracrine pathways that control fibroblast/myofibroblast function in wounds. Consistently, some keratinocyte integrins have been shown to modulate gene expression and/or bioavailability of ECM proteases that are already known to stimulate wound fibroblasts. For example, keratinocyte integrins αvβ6 and α3β1 can induce expression and secretion of MMP-9, MMP-3, uPA, and/or other extracellular proteases (Ghosh et al., 2000; Iyer et al., 2005; Ramos et al., 2002; Thomas et al., 2001b) into the wound stroma. Indeed, recruitment of MMP-9 to the fibroblast surface triggers TGFβ activation, which coupled with mechanical tension and other ECM signals can induce myofibroblast differentiation (Dayer and Stamenkovic, 2015; Kobayashi et al., 2014; Van De Water et al., 2013). Other studies support integrin-mediated induction of IL-1α from the epidermis (Hobbs and Watt, 2003). Additional evidence that integrins may control epithelial-to-myofibroblast crosstalk comes from studies in a mouse lung fibrosis model, which showed that deletion of integrin α3β1 from lung epithelial cells led to diminished numbers of myofibroblasts (Kim et al., 2009).

Paracrine signaling to inflammatory cells

It is well known that chemokines produce by keratinocytes can recruit inflammatory cells to the wound, and that misregulation of this process contributes to prolonged inflammation, impaired reepithelialization, and altered myofibroblast differentiation (reviewed in (Van Linthout et al., 2014)). For example, interferon inducible protein-10 (IP-10/CXCL-10) is upregulated in keratinocytes during wound healing, and its overexpression results in an intensified immune response that is associated with delayed reepithelialization and a prolonged granulation phase, as well as reduced angiogenesis (Barrientos et al., 2008). In another example, macrophage chemoattractant protein (MCP-1/CCL2) that is produced by wound keratinocytes serves to recruit monocytes/macrophages, T-cells, and mast cells (DiPietro, 1995). Moreover, persistent expression of MCP-1 leads to a prolonged inflammatory response in chronic wounds (Wetzler et al., 2000), and MCP-1 knockout mice display delayed wound healing (Low et al., 2001). While roles for epidermal integrins in paracrine signaling to inflammatory cells have not been explored extensively, treatment of epithelial cells with an antibody that targets integrin α3β1 was shown to suppress the induction of MCP-1, IL-6 and IL-8 that occurred in response to treatment with IL-1 (Lubin et al., 2003). Moreover, expression of a β1 integrin transgene in the suprabasal layers of the epidermis enhanced IL-1α secretion, providing a potential signal for crosstalk to inflammatory cells (Hobbs and Watt, 2003).

Potential mechanisms of integrin-mediated, long-distance signaling from the epidermis to other wound cells

Signaling through growth factors and cytokines

Regulating the bioavailability of growth factors, cytokines or chemokines is a critical point of control over the inflammatory phase of wound healing, and failure to control or resolve inflammation can contribute to both chronic wounds and fibrotic pathologies. The cytokine network is also critical for controlling protease-mediated degradation of fibrillar collagen and other matrix proteins that is required for the remodeling phase of wound healing (Singer and Clark, 1999). Although the epidermis is spatially separated from the stromal compartment of the skin, keratinocyte-derived growth factors and cytokines can diffuse to other cellular compartments within the wound microenvironment. Importantly, some epidermal integrins can modulate growth factor/cytokine production that can then stimulate distal wound cells such as fibroblasts, endothelial cells, and inflammatory cells, thereby providing a means of integrin-dependent paracrine signaling. For example, as already mentioned, we reported that keratinocyte α3β1 promotes MRP3 secretion, which stimulates pro-angiogenic functions of endothelial cells (Mitchell et al., 2009). As also mentioned, expression of β1 integrin in suprabasal keratinocytes leads to IL-1 expression (Hobbs and Watt, 2003), which stimulates fibroblast growth and collagen synthesis (Sauder et al., 1990), and may regulate TGFβ-mediated myofibroblast differentiation (Shephard et al., 2004). Epidermal-derived cytokines and growth factors may also feedback to regulate epidermal integrin expression. For example, α6β4-mediated activation of latent TGFβ in keratinocytes is associated with up-regulation of some epidermal integrins (e.g., α5β1, α2β1, αvβ5, αvβ6) and down-regulation of others (e.g., α3β1) (Zambruno et al., 1995), raising the possibility that α6β4/TGFβ signaling indirectly regulates integrin-dependent paracrine pathways that stimulate other cells. These complex regulatory interactions between growth factors/cytokines and epidermal integrins indicate the likely importance of tight spatial-temporal control over these interactions, perhaps through bioavailability of key factors.

Signaling through extracellular proteases

Proteolytic remodeling of the ECM is an essential feature of normal wound healing (Steffensen et al., 2001), and defects in ECM organization are associated with chronic wounds (Agren and Werthen, 2007; Lobmann et al., 2002). Indeed, MMPs are involved in all phases of wound healing, and abnormal MMP expression/function is well known to contribute to the pathogenesis of chronic wounds (Lobmann et al., 2002). It is well established that some keratinocyte integrins (e.g., α3β1, αvβ6) can regulate the expression or function of matrix-degrading extracellular proteases (e.g., MMP-9, uPA or uPAR) (Ghosh et al., 2000; Iyer et al., 2005; Thomas et al., 2001b), which may in turn control ECM remodeling and/or proteolytic release of ECM-bound growth factors or bioactive peptides that are crucial for proper wound healing (Gill and Parks, 2008; McCawley and Matrisian, 2001; Page-McCaw et al., 2007; Schenk and Quaranta, 2003). It follows that defects in integrin-dependent pathways of protease regulation in the epidermis may contribute to the pathogenesis of abnormal wound healing through effects on other cells in the wound microenvironment (Agren and Werthen, 2007; Lobmann et al., 2002). For example, as

described above, an α3β1-to-MMP-9 signaling axis (Iyer et al., 2005) may contribute to pro-angiogenic communication from the epidermis to the wound vasculature (Mitchell et al., 2009). Similar communication may occur from the epidermis to dermal fibroblasts/myofibroblasts, given the important roles that some MMPs play in myofibroblast differentiation and wound contraction (Hattori et al., 2009; Kobayashi et al., 2014; Mirastschijski et al., 2004).

Other potential mechanisms

There are other potential mechanisms of integrin-mediated, long-distance signaling from the epidermis that are relatively unexplored but warrant some discussion. For example, mechanical signaling, or mechanotransduction, is accomplished through ability of the constituent cells of a tissue to both exert force on the ECM and sense the ability of the ECM to resist that force (i.e., its stiffness) (Hinz, 2010; Van De Water et al., 2013). In their capacity as physical linkers of the ECM to the cytoskeleton, integrins function as transducers of mechanical signals across the plasma membrane (Hynes, 2002). This function can be influenced by changes in chemical or physical properties of the ECM that alter its stiffness, such as changes in organization of collagen fibers, fibronectin, or other matrix components that can be brought about by post-translational modifications, altered crosslinking, or proteolysis (Humphrey et al., 2014; Wells, 2008). Importantly, the biomechanical properties/stiffness of the ECM changes dramatically during the course of wound healing, as it progresses from the initial fibrin clot, to the provisional ECM of the granulation tissue, and finally to the remodeled stromal ECM and regenerated BM. Wound cells respond to these changes (Hinz, 2010), and increasing evidence links wound pathogenesis to alterations in ECM compliance and mechanical tension within the wound bed (Wong et al., 2011). Such alterations may be caused by changes in cell-generated forces, defective ECM deposition, or mis-regulated proteolysis of the ECM (Hermes et al., 2011; Lancerotto et al., 2012; Shirakawa and Isseroff, 2005; Trengove et al., 1999; Wong et al., 2013).

Since keratinocytes respond to matrix stiffness through alterations in migration and proliferation (Evans et al., 2013; Wang et al., 2012; Zarkoob et al., 2015)(reviewed in (Kenny and Connelly, 2015)), one could speculate that keratinocyte integrins can also transduce mechanical signals from the epidermis that influence behaviors of other wound cells (Kenny and Connelly, 2015). Indeed, epidermal keratinocytes generate relatively high intercellular tension, which is enhanced by cell-cell adhesion within the collectively migrating sheet of cells (Vedula et al., 2014), raising the possibility that forces transduced to the adjacent wound ECM may modulate its stiffness. In addition, keratinocytes might indirectly modulate stiffness of the wound ECM through release of matrix-degrading proteases. However, the extent to which mechanical signaling and ECM stiffness are an important mode of communication from the epidermis to other wound cells requires further investigation. Such studies will certainly require the development of cell culture or organotypic models wherein mechanical stimuli can be isolated from, and controlled independently of, diffusible factors (e.g. growth factors, cytokines) that also control wound healing (Kenny and Connelly, 2015).

A growing literature supports the cellular shedding of extracellular vesicles, including microvesicles and exosomes, as another potential mechanism of intercellular communication (for a review see (Camussi et al., 2010)). Such cell-to-cell crosstalk may occur through the ability of microvesicles/exosomes to directly stimulate receptors on target cells, or through their capacity to transport cargos that alter target cell function (e.g., membrane receptors, signaling proteins, mRNAs, or microRNAs). Interestingly, tumor cell-derived exosomes have been shown to trigger fibroblast-to-myofibroblast differentiation through transport of TGFβ (Webber et al., 2010). Similarly, keratinocytes have been shown to release exosomes/microvesicles that stimulate wound healing-associated genes (e.g., MMPs, interleukins, TGFβ signaling genes) and functions in dermal fibroblasts, suggesting a potential mechanism of paracrine signaling during wound healing (Chavez-Munoz et al., 2009). Interestingly, recent studies in cancer models have implicated important roles for integrins, or extracellular matrix proteins, in exosome-mediated signaling (Fedele et al., 2015; Sung et al., 2015), raising the intriguing possibility that epidermal integrins play a similar role in paracrine crosstalk from keratinocytes to other wound cells.

Implications for pathological wound healing

As discussed above, normal acute wounds heal by a series of overlapping phases (i.e., inflammation, proliferative phase and tissue remodeling) that optimize a prompt return to tissue homeostasis. Each of these phases entails dynamic and balanced interactions between soluble mediators (e.g., growth factors) extracellular matrix components and both resident and infiltrating cells. When these wound dynamics are disrupted, pathological wound healing ensues. The wound pathologies are manifested along a spectrum that includes, at one end, wounds that do not heal well (e.g., chronic wounds) and at the other end wounds that heal over-exuberantly (e.g., hypertrophic scars and keloids). While ongoing work in many labs has identified potential therapies, there has been a relatively low rate of success, renewing calls for robust cellular and molecular biology to support the development of novel therapies (Eming et al., 2014; Nunan et al., 2014). In addition to the cell-autonomous functions of integrins in wound keratinocytes, we believe that roles for integrins in paracrine signaling from wound epidermis are understudied. In the previous sections, we reviewed how keratinocyte integrins may regulate both autocrine and paracrine functions during wound healing (Fig. 1). In the current section, we will illuminate important areas in which disrupted keratinocyte integrin interactions with ECM may contribute to wound pathologies.

Chronic wounds

The term “chronic wounds” encompasses wound pathologies in which a defect in barrier function - normally assembled by keratinocytes occurs. An alarming increase in the number of chronic wounds has become apparent in recent years and is the focus of much concern, particularly in view of the rising tide of diabetic patients (Sen et al., 2009) (Eming et al., 2014). These wound pathologies occur in patients in which vascular function is compromised, either as a consequence of chronic venous insufficiency (e.g., venous leg ulcers), reduced arterial blood supply secondary to diabetes (e.g, foot ulcers), or pressure ulcers occurring in areas of skin that are compressed against underlying bone. Chronic wounds are characterized by a hyper-proliferative but stationary epidermis, persistent

bacterial infection and inflammation and a compromised wound vasculature. Moreover, recent gene expression analyses have revealed a different synthetic program in keratinocytes at the non-healing edges of chronic wounds compared to normal keratinocytes (Pastar et al., 2008). Of note, chronic wounds often display dramatic alterations in epidermal integrin expression, such as increased αvβ6 and decreased α5β1 expression, and these changes are likely to play causal roles in wound pathology ((Hakkinen et al., 2004; Koivisto et al., 2014; Morgan et al., 2004; Widgerow, 2013)). Below, we speculate on several areas in which keratinocyte integrin-ECM interactions may be critical in chronic wound pathologies.

With regard to wound infections, it is now well understood that bacteria exploit host ECM components and other proteins in order to colonize tissues (Foster et al., 2014). Among these are ECM proteins that are prominent in healing wounds, such as plasma and cellular forms of fibronectin. Cellular fibronectin includes an alternatively spliced segment, termed EDA (or EIIIA) that is undetectable in unwounded skin (Singh et al., 2004). Our recent work has demonstrated an important role for the EDA segment of fibronectin in promoting biofilm formation (Oliver-Kozup et al., 2013). The EDA segment binds to integrin α9β1, which promotes keratinocyte proliferation (Liao et al., 2002; Shinde et al., 2008; Singh et al., 2009), and we have observed that α9β1 exerts transdominant inhibition of keratinocyte integrin α3β1 function (W. M. Longmate and C. M. DiPersio, unpublished). Therefore, it will be important to determine if and how bacterial biofilm formation in chronic wounds disrupts normal interactions between keratinocyte integrins, and how such disruption impacts paracrine signaling via fibronectin- and integrin-dependent pathway(s). Because keratinocytes secrete paracrine mediators (e.g., IL-1, TNFα) that are known components of innate immunity pathways (see for example, see (Feldmeyer et al., 2010)), analyses of integrin-dependent mechanisms that regulate keratinocyte cytokine production in chronic inflammatory settings will likely prove important. The presence of persistent inflammation during wound infection also entails alterations in the spectrum of proteases elaborated by both immune cells and keratinocytes. Although there are clearly many proteases (e.g., serine proteases, MMPs) that are regulated by integrins and have critical roles, recent work from our group supports a model in which dysregulation of α3β1-ECM interactions could influence MMP-9-dependent homeostasis (Iyer et al., 2005; Lamar et al., 2008; Missan et al., 2015).

Dysregulation of angiogenesis and compromised wound vasculature is a cardinal feature of chronic wounds. Wound keratinocytes have long been known to secrete angiogenic factors (Johnson and Wilgus, 2014), yet the mechanisms that regulate this process remain poorly understood. As already discussed, keratinocyte integrin α3β1 governs the expression of pro-angiogenic factors, including MRP-3 (Mitchell et al., 2009) and MMP-9 (Iyer et al., 2005), suggesting a potential role for disrupted keratinocyte integrin function in modulating angiogenesis in chronic wounds.

Scarring pathologies

The healing that follows deep traumatic or serious burn injury is often complicated by the elaboration of keloids or hypertrophic scars (Ehrlich et al., 1994). Keloids are abnormal scars that contain abundant collagen deposits, extend beyond the boundary of the original

wound, rarely regress and occur in individuals who are genetically predisposed. Surgical resection reinitiates this process, and keloids have a high recurrence rate despite adjunct treatments including intralesional steroid treatment (Andrews et al., 2016). In contrast, hypertrophic scars are elevated above the skin surface and are characterized by redness and itching, but they remain within the boundaries of the initial injury. Although they often regress spontaneously over time, these scars can undergo disfiguring contractures that can limit motion, particularly over joints. Surgical scar revision remains a mainstay therapy, although many other therapeutic approaches have been attempted (Reish and Eriksson, 2008). Interestingly, occlusive dressings have been effective in both controlled animals studies and prospective, randomized studies (Mustoe and Gurjala, 2011). Importantly, these dressings are thought to promote epidermal function by prompt restoration of barrier function, thereby reducing water loss and potentially reducing epidermal paracrine signals to inflammatory cells and other wound cells (Mustoe and Gurjala, 2011; Reish and Eriksson, 2008). Given the emerging roles for keratinocyte integrins in controlling epidermal paracrine signals, their potential roles in hypertrophic scarring should not be overlooked and warrants investigation.

Concluding remarks

In summary, it has become clear in recent years that integrins control both autocrine and paracrine functions of wound keratinocytes that extend well beyond established roles in epidermal adhesion and migration (Fig. 1, arrow 1). Indeed, keratinocyte integrins also play important roles in enabling the epidermis to modify the wound microenvironment, either through alterations in the wound ECM or through communication with other wound cells. It is clear that certain epidermal integrins can influence angiogenesis by promoting paracrine pathways that stimulate endothelial cells (Fig. 1, arrow 2), and it seems likely that such paracrine stimulation extends to other wound cells, such as fibroblasts/myofibroblasts or inflammatory cells (Fig. 1, arrow 3). Since many epidermal functions are altered in wound pathologies such as chronic wounds and hypertrophic scars, there are promising opportunities for basic research on integrin-mediated keratinocyte-ECM interactions that may provide a foundation for novel wound healing therapies. Indeed, results of genetic studies in mice support the concept that wound re-epithelialization might be facilitated through therapeutic manipulation of epidermal integrins. However, this strategy will likely require combinatorial targeting of several integrins with both distinct and overlapping functions. In addition, targeting gene regulatory functions of epidermal $\alpha 3\beta 1$ (and possibly other integrins) may allow the therapeutic modulation of gene groups with predicted roles in altering the wound microenvironment, including secreted growth factors, cytokines, proteases, or ECM/matricellular proteins. Nevertheless, while good progress has been made towards identifying wound-related functions of individual integrins, we are only beginning to understand how the functions of multiple integrins are coordinated within the epidermis to ensure normal wound healing. Formidable challenges lie ahead as we attempt to translate this knowledge into the development of therapeutic approaches to treat wound healing deficiencies in the clinic. Adding to this challenge, it is likely that integrin-mediated control over diverse epidermal wound functions is precisely timed, in order to maintain properly coordinated regulation of epidermal function throughout the stages of wound healing.

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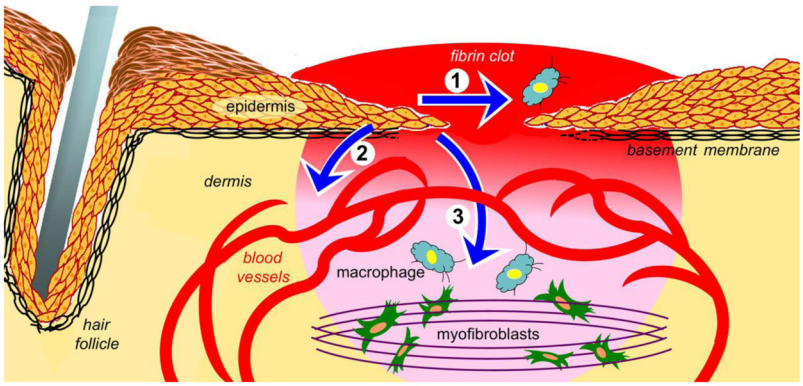

Fig. 1.

Illustration depicts functions of wound epidermis that may be controlled by keratinocyte integrins. Arrow 1 indicates wound re-epithelialization, which is driven by keratinocyte proliferation, local matrix remodeling, and migration. Arrow 2 indicates paracrine signaling from the epidermis to vascular endothelial cells that promotes wound angiogenesis. Arrow 3 indicates paracrine signaling from the epidermis to other wound cells, including inflammatory cells (blue cells) and fibroblasts/myofibroblasts that promote wound contraction (green cells). The wound bed is indicated in red-to-pink gradient.

Table 1

Summary of epidermal integrins, their ECM ligands, and their known functions in the skin

Integrin	ECM ligands in skin	Known functions in unwounded epidermis	Known functions in wound epidermis
α3β1	LN (mainly LN-332)	Expressed constitutively. Essential for basement membrane organization during skin development, and epidermal-dermal adhesion in newborn mice.	Required for maturation of the basement membrane, epidermal-dermal adhesion, and pararcine stimulaton of angiogenesis. May modulate epidermal migration.
α6β4	LN (mainly LN-332)	Expressed constitutively. Essential for hemidesmosome formation and epidermal-dermal adhesion.	Presumably required for hemidesmosome assembly and epidermal adhesion following re-epithelialization. Roles in epidermal migration are unclear.
α9β1	FN (via EDA segment), TN, OPN, TSP, ADAMs, EMILIN1, VEGF-C & -D	Expressed constitutively at low levels. Not essential for epidermal development or adhesion.	Upregulated. Essential for normal keratinocyte proliferation during wound re-epithelialization.
α2β1	collagens	Expressed constitutively. Not essential for epidermal development or adhesion.	Upregulated. No essential roles reported, but may contribute to epidermal migration over collagen.
α5β1	FN (via RGD)	Expressed at very low levels. Not essential for epidermal development or adhesion.	Upregulated. No essential roles reported, but likely contributes to epidermal migration on fibronectin.
αvβ6	FN, TN, LAP of TGFβ-l and -3 (via RGD)	Restricted to follicular cells. Not essential for epidermal development or adhesion, although required in juvenile mice for normal hair growth.	Upregulated. Required for efficient wound healing in aged mice. May regulate ECM proteolysis, keratinocyte survival, and keratinocyte-mediated activation of latent TGFβ. Over-expression associated with chronic wounds.
αvβ5	VN (via RGD)	Expressed at low levels. Not essential for epidermal development or adhesion.	Upregulated. May contribute to keratinocyte-mediated activation of latent TGFβ.

Table adapted from Longmate and DiPersio (2014). See text for supporting literature. ECM, extracellular matrix; LN, laminin; FN, fibronectin; TGFβ, transforming growth factor β; TN, tenascin-C, OPN, osteopontin; VEGF, vascular endothelial cell growth factor; TSP, thrombospondin-1; LAP, latency-associated proteins; VN, vitronectin.