COMPREHENSIVE INVITED REVIEW

Integrins in Wound Healing

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Significance: Regulation of cell adhesions during tissue repair is fundamentally important for cell migration, proliferation, and protein production. All cells interact with extracellular matrix proteins with cell surface integrin receptors that convey signals from the environment into the nucleus, regulating gene expression and cell behavior. Integrins also interact with a variety of other proteins, such as growth factors, their receptors, and proteolytic enzymes. Re-epithelialization and granulation tissue formation are crucially dependent on the temporospatial function of multiple integrins. This review explains how integrins function in wound repair.

Recent Advances: Certain integrins can activate latent transforming growth factor beta-1 (TGF-β1) that modulates wound inflammation and granulation tissue formation. Dysregulation of TGF-β1 function is associated with scarring and fibrotic disorders. Therefore, these integrins represent targets for therapeutic intervention in fibrosis.

Critical Issues: Integrins have multifaceted functions and extensive crosstalk with other cell surface receptors and molecules. Moreover, in aberrant healing, integrins may assume different functions, further increasing the complexity of their functionality. Discovering and understanding the role that integrins play in wound healing provides an opportunity to identify the mechanisms for medical conditions, such as excessive scarring, chronic wounds, and even cancer.

Future Directions: Integrin functions in acute and chronic wounds should be further addressed in models better mimicking human wounds. Application of any products in acute or chronic wounds will potentially alter integrin functions that need to be carefully considered in the design.

Abbreviations and Acronyms

αSMA = alpha–smooth muscle actin
ADAM = a disintegrin and metalloproteinase
BM = basement membrane
CCN = Cyr61-CTGF-Nov
COL = collagen
CT = connective tissue
CTGF = connective tissue growth factor
EC = endothelial cell
ECM = extracellular matrix
EDA/B = extra domain A/B
EGF = epidermal growth factor
EGFR = EGF receptor
EMILIN = elastic microfibril interface–located protein
FAK = focal adhesion kinase

(*continued*)

SCOPE AND SIGNIFICANCE

Wounds are common in skin and oral mucosa, and they are caused by either trauma or surgery. Wound healing is a coordinated, progressive process which is used to restore the barrier function and integrity of the epithelium that involves blood coagulation, inflammation, re-epithelialization by migrating keratinocytes, granulation tissue formation, angiogenesis, and, eventually, tissue remodeling. The formation and regulation of cell adhesions via integrin receptors play a fundamental role during all phases of wound healing.[1,2] In the present review, our main focus will be on integrin expression and functions during re-epithelialization and granulation tissue formation.

TRANSLATIONAL RELEVANCE

Oral mucosal wounds heal with minimal scarring compared with skin wounds. Integrins are likely to play a role in regulating this differential

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healing outcome, although direct evidence is still lacking. Understanding the pathways that are important for scarless healing will help in the development of therapies for the prevention of scar formation in skin.[3] There are no commercial wound healing products in the market at the present time that are based on integrin functions. However, some therapies targeting $\alpha_v\beta_6$ integrin are being developed that show promise in reducing fibrosis.[4] In addition, transferring oral cells to an extra-oral location to improve healing outcomes has been proposed.[5]

CLINICAL RELEVANCE

Wound healing problems are very common, affecting millions of people worldwide every year. Some wounds cause morbidity, because they over-heal with extensive scarring and others, because they fail to heal, becoming chronic. At the molecular level, integrin-mediated adhesion is likely to participate in both conditions.

OVERVIEW

The process of wound healing has been recently reviewed and is, therefore, only briefly covered here (Fig. 1).[6–8] Wound healing starts with blood clotting that initially seals the wound.[9] Platelet activation during the primary hemostasis releases a number of important cytokines that provide chemotactic signals to inflammatory and resident cells. During this innate immune response, inflammatory cells (first neutrophil granulocytes, later macrophages, lymphocytes, and mast cells) which have been recruited to the wound site release more cytokines and chemokines that activate and recruit the resident epithelial cells and fibroblasts at the wound margins.[10] Within 24 h after wounding, epithelial cells at the wound margins start to form cellular extensions into the clot and dissolve their hemidesmosomal adhesions to the basement membrane. Keratinocytes behind the leading edge start proliferating to seed more cells into the wound site. Keratinocytes migrate over the wound bed until they contact the front of the leading cells coming from the other side of the wound.[11] The formation of granulation tissue starts simultaneously with re-epithelialization.[8] Granulation tissue replaces the provisional wound matrix and provides a scaffold for connective tissue formation. Injury to the tissue also initiates angiogenesis (formation of new blood vessels from pre-existing blood vessels).[12] Wound angiogenesis is tightly associated with granulation tissue formation and has many similarities to re-epithelialization. Similarly to the epithelial cells, the endothelial cells or their precursor cells in the pre-existing blood vessels become activated by cytokines and start to migrate to the wound provisional matrix. They create the granulation tissue along with the activated fibroblasts, mesenchymal progenitor cells (pericytes and other mesenchymal stem cells), and circulating fibroblast-like cells (fibrocytes) that also migrate to the provisional matrix. When a sufficient amount of collagen is produced into the granulation tissue, wound contraction is started by myofibroblasts that differentiate from local resident fibroblasts or other progenitor cells. This process pulls wound margins closer together, reducing the wound area and accelerating the wound closure. After wound contraction, granulation tissue remodeling takes place. During this process, myofibroblasts degrade, remodel, and re-organize the wound extracellular matrix (ECM). The maturation to connective tissue is slow and can continue for months if not years.

Abbreviations and Acronyms (*continued*)

FAP = fibroblast activating protein
FBL = fibroblast
FC = wound (fibrin) clot
FGF = fibroblast growth factor
FN = fibronectin
GT = granulation tissue
HB-EGF = heparin-binding EGF-like growth factor
ICAM = intercellular adhesion molecule
ILK = integrin-linked kinase
KC = keratinocyte
LAP = latency-associated peptide
LM = laminin
LTBP = latent TGF-β1–binding protein
MMP = matrix metalloproteinase
NK = natural killer cell
OPN = osteopontin
PDGF = platelet-derived growth factor
RGD = arginine-glycine-aspartic acid
ROS = reactive oxygen species
SPARC = secreted protein acidic and rich in cysteine
TGF = transforming growth factor
TN = tenascin
TSP = thrombospondin
uPAR = urokinase-type plasminogen activator receptor
VCAM = vascular cell adhesion molecule
VEGF = vascular endothelial growth factor
VN = vitronectin
VWF = von Willebrand factor

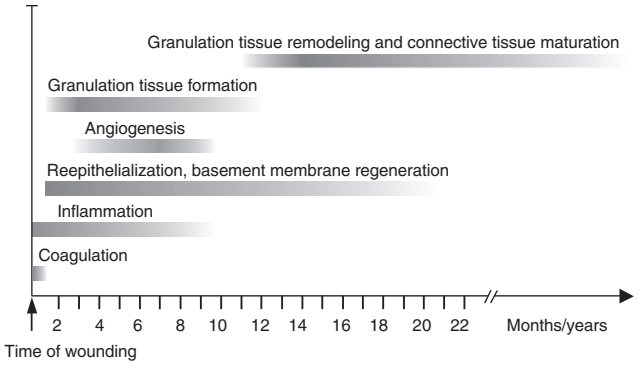

Figure 1. Wound healing phases. The approximate timing of coagulation, inflammation, re-epithelialization, angiogenesis as well as granulation tissue formation and remodeling. Adapted from Häkkinen *et al.*[8]

Oral soft tissue healing proceeds with the same principles as in skin. However, in some parts of oral mucosa (gingiva, palatal mucosa), the result is a clinically scar-free healing with histological features of almost normal connective tissue; while healing in the skin often ends in a formation of a connective tissue scar with reduced tensile strength, disoriented collagen fibers, and other molecular alterations.[8] Differences in integrin–ECM interactions between these two tissues likely influence the divergent healing outcomes.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

The playing field of wound healing: specialized ECM molecules in the provisional wound matrix and granulation tissue

The ECM is a highly dynamic structure that comprises hundreds of different proteins.[13,14] The interactions between cells and their environment are bidirectional and dynamic—the cells can modulate the structure and composition of ECM, and the ECM, in turn, guides cell morphology and behavior, including proliferation, differentiation, survival, and migration in tissue homeostasis and during wound healing.[1,2] Micro RNAs have been recently shown to provide one mechanism for the cells to control the composition of the ECM and the cell phenotype.[15]

In wounds, keratinocytes and fibroblasts encounter a multifaceted environment of ECM molecules, matrix-degrading enzymes, growth factors, and cytokines that are not present in their normal surroundings.[8,11] The initial plasma-derived proteins, including fibrinogen, fibronectin, and vitronectin form the provisional wound matrix of the blood clot and act as a scaffold for further ECM accumulation.[16–18] In addition, the developing granulation tissue contains ECM proteins that are released or synthesized by the wound cells at the injury site, such as osteopontin, thrombospondins, secreted protein acidic and rich in cysteine (SPARC), tenascins, collagens, and alternatively spliced forms of fibronectin.[8,19–21] These proteins are only transitionally present in wounds, although their expression may continue long after the wound has clinically and histologically healed. The provisional basement membrane that supports keratinocyte migration during re-epithelialization contains extra domain A (EDA) fibronectin, tenascin-C, and laminin-332.[11,22] Studies in knockout mice have provided considerable insight into the roles that ECM molecules play during various phases of wound healing *in vivo* (Table 1).[23,24]

In this section, we briefly focus on ECM molecules that have an important role in the regulation of fibroblast and keratinocyte behavior and functions during wound healing, namely fibronectin, tenascin-C, collagens, and laminin-332.

Fibronectin. Fibronectins are ECM proteins that have a multidomain structure, in which the various domains serve different functions, such as binding to specific integrins and ECM molecules (Fig. 2A).[18,25,26] Plasma fibronectin is produced by hepatocytes and circulates in blood. It becomes incorporated into the fibrin clot during blood clotting process either noncovalently or through covalent crosslinking by transglutaminase (activated factor XIII).

Wound fibroblasts and keratinocytes produce cellular fibronectins that contain variable amounts of alternatively spliced extra domains A and B (EDA and EDB, respectively; Fig. 2A), which are not present in plasma fibronectin.[18] Interestingly, fetal wounds in skin and airway mucosa that heal without scars show no induction of EDA fibronectin expression.[27] Similarly, its expression is induced more transiently in porcine oral mucosal wounds that show minimal scarring than in scar forming skin wounds in the same animals.[28] In addition, EDA fibronectin expression is associated with many fibrotic conditions, suggesting its important involvement in the regulation of fibroblast differentiation into myofibroblasts and matrix production.[18]

Tenascin-C. Tenascins belong to the family of matricellular proteins that regulate cell adhesion and cytokine activation. Other members of this group include thrombospondins and SPARCs.

Table 1. *Effect of deficiency or overexpression of certain extracellular matrix molecules on wound healing in mice*

ECM Molecule	*Animal Model*	*Wound Healing Phenotypes*
Fibrinogen	Knockout	Wound closure not affected but somewhat increased initial bleeding, defects in granulation tissue formation and reduced wound tensile strength, altered pattern of epithelial cell migration, and increased epithelial hyperplasia
Fibronectin	Knockout	Embryonic lethal phenotype
Plasma fibronectin	Hepatocyte-targeted knockout	Normal fibrinogenesis, hemostasis, and wound healing
Fibronectin EDA	Exclusion of EDA domain	Keratinocyte migration normal; blurred border between the new epidermis and granulation tissue; ulceration in the newly formed epidermis; influx of inflammatory cells to ulcerated area
Fibronectin EDA	Constitutive inclusion of EDA domain	Normal wound healing but a striking decrease in the levels of fibronectin in most of the organs
Laminin-332	Knockout of α_3 or γ_2 subunit of laminin-332	No wound healing data due to neonatal lethal phenotype; the animals exhibit epidermal/dermal blistering
Tenascin-C	Knockout	Skin wound re-epithelialization normal; defects in corneal wound re-epithelialization; reduced fibronectin expression in wounds
Vitronectin	Knockout	Re-epithelialization normal but slightly delayed dermal wound healing, decreased angiogenesis, and formation of larger blood vessels
Thrombospondin-1	Overexpression (K14-promoter)	Healing of full-thickness skin wounds was greatly delayed with reduced granulation tissue formation and highly diminished wound angiogenesis
Thrombospondin-2	Knockout	Accelerated wound healing with reduced inflammation and scarring but with irregularly organized and highly vascularized granulation tissue and thickened epithelium, possibly due to elevated levels of MMP-2 and MMP-9
Osteopontin	Knockout	Significantly decreased level of debridement, greater disorganization of matrix, and altered collagen fibrillogenesis with small-diameter collagen fibrils
Osteonectin/SPARC	Knockout	Accelerated wound closure potentially due to decreased granulation tissue collagen content resulting in enhanced granulation tissue contractibility
EMILIN1	Knockout	Accelerated wound closure due to fibroblast and keratinocyte hyperproliferation

The table is adapted from Koivisto *et al.*,[11] with the following additional articles cited: Maclauchlan *et al.*[23] and Danussi *et al.*[24]
ECM, extracellular matrix; EMILIN, elastic microfibril interface–located protein; MMP, matrix metalloproteinase; SPARC, secreted protein acidic and rich in cysteine.

Collectively, these proteins appear to have their main function in reducing fibroblasts migration in the healing wounds, as evidenced by accelerated wound closure in the respective knockout mice (Table 1).[21] Tenascin-C is a large, multi-domain hexameric glycoprotein that is capable of binding a multitude of matrix proteins and receptors (Fig. 2B).[29] In normal oral mucosa (gingiva), it is strongly and constitutively expressed in the subepithelial connective tissue, whereas it is weakly expressed in or absent from healthy skin.[28,30,31] During wound healing, its expression is strongly upregulated in both tissues. Tenascin-C has both adhesive and anti-adhesive functions depending on the cellular context. During wound healing, it can interact with EDA fibronectin and reduce fibroblast and keratinocyte adhesion to it, thus allowing faster cell migration.[32] Tenascin-C can also promote fibroblast migration into fibrin-fibronectin matrix via its fibronectin type III repeats.[33] Low tenascin-C expression may contribute to scarring. Oral mucosal and fetal skin wounds that heal with minimal scarring exhibit early and continuing expression of tenascin-C even after the tissue morphology is normalized, whereas skin wounds that form scars show transient expression, and tenascin-C is, thus, effectively downregulated before remodeling is complete.[28,34] However, its aberrant expression may also be involved in fibrosis, as tenascin-C is highly expressed in scars, keloids, and lung fibrosis; whereas mice lacking its expression are protected from bleomycin-induced lung fibrosis.[35,36] This protection is attributed to reduced accumulation myofibroblasts and impaired transforming growth factor (TGF)-β responsiveness of the tenascin-C null cells.

Collagens

During the active granulation tissue formation in the scarlessly healing human oral mucosal wounds, a number of collagen genes (collagen types I, III, IV, V, VI, and XV) are significantly upregulated as compared with the unwounded tissue.* Almost identical sets of genes continue to be elevated in human and pig hypertrophic scars in the skin,[28,37] suggesting that the expression of these genes relates to both scarless and scar-forming wounds but that they may be ineffectively downregulated in scars. Early wounds contain mainly fibrillar types III and I collagen produced and then organized into fibrils by myofibroblasts that

*Larjava H and Häkkinen L, unpublished gene expression profiling of pig wounds performed in 2006, University of British Columbia.

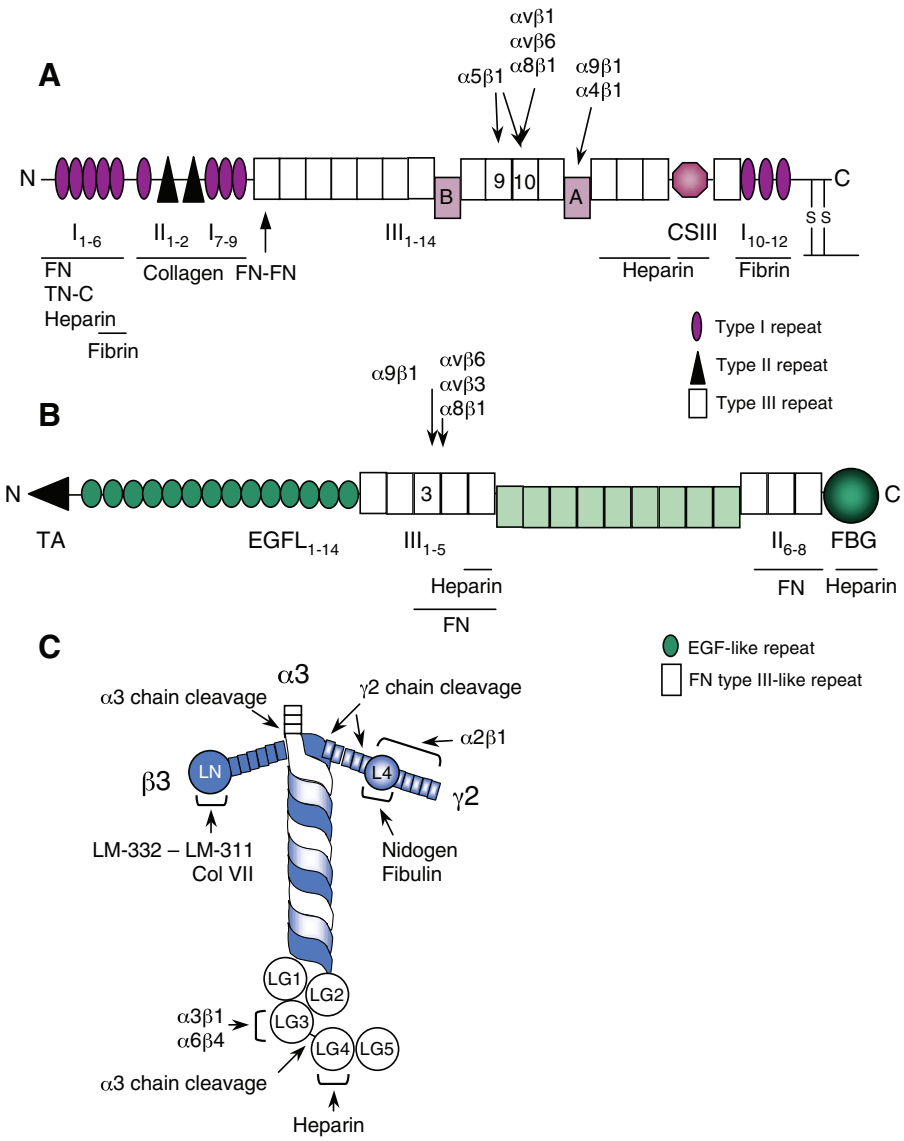

Figure 2. Structural and functional domains in fibronectin (FN), tenascin-C, and laminin-332, including major ECM and keratinocyte and fibroblast integrin binding sites. **(A)** FN consists of two similar subunits that are linked in an antiparallel orientation by two disulphide bridges at their C-termini. It is formed by repeating homologous type I, II, and III units, and it binds to a number of biologically important molecules, including heparin (and heparan sulfate proteoglycans), denatured collagen, fibrin, and tenascin-C (TN-C). FN has three sites of alternative splicing: type III repeats A and B as well as the CSIII segment. The binding site for $\alpha_5\beta_1$, $\alpha_v\beta_1$, $\alpha_8\beta_1$, and $\alpha_v\beta_6$ integrins is located in module III_{10}. In addition, $\alpha_5\beta_1$ integrin interacts with a second site, located in module III_9. Integrins $\alpha_4\beta_1$ and $\alpha_9\beta_1$ bind to module IIIA. FN is present in blood plasma in a soluble, globular form, and its cell-binding sites are unexposed. The cell-binding sites become exposed when it is absorbed to fibrin and polymerizes into insoluble fibrils. **(B)** Three tenascin-C monomers are joined together via their N-terminal tenascin-C assembly (TA) domains to form a trimer. Two trimers are further linked together to form a hexamer. Each arm of mammalian tenascin-C consists of EGF-like repeats (EGFL) that are recognized by EGFR, FN type III-like repeats that contain binding sites for FN and heparin, and a C-terminal fibrinogen globe (FBG), also interacting with heparin. Nine additional type III repeats can be included or excluded by alternative RNA splicing (light green). Binding sites for integrins are located in module III_3. **(C)** Laminin (LM) 332 is a T-shaped molecule consisting of three genetically distinct polypeptide chains, α_3, β_3, and γ_2. The α_3 chain contains five C-terminal globular domains (LG), the β_3 chain an N-terminal globular domain (LN), and the γ_2 chain an interrupting globular domain (L4) in the short arm. Proteolytic cleavage between LG3 and LG4 domains of the α_3 chain results in a functional conversion of laminin-332 from a motility to an adhesion factor. LG3 domain contains the binding site for $\alpha_3\beta_1$ and $\alpha_6\beta_4$ integrins, whereas LG4 includes a heparin/heparan sulfate proteoglycan-binding site. The β_3 and γ_2 chains can also be cleaved. The γ_2 L4 domain contains binding sites for nidogen and fibulin, which aid the incorporation of laminin-332 to the basement membrane. This arm also contains the binding site for $\alpha_2\beta_1$ integrin. The β_3 LN domain contains a binding site for type VII collagen and a laminin-332–laminin-311 interaction site, which facilitate laminin-332 integration to the ECM. Adapted from Larjava *et al.*[25] ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, EGF receptor. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

highly express these collagen types.[28,38] Fibrillogenesis of type I collagen also requires type III and V collagens, fibronectin, and integrins.[39,40] When the granulation tissue matures, active remodeling of collagen fibers will follow, leading to either a normal connective tissue orientation (basket weave) or a scar (parallel orientation).[8]

Laminin-332. Laminins are heterotrimers of α, β, and γ chains. They can be incorporated into the ECM by interactions with other ECM molecules.[41] Laminin-332 ($\alpha_3\beta_3\gamma_2$, formerly known as laminin-5) is essential for the formation of hemidesmosomes and basement membranes, where it interacts with types VII (anchoring fibrils) and XVII collagen (BP180).[41] Mutations to laminin-332 cause junctional epidermolysis bullosa, in which the affected patients suffer severe skin blistering due to the absence or poor development of hemidesmosomes.[42]

Laminin-332 polymerization and proteolytical processing affect its biological functions (Fig. 2C).[22,41,43] For example, activated keratinocytes at the leading edges of wounds express high levels of unprocessed laminin-332 α_3 chains; while in quiescent keratinocytes, these chains are cleaved, which changes laminin-332 function from migratory to adhesive and promotes hemidesmosome formation.[44] Moreover, *in vitro* studies demonstrate that the leading migrating keratinocytes deposit the unprocessed laminin-332 at the rear of the cell, forming a trail of laminin-332 deposits.[41] The laminin-332 β_3 and γ_2 chains can also be processed to promote epithelial cell migration (Fig. 2C).[22,41]

In addition to regulating epithelial cell functions, laminin-332 may also modulate granulation tissue formation, and mutations leading to deletion of the N-terminus of the α_3 chain are associated with laryngo-onycho-cutaneous syndrome that leads to excessive granulation tissue formation in mucosal tissues.[45]

Integrins: cell attachment receptors and mediators of cellular signaling

Composition and extracellular ligand specificities of the integrin heterodimers. Integrins are the main mediators of cell attachment to ECM.[46] All 24 integrin-type adhesion receptors are formed by 1 of the 18 α subunits and 1 of the 8 β subunits, which are bound together in a noncovalent manner (Fig. 3; Table 2).[46–65] Integrins can be divided into four subfamilies based on their ligand specificity and/or phylogenetic comparison of the α subunits (Fig. 3).[66] All multicellular animals have integrin heterodimers that recognize a specific three amino acid motifs, arginine-glycine-aspartic acid (RGD)

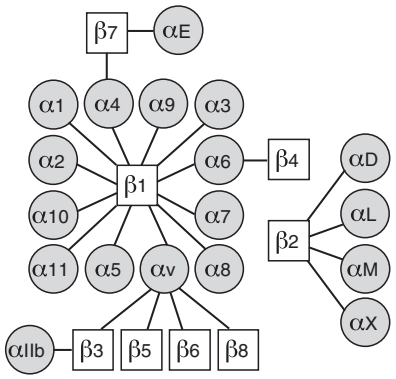

Figure 3. Integrin heterodimers. Schematic presentation of the 24 integrin receptors. Integrins $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_{10}\beta_1$, and $\alpha_{11}\beta_1$: αI domain-containing collagen receptors; $\alpha_5\beta_1$, $\alpha_8\beta_1$, $\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, and $\alpha_{IIb}\beta_3$: RGD-binding integrins; $\alpha_3\beta_1$, $\alpha_6\beta_1$, $\alpha_7\beta_1$, and $\alpha_6\beta_4$: laminin receptors; $\alpha_4\beta_1$, $\alpha_9\beta_1$, and $\alpha_4\beta_7$: $\alpha_4/\alpha_9\beta_1$ integrin family; $\alpha_D\beta_2$, $\alpha_L\beta_2$, $\alpha_M\beta_2$, $\alpha_X\beta_2$, and $\alpha_E\beta_7$: leukocyte integrin subgroup. RGD, arginine-glycine-aspartic acid.

in their extracellular ligands. The vertebrate heterodimers in this subfamily of the integrins are named $\alpha_5\beta_1$, $\alpha_8\beta_1$, $\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, and $\alpha_{IIb}\beta_3$, and their RGD-containing ECM and plasma protein ligands include fibronectin, vitronectin, fibrinogen, and thrombospondins (Table 2). The members of the laminin receptor subfamily, $\alpha_3\beta_1$, $\alpha_6\beta_1$, $\alpha_7\beta_1$, and $\alpha_6\beta_4$ integrins, can mediate cell adhesion to basement membranes in various tissues (Fig. 4A). Integrins $\alpha_4\beta_1$, $\alpha_4\beta_7$, and $\alpha_9\beta_1$ form their own subfamily. They can recognize ECM ligands such as fibronectin, but in an RGD-independent manner. Integrins $\alpha_4\beta_1$ and $\alpha_4\beta_7$ can also bind to counter receptors in other cells, such as vascular cell adhesion molecule. Integrin α subunits with a special inserted (αI) domain or von Willebrand factor type A (αA) domain form the fourth subfamily. Integrin subunits α_1, α_2, α_{10}, and α_{11} combine with the β_1 subunit, and they bind numerous collagen types (Table 2). Integrins $\alpha_D\beta_2$, $\alpha_L\beta_2$, $\alpha_M\beta_2$, $\alpha_X\beta_2$, and $\alpha_E\beta_7$ are expressed in leukocytes, and their ligands include counter receptors such as intercellular adhesion molecules (ICAMs) and plasma proteins, including complement component C3b (Table 2; Fig. 4B).

Integrin participation in embryonic development and distinct biological processes has been extensively studied using knockout and transgenic mouse models.[48,67] In general, integrin heterodimers containing either β_2 or β_7 subunit participate in immunodefence, for example, by recognizing components of the complement system or by mediating leukocyte extravasation.[65,68] The most important task of most other integrins is to anchor cells to tissues. However, these receptors also often participate in other processes, including innate immunity and cell regulation by growth

Table 2. *Integrin expression and function in wound cells*

Integrin	*Wound Cells Expressing*	*Ligands in Wounds*	*Cellular Functions in Wound Healing*	*Wound Phenotypes in Animal Models*
$\alpha_1\beta_1$	ECs, FBLs, monocytes, macrophages, and myofibroblasts	COL I, III, IV, and V, LM-111	Mediates VEGF-driven angiogenesis, negative feedback regulation of collagen synthesis in FBLs	The integrin α_1 null mice exhibit increased collagen gene expression during early granulation tissue development and altered collagen fibril distribution
$\alpha_2\beta_1$	Platelets, KCs, ECs, and FBLs	COLs (types I and III with high affinity), LM-332, TN-C, MMP-1, and CCN1/Cyr6	Mediates KC migration and VEGF-driven angiogenesis, may mediate platelet adhesion to COL, and contribute to collagen polymerization by FBLs	Increased wound angiogenesis in α_2 integrin knockout mice
$\alpha_3\beta_1$	KCs, ECs, and FBLs	LM-332, other LMs	Regulates KC polarization during re-epithelialization, controls angiogenesis and TGF-β1–mediated responses	Integrin α_3 null mice die shortly after birth with skin blisters and disrupted basement membranes; KC-targeted α_3 integrin knockout mice exhibit slightly accelerated or not affected wound closure but impaired wound angiogenesis; retarded re-epithelialization α_3 integrin null mouse skin grafts
$\alpha_4\beta_1$	Leukocytes, FBLs, and ECs	EDA-FN, OPN, several ADAMs, VCAM-1, and EMILIN1	Interaction with EMILIN1 may control FBL proliferation and TGF-β1 processing	Genetic ablation of α_4 integrin causes an embryonic lethal phenotype
$\alpha_5\beta_1$	Platelets, KCs, ECs, FBLs, and leukocytes	FN, CCN2/CTGF, and CCN3/NOV	Promotes KC migration, may be involved in platelet–blood vessel wall interactions	Genetic ablation of α_5 integrin causes an embryonic lethal phenotype
$\alpha_6\beta_1$	Platelets, ECs, leukocytes, and FBLs	LMs, TSPs, CCN1/Cyr6, CCN2/CTGF, and CCN3/NOV	May be involved in platelet–blood vessel wall interactions and angiogenesis; interaction with CCN1/Cyr61 promotes myofibroblast senescence and controls fibrogenesis	Genetic ablation of α_6 integrin causes a neonatal lethal phenotype; endothelial cell-targeted deletion of α_6 integrin increases tumor angiogenesis but reduces postischemic vascular repair—these phenotypes may be partly caused by the loss of $\alpha_6\beta_4$ in these cells as well; no wound healing data available
$\alpha_7\beta_1$	N/A (expressed by muscle cells, vascular smooth muscle cells, and in neurons)	TN-C, LM		
$\alpha_8\beta_1$	Myofibroblasts	FN, VN, TN-C, and latent TGF-β1	May contribute to fibrotic responses	No wound healing data available
$\alpha_9\beta_1$	KCs, FBLs, neutrophils, and ECs	EDA-FN, TN-C, OPN, several ADAMs, EMILIN1, and VEGFs	Regulates KC and FBL growth, neutrophil chemotaxis as well as EC migration and angiogenesis	Reduced keratinocyte proliferation and delayed wound closure in keratinocyte-targeted α_9 integrin knockout mice; impaired formation of granulation tissue in mouse wounds treated with a blocking antibody against α_9 integrin because of reduced adhesion and migration of FBLs
$\alpha_{10}\beta_1$	FBLs?	COLs	May mediate FBL adhesion to collagen	No wound healing data available
$\alpha_{11}\beta_1$	FBLs	COLs	Controls myofibroblast differentiation and may mediate FBL adhesion to collagen and contribute to collagen reorganization	No wound healing data available
$\alpha_v\beta_1$	KCs, ECs	FN, VN, OPN, and latent TGF-β1	Mediates KC adhesion during re-epithelialization	Difficult to address the specific function of this receptor due to the wide array of α_v and β_1 integrins

(*continued*)

Table 2. *(continued)*

Integrin	*Wound Cells Expressing*	*Ligands in Wounds*	*Cellular Functions in Wound Healing*	*Wound Phenotypes in Animal Models*
$\alpha_v\beta_3$	ECs, platelets, FBLs, and macrophages	Fibrin(ogen),TN-C, OPN, latent TGF-β1, CCN1/Cyr6, CCN2/CTGF, and CCN3/NOV	Required for neoangiogenesis, modulates fibrin network structure and stability, mediates EC adhesion to CCN1/Cyr6 and CCN2/CTGF, EC survival, pericyte retention in blood vessels, and FBL proliferation	Mice lacking β_3 integrin subunit show enhanced re-epithelialization but reduced KC proliferation due to increased TGF-β1 and enhanced dermal fibroblast infiltration into the wound. They also exhibit reduced macrophage numbers in wounds and increased angiogenesis in late wound healing. Peptide antagonists of $\alpha_v\beta_3$ integrin reduce granulation tissue formation and wound-induced angiogenesis in porcine wounds
$\alpha_v\beta_5$	ECs, FBLs, and skin KCs	VN, OPN, latent TGF-β1, CCN1/Cyr6, CCN3/NOV, VEGF	May participate in FBL transformation to myofibroblasts, interaction with CCN1/Cyr61 mediates FBL migration	Wound healing is normal in β_5 integrin knockout mice
$\alpha_v\beta_6$	KCs	FN, VN, TN-C, latent TGF-β1 and -β3, and chromogranin A	Regulates inflammation and KC proliferation, contributes to basement membrane and granulation tissue remodeling	Re-epithelialization is normal in β_6 integrin knockout mice if not challenged by age or diabetes; mice with keratinocyte-targeted β_6 integrin overexpression are susceptible to chronic, nonhealing wounds but show faster re-epithelialization than wild-type mice after being challenged by a glucocorticoid treatment
$\alpha_v\beta_8$	Dentritic cells, FBLs, and ECs	LM-111, COL IV, FN, and latent TGF-β1	May regulate inflammation through TGF-β activation	No wound healing data available
$\alpha_6\beta_4$	KCs, ECs	LM-332, other LMs	Promotes KC adhesion, migration and proliferation, and EGFR signaling; regulates angiogenesis in ECs	Genetic ablation of β_4 integrin causes a neonatal lethal phenotype with severe epidermal blistering; deletion of β_4 integrin intracellular signaling domain caused decelerated wound re-epithelialization and reduced keratinocyte migration
$\alpha_{IIb}\beta_3$	Platelets	Fibrin(ogen), FN, COL, VWF, CCN1/Cyr6, and CCN2/CTGF	Mediates platelet aggregation in clot formation, modulates fibrin network structure and stability	An antagonist of $\alpha_{IIb}\beta_3$ integrin has an antithrombotic effect in mice
$\alpha_4\beta_7$	Leukocytes, dentritic cells	OPN, VCAM,	Involved in leukocyte extravasation	Impaired immune response in β_7 integrin knockout mice due to defective T-cell trafficking, no wound healing data available
$\alpha_E\beta_7$	T-lymphocytes, dentritic cells	E-cadherin	Mediates leukocyte extravasation	Inflammatory skin lesions in α_E integrin knockout mice, no wound healing data available
$\alpha_L\beta_2$ (LFA-1)	All leucocytes	Several ICAMs, JAM-1, and lumican	Mediates leukocyte extravasation across the endothelium	No wound healing data available
$\alpha_M\beta_2$ (Mac-1)	Monocytes, macrophages, NK, neutrophils, and T-cells	Fibrin(ogen), several ICAMs, heparin, plasminogen, FN, LMs, COL I, uPAR, CCN1/Cyr6, CCN2/CTGF, and others	Involved in leukocyte extravasation across the endothelium; promotes fibrinolysis and clearance of fibrin clots by monocytes and neutrophils in complex with uPAR and its ligand uPA	Attenuation of granulation tissue deposition and wound re-epithelialization in α_M integrin knockout mice
$\alpha_X\beta_2$	Monocytes, macrophages, dentritic cells, and NK	Fibrin(ogen), several ICAMs, COL I, heparin, and OPN	Involved in leukocyte extravasation	No wound healing data available
$\alpha_D\beta_2$	Macrophages, eosinophils	ICAM-3, VCAM-1, and CCN1/Cyr6	Involved in leukocyte extravasation	No wound healing data available

The data is consolidated from the following articles: Häkkinen *et al.*,[8] Koivisto *et al.*,[11] Senger and Davis,[12] Gardner *et al.*,[47] Bouvard *et al.*,[48] Grüner *et al.*,[49] Reynolds *et al.*,[50] AlDahlawi *et al.*,[51] Grenache *et al.*,[52] Sisco *et al.*,[53] Blue *et al.*,[54] Mitchell *et al.*,[55] Nieswandt *et al.*,[56] Germain *et al.*,[57] Jacobsen *et al.*,[58] Nakayama *et al.*,[59] Chen and Lau,[60] Oommen *et al.*,[61] Worthington *et al.*,[62] Bouvard *et al.*,[63] Høye *et al.*,[64] and Tan.[65]

ADAM, a disintegrin and metalloproteinase; CCN, Cyr61-CTGF-Nov; COL, collagen; CT, connective tissue; EDA, extra domain A; EC, endothelial cell; EGFR, epidermal growth factor receptor; FBL, fibroblast; FN, fibronectin; ICAM, intercellular adhesion molecule; KC, keratinocyte; LM, laminin; NK, natural killer cell; OPN, osteopontin; TGF, transforming growth factor; TN, tenascin; TSP, thrombospondin; uPAR, urokinase-type plasminogen activator receptor; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; VN, vitronectin; VWF, von Willebrand factor.

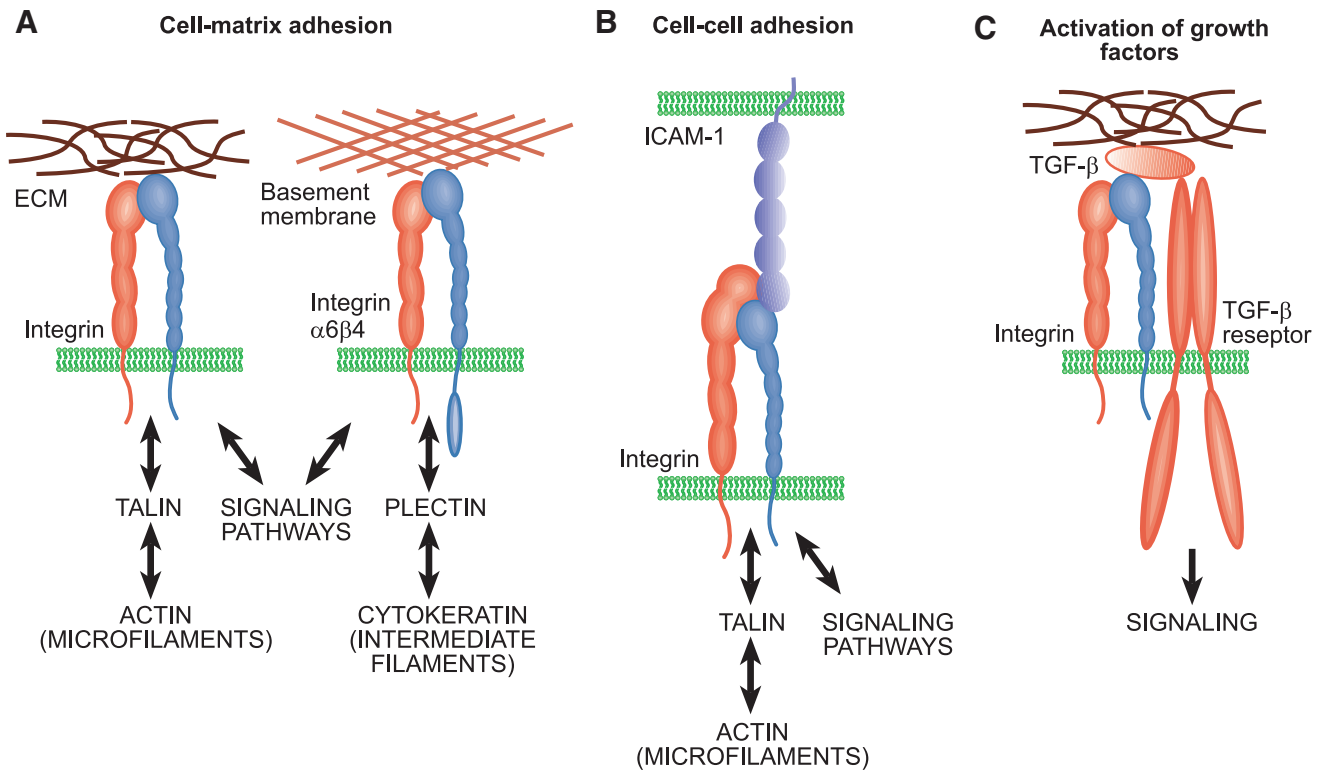

Figure 4. Basic functions of integrins. **(A)** Integrins mediate cell adhesion to ECM and form adhesion plaques and intracellular complexes with cytoskeletal and signaling proteins. Most integrins are connected to actin microfilaments, whereas hemidesmosomal $\alpha_6\beta_4$ integrin is linked to cytokeratins via plectin protein. **(B)** Leukocyte integrins can mediate cell–cell adhesion. **(C)** Integrins also have numerous other functions, such as binding to growth factors. For example, integrins $\alpha_v\beta_6$ and $\alpha_v\beta_8$ are critical for *in vivo* activation of TGF-β1. TGF, transforming growth factor. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

factors. For example, the collagen receptor $\alpha_2\beta_1$ integrin can also recognize members of the collectin family, namely C1q complement protein, mannose-binding lectin, and surfactant protein A.[69] The same receptor can also bind to matrix metalloproteinase-1 (MMP-1; collagenase-1) to influence matrix remodeling.[70] Furthermore, it can promote cell locomotion. Another example of the specialized functions of the integrins is the binding and *in vivo* activation of the latent TGF-β by the fibronectin receptor integrins $\alpha_v\beta_6$ and $\alpha_v\beta_8$ (Fig. 4C).[62,71] Many other integrins can recognize various growth factors and act as assisting or enabling receptors for them.[72] In addition to chemical signals, the integrin-based adhesion sites also mediate the effects of mechanical stress from the ECM.[73]

Integrins are bidirectional signaling molecules. Integrins mediate two-directional signaling across the plasma membrane—extracellular ligand binding to integrin promotes outside-in signaling, whereas binding of intracellular signalling molecules (*e.g.,* talin) to the cytoplasmic tail of an integrin β subunit can initiate integrin inside-out signaling. Recent development has revealed the structural basis of the integrin-mediated activation of cellular signaling pathways.[74,75] At the molecular level, the difference between an inactive and a fully activated receptor depends on a conformational change from a bent to an extended form with the integrin standing with the legs of the α and β subunits apart from each other.

In inside-out integrin activation, the relatively short intracellular parts of the integrin β subunits seem to play a critical role, as they contain binding sites for many cytoskeletal and signaling proteins.[76,77] Talin, an actin-binding protein, can break the bonds between the α and β subunits and, consequently, induce an extension of the extracellular part, and it seems essential for integrin activation and for the formation of matrix adhesion sites or adhesion plaques (Figs. 4A and 5).[77] The three members of the kindlin family can also bind to the intracellular tails of integrin β subunits and activate the receptors.[78] Tyrosine phosphorylation is fundamentally linked with the regulation of integrin activity, and protein tyrosine kinases, such as focal adhesion kinase (FAK), p130Cas, and Src may

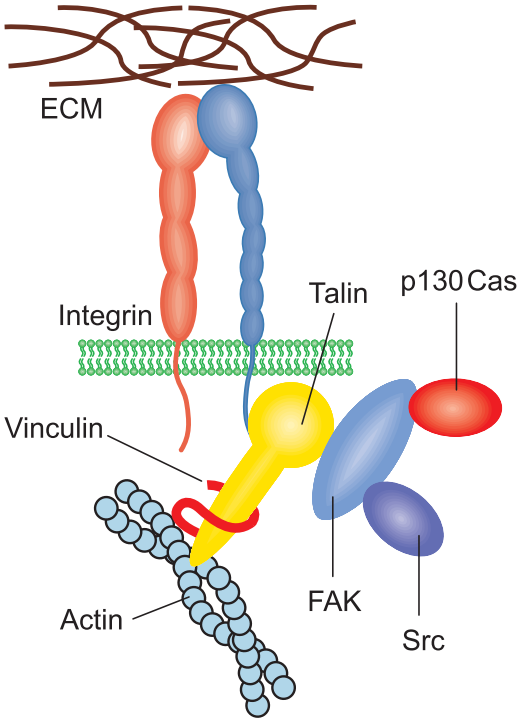

Figure 5. Cytoplasmic integrin signaling complexes. Binding of talin to the cytoplasmic tail of integrin β subunit causes a conformational change in the receptor that allows for binding of intracellular signaling molecules, such as tyrosine kinases FAK, Src, and p130Cas as well as other structural proteins, such as vinculin, which mediate integrin interaction with the actin cytoskeleton. These intracellular protein complexes allow for the translation of the integrin-ECM interaction to a change in cell shape and behavior (*e.g.,* motility). FAK, focal adhesion kinase. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

initiate signaling cascades (Fig. 5).[79] To date, the integrin adhesome network is reported to include at least 180 different scaffold and signaling proteins that can form more than 700 direct protein–protein interactions.[80] Intracellular proteins that mediate integrin binding to actin microfilaments include vinculin, paxillin, tensin, filamin, and α-actinin; whereas signaling proteins such as RhoA family GTPases regulate reorganization of actin microfilaments in the adhesion plaques. In epithelial hemidesmosomes, $\alpha_6\beta_4$ integrins are connected to intermediate filaments formed by cytokeratins (Fig. 4B).[81] In these structures, plectin is a critical protein that is responsible for the β_4 integrin–keratin interaction. Integrins also have links to microtubules. A pseudokinase/adaptor protein integrin-linked kinase (ILK) is essential for this interaction.[82]

In outside-in activation, ligand binding to an activated receptor leads to further conformational changes. Fibronectin and laminins attach to the integrin βI domain (also called βA domain) and trigger movement of the leg of the β subunit apart from that of the α subunit. In leukocyte and collagen receptor integrins, ligands bind to the αI domain (αA domain), inducing a conformational change first in this domain and, consequently, in the β subunit. In both cases, the separation of integrin legs promotes the binding of signaling proteins to integrin cytoplasmic tails to initiate cellular signaling.

In addition to the conformational changes, receptor clustering plays a major role in the regulation of integrin avidity and signaling. Many extracellular ligands are multivalent to promote receptor clustering, and they may also contain binding motifs with different affinity or integrin subtype specificity.

Integrins collaborate with other cell surface receptors and molecules to regulate cellular signaling. Many integrins associate functionally with growth factor receptors and regulate their number and stability on the cell surface by influencing their endocytosis and recycling.[71,72] In addition, other cell surface receptors (*e.g.,* urokinase-type plasminogen activator receptor [uPAR]), transmembrane adaptor proteins such as caveolin-1, or members of the transmembrane-4 superfamily (also called tetraspanins or tetraspans) and membrane lipids (gangliosides) modulate integrin function and cellular signaling.[83–86] These binding partners may alter integrin conformation and affinity directly, modulate the avidity of integrins by regulating their clustering, assist in recruiting signaling molecules to cell adhesion sites, regulate receptor endocytosis, or facilitate cell migration through tissues. Integrins also cross talk with cadherins via reactive oxygen species (ROS)-mediated signaling to coordinate cell–matrix and cell–cell adhesions during tissue remodeling.[87]

Integrin-mediated cell migration

Cell movement involves focalized cell–matrix interactions. Integrins play a central role in cell migration, where cell adhesion contacts function as signaling centers, and the linkages between ECM and actin cytoskeleton allow adhesion sites to serve as traction sites for cell movement.[88,89] Directional cell migration involves coordinated assembly of new adhesions at the front of the migrating cell into cellular protrusions and dissolution of adhesion contacts at their rear end. This process also involves integrin endocytosis and trafficking. Molecules that have been recently shown to regulate front–rear polarity in migrating cells include the small GTPases Rac1 and RhoG, ILK, Engulfment and Cell Motility-2, phosphatidylinositol-4,5-biphosphate, actinin-4, and syndecan-4.[90–93] The maximum cell migration

speed is facilitated by medium strength of cell adhesion—weak adhesion does not provide sufficient traction for cell movement, whereas too strong an adhesion will render the cells stationary.[88] The substratum ligand level, the level of integrin expression in cells and integrin ligand-binding affinity contribute to the strength of cell adhesion. Therefore, the strength and turnover rates of cell attachments to the extracellular environment determine which cell shapes and forces are being generated during migration. For example, fibroblasts exhibit relatively slow invasive migration into the loose provisional wound matrix, whereas keratinocytes migrate relatively fast.[88] Cells also have ways to modify the strength of their cellular adhesions to promote more efficient movement, for example, by focalized matrix degradation, by utilizing several low-to-moderate affinity integrins in concert or by expressing anti-adhesive ECM molecules underneath themselves.

Integrins regulate many aspects of wound healing, including cellular crosstalk. During wound healing, cells interact with the wound ECM molecules with their integrin receptors. Concomitantly, many integrins are functionally activated or their expression is either induced or upregulated in response to their contact with these ECM molecules. As evidenced earlier, many integrins can bind various ECM molecules and, conversely, many ECM molecules are recognized by several different integrin heterodimers. Due to their overlapping specificities and functional compensation, many integrin knockout animals display surprisingly mild wound healing phenotypes (Table 2).

There is extensive interaction between the different types of wound cells. ECM proteins and integrins play key roles in these interactions.[94] For example, knocking out neutrophil and monocyte integrin $\alpha_M\beta_2$ delays skin wound re-epithelialization in mice; whereas elimination of $\alpha_v\beta_3$ integrin, which is expressed in wounds by platelets, endothelial cells, macrophages, and fibroblasts, accelerates it (Table 2).[50,53] The formation of a new basement membrane zone is an example where interaction between keratinocytes and fibroblasts is crucially involved, as the basement membrane components are produced jointly by the two types of cells.[94] Similarly, endothelial cells and pericytes collaborate in the assembly of vascular basement membranes during wound angiogenesis.[95] Keratinocytes also cross talk with endothelial cells via integrins. For example, epidermal deletion of the α_3 integrin subunit leads to impaired wound angiogenesis due to decreased expression of the pro-angiogenic mitogen-related protein-3 by the keratinocytes.[55] Moreover, fibroblasts acquire the myofibroblast phenotype (see below) under the control of keratinocytes.[94]

Next, we will focus on integrin expression and functions during re-epithelialization and granulation tissue formation. Integrin functions in other wound cells (*e.g.,* platelets or infiltrating macrophages) have been comprehensively reviewed elsewhere (Table 2).[56,65,68] Much of the data presented are drawn from reports on human and animal skin wound healing and from experiments with cultured cells. Information about integrin functions during oral mucosal healing is also presented when available. It also needs to be kept in mind that, in addition to integrins, several non-integrin adhesions regulate cell functions.[1]

Integrins control epithelial cell migration and proliferation during re-epithelialization

Mechanisms of re-epithelialization. After wounding, keratinocytes are exposed to a new pericellular environment that consists of proteins of the underlying connective tissue at the wound edge and the plasma-derived proteins present in the blood clot (Fig. 6A).[11] Their contact with these pro-migratory ECM molecules, in collaboration with other factors that influence wound re-epithelialization, such as proteinases, which cleave matrix molecules and release matrix-bound growth factors, growth factors, and cytokines (such as the members of the epidermal growth factor [EGF] family, TGF-β1, and fibroblast growth factors [FGFs]) synthesized by other wound cells and by keratinocytes themselves, loss of cell–cell contacts as well as changes in the direction of the intraepithelial electrical field, and the concentrations of Mg^{2+} and Ca^{2+} in the wound fluid, promote keratinocyte transition to a migratory phenotype.[11] The autocrine expression of heparin-binding EGF-like growth factor by the keratinocytes is, however, needed for the sustenance of the re-epithelialization process (Fig. 6A).[96]

The activated keratinocytes at the wound edge dissolve their hemidesmosomal contacts with the basement membrane, and their morphology becomes flattened and elongated with long lamellipodia that extend into the wound provisional matrix (Fig. 6A). Unlike epidermal keratinocytes that migrate under the blood clot, oral mucosal keratinocytes invade into and migrate through it (Fig. 7A, B).[97] The leading keratinocytes need to proteolytically dissolve and remodel the fibrin barrier ahead of them via focalized activation of plasmin by the collaboration of integrins and uPAR on the keratinocyte cell

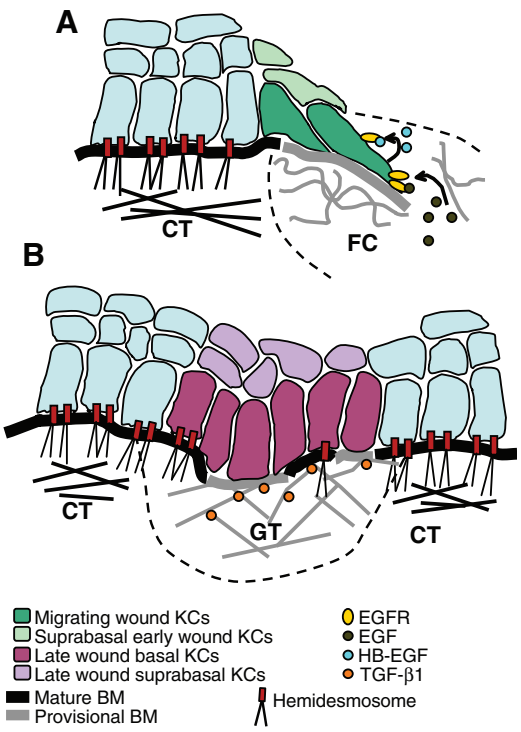

Figure 6. A schematic presentation of KC integrin expression and ECM molecule distribution during human oral mucosal healing. **(A)** The contact with the ECM molecules and pro-migratory growth factors (*e.g.,* EGF) present in the wound clot activate the wound edge basal KCs. They dissolve their hemidesmosomal contacts with the BM and extend into the wound clot. As they migrate, wound KCs interact with the provisional BM they deposit underneath themselves. In this provisional matrix, they interact with EDA FN via $\alpha_5\beta_1$, $\alpha_9\beta_1$, and $\alpha_v\beta_1$ integrins, with TN-C via $\alpha_9\beta_1$ integrin and with laminin-332 via $\alpha_2\beta_1$, $\alpha_3\beta_1$, and $\alpha_6\beta_4$ integrins. KC migration is sustained by their autocrine expression of HB-EGF. **(B)** After wound edges have joined, BM is regenerated, and hemidesmosome re-assembly is initiated. At this point, $\alpha_v\beta_6$ integrin expression is induced in the wound KCs. It potentially interacts with and activates latent, ECM-bound TGF-β1 to regulate KC proliferation, inflammation, and granulation tissue remodeling. Migrating wound KCs express $\alpha_2\beta_1$, $\alpha_3\beta_1$, $\alpha_5\beta_1$, $\alpha_9\beta_1$, $\alpha_v\beta_1$, and $\alpha_6\beta_4$ integrins; suprabasal early-wound KCs express β_1 integrins; late-wound basal KCs express mainly $\alpha_2\beta_1$, $\alpha_3\beta_1$, $\alpha_9\beta_1$, $\alpha_v\beta_6$, and $\alpha_6\beta_4$ integrins, whereas the expression of $\alpha_5\beta_1$ and $\alpha_v\beta_1$ integrins is downregulated; late wound suprabasal KCs express $\alpha_v\beta_6$ integrin. Mature BM consists mainly of laminin-332, other laminins, collagen types IV and VII, and tenascin-C; provisional BM consists mainly of laminin-332, EDA FN, and tenascin-C. Connective tissue (CT) contains type I collagen, other collagens, and FN. Wound clot (FC) contains fibrin, FN, and vitronectin. Granulation tissue (GT) contains EDA and EDB FNs, collagen types I and III, other collagens, tenascin-C, fibrin, vitronectin. KC, keratinocyte; BM, basement membrane; EDA/B, extra domain A/B; HB-EGF, heparin-binding EGF-like growth factor. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

surface to be able to migrate into the wound clot.[98] In re-epithelialization, the keratinocytes move as a sheet and maintain some of their cell–cell connections, but the exact mechanism of their migration has not yet been conclusively established (Fig. 7A).[11,99]

Keratinocytes adapt to the wound environment via changes in their integrin expression and localization

In healthy skin and oral mucosa, the basal epithelial cells express mainly $\alpha_3\beta_1$, $\alpha_2\beta_1$, $\alpha_9\beta_1$, and $\alpha_6\beta_4$ integrins, which anchor the cells to the underlying basement membrane and maintain the normal epithelial proliferation and differentiation patterns as well as the innate epithelial immune system, with additional weak expression of $\alpha_5\beta_1$ and $\alpha_v\beta_5$ integrins.[11,100] As an adaptation to the new extracellular environment in the wound as well as to the provisional basement membrane the keratinocytes assemble underneath themselves against the provisional wound matrix, there is a change in the expression levels and/or localization of the existing keratinocyte integrins and an induction of fibronectin-recognizing $\alpha_5\beta_1$, $\alpha_v\beta_1$, and $\alpha_v\beta_6$ integrins.[11] Expression of $\alpha_v\beta_5$ integrin in the migrating keratinocytes may depend on the severity of the trauma, as it is expressed in deep human and porcine excisional skin wounds, but not in smaller incisional human skin or oral mucosal wounds.[101,102] For optimal motility on the wound composite matrix, keratinocytes seem to utilize several intermediate strength integrin–matrix interactions in cooperation. The strength of their cell adhesion may be regulated by focalized digestion of strong cell adhesion ligands, by assembly of matrices with reduced adhesiveness, by reduction of the strength of integrin affinity through cellular signaling, and by robust expression of low-affinity integrins.

Integrins guide keratinocyte migration directionality during re-epithelialization. Integrins are involved in the guidance of the migration directionality of wound edge keratinocytes. Integrin $\alpha_2\beta_1$ binding to fibrillar dermal collagen at the wound edge and in the granulation tissue with high affinity leads to induction of MMP-1 expression and focalized denaturation of the collagen matrix.[103] Keratinocytes do not express any known receptors for denatured collagen, but it can bind other pro-migratory ECM molecules, such as fibronectin, and this process may help regulate the directionality of keratinocyte migration in wounds.[103] Integrin $\alpha_6\beta_4$ regulates the migratory behavior of keratinocytes by determining laminin-332 organization underneath the epithelial front, whereas $\alpha_3\beta_1$ integrin may help in maintaining keratinocyte migration directionality by binding to the laminin-332 that is newly deposited on the wound bed at the rear of the cell, thus regulating their polarization, adhesion, and migration velocity during re-epithelialization.[104,105]

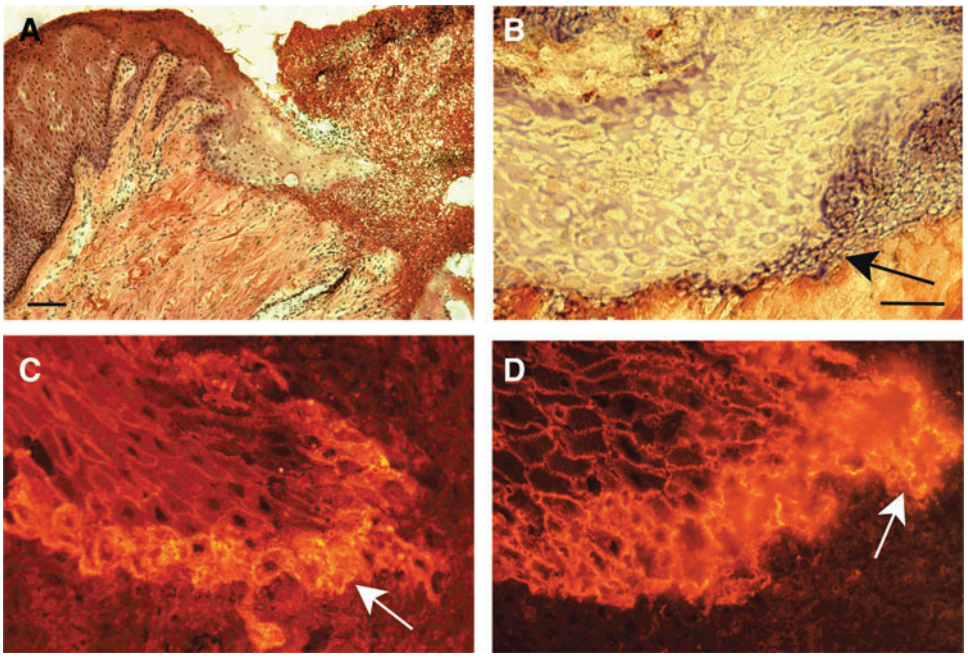

Figure 7. Active re-epithelialization of a 3-day-old human palatal mucosal wound. **(A)** Epithelial keratinocytes migrate into the wound provisional matrix (HE staining). Scale bar: 200 μm. **(B)** Higher magnification image illustrating fibrin (arrow) between the migrating cells and the CT collagen (Mallory's phosphotungstic acid hematoxylin staining). Scale bar: 50 μm. **(C)** High expression of $\alpha_6\beta_4$ integrin at the leading keratinocytes (indirect immunofluorescence image). **(D)** High expression of $\alpha_3\beta_1$ integrin at the leading keratinocytes (indirect immunofluorescence image). See Larjava *et al.* for experimental procedures.[97] To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

Pro-migratory signaling by $\alpha_6\beta_4$ integrin is needed for keratinocyte migration. Chemotactic factors (*e.g.,* EGF) promote the mobilization of $\alpha_6\beta_4$ integrin from hemidesmosomes to the keratinocyte protrusions by increasing the phosphorylation of the β_4 integrin cytoplasmic domain (Fig. 7C).[106,107] Signaling through this receptor is required for normal re-epithelialization (Table 2). Recently, $\alpha_6\beta_4$ integrin was shown to complex with C4.4A (a structural homologue of uPAR), MMP-14, and disintegrin-metalloproteinase TACE to promote keratinocyte migration on laminin-332, possibly through focalized laminin-332 degradation.[108] In addition, it may regulate the expression of $\alpha_2\beta_1$ and $\alpha_3\beta_1$ integrins in keratinocytes.[109]

Integrins of the β_1 family are essential for wound re-epithelialization. The expression of β_1 integrins is strongly upregulated after wounding in the wound-edge keratinocytes and in several suprabasal keratinocyte layers, and they are critical for proper re-epithelialization (Fig. 6A).[110] Recently, it was shown that adaptor protein 4.1R regulates the expression of β_1 integrins in wound keratinocytes, and its loss results in defective re-epithelialization.[111] Wounding causes an increase in the expression of $\alpha_2\beta_1$, $\alpha_3\beta_1$, and $\alpha_9\beta_1$ integrins as well as their relocation onto the basal cell membrane of the basal keratinocytes and an induction of $\alpha_v\beta_1$ and $\alpha_5\beta_1$ integrin expression (Fig. 6A).[25] The importance of these individual β_1 integrins for re-epithelialization is not yet completely understood. For example, $\alpha_3\beta_1$ integrin, which is upregulated in migrating epithelial front in wounds (Fig. 6D), has been reported to either promote or inhibit keratinocyte migration and re-epithelialization depending on the experimental model both *in vitro* and *in vivo* (Table 2). β_1 integrins can also modify each other's ligand binding. For example, $\alpha_3\beta_1$ integrin is a trans-dominant inhibitor of $\alpha_2\beta_1$ and $\alpha_5\beta_1$ integrins, and it can moderate their binding affinity toward collagen and fibronectin, respectively, during re-epithelialization.[112]

Fibronectin receptors $\alpha_5\beta_1$ and $\alpha_v\beta_1$ are induced in the migrating wound keratinocytes (Fig. 6A). Unlike $\alpha_5\beta_1$ integrin, which is required for keratinocyte migration and fibronectin matrix assembly, $\alpha_v\beta_1$ integrin is a low-affinity fibronectin receptor that only weakly supports keratinocyte migration.[113] It may, thus, facilitate keratinocyte migration on the underlying EDA fibronectin during re-epithelialization by supporting cell attachment without decelerating the migration speed. In addition, deposition of tenascin-C underneath the migrating epithelium reduces the affinity of $\alpha_5\beta_1$ integrin toward fibronectin to facilitate keratinocyte

migration.[32] Migrating keratinocytes also express low levels of $\alpha_v\beta_6$ integrin in the re-epithelializing oral mucosal and skin wounds, where it co-localizes with tenascin-C and EDA fibronectin, but its main role comes later in the wound healing.

Integrins regulate keratinocyte proliferation in wounds. While migrating wound keratinocytes do not divide, the basal keratinocytes adjacent to the wound edge start proliferating 48–72 h after the injury to supply more migratory cells to the wound, and these cells may be amended by a putative keratinocyte stem cell population that is localized in the basal keratinocyte layer against the connective tissue papilla area in oral mucosal epithelium and in interfollicular epidermis in skin.[114–116] In addition, epidermal stem cells residing in hair follicle bulges and sebaceous glands contribute to skin re-epithelialization.[116] Apart from mediating keratinocyte migration, integrins also influence their proliferation during re-epithelialization. Integrin $\alpha_9\beta_1$ seems essential for keratinocyte proliferation at the wound edge, as mice with α_9 integrin-deficient keratinocytes exhibit retarded wound re-epithelialization due to reduced proliferation of keratinocytes (Table 2). In addition to tenascin-C and EDA fibronectin, $\alpha_9\beta_1$ integrin was recently shown to interact with another ECM component, elastic microfibril interface–located protein 1 (EMILIN1), to regulate keratinocyte proliferation.[24] The interaction of $\alpha_5\beta_1$ integrin with fibronectin may also contribute to keratinocyte proliferation in addition to promoting their adhesion and motility on this matrix.[117]

Epithelial $\alpha_v\beta_6$ integrin regulates inflammation and granulation tissue remodeling. When the migrating epithelial fronts originating from the wound edges have joined and cover the wound surface, β_1 integrin expression is downregulated, and $\alpha_6\beta_4$ integrin binding to laminin-332 is restored.[25,43] New hemidesmosomes start forming along the wound epithelium, and they function as nucleation sites for the basement membrane restorations (Fig. 6B).[44] During this later phase of wound healing, $\alpha_v\beta_6$ integrin expression is significantly upregulated in the basal and several suprabasal keratinocyte layers (Fig. 6B).[102] It may mediate TGF-β1 activation and regulate ECM deposition in the granulation tissue (Fig. 8),[62] as its expression coincides with the peak expression and activity of this cytokine.[118] In addition, $\alpha_v\beta_6$ integrin may

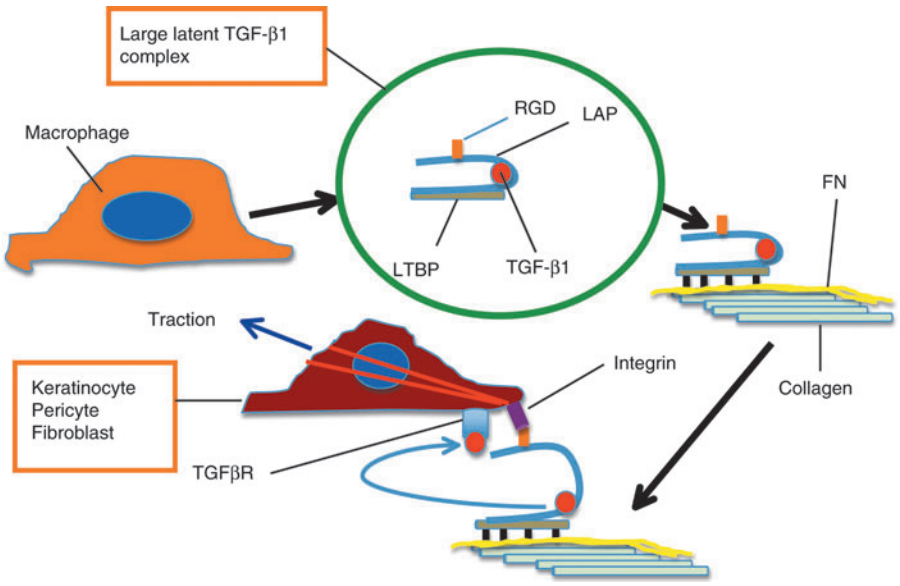

Figure 8. Schematic presentation illustrating how integrins could activate latent TGF-β1 during wound healing. In wounds, macrophages are the main source of TGF-β1, although other cells produce it as well. TGF-β1 is produced in a latent form, in which active TGF-β1 (red circle) is confined inside latency-associated peptide (LAP) that renders it inactive. LAP contains the RGD recognition signal for integrins. LAP further binds latent TGF-β1-binding protein (LTBP) to create a "large latent complex" that subsequently binds to ECM, specifically to FN. Target cells with LAP RGD-recognizing integrins (keratinocytes with $\alpha v\beta 6$ integrin and fibroblasts with $\alpha v\beta 5$ integrin) attach to the large complex, create a tractional force with their cytoskeleton (red actin filaments), and pull, leading to a conformational change in the complex and release of the active TGF-β1 that can now bind to its receptor complex (TGFβR). Active TGF-β1 signals via smad proteins and stimulate keratinocyte migration and ECM production but inhibit their proliferation. In pericytes and fibroblasts, active TGF-β1 stimulates cell differentiation to myofibroblasts and their ECM production. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

have other functions, such as regulation of keratinocyte proliferation and inflammation as well as remodeling of the basement membrane zone and removal of the fibrin provisional matrix during late wound healing.[11,119]

Fibroblast integrins mediate cell migration as well as granulation tissue formation and remodeling

Connective tissue is repaired by fibroblasts or progenitor cells (pericytes and other mesenchymal stem cells) that are activated by serum and other factors (*e.g.,* TGF-β1, platelet-derived growth factor [PDGF], and FGF-2) that are released from platelets and by other wound cells, such as macrophages and keratinocytes.[8] Additional activating signals include the disruption of cell–cell connections, changes in oxygen tension, exposure to new ECM molecules, and changes in mechanical tension in the tissue itself.[8,120–122] In addition, the circulating fibroblast-like cells (fibrocytes) may serve as important precursor cells to pericytes in wound healing.[123] Connective tissue cell activation extends far from the wound edge, as evidenced by localization of the induction of fibroblast activating protein (FAP or seprase) expression at cells distant from the wound edge.[124]

Activated fibroblasts and pericytes migrate from the adjacent subepithelial connective tissue and blood vessels, respectively, to the wound bed where they differentiate into myofibroblasts, synthesize the granulation tissue ECM, and remodel it to either normal or scar tissue.[8] Cytokines, such as TGF-β1, PDGF, and Cyr61-CTGF-Nov (CCN)2/connective tissue growth factor (CTGF), that are secreted by platelets and macrophages are important for pericyte and connective tissue fibroblast differentiation into myofibroblasts (Fig. 9). In addition, their differentiation depends on the presence of EDA fibronectin and mechanical tension experienced by the cells from the ECM through integrin-mediated signaling (Fig. 9).[125]

Integrins are required for fibroblast infiltration into the wound clot. Normal fibroblasts and granulation tissue fibroblasts (mixture of fibroblasts and myofibroblasts) express a large repertoire of integrins, including $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_3\beta_1$, $\alpha_5\beta_1$, $\alpha_{11}\beta_1$, $\alpha_v\beta_1$, $\alpha_v\beta_3$, and $\alpha_v\beta_5$, that the cells can use for binding to a variety of ECM molecules such as collagens, fibronectins, other blood clot components, CCN2/CTGF, and others (Table 2).[8] However, many individual integrins are dispensable for normal connective tissue healing at least in the mouse (Table 2), although they

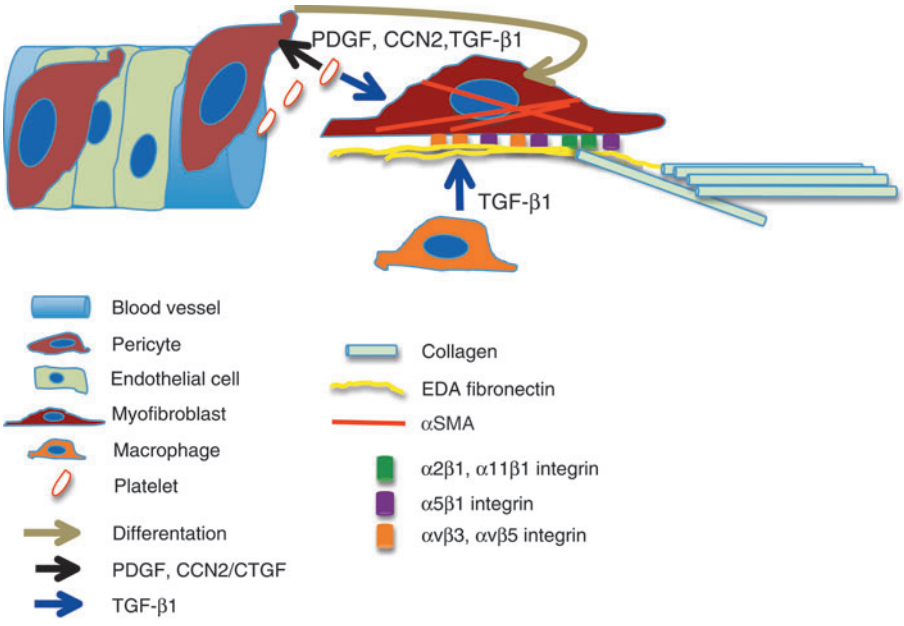

Figure 9. A simplified illustration depicting how pericytes differentiate to matrix-producing myofibroblasts. Chemotactic PDGF, TGF-β1, and CCN2/CTGF signaling by platelets and macrophages causes the pericytes to detach from the vessel wall and produce EDA FN and collagen. Full differentiation of pericytes into myofibroblasts, evidenced by αSMA expression, depends on three essential elements, namely TGF-β1, EDA FN, and tension that can be created in the matrix produced by the pericytes. Myofibroblasts interact with EDA FN via $\alpha_5\beta_1$, $\alpha_v\beta_3$, and $\alpha_v\beta_5$ integrins and with collagen via $\alpha_2\beta_1$ and $\alpha_{11}\beta_1$ integrins. Latent TGF-β1 complex is bound into the FN matrix and possibly activated via $\alpha_v\beta_5$ integrin and by other mechanisms. Whether the wound heals scarless, with scars, or becomes fibrotic depends on both the presence of myofibroblasts and macrophage-derived TGF-β1. αSMA, alpha–smooth muscle actin; CCN, Cyr61-CTGF-Nov; CTGF, connective tissue growth factor. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

appear to have specific functions in cultured fibroblasts. This may be due to compensatory mechanisms by other integrins with overlapping functions. Due to significant differences between murine and human wound healing, the consequences of integrin deficiencies in human beings may be more significant.

Fibroblasts express many β_1 integrins. Of these, it can be speculated that $\alpha_5\beta_1$ integrin plays the most critical role *in vivo* during connective tissue cell invasion into the wound clot and their subsequent migration in the fibrin–fibronectin-containing 3D wound environment.[1] It was recently shown that dermatopontin, a dermal ECM protein, colocalizes with fibrin and fibronectin in the wound clot, where it may enhance fibroblast adhesion to the provisional matrix via $\alpha_5\beta_1$ integrin, accelerating fibroblast cell adhesion to the provisional matrix in the initial stage of wound healing.[126] Syndecan-4 triggers the endocytosis and trafficking of the fibroblast $\alpha_5\beta_1$ integrin, which leads to immigration of the cells into the wound bed.[127] Interestingly, granulation tissue fibroblasts seem to have a reduced ability to adhere to fibronectin via $\alpha_5\beta_1$ integrin that may help them in being more mobile in the early fibronectin-rich granulation tissue matrix.[128] The presence of tenascin-C can also promote the $\alpha_5\beta_1$ integrin-dependent fibroblast migration into the granulation tissue.[33]

Integrin $\alpha_v\beta_3$ may be inhibitory to fibroblast infiltration into the wound clot, because it can suppress TGF-β1–mediated signaling. Notably, mice lacking β_3 integrins show faster epidermal wound healing with enhanced dermal fibroblast infiltration into wounds (Table 2).[50]

Both β_1 and α_v integrins are involved in myofibroblast differentiation and in granulation tissue synthesis and remodeling. About 1 week after wounding, the connective tissue cells within the wound granulation tissue start expressing alpha–smooth muscle actin (αSMA) in the cytoskeletal stress fibers, becoming myofibroblasts. The integrins of the β_1 family appear important in myofibroblast differentiation and function. Mouse fibroblasts deficient in β_1 integrins show reduced expression of αSMA, CCN2/CTGF, and type I collagen as well as lowered ability to activate latent TGF-β, and they fail to differentiate into myofibroblasts.[129] This leads to delayed cutaneous wound closure and diminished granulation tissue formation in the β_1 integrin null animals. *In vitro*, TGF-β1–induced αSMA expression and collagen matrix contraction are blocked by antibodies against α_5 integrin in both human oral mucosal and dermal fibroblasts.[130] TGF-β1 from macrophages can upregulate both EDA fibronectin and $\alpha_5\beta_1$ integrin expression in fibroblasts, leading to activation of FAK, an essential signaling protein for myofibroblast differentiation.[131] Integrin signaling proteins kindlin-2 and ILK are also required for the TGF-β1–induced myofibroblast differentiation and function.[132,133] Indeed, defective granulation tissue formation is seen in mice with fibroblast-specific ILK ablation.[134] Inhibition of $\alpha_9\beta_1$ integrin by a specific antibody also inhibits granulation tissue formation during skin wound healing.[59]

Fibroblasts interact with fibrillar collagens via $\alpha_1\beta_1$, $\alpha_2\beta_1$, and $\alpha_{11}\beta_1$ integrins (Table 2). Mice lacking individual collagen receptors show only subtle changes in granulation tissue ECM remodeling, however (Table 2). It is likely that in the absence of $\alpha_1\beta_1$ or $\alpha_2\beta_1$ integrin, the other collagen receptors can compensate in most functions, such as regulation of MMP expression and collagen fibrillogenesis. Interestingly, it was recently shown that $\alpha_{11}\beta_1$ is induced by mechanical strain and by members of the TGF-β family, and it promotes myofibroblast differentiation.[135,136] However, there is no wound healing data available that show the effects of $\alpha_{11}\beta_1$ deficiency or blockage in granulation tissue formation or remodeling.

In addition, α_v integrins may be involved in myofibroblast differentiation. Blocking of $\alpha_v\beta_5$ or $\alpha_v\beta_3$ integrin suppresses TGF-β1-induced myofibroblast differentiation of both oral and dermal fibroblasts in cell culture.[137] Furthermore, increased expression of $\alpha_v\beta_5$ integrin induces αSMA expression in fibroblasts and promotes their responsiveness to TGF-β1 via RGD motif-dependent recruitment of latent TGF-β complex into the cell surface and its activation (Fig. 8).[138] Integrin $\alpha_v\beta_5$ also appears to regulate $\alpha_2\beta_1$ integrin function in myofibroblasts, promoting their persistent myofibroblast phenotype.[139]

Tension within granulation tissue increases as it is getting compacted by myofibroblasts. Cells under minimal tension in early granulation tissue express $\alpha_2\beta_1$ integrin that regulates fine collagen fibril organization into thick collagen fibers.[140] Thicker fibers create a rigid matrix, generating more tension, which leads to cell switching to $\alpha_v\beta_3$ integrin and noncollagen ECM interactions.[140] However, fibroblast differentiation into myofibroblasts and wound contraction are not affected by $\alpha_v\beta_3$ integrin deficiency at least in the mouse skin wound healing model (Table 2),[50] suggesting that compensatory mechanisms exist *in vivo*.

Usually, myofibroblasts are driven into senescence and converted from ECM-producing cells into ECM-degrading cells in the remodeling phase

of wound repair.[141,142] This process is mediated by collaborative interaction of $\alpha_6\beta_1$ integrin and cell surface heparan sulphate proteoglycans with matricellular protein CCN1/Cyr61 and by subsequent production of ROS.[142] Myofibroblasts persist in fibrotic conditions and pathological scars, where they continue to produce matrix.[141] However, the number of myofibroblasts in the oral mucosal wounds, which heal with minimal scarring, is higher than in skin wounds,[143] suggesting that the presence of myofibroblasts *per se* does not predict scarring or fibrosis.

Integrins are essential for angiogenesis

Wound angiogenesis is an integral part of granulation tissue formation. It begins with endothelial cell activation by hypoxia-induced production of vascular endothelial growth factor (VEGF), FGF-2/bFGF, and other pro-angiogenic growth factors by various types of wound cells, such as macrophages.[12] Consequently, the vascular basement membrane is degraded, and vascular sprouting is initiated into the provisional wound matrix; this process involves proliferation and migration of endothelial cells (as well as endothelial progenitor cells) and vessel-associated pericytes.[12] Integrins play a central role in wound neo-vascularization. In addition to supporting endothelial cell and pericyte migration, they act as co-receptors for growth factor receptors, such as the VEGF and angiopoietin receptors, and support vascular basement membrane assembly.[12] The exact roles of individual integrins in wound angiogenesis are still unclear. Deposition of fibronectin is critical for angiogenic development. However, endothelial cells can interact with it by using several different fibronectin receptors in a compensatory manner and in collaboration with pericyte integrins.[12,144] Information about the role of integrins in adult vascular remodeling comes mostly from studies on tumor angiogenesis, which may be mechanistically different from wound vascularization. These studies point to $\alpha_6\beta_4$ integrin-mediated signaling playing a role in the initial endothelial cell activation, whereas at least $\alpha_v\beta_3$ and $\alpha_v\beta_5$ (when attached to matrix-bound ECM molecules), $\alpha_9\beta_1$ (in interaction with VEGFs) as well as $\alpha_1\beta_1$ and $\alpha_2\beta_1$ integrins can participate in vascular sprouting.[12,61,145]

Integrin expression and functions may be altered in chronic wounds and hypertrophic scars

Disruption of the normal wound healing sequence, especially prolonged inflammation, may result in over-healing (hypertrophic scar) or a failure to heal (chronic wound). Impaired wound healing may result from inadequate or excessive integrin signaling, which is accompanied by defective ECM that fails to support re-epithelialization and normal fibroblast function as well as from insufficient angiogenesis which results in poor tissue oxygenation. Therefore, activation or inhibition of certain integrins may provide an effective way to influence wound healing outcomes.

Many ECM molecules (*e.g.,* fibronectin and collagen) are abnormally glycated in chronic wounds that are associated with diabetes. This reduces the binding of different ECM molecules to each other and integrin-mediated epithelial adhesion to ECM, resulting in defective re-epithelialization.[2] Notably, chronic wounds exhibit drastically decreased epithelial expression of $\alpha_5\beta_1$ integrin, which results in reduced integration of fibronectin into the provisional basement membrane, increased fibronectin degradation, and a failure in keratinocyte migration and re-epithelialization.[146] In addition, increased keratinocyte integrin expression may contribute to the formation of chronic wounds. The expression of $\alpha_v\beta_6$ integrin is strongly upregulated in the epidermis of human chronic wounds, and its constitutive overexpression in mouse epidermis is associated with over activation of TGF-β1 and increased susceptibility for chronic fibrotic ulcers in these animals.[147] However, the responsiveness of myofibroblasts to the stimulatory action of TGF-β1 is diminished in chronic wounds; this is possibly due to a failure in myofibroblast integrin activation and cross-talk, which is caused by the degraded wound ECM, especially EDA fibronectin.[141,146] Integrin $\alpha_v\beta_6$ signaling may also promote the production of MMP-9 by the keratinocytes, which is shown to be upregulated in chronic wounds where it contributes to the excessive ECM degradation.[146,148]

Members of the CCN family of matricellular proteins are ligands for many integrins (Table 2),[60] and they critically regulate myofibroblast fate as well as ECM production and remodeling in wounds.[142] In chronic human wounds, the expression of CCN1/Cyr61 is increased, and CCN2/CTGF is significantly reduced compared with normally healing wounds.[149] The excessive expression of CCN1/Cyr61 may result in premature $\alpha_6\beta_1$-integrin-mediated myofibroblast senescence that is associated with early down-regulation of ECM (*e.g.,* collagen) production, up-regulation of matrix-degrading proteases, and ongoing breakdown of the granulation tissue before the re-epithelialization is completed, contributing to the wound chronicity.[142,146] In hypertrophic scars, myofibroblasts persist and

they continue to produce excessive matrix possibly because of a reversed CCN1/Cyr61 and CCN2/CTGF balance.[147] Elevated levels of CCN2/CTGF are one of the hallmarks of fibrosis, and it potentiates TGF-β1 actions in myofibroblasts to produce a sustained fibrotic response.[60]

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TAKE-HOME MESSAGES

- Integrins are essential cell surface receptors that bind proteins in the extracellular and wound provisional matrix.
- Keratinocytes and fibroblasts have multiple integrins with overlapping matrix-binding capabilities, and one can compensate for the lack of another.
- Expression of many integrins is induced during wound healing, and their localization in tissues may be altered.
- Integrins regulate wound re-epithelialization and granulation tissue formation at several levels. The most important integrins for epithelial migration are $\alpha_5\beta_1$ and $\alpha_6\beta_4$ integrins, while $\alpha_5\beta_1$ integrin appears critical for granulation tissue formation. In addition, other integrins participate, especially when healing is compromised or when it leads to fibrotic outcomes.
- Certain integrins can activate TGF-β1 and potentially regulate fibrosis. These integrins are potential targets for anti-fibrosis therapies.
- Most of the information regarding wound healing is derived from mouse or cell culture studies that poorly reflect human mucosal or skin healing. Therefore, future research should dissect integrin functions in animal models that better mimic human mucosal and skin wound healing.

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