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Integrins regulation of wound healing processes: insights for chronic skin wound therapeutics

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Integrins are heterodimers composed of non-covalently associated alpha and beta subunits that mediate the dynamic linkage between extracellular adhesion molecules and the intracellular actin cytoskeleton. Integrins are present in various tissues and organs and are involved in different physiological and pathological molecular responses *in vivo*. Wound healing is an important process in the recovery from traumatic diseases and consists of three overlapping phases: inflammation, proliferation, and remodeling. Integrin regulation acts throughout the wound healing process to promote wound healing. Prolonged inflammation may lead to failure of wound healing, such as wound chronicity. One of the main causes of chronic wound formation is bacterial colonization of the wound. In this review, we review the role of integrins in the regulation of wound healing processes such as angiogenesis and re-epithelialization, as well as the role of integrins in mediating bacterial infections during wound chronicity, and the challenges and prospects of integrins as therapeutic targets for infected wound healing.

KEYWORDS

integrin, wound healing, wound chronicity, bacterial infection, targeted therapy

1 Introduction

Integrins are heterodimers composed of non-covalently associated α and β subunits that link the extracellular matrix (ECM) to the cytoskeleton and mediate dynamic connections between extracellular adhesion molecules and the intracellular actin cytoskeleton as well as intermediate filaments (Hynes, 2004). Intracellular proteins that bind to the cytoplasmic tail of integrins regulate the binding of integrins to extracellular ligands and integrin localization and transport. Cytoplasmic integrin-binding proteins also function downstream of integrins, mediating connections to the cytoskeleton and signaling cascades that affect cell motility, growth, and survival (Morse et al., 2014). In mammals, integrins are composed of 18 α and eight β subunits, classified into laminin-binding integrins (Figure 1): α1β1, α2β1, α3β1, α6β1, α7β1, and α6β4, collagen-binding integrins: α1β1, α2β1, α3β1, α10β1, and α11β1, leukocyte integrins: αLβ2, αMβ2, αXβ2, and αDβ2

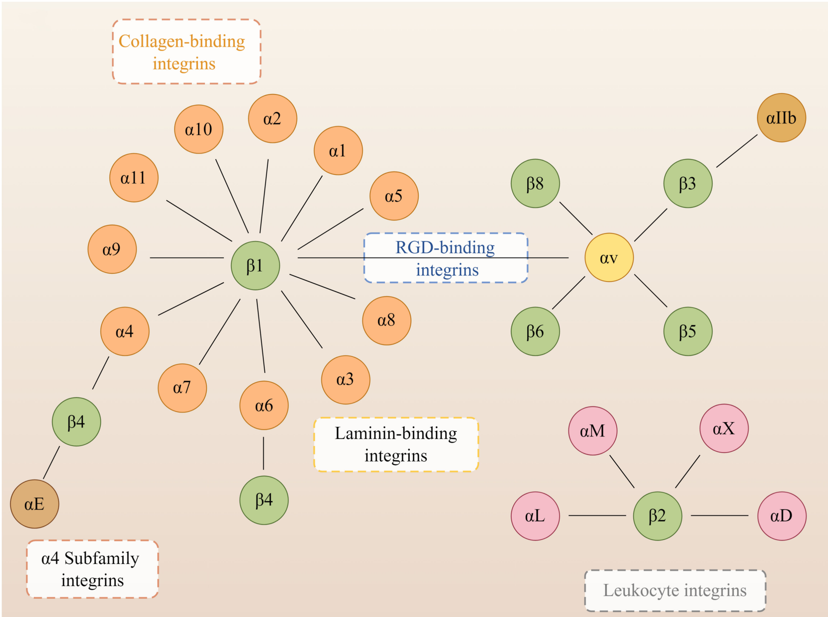

FIGURE 1
Members of the human integrin superfamily. At least 18 α subunits and eight β subunits have been identified in humans, and they can produce 24 different integrins. The integrin subunits that bind to each other to form heterodimers are connected by solid lines. By Figdraw.

and RGD-recognizing integrins: α5β1, αVβ1, αVβ3, αVβ5, αVβ6, αVβ8, and αIIbβ3, and with different binding properties and different tissue distribution (Takada et al., 2007). Integrins are involved in various bodily processes, including trauma, immunity, infection, cell proliferation, inflammation, angiogenesis, and tumors (Hostetter, 1996; LaFlamme and Auer, 1996; Desgrosellier and Cheresh, 2010; Mezu-Ndubuisi and Maheshwari, 2021).

Skin wounds, in the context of successful healing, include dynamic processes in three overlapping phases: inflammation, proliferation, and tissue remodeling (Martin, 1997). Wound repair is tightly regulated by many factors, including cell-ECM interactions (Martin, 1997), growth factors, and matrix metalloproteinases (MMP) (Gál et al., 2017). The integrin family regulates all processes of wound healing (Table 1), such as hemostasis, inflammation, angiogenesis (Figure 2), re-epithelialization (Figure 3), and fibrosis. Disruption of these regulatory mechanisms at any stage can lead to chronic or non-healing wounds where factors such as persistent inflammation and impaired barrier (Brem and Tomic-Canic, 2007; Harding et al., 2002), oxygenation response (Bishop, 2008), bacterial infection (Edwards and Harding, 2004), age (Swift et al., 2001), and disease state (Brem and Tomic-Canic, 2007) can impede the skin's ability to repair wounds effectively. In reality, chronic wounds are often accompanied by bacterial infections, and some bacteria, such as *Staphylococcus aureus (S. aureus)* and *Pseudomonas aeruginosa (P. aeruginosa)*, can mediate the integrin family to promote the formation of chronic wounds and thus cause them to persist (Edwards and Harding, 2004; Canchy et al., 2023). Abnormal wound healing is a major challenge in the treatment of skin wounds, and chronic wounds pose a serious emotional and financial burden to patients (Olsson et al., 2019). In this review, we review the role of integrins as bridges in bacterial-cell interactions in the context of wound healing and assess the role of integrins as nodes to inhibit bacteria in wound chronicity, as well as the challenges and perspectives of integrins as targets for therapeutic wound healing.

2 Role of integrins in bacterial infections

Prolonged inflammation may result in wounds that do not heal, such as chronic ulcers (Wang et al., 2018). The causes of chronic wounds are complex: local tissue hypoxia, wound bacterial colonization, and repetitive ischemia-reperfusion injury can all lead to chronic wounds (Mustoe et al., 2006), and inflammation due to bacterial colonization of wounds remains one of the most causes of persistent wound healing (Mustoe et al., 2006). The ECM is a non-cellular, three-dimensional macromolecular network composed of collagen, proteoglycan/glycosaminoglycan, elastin, fibronectin, laminin, and several other glycoproteins that regulate a variety of cellular functions and are essential for the maintenance of normal body homeostasis (Theocharis et al., 2016). The ECM serves as the primary microenvironment for wound healing, and integrin-mediated adhesion to the ECM may play an important role. Most chronic wounds at this stage are accompanied by bacterial infections, the most common causative agents being *S. aureus* and *P. aeruginosa* (Rhoads et al., 2012; Silva et al., 2018). Mechanisms such as the formation of bacterial biofilm, among others (Bjarnsholt, 2013; Wu et al., 2019). Such as in mouse periodontal disease (PD), bacterial biofilms inhibit β6 integrin expression and transforming growth factor-β1 signaling, leading to gingival inflammation (Uehara et al., 2022). Bacterial biofilms present in periodontal pockets inhibit αvβ6 integrin expression levels in periodontal disease and exacerbate the inflammatory

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

Type	Ligands	Secretion sites	Functional roles
$\alpha_1\beta_1$	Laminin, collagen	EC, FBL, monocytes, macrophages, and myofibroblasts	Mediating VEGF-driven angiogenesis, negative feedback regulation of collagen synthesis in FBL (Senger and Davis, 2011; Gardner et al., 1999; Senger et al., 1997)
$\alpha_2\beta_1$	Laminin, collagen	Platelets, KC, EC and FBL	Mediates KC migration and VEGF-driven angiogenesis (Senger et al., 1997; Grenache et al., 2007)
$\alpha_3\beta_1$	Laminin, platelet-reactive protein	KC、EC and FBL	Regulation of KC migration during re-epithelialization (Margadant et al., 2009), control of angiogenesis and TGF-β1-mediated responses (da Silva et al., 2010)
$\alpha_4\beta_1$	Thrombospondin, fibronectin, bone bridge protein, ADAM, EDA, VCAM, etc (Huhtala et al., 1995; Shinde et al., 2015; Abonia et al., 2006)	Leukocytes, FBL, and EC	Regulation of FBL proliferation and TGF-β1 processing (Shinde et al., 2015)
$\alpha_5\beta_1$	Fibronectin, bone bridging protein, pro-fibronectin, ADAM, CCN, etc (Huhtala et al., 1995; Lau, 2016)	Platelets, KCs, ECs, FBLs	Promote KC migration (Di Russo et al., 2021), etc.
$\alpha_6\beta_1$	Laminin, coagulation-reactive protein, Cyr61, CCN, etc (Lau, 2016)	Platelets, EC, leukocytes, and FBL	may be involved in platelet-vessel wall interactions and angiogenesis (Huang et al., 2016); interaction with CCN1/Cyr61 promotes myofibroblast senescence and controls fibrogenesis (Jun and Lau, 2010)
$\alpha_7\beta_1$	Laminin	Expressed by muscle cells, vascular smooth muscle cells, etc (Riederer et al., 2015; Burkin and Kaufman, 1999)	
$\alpha_8\beta_1$	FN, TGF-β1, etc.	Myofibroblasts	Lead to fibrotic reaction (Bouzeghrane et al., 2004)
$\alpha_9\beta_1$	EDA-FN, VEGF, etc (Shinde et al., 2015; Eto et al., 2002; Vlahakis et al., 2005)	KCs, FBLs, neutrophils, and ECs	Regulation of KC and FBL growth, neutrophil chemotaxis, and EC migration and angiogenesis (Nakayama et al., 2010; Oommen et al., 2011; Høye et al., 2012)
$\alpha_{10}\beta_1$	Collagen	FBL	May mediate the adhesion of FBL to collagen and dynamic connective tissue remodeling events (Zeltz and Gullberg, 2016)
$\alpha_{11}\beta_1$	Collagen	FBL	Controls myofibroblast differentiation and may mediate adhesion of FBL to collagen and contribute to collagen reorganization (Zeltz and Gullberg, 2016)
$\alpha_v\beta_1$	FN, TGF-β1, etc.	KC、EC	Mediating KC adhesion during re-epithelialization (Jakhu et al., 2018)
$\alpha_v\beta_3$	Fibronectin(pro), FGF-2, TGF-β1, CCN1/Cyr6, CCN2/CTGF and CCN3/NOV, etc (Lau, 2016; Rusnati et al., 1997; Lin et al., 2005)	EC, platelets, FBL, and macrophages	Required for neoangiogenesis; regulates fibronectin network structure and stability; mediates EC adhesion to CCN1/Cyr6 and CCN2/CTGF; EC survival; pericyte retention in the vasculature; and FBL proliferation (Mitchell et al., 2009)
$\alpha_v\beta_5$	TGF-β1, VEGF, CCN1/Cyr6, CCN3/NOV, etc (Lau, 2016; Lin et al., 2005)	EC, FBL, and Skin KC	may be involved in the conversion of FBL to myofibroblasts (Geuijen and Sonnenberg, 2002), and the interaction with CCN1/Cyr61 mediates FBL migration (Lygoe et al., 2004)
$\alpha_v\beta_6$	FN, TGF-β1 and -β3, etc.	KCs	Regulates inflammation and KC proliferation, contributing to the basement membrane and granulation tissue remodeling (Jakhu et al., 2018)
$\alpha_v\beta_8$	FN, and TGF-β (Lainé et al., 2021)	Dendritic cells, FBLs and ECs	Mediates TGF-β to regulate inflammation (Worthington John et al., 2015)
$\alpha_6\beta_4$	Laminin-332, Other LM (Sehgal et al., 2006)	KC、EC	Promotes KC adhesion and migration (Geuijen and Sonnenberg, 2002); regulates angiogenesis in EC (Mercurio et al., 2001; Nikolopoulos et al., 2004)
$\alpha_{IIb}\beta_3$	Fibronectin(pro), FN, CCN1/Cyr6 and CCN2/CTGF, etc (Lau, 2016; Andre et al., 2002)	Platelets	Mediates platelet aggregation in clot formation and regulates fibrin network structure and stability (antithrombotic effect) (Blue et al., 2009)
$\alpha_4\beta_7$	VCAM, etc (Abonia et al., 2006)	Leukocytes, dendritic cells	Involved in leukocyte transport (Gubatan et al., 2021)
$\alpha_E\beta_7$	Calcineurin	T lymphocytes, dendritic cells	Mediated leukocyte transport (Kilshaw, 1999)

(Continued)

TABLE 1 Continued

Type	Ligands	Secretion sites	Functional roles
$\alpha_L\beta_2$	Lumican, etc.	Leukocytes	Mediated leukocyte extravasation through the endothelium (Tan, 2012)
$\alpha_M\beta_2$	Fibronectin(pro), FN, CCN1/Cyr6, CCN2/CTGF, etc (Lau, 2016)	Monocytes, macrophages, NK, neutrophils, and T cells	Involved in leukocyte transport across the endothelium (Tan, 2012); complexed with uPAR and its ligand uPA to promote fibrinolysis and fibrin clot clearance by monocytes and neutrophils (Sisco et al., 2007)
$\alpha_X\beta_2$	Fibronectin (Garnotel et al., 2000)	Monocytes, macrophages, dendritic cells, and NK	Involved in leukocyte transport (Tan, 2012)
$\alpha_D\beta_2$	VCAM-1 and CCN1/Cyr6, etc (Lau, 2016; Grayson et al., 1998)	Macrophages, eosinophils	Involved in leukocyte transport (Tan, 2012)

FBL, 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.

response (Bi et al., 2017). Biofilm formation is tied to the regulated synthesis of extracellular matrix components (Rowan-Nash Aislinn et al., 2019), a structural group of different bacterial species that contribute to the chronicity of most wound healing, and bacteria associated with biofilms are highly resistant to antibiotics (Venkatesan et al., 2015). In addition, there are other pathogenic bacteria, such as anaerobic bacteria (Choi et al., 2019) and Streptococcus hemolytic type B (Silva et al., 2018).

2.1 Integrins and *S. aureus*

S. aureus is one of the most important human pathogens. *S. aureus* is known for its role in hospital-acquired infections and methicillin resistance and is now considered a global clinical problem (Chambers and DeLeo, 2009). This microorganism causes a variety of surface and systemic diseases and is frequently associated with oral mucositis. It is also a causative or worsening agent in various skin conditions, including atopic dermatitis, carbuncles, cellulitis, boils, hair follicles, Kawasaki syndrome, impetigo, psoriasis, and scalded skin syndrome (Morishita et al., 1999; Skov and Baadsgaard, 2000; Yarwood et al., 2000; Chiller et al., 2001; Cho et al., 2001a; Cho et al., 2001b; Breuer et al., 2002; Patel and Finlay, 2003). *S. aureus* is a major cause of wound infections and is thought to delay wound healing (Bowler et al., 2001) (Table 2). A prominent feature common to almost all *S. aureus* isolates is the expression of ECM-binding proteins, collectively referred to as microbial surface component

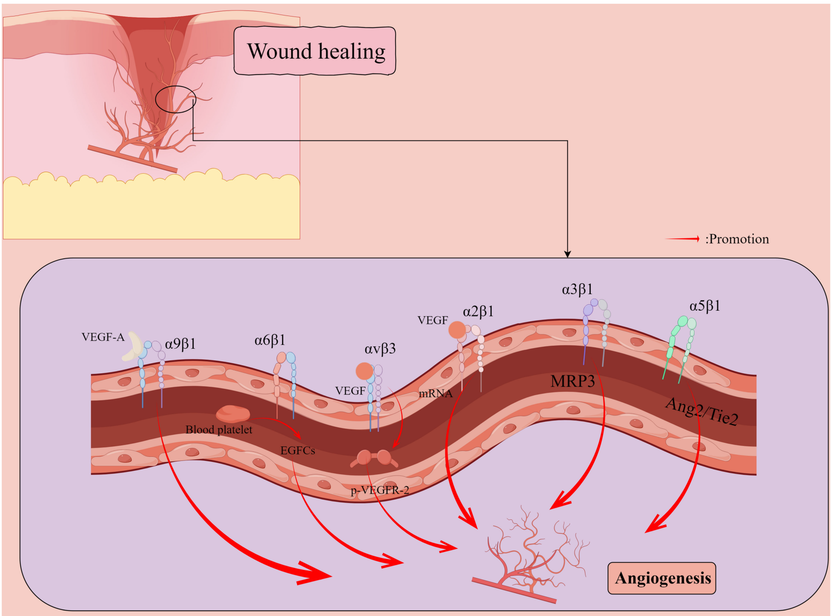

FIGURE 2
Promotion of new capillary formation by integrins during wound healing. Vascular endothelial growth factor (VEGF) induces a 5- to 7-fold increase in the protein expression of two collagen receptors, α1β1 and α2β1 integrins, on the surface of dermal microvascular endothelial cells (ECs) through the induction of mRNAs encoding α1 and α2 integrins subunits. α5 integrin localizes to cell junctions and participates in the angiopoietin (Ang)/Tie2 signaling pathway to maintain vascular homeostasis. αvβ3 integrin synergizes with VEGF to activate angiogenesis in ECs through VEGFR-2 phosphorylation. α6β1 integrin appears to promote platelet pro-mediated angiogenesis associated with endothelial colony forming cells (ECFCs). VEGF-A can induce endothelial and cancer cell migration by directly binding α9β1 integrin. By Figdraw.

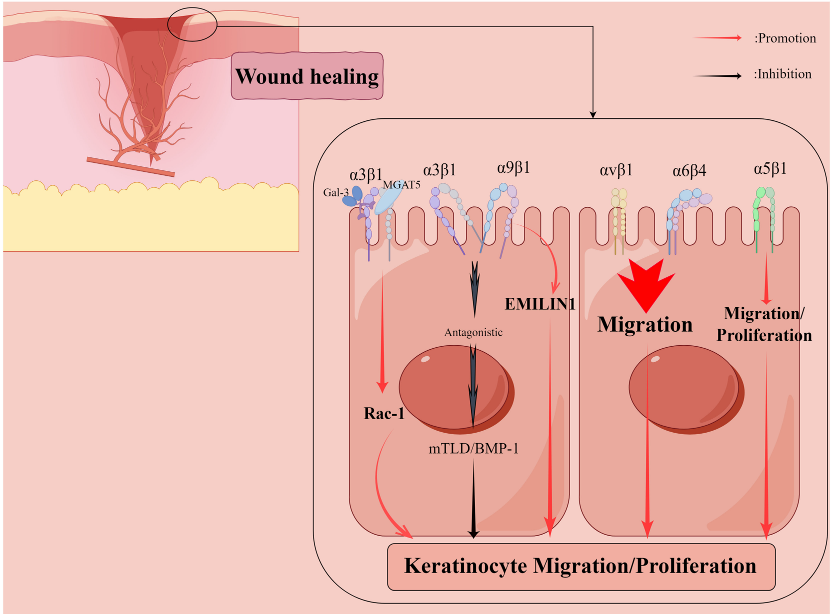

FIGURE 3
Shows that integrins regulate the re-epithelialization phase of the wound healing process. Galectin-3 promotes epithelial cell migration by cross-linking Mannoside Acetylglucosaminyltransferase 5 (MGAT5)-modified complex N-glycans on α3β1 integrins and subsequently activating α3β1-integrin-Rac1 signaling to promote lamellar pseudopod formation. The interaction of α5β1 integrins with fibronectin may contribute to keratinocyte proliferation in addition to promoting keratinocyte adhesion and motility on this matrix. α9β1 integrin interacts with another ECM component, elastic microfibril interface localization protein 1 (EMILIN1), to regulate keratinocyte proliferation, but α9β1 integrin antagonizes α3β1-dependent mTLD/BMP-1 expression and skin basement membrane reorganization and maturation. αvβ1 and α6β4 integrins also regulate keratinocyte migration. By Figdraw.

recognition adhesion matrix molecules (MSCRAMMs) (Patti et al., 1994; Foster and Höök, 1998). It is possible to colonize the host by attaching to components of the ECM to initiate infection (Foster and Höök, 1998), such as cell wall-attached fibronectin-binding proteins A and B that allow bacteria to bind tightly to the ECM protein fibronectin (FN) (Flock et al., 1987; JÖNsson et al., 1991).

Integrin β1-containing receptors are known for their role in cell adhesion and their ability to signal the transduction of cell attachment to the ECM (Schwartz and Ginsberg, 2002). In the *in vitro* experiments, *S. aureus* can invade eukaryotic cells by indirectly engaging the β1 integrin-containing host receptor, but non-pathogenic Staphylococcus carnosus is not invasive (Agerer et al., 2003). α5β1 integrin is a vital cell surface receptor that mediates the attachment of eukaryotic cells to the ECM protein fibronectin (Hynes, 1996). FN has recently been shown to act as a molecular bridge linking FN-binding proteins (FnBP) -expressing *S. aureus* to α5β1 integrin on the surface of human cells (Joh et al., 1999). This interaction not only tightly anchors *S. aureus* to its eukaryotic host cells but also promotes the internalization of the microbe by human epithelial and endothelial cell and mouse fibroblasts (Dziewanowska et al., 1999; Sinha et al., 1999; Fowler et al., 2000; Jett Bradley and Gilmore Michael, 2002) (Figure 4). In addition, an *in vitro* study found that one study found that necrotizing soft tissue infections with *S. aureus* isolates showed high rates of internalization and cytotoxicity to human myocytes, and the cellular basis of the high internalization rate in myocytes was attributed to the higher expression of α5β1 integrins in myocytes (Baude et al., 2019). The ability of *S. aureus* to be internalized by and survive in host cells, such as keratinocytes, may contribute to developing persistent or chronic infections, eventually leading to deeper tissue infection or dissemination. Internalization of *S. aureus* by immortalized keratinocytes requires bacterial FnBPs and is mediated by the significant fibronectin-binding α5β1 integrin. However, unlike the internalization of immortalized keratinocytes, the internalization of *S. aureus* by native keratinocytes can occur through FnBP-dependent and non-dependent pathways (Kintarak et al., 2004). In addition, in oral infections, multi-strain oral biofilms inhibit αvβ6 integrin expression in gingival epithelial cells (Bi et al., 2017). And

TABLE 2 Role of different integrins in normal wound healing (granulation tissue) and bacterial infection.

Type	Granulation tissue	Bacterial infections
α5β1	Regulates re-epithelialization and promotes migration of keratin-forming cells (Di Russo et al., 2021)	Mediating the attachment of eukaryotic cells to the extracellular matrix protein fibronectin (JÖNsson et al., 1991)
αvβ3	Regulates angiogenesis and promotes FBL proliferation (Mitchell et al., 2009)	Mediated Staphylococcus aureus bloodstream infection (Flock et al., 1987)
αvβ6	Regulates inflammation and keratin-forming cells proliferation (Jakhu et al., 2018)	Regulation of bacterial biofilms (Hynes, 1996; Mathelié-Guinlet et al., 2020)
αIIbβ3	Mediated platelet aggregation (Blue et al., 2009)	Mediated adhesion of Aureus to platelets (Miajlovic et al., 2010; Zapotoczna et al., 2013)

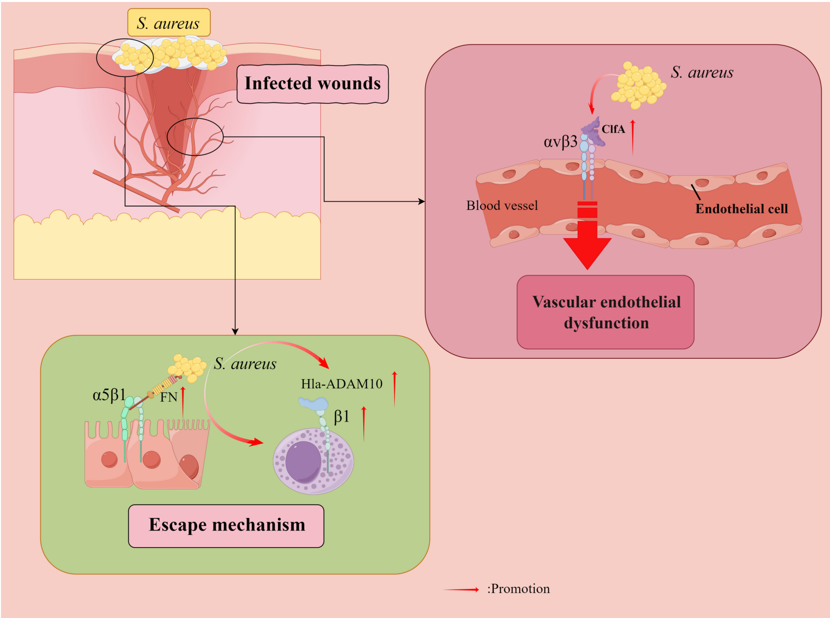

FIGURE 4
Staphylococcus aureus (S. aureus) evades bactericidal mechanisms. Fibronectin (FN) acts as a molecular bridge linking FnBP-expressing *S. aureus* to α5β1 integrin on the surface of human cells, tightly anchoring *S. aureus* to its eukaryotic host cells, and also facilitating microbial internalization by human epithelial and endothelial cells (ECs) and mouse fibroblasts. Furthermore, internalization of *S. aureus* by immortalized keratinocytes requires bacterial FnBPs and is mediated by the significant fibronectin-binding α5β1 integrin. *S. aureus* counteracts the extracellular bactericidal machinery of mast cells (MCs) by increasing fibronectin-binding protein expression and inducing Hla-ADAM10-mediated upregulation of β1 integrins in MCs. Vascular endothelial dysfunction is attributed to *S. aureus* aggregation factor A (ClfA) to adhere to αvβ3 integrins expressed on endothelial cells, where fibrinogen (FG) plays a key role. Direct binding of the *S. aureus* surface protein IsdB to endothelial αvβ3 integrins plays a vital role in host cell adhesion and invasion, ultimately leading to life-threatening disease. By Figdraw.

periodontal inflammation caused by αvβ6 integrin deficiency also resulted in significant alterations in the oral microbiome (Uehara et al., 2022). However, the second fibronectin-binding integral protein αvβ6 found on keratin-forming cells does not mediate *S. aureus* internalization (Kintarak et al., 2004).

In vitro infection tests have shown that *S. aureus* counteracts the extracellular bactericidal mechanism of mast cells (MCs) by increasing fibronectin-binding protein expression and inducing Hla-ADAM10 (a disintegrin and metalloproteinase 10)-mediated upregulation of β1 integrins in MCs (Goldmann et al., 2016). An experiment on mice showed that IFN-gamma intervention, partly by β1 integrins, drives enhanced antimicrobial and pro-inflammatory responses of human MCs to *S. aureus* (Swindle et al., 2015). An *in vitro* study found that a protein exported by S.aureus, α-toxin interacts with β1-integrin, a receptor for the host ECM protein, suggesting that β1-integrin may be a potential receptor for α-toxin on epithelial cells. The α-toxin inhibits *S. aureus* adhesion and internalization by interfering with integrin-mediated pathogen-host cell interactions (Liang and Ji, 2006).

In addition, an α5β1/αvβ3 integrin antagonist has been found to inhibit *S. aureus* invasion of epithelial cells (Melby et al., 2000). A study of mouse models found that vascular endothelial dysfunction was attributed to the ability of *S. aureus* aggregation factor A (ClfA) to adhere to αvβ3 integrins expressed on endothelial cell (EC), with fibrinogen (Fg) playing a pivotal role (McDonnell et al., 2016a). The direct binding of the *S. aureus* surface protein iron-regulated surface determinant B (IsdB) to EC αvβ3 integrins plays an essential role in host cell adhesion and invasion, ultimately leading to life-threatening disease (Mathelié-Guinlet et al., 2020). Therefore, αvβ3 integrin blockade represents an attractive target for treating *S. aureus* blood-borne infections. Furthermore, force-enhanced adhesion between IsdB and integrins may be one of the multiple mechanisms that have been developed by staphylococci to effectively colonize or invade their hosts while resisting the shear forces encountered in various environments after infection (Otto, 2014), and *S. aureus* can adhere to platelets through the high-affinity form of IsdB bound to the platelet integrin αIIbβ3 integrin without the need for additional ECM proteins (Miajlovic et al., 2010; Zapotoczna et al., 2013). In addition, αDβ2 integrins have been observed to have a role in Salmonella typhimurium and *S. aureus* infections (Nascimento et al., 2008).

Integrin-linked kinases and Rac1 mediate the invasion of *S. aureus* into keratinocytes, and the bacteria can invade keratinocytes via the integrin-linked kinase-Rac1 pathway. Thus, integrin-linked kinase may be a critical factor in preventing staphylococcal skin infections (Sayedyahossein et al., 2015), and therefore, this is speculated to be a biological target for the treatment of *S. aureus* infections.

2.2 Integrins and *P. aeruginosa*

P. aeruginosa is a ubiquitous gram-negative environmental bacterium that can cause serious infections in skin wounds, such as in patients with severe burns (Azzopardi et al., 2014). It can form biofilms (Mah et al., 2003) and invade and increase the host cells. *P. aeruginosa* has been shown to have the propensity to enter and colonize injured epithelial cells (Engel and Eran, 2011), and there is ample experimental evidence that loss of epithelial polarity increases the harmful effects of *P. aeruginosa* on host cells (Engel and Eran, 2011). *P. aeruginosa* has evolved ways of manipulating host epithelial cell polarity to promote infection (Engel and Eran, 2011; Tran Cindy et al., 2014). Integrins are usually restricted to the basolateral plasma membrane of epithelial cells, and when reaching the basolateral side, *P. aeruginosa* has access to integrins (Thuenauer et al., 2020). Current studies on integrin-mediated *P. aeruginosa* are mostly limited to α5β1 and αvβ5 integrins in respiratory epithelial cells (Buommino et al., 2014; Roger et al., 1999; Leroy-Dudal et al., 2004). The *P. aeruginosa* lectin the fucose-specific lectin LecB clears integrins from the surface of cells at the wound margin and blocks cell migration and wound healing dose-dependent manner (Thuenauer et al., 2020). Further studies are needed to determine the role of integrins in *P. aeruginosa* infections in infected wounds, which seems to be a clear direction for treating *P. aeruginosa* infections.

2.3 Integrins and other bacterial

Integrins also mediate the infectious effects of some other species of bacteria on the organism. Entry into epithelial cells and prevention of primary immune responses are prerequisites for successful colonization and subsequent infection of human hosts by *Streptococcus pyogenes* (group A streptococci, GAS). The interaction of GAS with fibrinogen promotes integrin-mediated internalization of bacteria into keratin-forming cells, and α1β1 and α5β1 integrins are the major keratin-forming cell receptors involved in this process (Siemens et al., 2011). Excessive bacterial invasion disrupts the attachment between the tooth surface and epithelium, leading to periodontitis. Integrin α5 may be involved in the invasion of aggregatibacter actinomycetemcomitans Y4 into gingival epithelial cells, and the resulting signal transduction cascade decreases cell adhesion and reduces the defensive role of gingival epithelial cells by reducing integrin expression (Kochi et al., 2017). Adhesion of *Candida albicans* germ tube human endothelial cell lines is mediated by αvβ3 and this adhesion is significantly blocked by the anti-β3 monoclonal antibody Gly-Arg-Gly-Asp-Ser-Pro (GRGDSP) peptide or heparin and completely eliminated by their combination (Santoni et al., 2001). Therefore, αvβ3 blockade may be used as one of the therapeutic options against *Candida albicans* infection. In addition, *H. pylori* induces the expression of integrin α5β1 and activates H. pylori-infected gastric epithelial cells via proteinase-activated receptor-2 (PAR2)-induced trypsin, which may play an important role in *H. pylori*-associated carcinogenesis (Seo et al., 2009).

2.4 Integrins and targeted therapy for bacterial infections

The integrin family, a large group of proteins in the human body, is involved in a variety of physiological processes, and for this family of proteins, we can effectively use them to regulate a number of pathophysiological processes in the organism. Based on the mechanism of integrin-mediated bacterial infection in wound healing, it appears that bacterial infection in the vast majority of cases requires the regulation of integrins. Earlier, it was found that the interaction of staphylococcal alpha toxin with α5β1 integrin and the overproduction of TNF-α may contribute to the destruction of epithelial cells during *S. aureus* infection (Liang and Ji, 2007). Recently, *S. aureus* has also been found to counteract the extracellular bactericidal mechanism of mast cell by increasing the expression of fibronectin-binding proteins and inducing Hla-ADAM10-mediated upregulation of β1 integrins in mast cell (Goldmann et al., 2016). At this point, it may be possible to effectively treat *S. aureus* infections by inhibiting targets associated with integrins. As inhibition of the major integrin αVβ3 reduces the attachment of *S. aureus* to sheared human endothelial cells (McDonnell et al., 2016b), blocking αVβ3 is an attractive target for the treatment of *S. aureus* blood-borne infections. There is evidence that alpha-melanocyte-stimulating hormone (α-MSH), a neuropeptide produced primarily by the pituitary gland but which is also produced by many extra-pituitary cells, including skin keratin-forming cells, has anti-inflammatory and antimicrobial effects and reduces the internalization of *S. aureus*. α-MSH prematurely downregulates the production of integrins such as beta1 and heat shock surface protein 70 (Donnarumma et al., 2004), to reduce infection and the inflammatory response.

In contrast, one study found that in mouse skin lacking integrin-linked kinase in the epidermis, *S. aureus* penetrated the skin 35 times more than normal skin; thus, integrin-linked kinase has potential as a targeted therapy for the prevention of *S. aureus* skin infections (Sayedyahossein et al., 2015). Fibronectin or β1 integrin-blocking antibodies completely eliminate IFN-γ-dependent *S. aureus* junctions, and IFN-γ can trigger human mast cells mediated by β1 integrins to enhance antibacterial and pro-inflammatory responses to IFN-γ-dependent *S. aureus* (Swindle et al., 2015). In these cases, increasing integrin levels requires integrin activation, and common activators such as talin, kindlin, and mechanical force (Sun et al., 2019; Lu et al., 2022). It has also been found that *P. aeruginosa* can produce the fucose-specific lectin LecB, which specifically removes integrins from the surface of cells located at the wound edge and blocks cell migration and wound healing in a dose-dependent manner (Rowan-Nash Aislinn et al., 2019; Thuenauer et al., 2020). When appropriate, integrin supplementation may antagonize this blocking effect and promote wound healing.

In clinical trials for the treatment of sepsis, cilengitide prevented ClfA from binding αVβ3 on endothelial cells, slowing infection without affecting normal endothelial cell function (McDonnell et al., 2016b). Thus, targeted inhibition of αVβ3 treatment seems to be locally applied for wound healing. The α5β1 integrin is one of the staphylococcal α-toxin receptors involved in mediating the cytotoxicity of α-toxin (Liang and Ji, 2007). α-MSH exerts a protective effect on the skin by reducing infection and inflammatory processes through the downregulation of β1 integrins (Donnarumma et al., 2004). LecB inhibitors can also be used as a treatment strategy in addition to antibiotics (Sommer et al., 2018; Thuenauer et al., 2020). In contrast, integrin receptors promoted increased binding of *S. aureus* to IFN γ-treated huMCs (Swindle et al., 2015), demonstrating the complexity of the MC response in relation to the cytokine environment. For these, there are no practical clinical studies yet, so appropriate drug development and clinical trials become a top priority for integrin-targeted therapy.

3 Conclusion and prospect

The integrin family is a group of functionally diverse protein families that play key roles in various physiological and pathological mechanisms by acting as a bridge between protein-cell, cell-cell, and bacterial-cell. The integrin family's role in bacterial-cell linkage during wound healing suggests that treatment targeting integrins can effectively promote wound healing and reduce bacterial infections. However, the human body is a unified organic whole, and integrins can largely regulate the promotion of overall wound healing. Therefore, activation of integrins is preferred in most cases. At this stage, there are few studies on the activation of integrins to block bacterial infections, which is a wide research space and requires our joint efforts to fill the gap. However, in order to treat bacterial infections in pathological wound healing, the targeting of integrins needs to be context-specific and, when certain conditions allow, appropriately inhibited, and these need to be explored and evaluated more. *S. aureus* and *P. aeruginosa*, the two most common gram-positive and gram-negative bacteria in hospital-acquired infections, are reviewed in the article, which focuses on the mechanism of their invasion into the organism via integrins and provides a systematic review for the treatment of clinical bacterial infections as well as a summary of recent studies on integrins and their related derivatives as target therapeutics. In conclusion, the use of integrins as targets for blocking bacterial infections has very high potential.

Author contributions

DY: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. ZL: Data curation, Formal Analysis, Writing – review & editing. FN: Formal Analysis, Investigation, Methodology, Writing – review & editing. YC: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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