

Review

Integrins as a bridge between bacteria and cells: key targets for therapeutic wound healing

Dong Yu^{1,2}, Zhaoyu Lu^{1,2} and Yang Chong^{1,2,*}

¹Department of Traditional Chinese Medicine, The Affiliated Hospital of Yangzhou University, Yangzhou University, No. 368 Hanjiang Middle Road, Yangzhou 225000, Jiangsu, China and ²Department of General Surgery, The Affiliated Hospital of Yangzhou University, Yangzhou University, No. 368 Hanjiang Middle Road, Yangzhou 225000, Jiangsu, China

*Correspondence. 092016@yzu.edu.cn

Received 25 June 2023; Revised 17 December 2023; Accepted 22 April 2024

Abstract

Integrins are heterodimers composed of α and β subunits that are bonded through non-covalent interactions. Integrins mediate the dynamic connection between extracellular adhesion molecules and the intracellular actin cytoskeleton. Integrins are present in various tissues and organs where these heterodimers participate in diverse physiological and pathological responses at the molecular level in living organisms. Wound healing is a crucial process in the recovery from traumatic diseases and comprises three overlapping phases: inflammation, proliferation and remodeling. Integrins are regulated during the entire wound healing process to enhance processes such as inflammation, angiogenesis and re-epithelialization. Prolonged inflammation may result in failure of wound healing, leading to conditions such as chronic wounds. Bacterial colonization of a wound is one of the primary causes of chronic wounds. Integrins facilitate the infectious effects of bacteria on the host organism, leading to chronic inflammation, bacterial colonization, and ultimately, the failure of wound healing. The present study investigated the role of integrins as bridges for bacteria–cell interactions during wound healing, evaluated the role of integrins as nodes for bacterial inhibition during chronic wound formation, and discussed the challenges and prospects of using integrins as therapeutic targets in wound healing.

Key words: Integrins, Wound healing, Wound chronicity, Bacterial infection, Extracellular adhesion molecules, Actin, Cytoskeleton, Inflammation

Highlights

- A summary of the mechanism of action of integrins in the wound healing process is provided.
- Integrins and the mechanism of connectivity of different cells in wound healing are introduced.
- Mechanisms underlying the interaction of integrins within different species of bacterial cells are discussed.
- Advancements and prospects associated with integrin-targeted drug delivery for wound healing and bacterial infections are summarized.

Background

Integrins are heterodimers composed of 18 α -subunits and 8 β -subunits. Integrins mediate the dynamic connections of extracellular adhesion molecules with the intracellular actin

cytoskeleton and intermediate filaments. These connections are noncovalent in nature and serve to connect the extracellular matrix (ECM) to the cytoskeleton [1]. Cytoplasmic integrin-binding proteins regulate the binding of integrins to

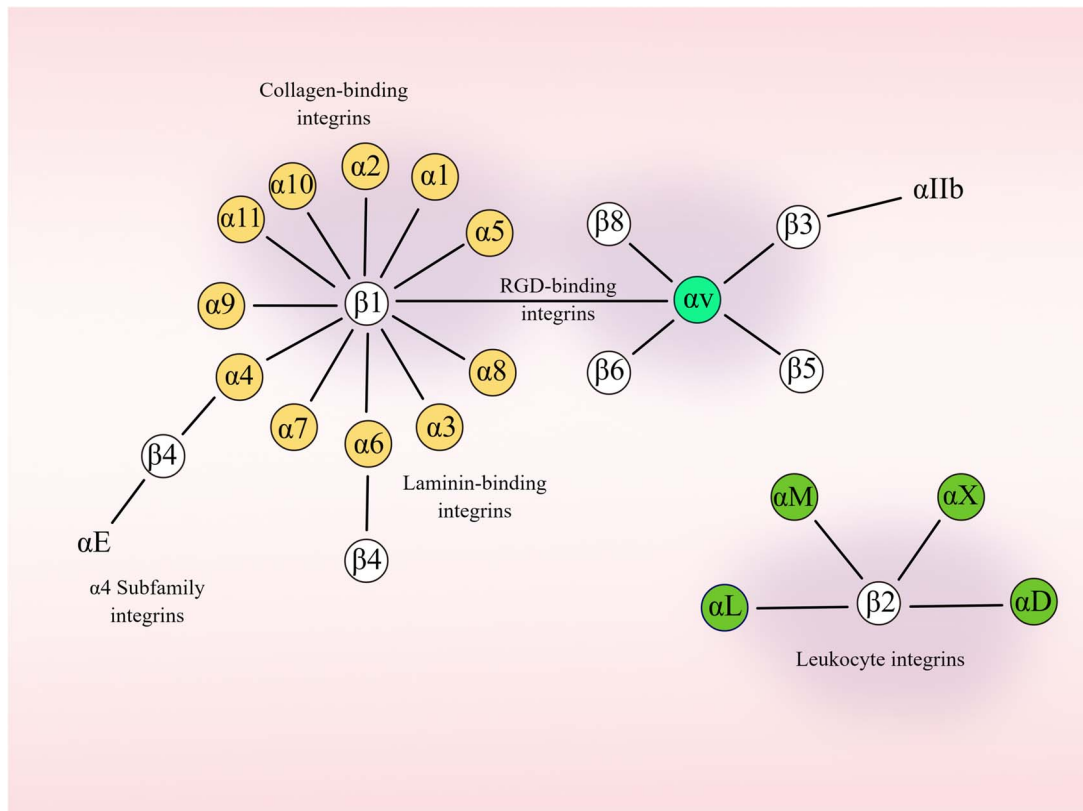


Figure 1. Members of the human integrin superfamily. A minimum of 18 α subunits and eight β subunits have been identified in humans, which together produce 24 different integrins. The integrin subunits that bind to each other to form heterodimers are connected using solid lines. Each integrin has a distinct ligand-binding specificity and tissue and cellular distribution. Reprinted with permission from Figdraw (www.figdraw.com)

extracellular ligands and play a crucial role in integrin localization and transport. These proteins bind to the cytoplasmic tail of integrins and thereby mediate their connections to the cytoskeleton and signaling cascades that affect cell motility, growth and survival [2]. The targeting integrin sequence may be a simple tripeptide, such as Arg-Gly-Asp (RGD) or Leu-Asp-Val (LDV), or a more complex peptide such as GFOGER [3]. Integrins are classified into four types based on their binding properties. The integrins involved in leukocyte cell adhesion include $\alpha 4\beta 1$, $\alpha 9\beta 1$, $\alpha L\beta 2$, $\alpha M\beta 2$, $\alpha X\beta 2$, $\alpha D\beta 2$, $\alpha 4\beta 7$ and $\alpha E\beta 7$. Among these, the integrins $\alpha 4\beta 1$, $\alpha 4\beta 7$, $\alpha 9\beta 1$ and $\alpha E\beta 7$ recognize short specific LDV peptide sequences, which are also present in fibronectin. The most common integrin mediating leukocyte adhesion and migration is $\beta 2$, which is characterized by sites in the ligand that are structurally similar to the LDV motifs [4]. RGD-binding integrins include $\alpha v\beta 1$, $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 6$, $\alpha v\beta 8$, $\alpha 8\beta 1$, $\alpha 5\beta 1$ and $\alpha IIb\beta 3$, and are known to share RGD peptides with extracellular matrices (e.g. fibronectin, osteoadhesins, vitronectin and fibrinogen) via a common binding motif [5]. Collagen (GFOGER)-binding integrins, including $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$ and $\alpha 11\beta 1$, recognize the triple-helical GFOGER sequences in major collagens. Laminin-binding integrins, including $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 7\beta 1$, and $\alpha 6\beta 4$. In addition, $\alpha 10\beta 1$, $\alpha 2\beta 1$ and $\alpha 1\beta 1$, contain three αI structural domains and form a distinct laminin/collagen-binding subfamily [3,6]. In addition, these

integrins exhibit different binding properties and varied tissue distribution (Figure 1 and Table 1) [7]. Integrins are involved in various physiological processes, including those related to trauma, immunity, infection, cell proliferation, inflammation, angiogenesis and tumors [8–11].

Skin wounds heal successfully through various dynamic processes that occur in three overlapping phases— inflammation, proliferation and tissue remodeling [12]. Wound repair is tightly regulated by various factors, including cell-ECM interactions [12], growth factors and matrix metalloproteinases [13]. The integrin family of proteins regulates all aspects of the wound healing process, including hemostasis, inflammation, angiogenesis (Figure 2), re-epithelialization (Figure 3) and fibrosis (Table 1) [6,7,14–52]. Any disruption in these regulatory mechanisms at any of the three phases could result in chronic or non-healing wounds, and factors such as persistent inflammation and impaired barrier function [53,54], oxygenation response [55], bacterial infection [56], age [57] and disease state [53] could hinder effective wound repair. In real-life scenarios, chronic wounds are frequently accompanied by bacterial infections, with a few of these bacteria, such as *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*), capable of exploiting the integrin family to facilitate the development of chronic wounds, thereby perpetuating the presence of these wounds [56,58]. RGD-binding integrins, such as $\alpha 5\beta 1$

Table 1. Main secretory sites and functional roles of different types of integrins

Type		Ligands	Secretion sites	Wound healing (granulation tissue)
RGD binding integrins	$\alpha v \beta 1$	TGF- β 1, fibronectin, osteoblastin [7]	KC, EC	Modulation of the ECM Induces TGF- β activation [14] and mediates KC adhesion Mediates vascular remodeling [15]
	$\alpha v \beta 3$	Fibronectin, FGF-2, TGF- β , vitronectin (hyaluronan), osteoblastin, platelet reactive protein, fibronectin [7,16]	EC, platelets, FB and macrophages	ECM regulation Angiogenesis: EC survival and FB proliferation [17,18] Inflammation: regulation of monocyte, macrophage and neutrophil migration [19,20]
	$\alpha v \beta 5$	TGF- β , VEGF, osteoblastin, hyaluronan, platelet reactive protein [7]	EC, FB and skin KC	Fibrosis: induction of TGF- β activation mediates conversion of FB into myofibroblasts and matrix production [21,22]
	$\alpha v \beta 6$	TGF- β 1 and - β 3, TGF- β , fibronectin, osteoblasts and metalloproteinases (ADAM)	KCs	Activation of TGF- β Inflammation/re-epithelialization: regulation of inflammation and KC proliferation [23,24]
	$\alpha v \beta 8$	FN and TGF- β	Dendritic cells, FBs and ECs	Inflammation: may regulate inflammation by activating TGF- β [25]
	$\alpha 8 \beta 1$	TGF- β , tendonin, fibronectin, osteoblastin, hyaluronidase [7]	Myofibroblasts; vascular smooth muscle cells	Fibrosis [26]
	$\alpha 5 \beta 1$	Fibronectin, bone bridging protein, protofibronectin, thrombospondin, ADAM [27]	KC, EC, FB and leukocytes	Modulation of inflammation [6] Re-epithelialization: promotes KC migration [28]
	$\alpha IIb \beta 3$	Fibrinogen, fibronectin, platelet reactive protein, hyaluronan, vascular hemophilic factor [7]	Platelets	Platelet activation and arterial thrombosis [29]
	Leukocyte cell adhesion integrin	$\alpha 4 \beta 1$	Thrombospondin, VCAM-1, fibronectin, osteoblastin [30]	Regulation of inflammation Regulation of FB proliferation and differentiation [30]
		$\alpha 9 \beta 1$	EDA-FN, TN-C, ADAM, EMILIN1, and VEGF [31,32], bone bridging proteins, metalloproteinases-12 and 15	Regulates KC and FB growth [33], neutrophil chemotaxis, and EC migration and angiogenesis [34–36]
		$\alpha L \beta 2$	ICAM, JAM-1 intercellular adhesion molecule [ICAM]-1	Mediates leukocyte extravasation through the endothelium [37]; enhances phagocytosis of bacteria by neutrophils [38]
		$\alpha M \beta 2$	Fibrinogen, ICAM, heparin, FN, uPAR etc	Involved in leukocyte extravasation across the endothelium [37] Complexes with uPAR and its ligand uPA to promote fibrinolysis and clearance of fibrin clots from monocytes and neutrophils [39] Modulates inflammation and defends against microbial infection [38]
		$\alpha X \beta 2$	Fibrous protein, ICAM, COL I [40]	Involved in leukocyte extravasation [37] Regulates macrophages [41]
		$\alpha D \beta 2$	ICAM-3, VCAM-1 and CCN1/Cyr6	Involved in leukocyte extravasation [37] Modulation of inflammation and microbial infections [42]
		$\alpha 4 \beta 7$	VCAM	Involved in leukocyte extravasation
		$\alpha E \beta 7$	Calcineurin	
		$\alpha 1 \beta 1$	Laminin, collagen	Mediation of VEGF-driven angiogenesis, negative feedback regulation of collagen synthesis in FBL [43]
Collagen (GFOGER)/ laminin-binding integrins	$\alpha 2 \beta 1$	Laminin, collagen, thrombomodulin, e-calmodulin, tendonin	Platelets, KC, EC and FB, megakaryocytes	Mediates KC migration and VEGF-driven angiogenesis and keratinocyte adhesion [43,44]
	$\alpha 10 \beta 1$	Collagen type II	FB	May mediate FBL adhesion to collagen

(Continued)

Table 1. Continued

Type	Ligands	Secretion sites	Wound healing (granulation tissue)
Collagen (GFOGER) protein-binding integrins	$\alpha 11\beta 1$ Collagen	FB	Mediates collagen gel reorganization, cell migration and proliferation [45]
Laminin-binding integrins	$\alpha 3\beta 1$ Laminin Laminin-332 and laminin-511	Lungs, stomach, intestines, kidneys, bladder and skin	Mediates cell adhesion to the basement membrane and intercellular communication [46]
	$\alpha 6\beta 1$ Laminin, platelet-derived growth factor	Platelets, EC, leukocytes and FB	May be involved in platelet–vessel wall interactions and angiogenesis [47], mediates keratinocyte migration [48], interaction with CCN1/Cyr61 promotes myofibroblast senescence and controls fibrogenesis [49]
	$\alpha 7\beta 1$ Laminin	Cardiac and skeletal muscle	Mediates the binding of muscle fibers to the tendon junction [50]
	$\alpha 6\beta 4$ LM-332	KC, EC	Vascular development and integrity [51]. Promotes KC adhesion, migration and proliferation as well as EGFR signaling, regulates angiogenesis in the EC [52]

FB fibroblasts, KC keratin-forming cells, EC endothelial cells, VEGF vascular endothelial cell growth factor, FN fibronectin, TGF- β transforming growth factor beta, EDA extra domain A, ADAM a disintegrin and metalloproteinase, CCN Cyr61-CTGF-Nov, Cyr6 cysteine-rich protein 6, VCAM vascular cell adhesion molecule, uPAR urokinase-type plasminogen activator receptor, EMILIN1 elastic microfibril interface localization protein 1

and $\alpha v\beta 3$, are the primary types of integrins identified to be mediating bacterial infection [59,60]. Therefore, the present review focuses on discussing the role of RGD-binding integrins as mediators in the bacteria–cell interactions occurring during the wound healing process. In addition, the potential of integrins as targets to impede bacterial involvement during wound chronicity is explored. Finally, the challenges and prospects of using integrins as targets in therapeutic wound healing are discussed.

Review

General mechanism of integrin attachment to the ECM
Integrins are the central mediators of cell–ECM and cell–cell adhesions. The cytoplasmic tails in the structure of integrins contain extracellular structural domains along with cytoskeletal and signaling proteins that bind to different components of the ECM. Such binding of integrins facilitates transmembrane signaling between the ECM and the cytoskeleton, allowing for the transmission of chemical and mechanical signals in and out of the cell [61]. The ECM in living organisms predominantly comprises a heterogeneous mixture. Moreover, cells express multiple isoforms of integrins, allowing for crosstalk among the different integrins and also between the integrin and non-integrin co-receptors [62]. Further detailed information on the general mechanisms through which integrins interact with the ECM may be obtained by referring to certain comprehensive reviews reported previously [6,63–65].

Connection of RGD integrins to cells in wound healing
Platelets, neutrophils, macrophages, endothelial cells, fibroblasts and keratinocytes are the main cells involved in the wound-healing process.

Connection of RGD integrins to platelets
Platelets contain three $\beta 1$ integrins ($\alpha 2\beta 1$, $\alpha 5\beta 1$ and $\alpha 6\beta 1$) and two $\beta 3$ integrins ($\alpha v\beta 3$ and $\alpha IIb\beta 3$). These integrins promote platelet adhesion to ECM proteins, such as collagen, fibronectin and laminin, in addition to facilitating platelet aggregation [66].
In addition, $\alpha v\beta 3$ facilitates cell adhesion and migration on immobilized ligands containing RGD motifs [67]. The widespread expression of $\alpha v\beta 3$ could explain its lack of a distinct hemostatic function [66].
Expression of $\alpha IIb\beta 3$ is reportedly limited to platelets [68], and this integrin is also the one present most abundantly on the platelet surface, where it facilitates both platelet adhesion and aggregation by binding to fibrinogen [69]. Platelet activation induces aggregation through interaction between integrin $\alpha IIb\beta 3$ and plasma fibrinogen, which leads to hemostasis under pathological or physiological conditions [70,71]. The detailed role of platelet integrins in hemostasis and arterial thrombosis is thoroughly summarized in the report by Janus-Bell and Mangin [66].
Integrin $\alpha 5\beta 1$ facilitates platelet adhesion, activation and aggregation on fibronectin and participates in thrombus growth [72]. The inhibition of $\alpha 5\beta 1$ integrin was demonstrated to reduce soluble CD40 ligand (sCD40L)-mediated platelet activation [73].

RGD integrins connect with inflammatory cells
Integrin $\alpha v\beta 3$ is expressed in leukocytes, where it regulates the migration of monocytes, macrophages and neutrophils and the phagocytotic process in dendritic cells and macrophages, thereby modulating the progression of inflammation [19,20].
Integrin $\alpha v\beta 5$ is expressed highly in mature intestinal macrophages. This integrin mediates the phagocytosis

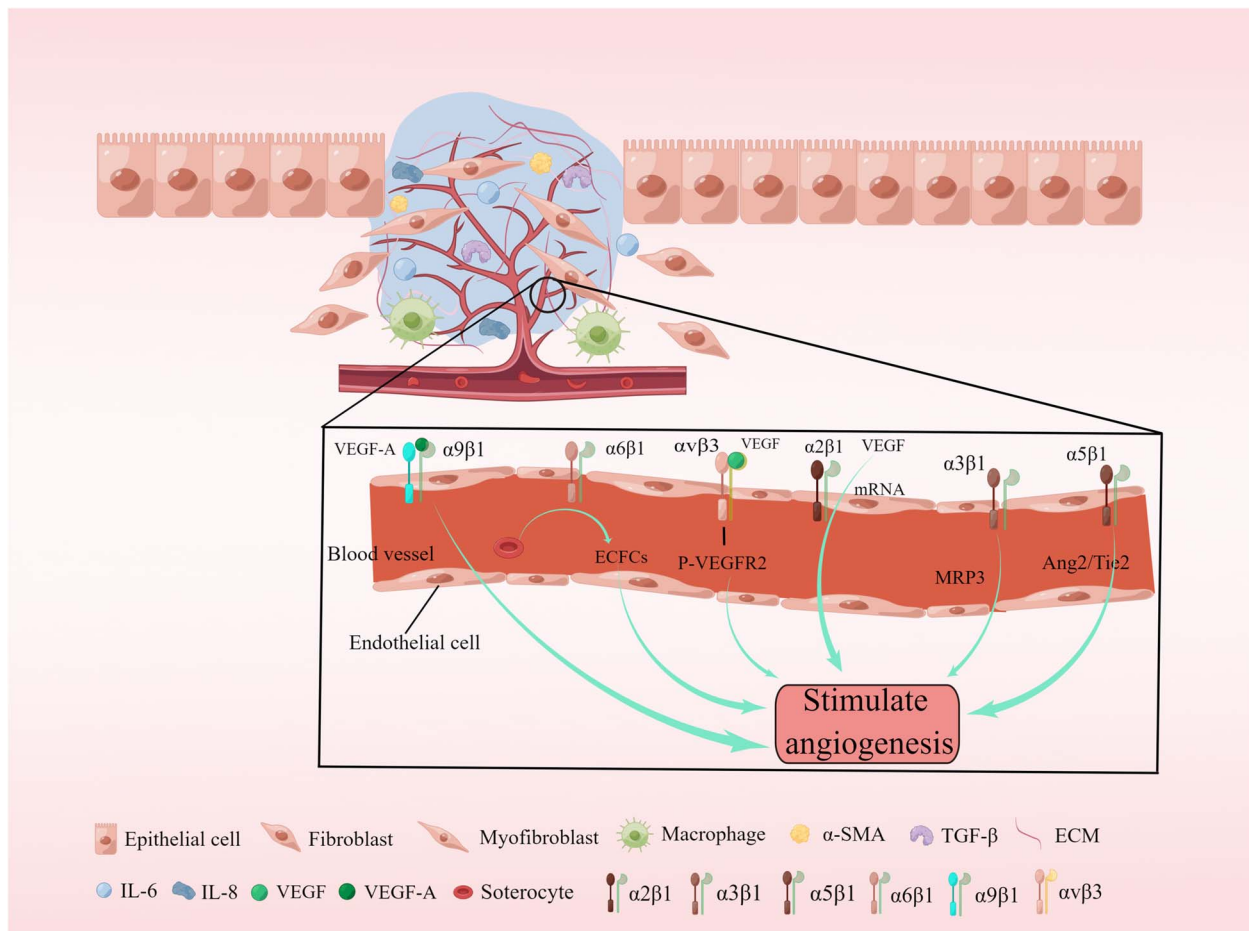


Figure 2. Stages of formation of new capillaries during wound healing. Vascular endothelial growth factor (VEGF) induces a 5- to 7-fold increase in the protein expression of two collagen receptors, namely, α 1 β 1 and α 2 β 1 integrins, on the surface of dermal microvascular endothelial cells (ECs) through the induction of mRNAs encoding α 1 and α 2 integrins subunits. The α 5 integrin localizes to cell junctions and participates in the angiopoietin (Ang)/Tie2 signaling pathway to maintain vascular homeostasis. The α v β 3 integrin acts in synergy with VEGF to activate angiogenesis in ECs through VEGF receptor 2 (VEGFR2) phosphorylation. The α 6 β 1 integrin appears to promote platelet mediated angiogenesis associated with endothelial colony forming cells (ECFCs). VEGF-A induces endothelial and cancer cell migration by directly binding to the α 9 β 1 integrin. ECM extracellular matrix, IL-6 interleukin 6, TGF- β transforming growth factor beta, MRP3 multidrug resistance-associated protein 3, α -SMA α -Smooth Muscle Actin, Tie2 Tyrosine kinase with Ig and EGF homology domains 2. Reprinted with permission from Figdraw (www.figdraw.com)

of apoptotic cells by macrophages and promotes tissue repair by regulating the homeostatic properties of intestinal macrophages [74]. Immature dendritic cells phagocytize apoptotic cells via α v β 5 and CD36 and cross-present antigens to cytotoxic T lymphocytes [75].

The expression of α v β 6 integrin is significantly elevated during tissue repair and malignancy [76]. The expression of integrin α v β 6 is correlated to the severity of inflammation, and integrin β 6 deficiency significantly reduces the release of pro-inflammatory cytokines, such as TNF- α , interleukin 6 (IL-6) and IL-1 β , in intestinal tissues with colitis. The inhibition of integrin α v β 6 expression was demonstrated to inhibit the polarization of macrophages toward the M1 phenotype while promoting macrophage polarization toward the M2 phenotype, thereby attenuating the dextran Sulfate Sodium (DSS)-induced inflammatory response in the mice with colitis [77].

The expression of integrin α v β 8 by human monocytes and macrophages activates transforming growth factor

beta (TGF- β), a component that inhibits the production of pro-inflammatory cytokines and is disrupted in inflammatory bowel disease [78]. Studies have demonstrated that tumor cells expressing integrin α v β 8 evade host immunity by regulating TGF- β activation within immune cells [79].

As one of the fibronectin-binding integrins, α 5 β 1 mediates the adhesion of neutrophils to fibronectin [80]. In addition, α 5 β 1 regulates the adhesion behavior of neutrophils upon stimulation with various substances [81]. This is confirmed by the fact that during lung inflammation, α 5 β 1 was demonstrated to be involved in the migration of polymorphonuclear leukocytes to the lungs [82].

RGD integrins connect to endothelial cells

Integrins are the primary adhesion receptors that facilitate an interaction between endothelial cells and their extracellular microenvironment, thereby playing a crucial role in regulating the processes of cell proliferation, migration and survival [83]. The process of angiogenesis begins with the activation of

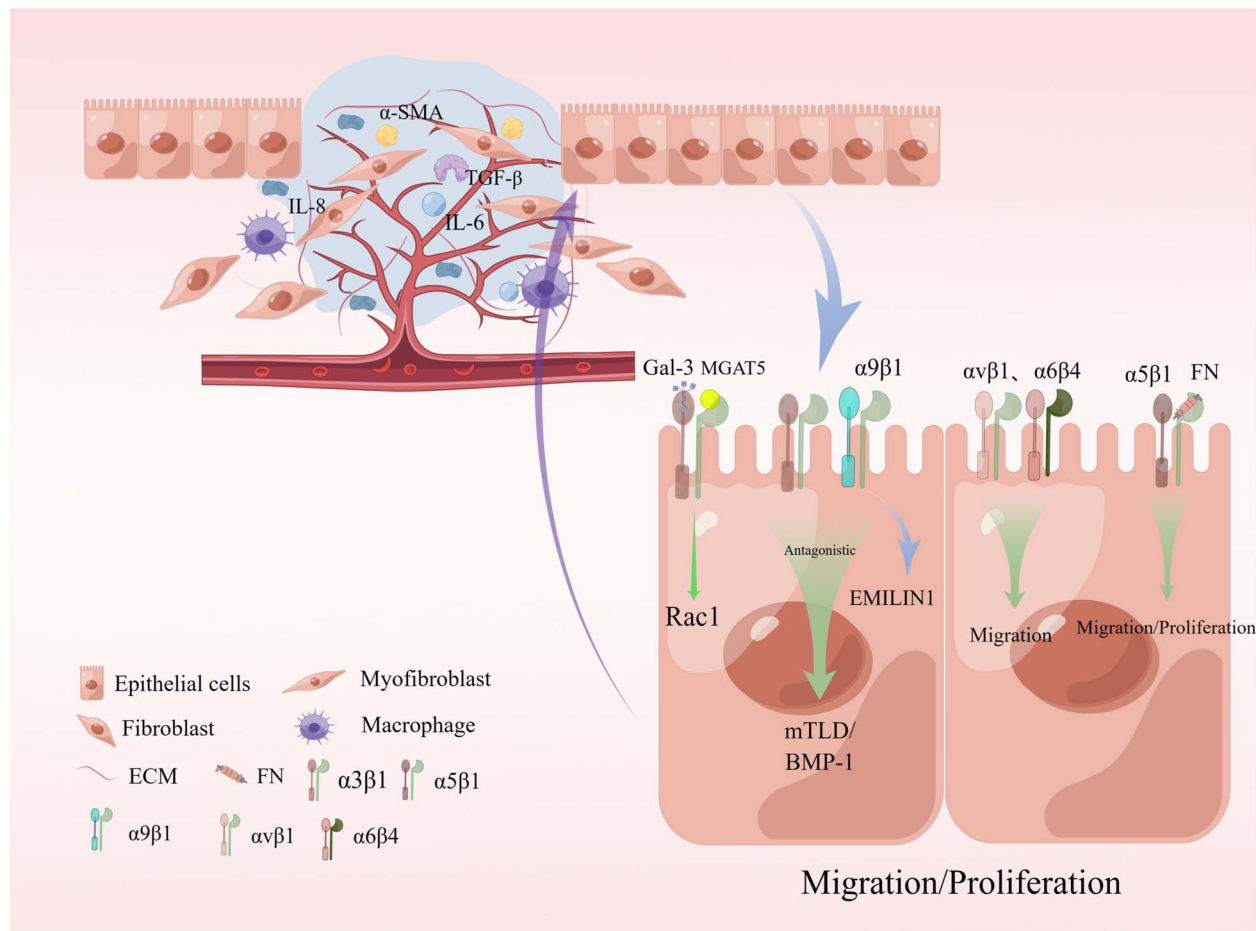


Figure 3. Stages of re-epithelialization during wound healing. Galectin-3 promotes epithelial cell migration by cross-linking with the MGAT5-modified complex N-glycans on $\alpha 3\beta 1$ integrins and subsequently activating $\alpha 3\beta 1$ -integrin-Rac1 signaling to promote lamellar pseudopod formation. The interaction of $\alpha 5\beta 1$ integrins with fibronectin (FN) contributes to keratinocyte proliferation in addition to promoting keratinocyte adhesion and motility on this matrix. The $\alpha 9\beta 1$ integrin interacts with another extracellular matrix (ECM) component named elastic microfibril interface localization protein 1 (EMILIN1) to regulate keratinocyte proliferation, although the $\alpha 9\beta 1$ integrin antagonizes the $\alpha 3\beta 1$ -dependent expression of mTLD/BMP-1 and skin basement membrane reorganization and maturation. The $\alpha v\beta 1$ and $\alpha 6\beta 4$ integrins also regulate keratinocyte migration. IL-6 interleukin 6, TGF- β transforming growth factor beta, MGAT5 mannosyl (Beta-1,6-) glycoprotein beta-1,6-N-acetyl-glucosaminyltransferase, mTLD/BMP1 mammalian tollid/bone morphogenetic protein 1, Gal-3 galectin-3, α -SMA α -Smooth Muscle Actin. Reprinted with permission from Figdraw (www.figdraw.com)

endothelial cells, followed by the degradation of the vascular basement membrane and the sprouting of blood vessels within the mesenchymal stroma. In this process, the binding of the ECM to integrins provides vital signaling support for endothelial cell proliferation, survival and migration [84], thereby contributing to embryonic angiogenesis and adult angiogenesis [85,86]. Both *in vitro* and *in vivo* data indicate that numerous integrins, including $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 4\beta 1$, $\alpha 5\beta 1$, $\alpha 6\beta 1$, $\alpha 6\beta 4$, $\alpha 9\beta 1$, $\alpha v\beta 3$ and $\alpha v\beta 5$, present on endothelial cells regulate cell growth, survival and migration during angiogenesis [87].

The essential role of endothelial $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins during angiogenesis was demonstrated through *in vitro* experiments involving a 3D assay conducted with bovine aortic and microvascular endothelial cells [88]. In addition, integrin $\alpha v\beta 3$ acts in synergy with vascular endothelial growth factor (VEGF) to activate angiogenesis in endothelial cells by inducing VEGF receptor 2 (VEGFR-2) phosphorylation [89]. The interaction between integrins $\alpha 5\beta 1$ and $\alpha v\beta 3$ within

endothelial cells having fibronectin is necessary for cell migration, and any disruption in this interaction impedes placental endothelial cell migration during fetal growth restriction [90]. Previous studies have demonstrated that focal adhesions of endothelial cells, which are concentrated on $\alpha 5\beta 1$ integrin-selective substrates, efficiently recruit $\alpha v\beta 3$ integrins [91]. In addition, catabolic inhibitors of $\alpha v\beta 3$ integrin were demonstrated to impede VEGFR-2 signaling, thereby disrupting the angiogenic mechanisms, even in the presence of VEGF [92]. Therefore, drugs targeting integrin $\alpha v\beta 3$ ligands enhance endothelial cell survival, implantation and angiogenesis [93].

ATN-161 is an antagonist of integrin $\alpha 5\beta 1$, which induces apoptosis in neovascular endothelial cells, thereby effectively inhibiting ocular neovascularization [94]. The presence of soluble VEGF receptor-1 in the microenvironment of endothelial cells facilitates $\alpha 5\beta 1$ integrin signaling, initiating cell migration and angiogenesis [95]. Moreover, the binding of Gln-362 in angiopoietin-2 to the $\alpha 5\beta 1$ integrin facilitates the migration of both tumor and endothelial cells [96].

RGD integrins connect to fibroblasts

Normal fibroblasts and granulosal fibroblasts, which are a combination of fibroblasts and myofibroblasts, express numerous integrins, including $\alpha1\beta1$, $\alpha2\beta1$, $\alpha3\beta1$, $\alpha5\beta1$, $\alpha11\beta1$, $\alpha v\beta1$, $\alpha v\beta3$ and $\alpha v\beta5$. Both kinds of cells are capable of binding to a wide range of ECM molecules, such as collagens, fibronectin, other components of blood clots, CCN2/CTGF, etc. [97].

The αv integrins reportedly play a role in the differentiation of myofibroblasts, and the inhibition of $\alpha v\beta5$ or $\alpha v\beta3$ integrins was demonstrated to hinder the TGF- $\beta1$ -induced differentiation of myofibroblasts in oral and dermal fibroblast cell cultures [98]. An increase in the expression of $\alpha v\beta5$ integrin induces α -Smooth Muscle Actin (α -SMA) expression in fibroblasts and enhances their activation by facilitating the recruitment of potential TGF- β complexes to the cell surface via the RGD motif. This activation then promotes their response to TGF- $\beta1$ [99]. Integrin $\alpha v\beta5$ also appears to regulate the function of $\alpha2\beta1$ integrin in myofibroblasts and promote the maintenance of their myofibroblast phenotype [100].

Integrin $\alpha v\beta3$ reportedly hinders the infiltration of fibroblasts into wound clots through the inhibition of TGF- $\beta1$ -mediated signaling [101]. However, the deficiency of $\alpha v\beta3$ integrin did not impact the differentiation of fibroblasts into myofibroblasts or wound contraction in a mouse model of cutaneous wound healing [101].

In the early stages of wound healing, an ECM protein named dermal bridging protein, which is present in the dermis, improves the adhesion of fibroblasts to the provisional matrix and facilitates the adhesion of these cells via $\alpha5\beta1$ integrins [102]. For instance, syndecan-4 initiates the process of the endocytosis and trafficking of fibroblast $\alpha5\beta1$ integrins, leading to the migration of cells toward the wound bed [103]. The presence of syndecan-C also facilitates the migration of fibroblasts into the granulation tissue via $\alpha5\beta1$ integrin-dependent mechanisms [104].

RGD integrin keratinocyte attachment

Epithelium reformation involves the collective migration of keratinocytes and the retention of certain cell-cell connections, although the precise mechanisms underlying their migration have not been definitively established [105,106]. While the key integrins for epithelial migration are $\alpha5\beta1$ and $\alpha6\beta4$ [107], several other types of integrins are also reportedly involved.

Injury may lead to upregulated expression of $\alpha2\beta1$, $\alpha3\beta1$ and $\alpha9\beta1$ integrins, which subsequently translocate to the basal cell membrane of basal keratinocytes, where they induce $\alpha v\beta1$ and $\alpha5\beta1$ integrins [108].

The interaction between $\alpha5\beta1$ integrins and fibronectin may, in addition to enhancing keratinocyte adhesion and movement on this substrate, contribute to keratinocyte proliferation [109]. In contrast to $\alpha5\beta1$ integrin, which is crucial for keratinocyte migration and fibronectin matrix assembly,

$\alpha v\beta1$ integrin acts as a low-affinity fibronectin receptor that provides minimal support for keratinocyte migration [110].

As the potential binding integrin for fibronectin and myosin, $\alpha v\beta6$ integrin is induced in keratinocytes during the fusion of epithelial layers in wound healing [111]. Biopsies of the inner surface of the upper arm from adult volunteers during wound healing revealed that in the early stages of this process, basal expression of the epidermis appeared to include $\alpha5\beta1$ and $\alpha v\beta5$ while $\alpha v\beta6$ was not present. In the middle stages, it was $\alpha5\beta1$, $\alpha v\beta5$, and $\alpha v\beta6$. After the completion of the re-epithelialization process, $\alpha5\beta1$ and $\alpha v\beta6$ were detected in all basal cells, while $\alpha v\beta5$ was not detected. Consequently, it was inferred that αv undergoes heterodimer binding, transitioning from $\beta5$ to $\beta6$ subunits during re-epithelialization [112]. In the later stages of wound healing, $\alpha v\beta6$ integrin expression is considerably upregulated in the basal lamina and multiple layers of basal lamina keratinocytes [111]. This upregulation could mediate TGF- $\beta1$ activation and regulate ECM deposition in the granulation tissue [113]. Enhanced keratinocyte integrin expression could potentially contribute to the development of chronic wounds. The expression of $\alpha v\beta6$ integrin is significantly upregulated in the epidermis during human chronic wounds, and its constitutive overexpression in mouse epidermis has been linked to the hyperactivation of TGF- $\beta1$ and increased vulnerability to chronic fibrotic ulcers in these animals [114].

In addition, keratinocytes interact with endothelial cells through integrins, and the removal of the $\alpha3$ integrin subunit in the epidermis leads to compromised wound angiogenesis [17].

Wound healing is a dynamic process comprising three overlapping phases of inflammation, proliferation and tissue remodeling. The process of wound healing includes hemostasis in the initial stages of wound formation, followed by inflammation and granulation tissue formation during wound recovery (including angiogenesis) (Figure 2), and then re-epithelialization as the final stage of wound closure (Figure 3). These three processes involve various cell types, including platelets, inflammatory cells, endothelial cells, fibroblasts and keratinocytes. A review of the literature suggests that integrin-mediated processes are inherently inclined to facilitate their progression. Specifically, the activation of integrins promotes wound healing, and supplementation of appropriate integrins may further expedite the healing process. According to these findings, numerous directions and strategies for wound treatment could be developed. Conversely, blocking integrins might impede wound healing, a process that shares common characteristics with the perpetual wounds occurring in tumors.

Integrins in bacterial infections

Prolonged inflammation may lead to non-healing wounds, such as chronic ulcers [115]. Chronic wounds may have complex causes, including local tissue hypoxia, wound bacterial colonization and repetitive ischemia-reperfusion injury, all

of which contribute to wound development [116]. Inflammation resulting from the bacterial colonization of wounds remains one of the primary factors that delay wound healing [116]. The ECM is a non-cellular, 3D macromolecular network comprising collagen, proteoglycan/glycosaminoglycan, elastin, fibronectin, laminin and other glycoproteins. ECM regulates various cellular functions and plays a crucial role in maintaining normal body homeostasis [117]. ECM serves as the primary microenvironment for wound healing, and integrin-mediated adhesion to ECM is believed to play a crucial role in this process. Most chronic wounds at this stage are infected with bacteria, primarily Gram-positive bacteria such as *S. aureus* and *Staphylococcus hemolyticus*, although infection with Gram-negative bacteria such as *P. aeruginosa*, *Acinetobacter baumannii* and *Escherichia coli* are also reported [118–120]. The main mechanisms of these bacterial colonization organisms such as bacterial biofilm formation [121,122]. Biofilm formation is associated with the regulated synthesis of ECM components [123]. Biofilms comprise different bacterial species and contribute to the chronic nature of most wound-healing processes. Further, bacteria with biofilms exhibit high resistance to antibiotics [124].

Integrins and *S. aureus*

S. aureus is a highly significant pathogen for humans and is recognized for its involvement in hospital-acquired infections and methicillin resistance. Accordingly, *S. aureus* is considered a global clinical concern [125]. *S. aureus* causes a range of surface and systemic diseases and has been commonly associated with oral mucositis. In addition, this bacterium plays a role in the development or exacerbation of several skin conditions, such as atopic dermatitis, carbuncles, cellulitis, boils, hair follicle infections, Kawasaki syndrome, impetigo, psoriasis and scalded skin syndrome [126–133]. *S. aureus* is considered the primary culprit for wound infections and is believed to impede the wound-healing process (Table 2) [17, 134–143]. A notable characteristic shared by almost all *S. aureus* isolates is the production of ECM-binding proteins, which are collectively referred to as microbial surface component recognition adhesion matrix molecules [144,145]. Microbial colonization of the host may occur when *S. aureus* attaches to ECM components, thereby initiating an infection [145]. For instance, cell wall-attached fibronectin-binding proteins A and B enable the bacteria to firmly adhere to the ECM protein fibronectin [146,147].

Integrin $\beta 1$ -containing receptors are recognized for their role in cell adhesion and their capability of cell attachment signal transduction to the ECM [148]. *S. aureus* is capable of invading eukaryotic cells by indirectly engaging the $\beta 1$ integrin-containing host receptor. However, non-pathogenic *S. carnosus* is not invasive [149]. The $\alpha 5 \beta 1$ integrin is a cell surface receptor and a vital mediator of the attachment of eukaryotic cells to the ECM protein fibronectin [136]. Fibronectin has recently been demonstrated to serve as a molecular bridge linking fibronectin-binding proteins

(FnBP)-expressing *S. aureus* to the $\alpha 5 \beta 1$ integrin present on the surface of human cells [150]. This interaction, besides allowing *S. aureus* to tightly anchor to its eukaryotic host cells, also promotes the internalization of the microbe by human epithelial and endothelial cells and mouse fibroblasts [151–154]. A study revealed that necrotizing soft tissue infections with *S. aureus* isolates had high rates of internalization and cytotoxicity to human myocytes, and the cellular basis of the high internalization rate in myocytes was the higher expression of $\alpha 5 \beta 1$ integrins in myocytes [155]. The ability of *S. aureus* to be internalized by and survive within the host cells, such as keratinocytes, might contribute to the development of persistent or chronic infections, eventually leading to deeper tissue infection or dissemination. The internalization of *S. aureus* by immortalized keratinocytes requires bacterial FnBPs and is mediated by the significant fibronectin-binding $\alpha 5 \beta 1$ integrin. However, unlike the internalization of immortalized keratinocytes, the internalization of *S. aureus* by native keratinocytes may occur via FnBP-dependent and non-dependent pathways [156]. Moreover, in oral infections, multi-strain oral biofilms inhibit the expression of $\alpha v \beta 6$ integrin in gingival epithelial cells [140]. In addition, the periodontal inflammation caused by $\alpha v \beta 6$ integrin deficiency reportedly results in a significantly altered oral microbiome [139]. However, the second fibronectin-binding integral protein $\alpha v \beta 6$ on keratin-forming cells does not mediate *S. aureus* internalization [156] (Figure 4).

S. aureus counteracts the extracellular bactericidal mechanism of mast cells (MCs) by increasing the expression of FnBP and inducing Hla-a disintegrin and metalloproteinase 10 (Hla-ADAM10)-mediated upregulation of $\beta 1$ integrins in MCs [157]. Interferon gamma (IFN- γ) intervention, partly by $\beta 1$ integrins, drives the enhanced antimicrobial and pro-inflammatory responses of human MCs to *S. aureus* [158]. A study revealed that α -toxin interacts with $\beta 1$ -integrin, a receptor for host ECM protein, suggesting $\beta 1$ -integrin as a potential receptor for α -toxin on epithelial cells. This α -toxin reportedly inhibits *S. aureus* adhesion and internalization by interfering with integrin-mediated pathogen–host cell interactions [159].

In addition, an $\alpha 5 \beta 1 / \alpha v \beta 3$ integrin antagonist was reported to inhibit the invasion of epithelial cells by *S. aureus* [160]. In a study, vascular endothelial dysfunction was attributed to the ability of *S. aureus* aggregation factor A (ClfA) to adhere to the $\alpha v \beta 3$ integrins expressed on endothelial cells, with fibrinogen playing a pivotal role in this process [60]. The direct binding of the *S. aureus* surface protein named the iron-regulated surface determinant B (IsdB) to the $\alpha v \beta 3$ integrins within endothelial cells plays an essential role in host cell adhesion and invasion, leading to a life-threatening disease [137]. Therefore, $\alpha v \beta 3$ integrin blockade appears to be an attractive target for the treatment of blood-borne infections caused by *S. aureus*. Further, a force-enhanced adhesion between IsdB and integrins could be one of the multiple mechanisms evolved by *Staphylococci* to effectively colonize or invade their hosts while resisting

Table 2. Roles of different integrins during normal wound healing (granulation tissue) and bacterial infection

Type	Granulation tissue	Bacterial infection
$\alpha 5 \beta 1$	Regulates re-epithelialization and promotes migration of keratin-forming cells [135]	Mediates the attachment of eukaryotic cells to the extracellular matrix protein fibronectin [136]
$\alpha v \beta 3$	Regulates angiogenesis and promotes fibroblasts proliferation [17]	Mediates <i>Staphylococcus aureus</i> bloodstream infection [137]
$\alpha v \beta 6$	Regulates inflammation and keratin-forming cell proliferation [138]	Regulates bacterial biofilms [139,140]
$\alpha I I b \beta 3$	Mediates platelet aggregation [141]	Mediates adhesion of <i>Staphylococcus aureus</i> to platelets [142,143]

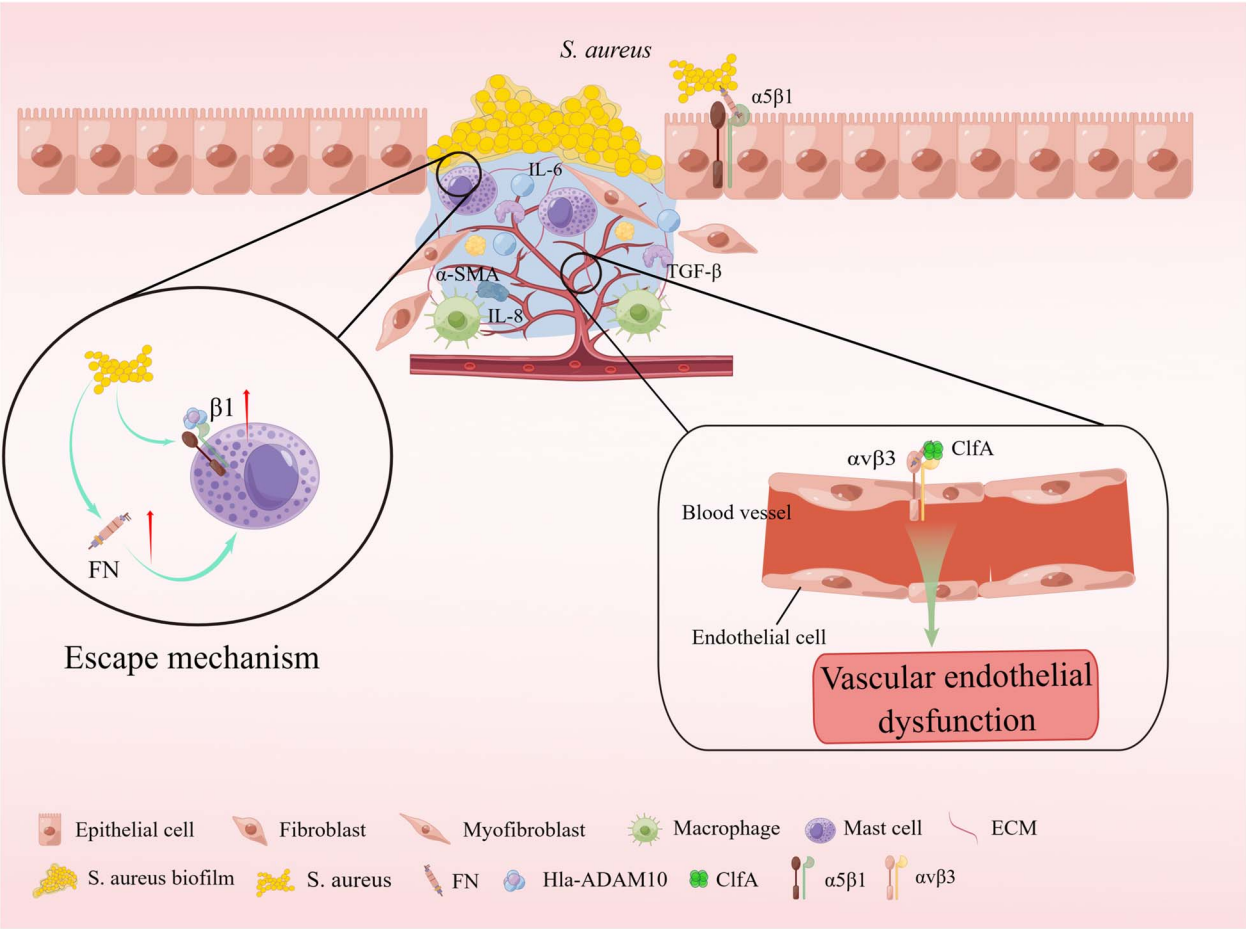


Figure 4. *S. aureus* evades the bactericidal mechanisms of the host cell. Fibronectin (FN) serves as a molecular bridge linking FN binding protein (FnBP)-expressing *S. aureus* to the $\alpha 5 \beta 1$ integrin present on the surface of human cells. FN tightly anchors *S. aureus* to its eukaryotic host cells and also facilitates the internalization of the microbe by human epithelial and endothelial cells and mouse fibroblasts. Further, the internalization of *S. aureus* by immortalized keratinocytes requires bacterial FnBPs and is mediated by the significant fibronectin-binding $\alpha 5 \beta 1$ integrin. *S. aureus* counteracts the extracellular bactericidal machinery of mast cells by increasing the expression of FnBP and inducing the Hla-ADAM10-mediated upregulation of $\beta 1$ integrins in mast cells. Vascular endothelial dysfunction is attributed to the adherence of the *S. aureus* aggregation factor A (ClfA) to the $\alpha v \beta 3$ integrins expressed on endothelial cells, with fibrinogen playing a key role during this process. The direct binding of the *S. aureus* surface protein iron-regulated surface determinant B iron-regulated surface determinant B (IsdB) to endothelial $\alpha v \beta 3$ integrins plays a vital role in host cell adhesion and invasion, ultimately leading to a life-threatening disease. IL-6 Interleukin 6, ECM extracellular matrix, Hla-ADAM10 Hla-a disintegrin and metalloproteinase 10, TGF- β transforming growth factor beta, α -SMA α -Smooth Muscle Actin. Reprinted with permission from Figdraw (www.figdraw.com)

the shear forces encountered in various environments after infection [161]. *Staphylococcus aureus* is capable of adhering to platelets via the high-affinity form of IsdB bound to the platelet integrin $\alpha I I b \beta 3$ without the requirement of additional ECM proteins [142,143]. In addition, the $\alpha D \beta 2$ integrins are

reported to play a role in *Salmonella typhimurium* and *S. aureus* infections [162].

Integrin-linked kinases (ILKs) and Rac1 mediate the invasion of keratinocytes by *S. aureus*, and these bacteria may invade keratinocytes via the ILK-Rac1 pathway. Therefore,

ILK could be a critical factor in preventing staphylococcal skin infections [163] and its use as a biological target in the treatment of *S. aureus* infections is speculated.

Integrins and *P. aeruginosa*

P. aeruginosa is a ubiquitous Gram-negative bacterial species present in the environment. This species is responsible for serious infections in skin wounds, such as in patients with severe burns [164]. *P. aeruginosa* infections are difficult to treat because these bacteria are highly resistant to antibiotics and rapidly acquire resistance to new antibiotics [165]. This species is capable of forming biofilms [166] and is known to invade and multiply in the host cells. *P. aeruginosa* has been demonstrated to have the propensity to enter and colonize injured epithelial cells [167]. Substantial experimental evidence suggests that loss of epithelial polarity increases the harmful effects of *P. aeruginosa* on host cells [167]. The bacterium has evolved ways of manipulating host epithelial cell polarity to promote its infection [167,168]. Integrins usually remain confined to the basolateral plasma membrane of epithelial cells, and when *P. aeruginosa* reaches the basolateral side, it gains access to integrins [169]. The current studies on integrin-mediated *P. aeruginosa* infections are mostly limited to $\alpha 5\beta 1$ and $\alpha v\beta 5$ integrins in respiratory epithelial cells [170–172]. The *P. aeruginosa* lectin is a fucose-specific lectin named LecB, which clears integrins from the surface of cells at the wound margin and blocks cell migration and wound healing in a dose-dependent manner [169]. Further studies are, we need to determine the role of integrins during *P. aeruginosa* infections in infected wounds, which appears to be a suitable direction for the treatment of *P. aeruginosa* infections.

Integrins and other bacteria

Integrins also mediate the infectious effects of a few other species of bacteria on their host organism. In the context of wound healing, no mechanistic studies to date have explored the interaction between integrins and *S. hemolyticus*. In addition, the current research on *A. baumannii* remains at the level of therapeutic applications to its infected organisms, such as a certain drug [173] or a therapeutic means for its treatment [174,175]. While no relevant research on the mechanism has been reported to date, this area appears to offer a broad scope for research.

Studies on the interaction between *E. coli* and integrins have focused mostly on intestinal infections [176] and urinary tract infections [177–179]. Hajj-Hussein *et al.* reported elevated levels of $\alpha v\beta 3$ and $\alpha ii\beta 3$ integrins in the treatment of colitis caused by *E. coli*, and this upregulation of integrins could be one of the reasons for increased inflammation and chronicity [176]. In addition, microRNA1976 is suggested to negatively regulate *E. coli*-induced vaginal inflammation in mice through the inhibition of CD105 and integrin $\alpha v\beta 6$ expression [179]. Recently, studies on the role of *E. coli* and platelets revealed that the interaction of *E. coli* $\alpha Iib\beta 3$ with

Fc gamma Receptor IIA (Fc γ RIIA) activated platelets, which then causes thrombophilia or sepsis [180,181].

Entry into epithelial cells and prevention of primary immune responses are prerequisites for the successful colonization and subsequent infection of human hosts by *Streptococcus pyogenes* (group A streptococci). The interaction of group A streptococci with fibrinogen promotes the integrin-mediated internalization of bacteria into keratin-forming cells, and integrins $\alpha 1\beta 1$ and $\alpha 5\beta 1$ are the major keratin-forming cell receptors involved in this process [182]. Excessive bacterial invasion disrupts the attachment between the tooth surface and the epithelium, leading to periodontitis. Integrin $\alpha 5$ could be involved in the invasion of *Aggregatibacter actinomycetemcomitans* Y4 into gingival epithelial cells, and the resulting cascade of signal transduction decreases cell adhesion and reduces the defensive role of gingival epithelial cells by reducing integrin expression [183]. The adhesion of *Candida albicans* germ tube human endothelial cell lines is mediated by $\alpha v\beta 3$, while this adhesion is significantly blocked by using either the anti- $\beta 3$ monoclonal antibody GRGDSP peptide or heparin, and eliminated by using the two in combination [184]. Therefore, $\alpha v\beta 3$ blockade could be used as a therapeutic tool against *C. albicans* infection. In addition, *Helicobacter pylori* induces the expression of integrin $\alpha 5\beta 1$ and activates *H. pylori*-infected gastric epithelial cells via proteinase-activated receptor-2)-induced trypsin, and this process might have an important role in *H. pylori*-associated carcinogenesis [185].

Integrins serve as suitable receptors for bacteria invading eukaryotic cells, including endothelial and epithelial cells, while evading the bactericidal actions of cells such as MCs. Activation of integrins, which act as pivotal mediators between bacteria and host cells during infections, creates a favorable environment for bacterial invasion of the host cell, facilitating the internalization and colonization of bacteria. This phenomenon contributes to the inflammatory response elicited in the host organism during the initial stages of infection. In addition, heightened integrin responsiveness aids the invading bacteria in evading the bactericidal cells of the host, thereby perpetuating the persistence of the wound. Therefore, inhibiting the activation of integrins could be an effective strategy in the treatment of bacterial infections.

Integrins and targeted therapy for bacterial infections

The integrin family is a large group of proteins in the human body that is involved in a variety of physiological processes. This family of proteins could be effectively utilized to regulate several pathophysiological processes in the organism. According to the mechanism of integrin-mediated bacterial infection in wound healing, it is speculated that bacterial infection in the vast majority of cases requires the regulation of integrins. Previously, it was believed that the interaction of staphylococcal alpha toxin with $\alpha 5\beta 1$ integrin and the overproduction of tumor necrosis factor alpha (TNF- α) contribute to the destruction of epithelial cells during *S. aureus* infection [186].

Recently, *S. aureus* was demonstrated to counteract the extra-cellular bactericidal mechanism of mast cells by increasing the expressions of FnBPs and inducing Hla-ADAM10-mediated upregulation of $\beta 1$ integrins in mast cells [157]. Therefore, inhibiting the targets associated with integrins could be an effective strategy for the treatment of *S. aureus* infections. Since the inhibition of the major integrin $\alpha V\beta 3$ reduces the attachment of *S. aureus* to sheared human endothelial cells [60], blocking $\alpha V\beta 3$ is considered an attractive strategy for the treatment of blood-borne infections caused by *S. aureus*. Alpha-melanocyte-stimulating hormone (α -MSH) is a neuropeptide produced primarily by the pituitary gland and also by several extra-pituitary cells, including skin keratin-forming cells. Evidence suggests that α -MSH exhibits anti-inflammatory and antimicrobial effects and reduces the internalization of *S. aureus*. In addition, α -MSH prematurely downregulates the production of integrins such as $\beta 1$ and heat shock surface protein 70 [187] to reduce the degree of infection and the inflammatory response.

In contrast, a study reported that in mice, *S. aureus* penetrated skin lacking ILK in the epidermis 35 times more than normal skin, indicating the great potential of ILK as a targeted therapy for the prevention of *S. aureus* skin infections [163]. Fibronectin or $\beta 1$ integrin-blocking antibodies reportedly eliminate the IFN- γ -dependent *S. aureus* junctions, and IFN- γ is capable of inducing human mast cells under the mediation of $\beta 1$ integrins to enhance antibacterial and pro-inflammatory responses to IFN- γ -dependent *S. aureus* [158]. The activation of integrins is perhaps more necessary in these cases. In addition, it is reported that *P. aeruginosa* produces the fucose-specific lectin LecB, which specifically removes the integrins from the surface of cells located at the wound margin and blocks cell migration and wound healing in a dose-dependent manner [123,169]. When appropriate, integrin supplementation could antagonize this blocking effect and promote wound healing.

In clinical trials for the treatment of sepsis, cilengitide prevented ClfA from binding $\alpha V\beta 3$ located on endothelial cells, thereby decelerating infection without affecting the normal functioning of endothelial cells [60]. Therefore, targeted inhibition of $\alpha V\beta 3$ treatment appears to be a locally applicable strategy for wound healing. The $\alpha 5\beta 1$ integrin is one of the staphylococcal α -toxin receptors that mediate α -toxin cytotoxicity [186]. According to a study, α -MSH exerts a protective effect on the skin by reducing infection and inflammatory processes through the downregulation of $\beta 1$ integrins [187]. LecB inhibitors could also be effective in the treatment strategy when used in combination with antibiotics [169,188]. In contrast, integrin receptors reportedly promote the increased binding of *S. aureus* to IFN γ -treated human Mast Cells (huMCs) [158], demonstrating the complexity of the MC response in the context of the cytokine environment. However, no relevant practical clinical studies have been conducted to date, and appropriate drug development and clinical trials are currently a top priority in the field of integrin-targeted therapy.

Therefore, under normal conditions without bacterial infection, supplementation of integrins is expected to promote wound healing. However, bacteria exploit integrins to invade the body and cause infections, turning integrins into accomplices. In this context, inhibiting integrins could be used as an effective approach to treat bacterial infections. The dual roles of promoting wound healing and inhibiting bacterial infection, however, raise a challenge in the treatment of chronic wound infections caused by bacteria, as integrins serve as a bridge between the bacteria and host cells. Therefore, developing a targeted drug specifically for integrins remains a challenge. For instance, in the case of *S. aureus*, supplementation of ILKs could potentially facilitate the penetration of the bacterium into the skin [163]. In the case of specific *Aureobacteria*, such as IFN- γ -dependent *S. aureus*, supplementation of $\beta 1$ integrins could potentially enhance the bactericidal effect of the organism [158]. With regard to *P. aeruginosa*, supplementation of integrins counteracts the integrin-scavenging effect caused by the bacterium's production of the fucose-specific lectin LecB, and under such circumstances, integrin supplementation would result in antimicrobial effects while also promoting wound healing, rendering it an advantageous approach. However, controlling the dynamic balance between the activation and inhibition of different fractional integrins during wound healing is key to wound healing and must be explored continuously.

Conclusions

The integrin family is a group of functionally diverse protein families that play key roles in various physiological and pathological mechanisms by serving as protein-cell, cell-cell and bacterium-cell bridges. The integrins and their metabolites, in addition to regulating wound healing, play an important role in bridging the gap between bacterial infection and the host cell in the wound. Bacterial adaptation to the environment and gradual familiarization with the immune system could result in diminished local immune defenses against infections, thereby exacerbating the progression toward chronic wound states. Simultaneously, the body's inherent healing mechanisms could become compromised, further impeding efficient wound healing. Therefore, a crucial initial endeavor to unravel the enigma of expediting chronic wound healing involves inducing an acute wound state. The involvement of the integrin family in mediating bacteria-host cell interactions during the intricate process of wound healing suggests the potential efficacy of incorporating selected integrin-related pharmaceutical agents or manipulating receptor expression to modulate integrin levels. Such interventions hold promise in regulating bacterial infections, thereby having the potential to interrupt the relentless progression toward chronic refractoriness, ultimately terminating the wound's transition to a chronic state. Therefore, utilizing integrin-based approaches in wound therapy appears to be a feasible strategy. Currently, only a few studies have explored the strategy of activating

integrins to block bacterial infections, and this area of research has a wide scope and warrants joint efforts to fill the existing gaps in research. *S. aureus* and *P. aeruginosa* are the two most common bacteria (Gram-positive and Gram-negative, respectively) detected in hospital-acquired infections. The two species have been discussed in the present review, with a focus on the mechanism of their invasion of the host organism via integrins, to provide a systematic review that will serve as a reference for advancing the treatment of clinical bacterial infections and a summary of recent studies on integrins and their related derivatives used as target therapeutics. In conclusion, the use of integrins as targets for blocking bacterial infections has great potential.

Acknowledgments

The authors acknowledge the administrative support of Yangzhou University. The figures were generated by Figdraw.

Funding

This work was supported by the National Natural Science Foundation of China [grant number 81802792], Project of Yangzhou University Medical Innovation and Transformation Special Fund New Medical Cross Innovation Team [grant number AHYZUCXTD 202108], Postgraduate Research & Practice Innovation Program of Jiangsu Province [grant number SJCX22_1822], Postdoctoral Science Foundation of Jiangsu Province [grant number 2020Z409], and Science and technology projects for social development of Yangzhou City [grant number YZ2022106].

Authors' contributions

YC had the idea for the article, DY drafted the manuscript, and ZYL and DY drew the table and figures. YC critically revised the work. All the authors were involved in revising the paper critically and read and approved the final manuscript.

Conflict of interest

None declared.

References

- Hynes RO. The emergence of integrins: a personal and historical perspective. *Matrix Biol.* 2004;23:333–40.
- Morse EM, Brahme NN, Calderwood DA. Integrin cytoplasmic tail interactions. *Biochemistry.* 2014;53:810–20.
- Humphries JD, Byron A, Humphries MJ. Integrin ligands at a glance. *J Cell Sci.* 2006;119:3901–3.
- Tselepis VH, Green LJ, Humphries MJ. An RGD to LDV motif conversion within the disintegrin kistrin generates an integrin antagonist that retains potency but exhibits altered receptor specificity. Evidence for a functional equivalence of acidic integrin-binding motifs. *J Biol Chem.* 1997;272:21341–8.
- Xiao T, Takagi J, Collier BS, Wang J-H, Springer TA. Structural basis for allostery in integrins and binding to fibrinogen-mimetic therapeutics. *Nature.* 2004;432:59–67.
- Pang X, He X, Qiu Z, Zhang H, Xie R, Liu Z, *et al.* Targeting integrin pathways: mechanisms and advances in therapy. *Signal Transduction and Targeted Therapy.* 2023;8:1.
- Takada Y, Ye X, Simon S. The integrins. *Genome Biol.* 2007;8:215.
- Hostetter MK. An integrin-like protein in *Candida albicans*: implications for pathogenesis. *Trends Microbiol.* 1996;4:242–6.
- LaFlamme SE, Auer KL. Integrin signaling. *Semin Cancer Biol.* 1996;7:111–8.
- Mezu-Ndubuisi OJ, Maheshwari A. The role of integrins in inflammation and angiogenesis. *Pediatr Res.* 2021;89:1619–26.
- Desgrosellier JS, Cheresch DA. Integrins in cancer: biological implications and therapeutic opportunities. *Nat Rev Cancer.* 2010;10:9–22.
- Martin P. Wound healing—aiming for perfect skin regeneration. *Science.* 1997;276:75–81.
- Gál P, Varinská L, Fáber L, Novák Š, Szabo P, Mitrengová P, *et al.* How Signaling molecules regulate tumor microenvironment: parallels to wound repair. *Molecules.* 2017;22:1818.
- Han Z, Ma Y, Cao G, Ma Z, Chen R, Cvijic ME, *et al.* Integrin $\alpha V\beta 1$ regulates procollagen I production through a non-canonical transforming growth factor β signaling pathway in human hepatic stellate cells. *Biochem J.* 2021;478:1689–703.
- Yamashiro Y, Thang BQ, Ramirez K, Shin SJ, Kohata T, Ohata S, *et al.* Matrix mechanotransduction mediated by thrombospondin-1/integrin/YAP in the vascular remodeling. *Proc Natl Acad Sci.* 2020;117:9896–905.
- Rusnati M, Tanghetti E, Dell'era P, Gualandris A, Presta M. $\alpha 5\beta 1$ integrin mediates the cell-adhesive capacity and biological activity of basic fibroblast growth factor (FGF-2) in cultured endothelial cells. *Mol Biol Cell.* 1997;8:2449–61.
- Mitchell K, Szekeres C, Milano V, Svenson KB, Nilsen-Hamilton M, Kreidberg JA, *et al.* $\alpha 3\beta 1$ integrin in epidermis promotes wound angiogenesis and keratinocyte-to-endothelial-cell crosstalk through the induction of MRP3. *J Cell Sci.* 2009;122:1778–87.
- Kokubo T, Uchida H, Choi ET. Integrin $\alpha v\beta 3$ as a target in the prevention of neointimal hyperplasia. *J Vasc Surg.* 2007;45:A33–8.
- Guermónprez P, Valladeau J, Zitvogel L, Théry C, Amigorena S. Antigen presentation and T cell stimulation by dendritic cells. *Annu Rev Immunol.* 2002;20:621–67.
- Bishop GG, McPherson JA, Sanders JM, Hesselbacher SE, Feldman MJ, McNamara CA, *et al.* Selective $\alpha v\beta 3$ -receptor blockade reduces macrophage infiltration and restenosis after balloon angioplasty in the atherosclerotic rabbit. *Circulation.* 2001;103:1906–11.
- Porte J, Jenkins G, Tatler AL. Myofibroblast TGF- β Activation Measurement In Vitro. In: Hinz L (ed). *Myofibroblasts: Methods and Protocols.* New York, NY: Springer US, 2021, 99–108.
- Asano Y, Ihn H, Jinnin M, Mimura Y, Tamaki K. Involvement of $\alpha 5\beta 1$ integrin in the establishment of autocrine TGF- β signaling in dermal fibroblasts derived from localized scleroderma. *J Invest Dermatol.* 2006;126:1761–9.
- Ansar M, Jan A, Santos-Cortez RLP, Wang X, Suliman M, Acharya A, *et al.* Expansion of the spectrum of ITGB6-related disorders to adolescent alopecia, dentogingival abnormalities and intellectual disability. *Eur J Hum Genet.* 2016;24:1223–7.

24. Xie Y, Gao K, Häkkinen L, Larjava HS. Mice lacking $\beta 6$ integrin in skin show accelerated wound repair in dexamethasone impaired wound healing model. *Wound Repair Regen.* 2009;17:326–39.
25. Zhou M, Niu J, Wang J, Gao H, Shahbaz M, Niu Z, *et al.* Integrin $\alpha v \beta 8$ serves as a novel marker of poor prognosis in colon carcinoma and regulates cell invasiveness through the activation of TGF- $\beta 1$. *J Cancer.* 2020;11:3803–15.
26. Nishimichi N, Tsujino K, Kanno K, Sentani K, Kobayashi T, Chayama K, *et al.* Induced hepatic stellate cell integrin, $\alpha 8 \beta 1$, enhances cellular contractility and TGF- β activity in liver fibrosis. *J Pathol.* 2021;253:366–73.
27. Hou J, Yan D, Liu Y, Huang P, Cui H. The roles of integrin $\alpha 5 \beta 1$ in human cancer. *Onco Targets Ther.* 2020;13:13329–44.
28. Kiwanuka E, Andersson L, Caterson EJ, Junker JPE, Gerdin B, Eriksson E. CCN2 promotes keratinocyte adhesion and migration via integrin $\alpha 5 \beta 1$. *Exp Cell Res.* 2013;319:2938–46.
29. Huang J, Li X, Shi X, Zhu M, Wang J, Huang S, *et al.* Platelet integrin $\alpha IIb \beta 3$: signal transduction, regulation, and its therapeutic targeting. *J Hematol Oncol.* 2019;12:26.
30. Baldassarro VA, Giraldo V, Giuliani A, Moretti M, Pagnotta G, Flagelli A, *et al.* Poly (l-lactic acid) scaffold releasing an $\alpha 4 \beta 1$ integrin agonist promotes nonfibrotic skin wound healing in diabetic mice. *ACS Applied Bio Materials.* 2023;6:296–308.
31. Eto K, Huet C, Tarui T, Kupriyanov S, Liu HZ, Puzon-McLaughlin W, *et al.* Functional classification of ADAMs based on a conserved motif for binding to integrin $\alpha 9 \beta 1$ - implications for sperm-egg binding and other cell interactions. *J Biol Chem.* 2002;277:17804–10.
32. Vlahakis NE, Young BA, Atakilit A, Sheppard D. The Lymphangiogenic vascular endothelial growth factors VEGF-C and -D are ligands for the integrin $\alpha 9 \beta 1$. *J Biol Chem.* 2005;280:4544–52.
33. Singh P, Chen C, Pal-Ghosh S, Stepp MA, Sheppard D, Van De Water L. Loss of integrin $\alpha 9 \beta 1$ results in defects in proliferation, causing poor re-epithelialization during cutaneous wound healing. *J Invest Dermatol.* 2009;129:217–28.
34. Nakayama Y, Kon S, Kurotaki D, Morimoto J, Matsui Y, Uede T. Blockade of interaction of $\alpha 9$ integrin with its ligands hinders the formation of granulation in cutaneous wound healing. *Lab Invest.* 2010;90:881–94.
35. Oommen S, Gupta SK, Vlahakis NE. Vascular endothelial growth factor a (VEGF-A) induces endothelial and cancer cell migration through direct binding to integrin $\alpha 9 \beta 1$: identification of a specific $\alpha 9 \beta 1$ binding site. *J Biol Chem.* 2011;286:1083–92.
36. Høye AM, Couchman JR, Wewer UM, Fukami K, Yoneda A. The newcomer in the integrin family: integrin $\alpha 9$ in biology and cancer. *Advances in Biological Regulation.* 2012;52:326–39.
37. Tan S-M. The leucocyte $\beta 2$ (CD18) integrins: the structure, functional regulation and signalling properties. *Biosci Rep.* 2012;32:241–69.
38. Yuki K, Hou L. Role of $\beta 2$ Integrins in neutrophils and sepsis. *Infect Immun.* 2020;88:e00031–20.
39. Sisco M, Chao JD, Kim I, Mogford JE, Mayadas TN, Mustoe TA. Delayed wound healing in mac-1-deficient mice is associated with normal monocyte recruitment. *Wound Repair Regen.* 2007;15:566–71.
40. Garnotel R, Rittie L, Poitevin S, Monboisse JC, Nguyen P, Potron G, *et al.* Human blood monocytes interact with type I collagen through $\alpha X \beta 2$ integrin (CD11c-CD18, gp150-95). *J Immunol.* 2000;164:5928–34.
41. Jawhara S, Pluskota E, Cao W, Plow Edward F, Soloviev DA. Distinct effects of Integrins $\alpha X \beta 2$ and $\alpha M \beta 2$ on leukocyte subpopulations during inflammation and antimicrobial responses. *Infect Immun.* 2016;85:e00644–16.
42. Miyazaki Y, Vieira-de-Abreu A, Harris ES, Shah AM, Weyrich AS, Castro-Faria-Neto HC, *et al.* Integrin $\alpha D \beta 2$ (CD11d/CD18) is expressed by human circulating and tissue myeloid leukocytes and mediates inflammatory Signaling. *PLoS One.* 2014;9:e112770.
43. Ghatak S, Niland S, Schulz J-N, Wang F, Eble JA, Leitges M, *et al.* Role of Integrins $\alpha 1 \beta 1$ and $\alpha 2 \beta 1$ in wound and tumor angiogenesis in mice. *Am J Pathol.* 2016;186:3011–27.
44. Grenache DG, Zhang Z, Wells LE, Santoro SA, Davidson JM, Zutter MM. Wound healing in the $\alpha 2 \beta 1$ integrin-deficient mouse: altered keratinocyte biology and dysregulated matrix metalloproteinase expression. *J Invest Dermatol.* 2007;127:455–66.
45. Erusappan P, Alam J, Lu N, Zeltz C, Gullberg D. Integrin $\alpha 11$ cytoplasmic tail is required for FAK activation to initiate 3D cell invasion and ERK-mediated cell proliferation. *Sci Rep.* 2019;9:15283.
46. Ramovs V, te Molder L, Sonnenberg A. The opposing roles of laminin-binding integrins in cancer. *Matrix Biol.* 2017;57:58:213–43.
47. Reynolds LE, D'Amico G, Lechertier T, Papachristodoulou A, Muñoz-Félix JM, De Arcangelis A, *et al.* Dual role of pericyte $\alpha 6 \beta 1$ -integrin in tumour blood vessels. *J Cell Sci.* 2017;130:1583–95.
48. Margadant C, Raymond K, Kreft M, Sachs N, Janssen H, Sonnenberg A. Integrin $\alpha 3 \beta 1$ inhibits directional migration and wound re-epithelialization in the skin. *J Cell Sci.* 2009;122:278–88.
49. Jun J-I, Lau LF. The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing. *Nat Cell Biol.* 2010;12:676–85.
50. Hayashi YK, Chou F-L, Engvall E, Ogawa M, Matsuda C, Hirabayashi S, *et al.* Mutations in the integrin $\alpha 7$ gene cause congenital myopathy. *Nat Genet.* 1998;19:94–7.
51. Flintoff-Dye NL, Welser J, Rooney J, Scowen P, Tamowski S, Hatton W, *et al.* Role for the $\alpha 7 \beta 1$ integrin in vascular development and integrity. *Dev Dyn.* 2005;234:11–21.
52. Blanco-Mezquita JT, Hutcheon AEK, Stepp MA, Zieske JD. $\alpha V \beta 6$ integrin promotes corneal wound healing. *Invest Ophthalmol Vis Sci.* 2011;52:8505–13.
53. Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. *J Clin Invest.* 2007;117:1219–22.
54. Harding KG, Morris HL, Patel GK. Healing chronic wounds. *BMJ.* 2002;324:160–3.
55. Bishop A. Role of oxygen in wound healing. *J Wound Care.* 2008;17:399–402.
56. Edwards R, Harding KG. Bacteria and wound healing. *Curr Opin Infect Dis.* 2004;17:91–6.
57. Swift ME, Burns AL, Gray KL, DiPietro LA. Age-related alterations in the inflammatory response to dermal injury. *J Invest Dermatol.* 2001;117:1027–35.
58. Canchy L, Kerob D, Demessant AL, Amici J-M. Wound healing and microbiome, an unexpected relationship. *J Eur Acad Dermatol Venereol.* 2023;37:7–15.

59. Robertin S, Brokatzky D, Lobato-Márquez D, Mostowy S. Regulation of integrin $\alpha 5\beta 1$ -mediated Staphylococcus aureus cellular invasion by the septin cytoskeleton. *Eur J Cell Biol.* 2023;102:151359.
60. McDonnell CJ, Garcarena CD, Watkin RL, McHale TM, McLoughlin A, Claes J, et al. Inhibition of major integrin $\alpha V\beta 3$ reduces Staphylococcus aureus attachment to sheared human endothelial cells. *J Thromb Haemost.* 2016;14:2536–47.
61. Kadry YA, Calderwood DA. Chapter 22: structural and signaling functions of integrins. *Biochim Biophys Acta Biomembr.* 2020;1862:183206.
62. Ivaska J, Heino J. Cooperation between Integrins and growth factor receptors in Signaling and endocytosis. *Annu Rev Cell Dev Biol.* 2011;27:291–320.
63. Sun Z, Guo SS, Fässler R. Integrin-mediated mechanotransduction. *J Cell Biol.* 2016;215:445–56.
64. Kolasangiani R, Bidone TC, Schwartz MA. Integrin conformational dynamics and Mechanotransduction. *Cells.* 2022;11:3584.
65. Kanchanawong P, Calderwood DA. Organization, dynamics and mechanoregulation of integrin-mediated cell–ECM adhesions. *Nat Rev Mol Cell Biol.* 2023;24:142–61.
66. Janus-Bell E, Mangin PH. The relative importance of platelet integrins in hemostasis, thrombosis and beyond. *Haematologica.* 2023;108:1734–47.
67. Hynes RO. Integrins: bidirectional, allosteric Signaling machines. *Cell.* 2002;110:673–87.
68. Litvinov RI, Mravic M, Zhu H, Weisel JW, DeGrado WF, Bennett JS. Unique transmembrane domain interactions differentially modulate integrin $\alpha v\beta 3$ and $\alpha IIb\beta 3$ function. *Proc Natl Acad Sci USA.* 2019;116:12295–300.
69. Wagner CL, Mascelli MA, Neblock DS, Weisman HF, Collier BS, Jordan RE. Analysis of GPIIb/IIIa receptor number by quantification of 7E3 binding to human platelets. *Blood.* 1996;88:907–14.
70. Jackson SP. Arterial thrombosis—insidious, unpredictable and deadly. *Nat Med.* 2011;17:1423–36.
71. Versteeg HH, Heemskerk JWM, Levi M, Reitsma PH. New fundamentals in Hemostasis. *Physiol Rev.* 2013;93:327–58.
72. Janus-Bell E, Yakusheva A, Scandola C, Receveur N, Ahmed UM, Mouriaux C, et al. Characterization of the role of integrin $\alpha 5\beta 1$ in platelet function, Hemostasis, and experimental thrombosis. *Thromb Haemost.* 2022;122:767–76.
73. Simic D, Bogdan N, Teng F, Otieno M. Blocking $\alpha 5\beta 1$ integrin attenuates sCD40L-mediated platelet activation. *Clin Appl Thromb Hemost.* 2015;23:607–14.
74. Kumawat AK, Yu C, Mann EA, Schridde A, Finnemann SC, Mowat AM. Expression and characterization of $\alpha v\beta 5$ integrin on intestinal macrophages. *Eur J Immunol.* 2018;48:1181–7.
75. Albert ML, Pearce SF, Francisco LM, Sauter B, Roy P, Silverstein RL, et al. Immature dendritic cells phagocytose apoptotic cells via alphavbeta5 and CD36, and cross-present antigens to cytotoxic T lymphocytes. *J Exp Med.* 1998;188:1359–68.
76. Koivisto L, Bi J, Häkkinen L, Larjava H. Integrin $\alpha v\beta 6$: structure, function and role in health and disease. *Int J Biochem Cell Biol.* 2018;99:186–96.
77. Sun Q, Lu Z, Ma L, Xue D, Liu C, Ye C, et al. Integrin $\beta 6$ deficiency protects mice from experimental colitis and colitis-associated carcinoma by altering macrophage polarization. *Front. Oncologia.* 2023;13:1190229.
78. Kelly A, Gunaltay S, McEntee CP, Shuttleworth EE, Smedley C, Houston SA, et al. Human monocytes and macrophages regulate immune tolerance via integrin $\alpha v\beta 8$ -mediated TGF- β activation. *J Exp Med.* 2018;215:2725–36.
79. Takasaka N, Seed RI, Cormier A, Bondesson AJ, Lou J, Elattma A, et al. Integrin $\alpha v\beta 8$ -expressing tumor cells evade host immunity by regulating TGF- β activation in immune cells. *JCI Insight.* 2018;3:e122591.
80. Pierini LM, Lawson MA, Eddy RJ, Hendey B, Maxfield FR. Oriented endocytic recycling of $\alpha 5\beta 1$ in motile neutrophils. *Blood.* 2000;95:2471–80.
81. Loike JD, Cao L, Budhu S, Marcantonio EE, El Khoury J, Hoffman S, et al. Differential regulation of beta1 integrins by chemoattractants regulates neutrophil migration through fibrin. *J Cell Biol.* 1999;144:1047–56.
82. Burns JA, Issekutz TB, Yagita H, Issekutz AC. The $\alpha 4\beta 1$ (very late antigen (VLA)-4, CD49d/CD29) and $\alpha 5\beta 1$ (VLA-5, CD49e/CD29) Integrins mediate $\beta 2$ (CD11/CD18) integrin-independent neutrophil recruitment to endotoxin-induced lung Inflammation1. *J Immunol.* 2001;166:4644–9.
83. Stupack DG, Cheresch DA. Integrins and Angiogenesis. In: Michael A. Rudnicki, F. Jeffrey Dilworth (eds.), *Current Topics in Developmental Biology*. United States: Academic Press, 2004, 207–38.
84. Senger DR, Davis GE. Angiogenesis. *Cold Spring Harb Perspect Biol.* 2011;3:a005090.
85. Davis GE, Senger DR. Endothelial extracellular matrix. *Circ Res.* 2005;97:1093–107.
86. Labat-Robert J. Cell–matrix interactions, the role of fibronectin and integrins. A survey. *Pathol Biol.* 2012;60:15–9.
87. Avraamides CJ, Garmy-Susini B, Varner JA. Integrins in angiogenesis and lymphangiogenesis. *Nat Rev Cancer.* 2008;8:604–17.
88. Nisato RE, Tille J-C, Jonczyk A, Goodman SL, Pepper MS. $\alpha v\beta 3$ and $\alpha v\beta 5$ integrin antagonists inhibit angiogenesis in vitro. *Angiogenesis.* 2003;6:105–19.
89. Soldi R, Mitola S, Strasly M, Defilippi P, Tarone G, Bussolino F. Role of $\alpha v\beta 3$ integrin in the activation of vascular endothelial growth factor receptor-2. *EMBO J.* 1999;18:882–92.
90. Gumina DL, Ji S, Flockton A, McPeak K, Stich D, Moldovan R, et al. Dysregulation of integrin $\alpha v\beta 3$ and $\alpha 5\beta 1$ impedes migration of placental endothelial cells in fetal growth restriction. *Development.* 2022;149:dev200717-dev.
91. Diaz C, Neubauer S, Rechenmacher F, Kessler H, Missirlis D. Recruitment of $\alpha v\beta 3$ integrin to $\alpha 5\beta 1$ integrin-induced clusters enables focal adhesion maturation and cell spreading. *J Cell Sci.* 2020;133:jcs232702.
92. Danilucci TM, Santos PK, Pachane BC, Pisani GFD, Lino RLB, Casali BC, et al. Recombinant RGD-disintegrin DisBa-01 blocks integrin $\alpha v\beta 3$ and impairs VEGF signaling in endothelial cells. *Cell Commun Signal.* 2019;17:27.
93. Hao D, Liu R, Gao K, He C, He S, Zhao C, et al. Developing an injectable Nanofibrous extracellular matrix hydrogel with an integrin $\alpha v\beta 3$ ligand to improve endothelial cell survival, engraftment and vascularization. *Front Bioeng. Biotechnol.* 2020;8:890.
94. Sui A, Zhong Y, Demetriades AM, Shen J, Su T, Yao Y, et al. ATN-161 as an integrin $\alpha 5\beta 1$ antagonist depresses ocular neovascularization by promoting new vascular endothelial cell apoptosis. *Med Sci Monit.* 2018;24:5860–73.

95. Orecchia A, Mettouchi A, Uva P, Simon GC, Arcelli D, Avitabile S, *et al.* Endothelial cell adhesion to soluble vascular endothelial growth factor receptor-1 triggers a cell dynamic and angiogenic phenotype. *FASEB J.* 2014;28:692–704.
96. Lee HS, Oh SJ, Lee K-H, Lee Y-S, Ko E, Kim KE, *et al.* Gln-362 of angiopoietin-2 mediates migration of tumor and endothelial cells through association with $\alpha 5\beta 1$ integrin. *J Biol Chem.* 2014;289:31330–40.
97. Schnittert J, Bansal R, Storm G, Prakash J. Integrins in wound healing, fibrosis and tumor stroma: high potential targets for therapeutics and drug delivery. *Adv Drug Deliv Rev.* 2018;129:37–53.
98. Lygoe KA, Norman JT, Marshall JF, Lewis MP. αv integrins play an important role in myofibroblast differentiation. *Wound Repair Regen.* 2004;12:461–70.
99. Asano Y, Ihn H, Yamane K, Jinnin M, Tamaki K. Increased expression of integrin $\alpha v\beta 5$ induces the Myofibroblastic differentiation of dermal fibroblasts. *Am J Pathol.* 2006;168: 499–510.
100. Wang L, Pedroja BS, Meyers EE, Garcia AL, Twining SS, Bernstein AM. Degradation of internalized $\alpha v\beta 5$ integrin is controlled by uPAR bound uPA: effect on $\beta 1$ integrin activity and α -SMA stress fiber assembly. *PLoS One.* 2012;7:e33915-e.
101. Reynolds LE, Conti FJ, Lucas M, Grose R, Robinson S, Stone M, *et al.* Accelerated re-epithelialization in $\beta 3$ -integrin-deficient mice is associated with enhanced TGF- $\beta 1$ signaling. *Nat Med.* 2005;11:167–74.
102. Kato A, Okamoto O, Ishikawa K, Sumiyoshi H, Matsuo N, Yoshioka H, *et al.* Dermatopontin interacts with fibronectin, promotes fibronectin fibril formation, and enhances cell adhesion*. *J Biol Chem.* 2011;286:14861–9.
103. Brooks R, Williamson RC, Bass MD. Syndecan-4 independently regulates multiple small GTPases to promote fibroblast migration during wound healing. *Small GTPases.* 2012;3:73–9.
104. Trebaul A, Chan EK, Midwood KS. Regulation of fibroblast migration by tenascin-C. *Biochem Soc Trans.* 2007;35: 695–7.
105. Friedl P, Gilmour D. Collective cell migration in morphogenesis, regeneration and cancer. *Nat Rev Mol Cell Biol.* 2009;10:445–57.
106. Koivisto L, Häkkinen L, Larjava H. Re-epithelialization of wounds. *Endod Top.* 2011;24:59–93.
107. Koivisto L, Heino J, Häkkinen L, Larjava H. Integrins in wound healing. *Advances in Wound Care.* 2013;3:762–83.
108. Larjava H, Koivisto L, Häkkinen L, Heino J. Epithelial Integrins with special reference to oral epithelia. *J Dent Res.* 2011;90:1367–76.
109. Bata-Csorgo Z, Cooper KD, Ting KM, Voorhees JJ, Hammerberg C. Fibronectin and $\alpha 5$ integrin regulate keratinocyte cell cycling. A mechanism for increased fibronectin potentiation of T cell lymphokine-driven keratinocyte hyperproliferation in psoriasis. *J Clin Invest.* 1998;101:1509–18.
110. Zhang Z, Morla A, Vuori K, Bauer J, Juliano R, Ruoslahti E. The $\alpha v\beta 1$ integrin functions as a fibronectin receptor but does not support fibronectin matrix assembly and cell migration on fibronectin. *J Cell Biol.* 1993;122:235–42.
111. Haapasalmi K, Zhang K, Tonnesen M, Olerud J, Sheppard D, Salo T, *et al.* Keratinocytes in human wounds express $\alpha v\beta 6$ integrin. *J Invest Dermatol.* 1996;106:42–8.
112. Clark RAF, Ashcroft GS, Spencer MJ, Larjava H, Ferguson MWJ. Re-epithelialization of normal human excisional wounds is associated with a switch from $\alpha v\beta 5$ to $\alpha v\beta 6$ integrins. *Br J Dermatol.* 1996;135:46–51.
113. Worthington JJ, Klementowicz JE, Travis MA. TGF β : a sleeping giant awoken by integrins. *Trends Biochem Sci.* 2011;36:47–54.
114. Sarrazy V, Billet F, Micallef L, Coulomb B, Desmouliere A. Mechanisms of pathological scarring: role of myofibroblasts and current developments. *Wound Repair Regen.* 2011;19:S10–5.
115. Wang P-H, Huang B-S, Horng H-C, Yeh C-C, Chen Y-J. Wound healing. *Journal of the Chinese Medical Association.* 2018;81:94–101.
116. Mustoe TA, O'Shaughnessy K, Kloeters O. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. *Plast Reconstr Surg.* 2006;117:35S–41.
117. Theocharis AD, Skandalis SS, Gialeli C, Karamanos NK. Extracellular matrix structure. *Adv Drug Deliv Rev.* 2016;97:4–27.
118. Rhoads DD, Cox SB, Rees EJ, Sun Y, Wolcott RD. Clinical identification of bacteria in human chronic wound infections: culturing vs. 16S ribosomal DNA sequencing. *BMC Infect Dis.* 2012;12:321.
119. Silva V, Marcoleta A, Silva V, Flores D, Aparicio T, Aburto I, *et al.* Prevalencia y perfil de susceptibilidad antimicrobiana en bacterias aisladas de úlceras crónicas infectadas en adultos. *Rev Chilena Infectol.* 2018;35:155–62.
120. Percival SL, Emanuel C, Cutting KF, Williams DW. Microbiology of the skin and the role of biofilms in infection. *Int Wound J.* 2012;9:14–32.
121. Bjarnsholt T. The role of bacterial biofilms in chronic infections. *APMIS.* 2013;121:1–58.
122. Wu Y-K, Cheng N-C, Cheng C-M. Biofilms in chronic wounds: pathogenesis and diagnosis. *Trends Biotechnol.* 2019;37: 505–17.
123. Rowan-Nash Aislinn D, Korry Benjamin J, Mylonakis E, Belenky P. Cross-domain and viral interactions in the microbiome. *Microbiol Mol Biol Rev.* 2019;83:e00044–18.
124. Venkatesan N, Perumal G, Doble M. Bacterial resistance in biofilm-associated bacteria. *Future Microbiol.* 2015;10: 1743–50.
125. Chambers HF, Deleo FR. Waves of resistance: Staphylococcus aureus in the antibiotic era. *Nat Rev Microbiol.* 2009;7: 629–41.
126. Breuer K, Haussler S, Kapp A, Werfel T. Staphylococcus aureus: colonizing features and influence of an antibacterial treatment in adults with atopic dermatitis. *Br J Dermatol.* 2002;147:55–61.
127. Chiller K, Selkin BA, Murakawa GJ. Skin microflora and bacterial infections of the skin. *J Invest Dermatol Symp Proc.* 2001;6:170–4.
128. Cho S-H, Strickland I, Boguniewicz M, Leung DYM. Fibronectin and fibrinogen contribute to the enhanced binding of Staphylococcus aureus to atopic skin. *J Allergy Clin Immunol.* 2001;108:269–74.
129. Cho S-H, Strickland I, Tomkinson A, Fehring AP, Gelfand EW, Leung DYM. Preferential binding of Staphylococcus aureus to skin sites of Th2-mediated inflammation in a murine model. *J Invest Dermatol.* 2001;116:658–63.
130. Morishita Y, Tada J, Sato A, Toi Y, Kanzaki H, Akiyama H, *et al.* Possible influences of Staphylococcus aureus on atopic dermatitis - the colonizing features and the effects of staphylococcal enterotoxins. *Clin Exp Allergy.* 1999;29:1110–7.

131. Skov L, Baadsgaard O. Bacterial superantigens and inflammatory skin diseases. *Clin Exp Dermatol*. 2000;25:57–61.
132. Patel GK, Finlay AY. Staphylococcal scalded skin syndrome. *Am J Clin Dermatol*. 2003;4:165–75.
133. Yarwood JM, Leung DYM, Schlievert PM. Evidence for the involvement of bacterial superantigens in psoriasis, atopic dermatitis, and Kawasaki syndrome. *FEMS Microbiol Lett*. 2000;192:1–7.
134. Bowler PG, Duerden BI, Armstrong DG. Wound microbiology and associated approaches to wound management. *Clin Microbiol Rev*. 2001;14:244–69.
135. Di Russo J, Young JL, Wegner JW, Steins T, Kessler H, Spatz JP. Integrin $\alpha 5 \beta 1$ nano-presentation regulates collective keratinocyte migration independent of substrate rigidity. *elife*. 2021;10:e69861.
136. Hynes RO. Targeted mutations in cell adhesion genes: what have we learned from them? *Dev Biol*. 1996;180:402–12.
137. Mathelie-Guinlet M, Viela F, Alfeo MJ, Pietrocola G, Speziale P, Dufrene YF. Single-molecule analysis demonstrates stress-enhanced binding between Staphylococcus aureus surface protein IsdB and host cell Integrins. *Nano Lett*. 2020;20:8919–25.
138. Jakhu H, Gill G, Singh A. Role of integrins in wound repair and its periodontal implications. *Journal of Oral Biology and Craniofacial Research*. 2018;8:122–5.
139. Uehara O, Bi J, Zhuang D, Koivisto L, Abiko Y, Häkkinen L, et al. Altered composition of the oral microbiome in integrin $\beta 6$ -deficient mouse. *Journal of Oral Microbiology*. 2022;14:2122283.
140. Bi J, Koivisto L, Pang A, Li M, Jiang G, Aurora S, et al. Suppression of $\alpha v \beta 6$ integrin expression by Polymicrobial oral biofilms in gingival epithelial cells. *Sci Rep*. 2017;7:4411.
141. Blue R, Kowalska MA, Hirsch J, Murcia M, Janczak CA, Harrington A, et al. Structural and therapeutic insights from the species specificity and in vivo antithrombotic activity of a novel αIIb -specific $\alpha IIb \beta 3$ antagonist. *Blood*. 2009;114:195–201.
142. Miajlovic H, Zapotoczna M, Geoghegan JA, Kerrigan SW, Speziale P, Foster TJ. Direct interaction of iron-regulated surface determinant IsdB of Staphylococcus aureus with the GPIIb/IIIa receptor on platelets. *Microbiology-SGM*. 2010;156:920–8.
143. Zapotoczna M, Jevnikar Z, Miajlovic H, Kos J, Foster TJ. Iron-regulated surface determinant B (IsdB) promotes Staphylococcus aureus adherence to and internalization by non-phagocytic human cells. *Cell Microbiol*. 2013;15:1026–41.
144. Patti JM, Allen BL, McGavin MJ, Höök M. MSCRAMM-mediated adherence of microorganisms to host tissues. *Ann Rev Microbiol*. 1994;48:585–617.
145. Foster TJ, Höök M. Surface protein adhesins of Staphylococcus aureus. *Trends Microbiol*. 1998;6:484–8.
146. Jönsson K, Signäs C, Müller H-P, Lindberg M. Two different genes encode fibronectin binding proteins in Staphylococcus aureus. *Eur J Biochem*. 1991;202:1041–8.
147. Flock JJ, Fröman G, Jönsson K, Guss B, Signäs C, Nilsson B, et al. Cloning and expression of the gene for a fibronectin-binding protein from Staphylococcus aureus. *EMBO J*. 1987;6:2351–7.
148. Schwartz MA, Ginsberg MH. Networks and crosstalk: integrin signalling spreads. *Nat Cell Biol*. 2002;4:E65–8.
149. Agerer F, Michel A, Ohlsen K, Hauck CR. Integrin-mediated invasion of Staphylococcus aureus into human cells requires Src family protein-tyrosine kinases*. *J Biol Chem*. 2003;278:42524–31.
150. Joh D, Wann ER, Kreikemeyer B, Speziale P, Höök M. Role of fibronectin-binding MSCRAMMs in bacterial adherence and entry into mammalian cells. *Matrix Biol*. 1999;18:211–23.
151. Dzievanowska K, Patti JM, Deobald CF, Bayles KW, Trumble WR, Bohach GA. Fibronectin binding protein and host cell tyrosine kinase are required for internalization of Staphylococcus aureus by epithelial cells. *Infect Immun*. 1999;67:4673–8.
152. Jett BD, Gilmore MS. Internalization of Staphylococcus aureus by human corneal epithelial cells: role of bacterial fibronectin-binding protein and host cell factors. *Infect Immun*. 2002;70:4697–700.
153. Sinha B, Francois PP, Nusse O, Foti M, Hartford OM, Vaudaux P, et al. Fibronectin-binding protein acts as Staphylococcus aureus invasin via fibronectin bridging to integrin $\alpha 5 \beta 1$. *Cell Microbiol*. 1999;1:101–17.
154. Fowler T, Wann ER, Joh D, Johansson S, Foster TJ, Höök M. Cellular invasion by Staphylococcus aureus involves a fibronectin bridge between the bacterial fibronectin-binding MSCRAMMs and host cell $\beta 1$ integrins. *Eur J Cell Biol*. 2000;79:672–9.
155. Baude J, Bastien S, Gillet Y, Leblanc P, Itzek A, Tristan A, et al. Necrotizing soft tissue infection Staphylococcus aureus but not S. Pyogenes isolates display high rates of internalization and cytotoxicity toward human myoblasts. *J Infect Dis*. 2019;220:710–9.
156. Kintarak S, Whawell SA, Speight PM, Packer S, Nair SP. Internalization of Staphylococcus aureus by human keratinocytes. *Infect Immun*. 2004;72:5668–75.
157. Goldmann O, Tuchscher L, Rohde M, Medina E. α -Hemolysin enhances Staphylococcus aureus internalization and survival within mast cells by modulating the expression of $\beta 1$ integrin. *Cell Microbiol*. 2016;18:807–19.
158. Swindle EJ, Brown JM, Radinger M, DeLeo FR, Metcalfe DD. Interferon-gamma enhances both the anti-bacterial and the pro-inflammatory response of human mast cells to Staphylococcus aureus. *Immunology*. 2015;146:470–85.
159. Liang XD, Ji YD. Alpha-toxin interferes with integrin-mediated adhesion and internalization of Staphylococcus aureus by epithelial cells. *Cell Microbiol*. 2006;8:1656–68.
160. Melby AK, Cue D, Mousa SA, Cleary PP. An $\alpha 5 \beta 1 / \alpha v \beta 3$ integrin antagonist inhibits Staphylococcus aureus invasion of epithelial cells. *Abstr Gen Meet Am Soc Microbiol*. 2000;100:71.
161. Otto M. Physical stress and bacterial colonization. *FEMS Microbiol Rev*. 2014;38:1250–70.
162. Nascimento DO, Vieira-De-Abreu A, Pacheco PS, Bozza PT, Zimmerman G, Castro-Faria-Neto HC. The role of $\alpha D \beta 2$ integrin in salmonella Typhimurium and Staphylococcus aureus infection. *Shock*. 2008;29:80–1.
163. Sayedyahosseini S, Xu SX, Rudkouskaya A, McGavin MJ, McCormick JK, Dagnino L. Staphylococcus aureus keratinocyte invasion is mediated by integrin-linked kinase and Rac1. *FASEB J*. 2015;29:711–23.
164. Azzopardi EA, Azzopardi E, Camilleri L, Villapalos J, Boyce DE, Dziewulski P, et al. Gram negative wound infection in hospitalised adult burn patients-systematic review and Meta-analysis. *PLoS One*. 2014;9:e95042.
165. Stover CK, Pham XQ, Erwin AL, Mizoguchi SD, Warrenner P, Hickey MJ, et al. Complete genome sequence of

- Pseudomonas aeruginosa* PAO1, an opportunistic pathogen. *Nature*. 2000;406:959–64.
166. Mah T-F, Pitts B, Pellock B, Walker GC, Stewart PS, O'Toole GA. A genetic basis for *Pseudomonas aeruginosa* biofilm antibiotic resistance. *Nature*. 2003;426:306–10.
 167. Engel J, Eran Y. Subversion of mucosal barrier polarity by *Pseudomonas aeruginosa*. *Front Microbiol*. 2011;2:2.
 168. Tran Cindy S, Eran Y, Ruch Travis R, Bryant David M, Datta A, Brakeman P, *et al*. Host cell polarity proteins participate in innate immunity to *Pseudomonas aeruginosa* infection. *Cell Host Microbe*. 2014;15:636–43.
 169. Thuenauer R, Landi A, Trefzer A, Altmann S, Wehrum S, Eierhoff T, *et al*. The *Pseudomonas aeruginosa* lectin LecB causes integrin internalization and inhibits epithelial wound healing. *MBio*. 2020;11:e03260–19.
 170. Roger P, Puchelle E, Bajolet-Laudinat O, Tournier JM, Debordeaux C, Plotkowski MC, *et al*. Fibronectin and alpha5beta1 integrin mediate binding of *Pseudomonas aeruginosa* to repairing airway epithelium. *Eur Respir J*. 1999;13:1301–9.
 171. Buommino E, Di Domenico M, Paoletti I, Fusco A, De Gregorio V, Cozza V, *et al*. $\alpha\beta 5$ integrins mediates *Pseudomonas fluorescens* interaction with A549 cells. *Frontiers in bioscience -Landmark*. 2014;19:408–15.
 172. Leroy-Dudal J, Gagnière H, Cossard E, Carreiras F, Di Martino P. Role of $\alpha\beta 5$ integrins and vitronectin in *Pseudomonas aeruginosa* PAK interaction with A549 respiratory cells. *Microbes Infect*. 2004;6:875–81.
 173. Vaze N, Demokritou P. Using engineered water nanostructures (EWNS) for wound disinfection: case study of *Acinetobacter baumannii* inactivation on skin and the inhibition of biofilm formation. *Nanomedicine*. 2022;42:102537.
 174. Farshadzadeh Z, Pourhajibagher M, Taheri B, Ekrami A, Modarressi MH, Azimzadeh M, *et al*. Antimicrobial and anti-biofilm potencies of dermcidin-derived peptide DCD-1L against *Acinetobacter baumannii*: an in vivo wound healing model. *BMC Microbiol*. 2022;22:25.
 175. Pourhajibagher M, Pourakbari B, Bahador A. Contribution of antimicrobial photo-sonodynamic therapy in wound healing: an in vivo effect of curcumin-nisin-based poly (L-lactic acid) nanoparticle on *Acinetobacter baumannii* biofilms. *BMC Microbiol*. 2022;22:28.
 176. Hajj-Hussein IA, Jurjus R, Saliba J, Ghanem S, Diab R, Assi TB, *et al*. Modulation of $\beta 2$ and $\beta 3$ integrins in experimental colitis induced by iodoacetamide and enteropathogenic *E. Coli*. *J Biol Regul Homeost Agents*. 2013;27:351–63.
 177. Petracchini S, Hamaoui D, Doye A, Asnacios A, Fage F, Vitiello E, *et al*. Optineurin links Hace1-dependent Rac ubiquitylation to integrin-mediated mechanotransduction to control bacterial invasion and cell division. *Nat Commun*. 2022;13:6059.
 178. Ristow Laura C, Tran V, Schwartz Kevin J, Pankratz L, Mehle A, Sauer J-D, *et al*. The extracellular domain of the $\beta 2$ integrin β subunit (CD18) is sufficient for *Escherichia coli* Hemolysin and *Aggregatibacter actinomycetemcomitans* Leukotoxin cytotoxic activity. *MBio*. 2019;10:e01459–19.
 179. Jiang L, Zhang L, Rui C, Liu X, Mao Z, Yan L, *et al*. The role of the miR1976/CD105/integrin $\alpha\beta 6$ axis in vaginitis induced by *Escherichia coli* infection in mice. *Sci Rep*. 2019;9:14456.
 180. Watson CN, Kerrigan SW, Cox D, Henderson IR, Watson SP, Arman M. Human platelet activation by *Escherichia coli*: roles for Fc γ RIIA and integrin α IIb β 3. *Platelets*. 2016;27:535–40.
 181. Moriarty RD, Cox A, McCall M, Smith SGJ, Cox D. *Escherichia coli* induces platelet aggregation in an Fc γ RIIA-dependent manner. *J Thromb Haemost*. 2016;14:797–806.
 182. Siemens N, Patenge N, Otto J, Fiedler T, Kreikemeyer B. *Streptococcus pyogenes* M49 plasminogen/plasmin binding facilitates keratinocyte invasion via integrin-integrin-linked kinase (ILK) pathways and protects from macrophage killing. *J Biol Chem*. 2011;286:21612–22.
 183. Kochi S, Yamashiro K, Hongo S, Yamamoto T, Ugawa Y, Shimoe M, *et al*. *Aggregatibacter actinomycetemcomitans* regulates the expression of integrins and reduces cell adhesion via integrin $\alpha 5$ in human gingival epithelial cells. *Mol Cell Biochem*. 2017;436:39–48.
 184. Santoni G, Spreghini E, Lucciarini R, Amantini C, Piccoli M. Involvement of $\alpha\beta 3$ integrin-like receptor and glycosaminoglycans in *Candida albicans* germ tube adhesion to vitronectin and to a human endothelial cell line. *Microb Pathog*. 2001;31:159–72.
 185. Seo JH, Lim JW, Yoon J-H, Kim H. Proteinase-activated Receptor-2 mediates the expression of integrin $\alpha 5$ and $\beta 1$ in *helicobacter pylori*-infected gastric epithelial AGS cells. *Gastroenterologia*. 2009;80:40–9.
 186. Liang X, Ji Y. Involvement of alpha 5 beta 1-integrin and TNF-alpha in *Staphylococcus aureus* alpha-toxin-induced death of epithelial cells. *Cell Microbiol*. 2007;9:1809–21.
 187. Donnarumma G, Paoletti I, Buommino E, Tufano MA, Baroni A. α -MSH reduces the internalization of *Staphylococcus aureus* and down-regulates HSP 70, integrins and cytokine expression in human keratinocyte cell lines. *Exp Dermatol*. 2004;13:748–54.
 188. Sommer R, Wagner S, Rox K, Varrot A, Hauck D, Wamhoff E-C, *et al*. Glycomimetic, orally bioavailable LecB inhibitors block biofilm formation of *Pseudomonas aeruginosa*. *J Am Chem Soc*. 2018;140:2537–45.