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Review

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Review

The role of the skin microbiome in wound healing

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Abstract

The efficient management of skin wounds for rapid and scarless healing represents a major clinical unmet need. Nonhealing skin wounds and undesired scar formation impair quality of life and result in high healthcare expenditure worldwide. The skin-colonizing microbiota contributes to maintaining an intact skin barrier in homeostasis, but it also participates in the pathogenesis of many skin disorders, including aberrant wound healing, in many respects. This review focuses on the composition of the skin microbiome in cutaneous wounds of different types (i.e. acute and chronic) and with different outcomes (i.e. nonhealing and hypertrophic scarring), mainly based on next-generation sequencing analyses; furthermore, we discuss the mechanistic insights into host–microbe and microbe–microbe interactions during wound healing. Finally, we highlight potential therapeutic strategies that target the skin microbiome to improve healing outcomes.

Key words: Skin microbiome, 16S Sequencing, Wound healing, Scarring

Highlights

- This paper summarizes recent research regarding the association of the skin microbiome with wound healing over different time courses and leading to different healing results.
- This paper also addresses the pathogenesis of microbiota dysbiosis in nonhealing or aberrantly healed wounds that could guide novel wound treatment modalities.

Background

The skin microbiota refers to the community of microorganisms residing on the skin, that together with their collective genomes, which have become detectable with the advent of next-generation sequencing technology targeting microbial-specific genes, are known as the microbiome. As skin is the largest and most exposed organ in the human body, the skin microbiota contains trillions of microorganisms, including bacteria, fungi and viruses, which intimately interact with the host to regulate host health and diseases.

Skin wounds are a broad category of injuries ranging from minor cuts and scratches to surgical incisions, burns and serious trauma. Minor and superficial injuries usually heal well in healthy individuals; however, larger and deeper injuries may result in a variety of pathological healing modalities,

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including chronic nonhealing ulcers and overly healed hypertrophic scars and keloids. Breakage of the skin barrier during injury allows for colonization of microbes that are not usually found on the skin and/or translocation of constituents of microbiota to places where they do not normally appear. Studies show that the microbiota might be beneficial for wound healing by modulating the innate immune response and facilitating regeneration [1–4]. However, the entrance of defined microorganisms with high proliferative and inflammatory potentials into the underlying skin tissue may induce a broad recall response by activating skin-resident microbiota-specific T cells and cause sustained inflammation and hence delayed healing [5].

In this review, we describe our current understanding of the skin microbiota and the physiology of wound healing. We highlight the association of the wound microbiome with clinical outcomes and gather mechanistic insights into the role of the microbiome in aiding or hampering wound healing. We also discuss how, based on an improved understanding of the microbe–host interactions in wounds, microbiota-based mechanisms may inform future therapeutic interventions.

Review

Skin microbiota and its role in homeostasis and diseases

The skin microbiota Using 16S rRNA gene sequencing, at least 19 bacterial phyla and over 1000 bacterial species have been identified on the human skin surface [6]. In general, skin bacteria predominantly belong to three phyla, *Actinobacteria* (51.8%), *Firmicutes* (24.4%) and *Proteobacteria* (16.5%), with the most represented genera being *Corynebacteria*, *Cutibacteria* (formerly *Propionibacteria)* and *Staphylococci* [6]. Both culture-based methods and genomic methodologies have confirmed that *Malassezia* spp. predominate among fungal communities on human skin, especially on the torso and the arm, whereas the foot is colonized by more diverse types of fungi [7]. For the skin viral community (virome), metagenomics has identified a large number of Caudovirales bacteriophage and single-stranded DNA viruses, including polyomaviruses, papillomaviruses and circoviruses [8–11]. In contrast to bacteria and fungi, viruses show little site specificity in skin colonization [12].

The initial colonization of skin microbes depends on the mode of delivery, with vaginally delivered babies acquiring microorganisms similar to their mother's vagina and babies delivered by Cesarean sections colonized with microbiota similar to that associated with the skin [13]. As the babies grow up, their skin microbiome gradually achieves a typical profile with site-specific colonization (Table 1), and most sites remain surprisingly stable over time [6, 12]. The major shift occurs at puberty when sex hormones drive the maturation of the sebaceous glands and initiate sebum production, favoring the expansion of lipophilic *Cutibacterium* spp., *Staphylococcus* spp. and *Malassezia* spp. on oily sites. The pilosebaceous unit is especially suitable for the existence of the anaerobe *Cutibacterium acnes* (*C. acnes*), which hydrolyses triglycerides in the sebum and releases free fatty acids to promote adherence [14, 15]. These bacteria also produce propionic acid to maintain an acidic pH in the pilosebaceous follicles and bacteriocins that prevent other microbes from colonizing the sebaceous ducts [16]. Skin sites with higher moisture and occlusion (e.g. the groin, axilla and umbilicus) are preferentially enriched with *Corynebacterium* spp. and *Staphylococcus* spp. [6]. *Staphylococcus epidermidis* (*S. epidermidis*) tolerates high salt concentrations and antibacterial molecules in sweat and may even use urea within sweat as a source of nutrients. The microbial profile of dry sites such as the forearm, hypothenar palm and buttock is more diverse and unstable, with a greater prevalence of *β-Proteobacteria* and *Flavobacteriales* [6]. In addition to intrinsic factors such as age, gender and body site, constituents of the skin microbiome vary according to the external environment, such as place of residence [17].

While the epidermal compartment harbors the vast majority of skin microorganisms, recent studies have shown that bacteria are also in the deeper dermis and dermal adipose tissue in healthy people, allowing for physical contact between microbes and immune cells, including innate immune cells, innate lymphoid cells and adaptive immune cells [18, 19]. The dermal microbiome exhibits a distinct profile compared to the epidermis, albeit with evident interpersonal variations. A higher proportion of *Proteobacteria* and *Actinobacteria* and a lower abundance of *Firmicutes* were observed in facial and palm skin samples from 6 healthy individuals [18], and *Clostridiales* and *Bacteroidetes* were found to be enriched in deep skin biopsies from 16 patients with noninflammatory skin diseases [20]. How these microbes that usually reside on the superficial skin translocate across the epidermal layer remains to be determined.

The microbiota helps maintain skin barrier function in homeostasis The skin establishes a symbiotic relationship with its resident microbiota that forms a first line of host defense against pathogens through several strategies (Figure 1). These include the cornified, stratified layers of keratinocytes as a physical barrier, an acidic or salty niche as a chemical barrier, surveillance by tissue-resident immune cells, and the microbial barrier itself [21]. The most abundant and stable skin microbes are beneficial for skin homeostasis, as they compete with other microbes for space and nutrients, secrete antimicrobial proteins and proteases, and have evolved mechanisms to interfere with pathways vital for their rivals' colonization [21] (colonization resistance).

Additionally, although the skin microbiota is not required for the seeding of immune cells residing in the skin due to the role of the gut microbiota in promoting gut-associated lymphoid structure development, it provides protective immunity for cutaneous infections as an adjuvant to the host's immune system [22]. For instance, skin microbes directly produce or regulate keratinocyte and immune cell

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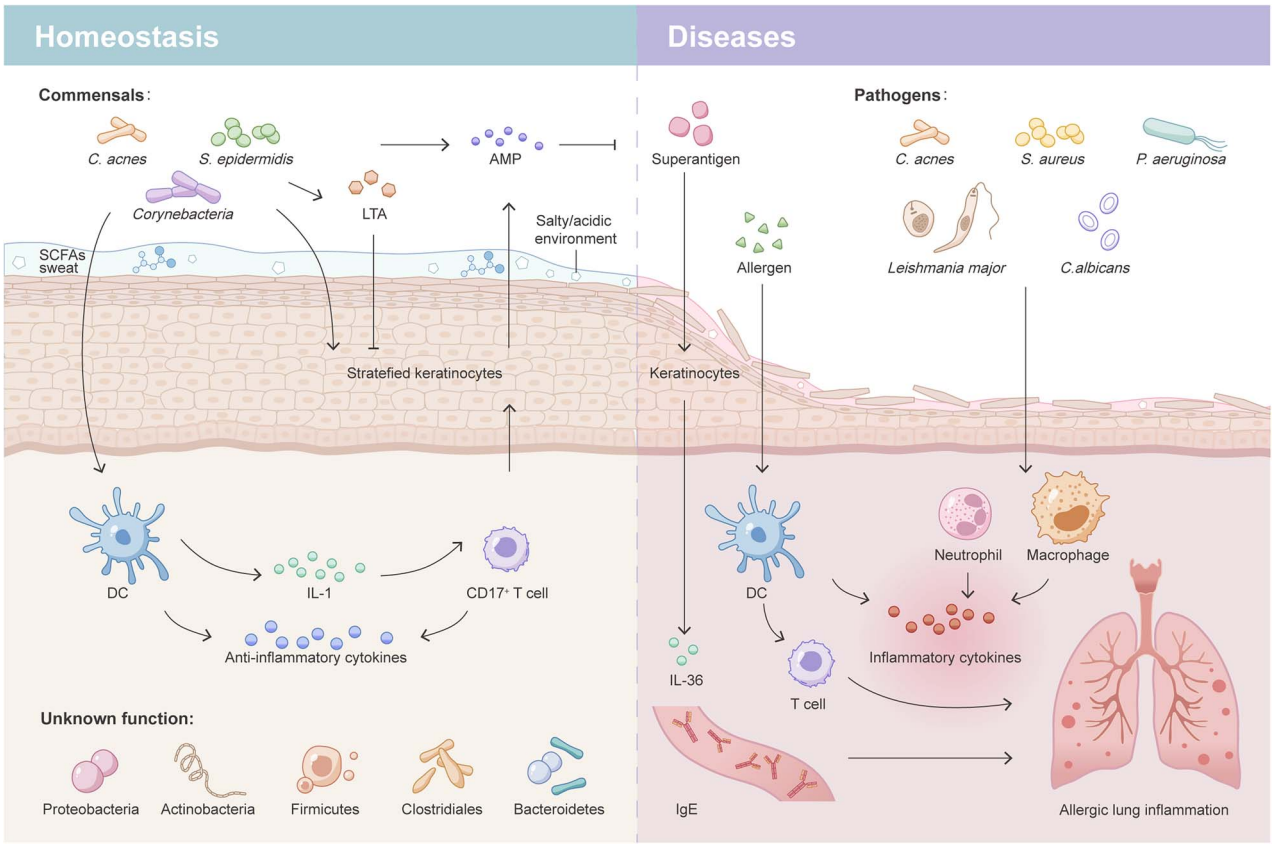

Figure 1. The microbiota in skin homeostasis and diseases. Skin commensals constitute an important microbial barrier of the skin in steady state. Microbiota-derived metabolites together with sweat create an uninhabitable chemical environment for other microbes on the skin surface. They directly produce or stimulate keratinocyte production of AMPs. Commensal-derived LTA attenuates keratinocyte-mediated cutaneous inflammation. Skin microbiobes also stimulate skin dendritic cell production of anti-inflammatory cytokines and IL-1 to prime CD17+ T cells for defense against pathogens such as *Leishmania major* and *C. albicans*. Bacteria are also found in the deep dermis in healthy skin, but their roles remain unknown. When the skin barrier is compromised due to the loss of an intact physical barrier (stratified keratinocytes), a change in the chemical niche or an overgrowth of pathogens, neutrophils and macrophages at early phases and effector T cells at later phases are recruited and activated to elicit skin inflammation. *S. aureus* amplifies skin sensitization to allergens, upregulates IL-36 and IgE expression and eventually contributes to a heightened risk of developing allergic lung inflammation. *C. acnes Cutibacterium acnes, S. epidermidis Staphylococcus epidermidis, S. aureus Staphylococcus aureus, P. aeruginosa Pseudomonas aeruginosa, C. albicans Candida albicans*, *LTA* lipoteichoic acid, *AMP* antimicrobial peptides, *SCFA* short-chain fatty acid, *DC* dendritic cell, *IL-1* interleukin-1, *IgE* immunoglobulin E

expression of innate factor antimicrobial peptides (AMPs), such as cathelicidins and β-defensins [23, 24]. They educate and prime skin-resident T cells for a better response to limit pathogen invasion. *S. epidermidis*-loaded dendritic cell-derived interleukin-1 (IL-1) could polarize skin-homing T cells into IL-17A-producing CD8+ T (Tc17) cells, which are important in promoting the keratinocyte production of AMPs [S100 calcium binding protein A8–A9 complex (S100A8/9)] to fight against pathogens such as *Leishmania major* and *Candida albicans (C. albicans)* [5, 22]. *S. epidermidis* can also prevent exaggerated inflammation by promoting monocyte-derived dendritic cell (DC) secretion of the anti-inflammatory cytokine IL-10 [25] and by producing lipoteichoic acid (LTA), which decreases keratinocyte cytokine production triggered by RNA released from damaged cells [1]. Intriguingly, in sharp contrast to immunity against pathogen invasion, such 'homeostatic immunity' happens silently without actively recruiting immune cells to the skin; thus, no inflammation occurs [2, 5, 26].

Microbiota dysbiosis is associated with diseases A delicate balance is achieved between the host and skin microbiota in the steady state, and various skin diseases can occur upon perturbation of the balance by either side (Figure 1). Normal constituents of the commensal microbiota can cause infections in certain cases (defined as opportunistic infection) and contribute to the initiation and/or amplification of skin disorders. Whether these microbes are friends or foes to humans is highly context dependent, profoundly influenced by the host's immune system, metabolism and genetic predisposition, bioburden, virulence and location of the microorganism, as well as microbe–microbe interactions. For instance, after the acute infection is resolved, herpes simplex virus 1 usually lurks in the host and establishes lifelong latency but can be reactivated when the host is immunocompromised [27]. As frequent opportunists of the skin, certain *C. acnes* strains with high inflammatory potential cause acne lesions, and *S. aureus*, when overwhelming the commensal microbiota, is responsible for most bacterial skin and soft tissue infections

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(e.g. furuncles and cellulitis) [28] and is also associated with immune diseases, including atopic dermatitis (AD) [24, 29] and psoriasis [30].

In addition to skin-specific disorders, the skin microbiota has been associated with systemic inflammatory diseases. Repetitive exposure to skin allergens due to skin barrier defects, such as those seen in AD patients with dysfunctional filaggrin, at early life stages leads to allergen sensitization and subsequent development of systemic allergies, including rhinitis and asthma [31]. This process is dependent on the recruitment of skin microbiota-induced antigen-presenting cells, as allergic inflammation was largely reduced in the absence of skin antigen-presenting cells in neonatal mice and adult germ-free mice [32]. The most common colonizer on AD skin, *S. aureus*, also plays important roles. Superantigen secreted by *S. aureus* augments ovalbumin-induced allergic lung inflammation by upregulating the IL-17A-associated immune response [33]. Epicutaneous exposure to *S. aureus* induces keratinocyte release of IL-36, increasing serum immunoglobulin E (IgE) levels and eventually leading to allergen-specific lung inflammation [34]. Through an undefined mechanism, chronic skin inflammation in psoriasis has been linked to an increased risk of atherosclerotic cardiovascular diseases [35–37]. Therefore, it is plausible that the unique skin microbiome in psoriasis patients might play a role in this [30, 38], which remains an interesting question and further studies are needed.

Wound healing processes

The cutaneous wound healing process is traditionally classified into the following three overlapping phases: inflammation, tissue regeneration/proliferation and remodeling [39]. Upon full-thickness skin injury, a blood clot forms to plug the defect as a temporary repair, which also initiates inflammation. The coagulation factors trigger classical and alternative complement cascades, and activated platelets release cytokines and growth factors that attract circulating neutrophils and monocytes to the injured site and activate them [40]. Neutrophils are phagocytosed by macrophages (i.e. efferocytosis) quickly once they eliminate infectious agents and devitalized host tissue, unless pathogens remain [40]. Monocyte-derived and tissue-resident macrophages, with the help of transforming growth factor (TGF)-β, degrade and remove injured tissue debris and apoptotic neutrophils [41]. These macrophages demonstrate a pro-inflammatory M1 phenotype [producing IL-1, tumor necrosis factor (TNF), inducible nitric oxide synthase (iNOS) and reactive oxygen species (ROS)] at the acute phase and convert to an anti-inflammatory M2 profile [producing IL-10, matrix metalloproteinase (MMP), TGF-β, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and epidermal growth factor (EGF)] at later stages, which is favorable for constructive tissue remodeling and guides tissue repair in a regenerative manner [42].

A few hours after injury, keratinocytes change their gene expression profile to initiate re-epithelialization, which is stimulated by keratinocyte growth factor 1 that is mainly produced by fibroblasts [43]. They migrate to damaged sites and proliferate in response to chemotactic cytokines and growth factors, including epidermal growth factor receptor (EGFR) ligands, the FGF family and TGF-α/β [44]. Meanwhile, granulation tissue consisting of macrophages, fibroblasts, loose connective tissue and new blood vessels is formed to replace the initial clot and start fibroplasia and neovascularization [40]. At this stage, growth factors, especially TGF-β, stimulate fibroblasts to proliferate and secrete collagen, fibronectin, glycosaminoglycans, proteoglycans and hyaluronic acid [45]. After granulation tissue formation, fibroblasts differentiate into α-smooth muscle actin-expressing myofibroblasts, which is a result of the increased stiffness of the wound compared to normal skin [46]. Then, large numbers of T cells infiltrate at the late proliferative phase and regulate the transition from inflammation to tissue remodeling [47, 48].

In the third phase, the cellularity of the wound gradually decreases. Macrophages, endothelial cells and myofibroblasts undergo apoptosis, representing the resolution of inflammation, involvement of vascularization and cessation of contraction, respectively [49, 50]. Under the regulation of MMPs and their inhibitors, collagen type III in the extracellular matrix (ECM) is replaced by collagen type I, the hyaluronan and glycosaminoglycan content decreases, and the more resilient and stiff molecules of the proteoglycan family increase [51]. Finally, a scar is formed that resembles normal skin tissue but is less elastic and resilient due to the altered organization and composition of the ECM. Not all wounds heal in a timely manner. Continuous infection exaggerates local inflammation and prevents the stage transition from inflammation to proliferation. In the case of redundant collagen deposition, dysfunctional fibrotic tissues are formed, namely, hypertrophic scars or keloids, according to the extent of fibroplasia.

The microbiome in acute wounds

Bacterial and fungal communities in acute wounds Because of the good prognosis, acute wounds are often overlooked in the field of wound microbiome study, and only limited information is available. Burn injury provides a typical acute wound model. It increases epithelial permeability, and thus, skin microbes are more likely to translocate to deeper tissue and cause infection. Burns can significantly alter the skin microbial profile, even in unaffected areas, increasing the abundance of thermophile microbes such as *Aeribacillus*, *Caldalkalibacilus* and *Nesterenkonia* while decreasing skin commensals such as *Cutibacteria*, *Staphylococci* and *Corynebacteria* [52, 53]. These changes are associated with certain outcomes of wound healing. The abundance of *Corynebacterium* correlates positively with wound infections, whereas *Staphylococci* and *Cutibacteria* have a negative correlation with postburn infections [52]. In terms of changes in bacterial diversity, contradictory results have been obtained by different studies, possibly due to the small sample size and use of antimicrobial agents [52, 53]. Investigation of recently healed

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burn wounds also revealed an altered composition, with *Staphylococcus* overgrowth, reduced community richness and increased bacterial diversity compared to healthy individuals [54]. Other forms of acute wounds also change skin microbial diversity and composition depending on the type of injury, and longitudinal observations suggest that those changes are dynamic in nature. Nevertheless, the microbiome in acute wounds gradually becomes similar to the adjacent skin microbiome with healing [55, 56]. Such a temporal and dynamic microbiome and its metabolome may be exploited to identify novel biomarkers that correspond to specific wound-healing processes [57].

As a known serious complication of traumatic wounds, the emergence of invasive fungal infection was identified in combat-related wounds of military personnel during the Afghanistan War [58], and it is associated with high mortality and morbidity, including residual limb shortening and high-level amputations (defined by either a hemipelvectomy or hip disarticulation) [58–60]. The presence of invasive molds (such as those of the order *Mucorales*, *Aspergillus* and *Fusarium* spp.) significantly delayed wound closure compared to wounds without fungal infection with similar injury pattern [59, 60], as measured by wound cultures. The coexistence of bacteria such as *Enterococci* is usually observed in invasive fungal infection, increasing the complexity of traumatic wounds [59]. However, no sequencing data regarding the fungal community in traumatic wounds and thus no comprehensive fungal profile are available to date.

Skin commensals may promote wound healing Sometimes, bacteria inhabit the wound bed as passive residents without arousing active infection and leave the healing process uninterrupted. Moreover, there is a growing body of evidence showing that a mixed population of skin commensals can actively interact with the immune system to promote wound healing. Constant encounter with symbionts, even a low level of bacteria, in the steady state leads to induction of microbiota-specific T-cell responses in the absence of inflammation, which are important in antimicrobial defense and tissue repair upon skin injury [2, 5, 26]. During skin injury, commensal bacteria stimulate neutrophils to express CXC ligand 10 (CXCL10), which eradicates wound-colonizing microbes and recruits activated plasmacytoid DCs (pDCs). pDC-derived type I interferons then accelerate wound repair by inducing growth factor production in fibroblasts and macrophages [3]. This result may alter our current understanding that inflammation in noninfected wounds is triggered by dying host cells; instead, this data suggests that commensals are required to elicit innate immune responses. In a separate study, resident commensals and even pathogenic *S. aureus* enhanced skin regeneration and wound-induced hair follicle neogenesis by inducing IL-1β and keratinocyte-dependent IL-1R-myeloid differentiation primary response 88 (MyD88) signaling [4]. In addition, *S. aureus* potently induces keratinocyte production of AMPs in a Toll-like receptor (TLR) 2-independent manner and, together with commensal-induced AMPs, may synergistically promote innate immune responses in wound healing [61]. When skin commensals were disturbed by oral vancomycin treatment, mice demonstrated decreased skin bacterial diversity and altered composition. Compared to the control, these mice showed delayed wound healing, possibly associated with downregulation of IL-17 and the regeneration of islet-derived protein-III γ, which are important for keratinocyte differentiation and proliferation [62].

However, when Canesso *et al*. compared the healing process in germ-free Swiss mice and conventional Swiss mice, they found that wound healing was accelerated and scarless in the absence of a commensal microbiota because of controlled inflammation, characterized by low accumulation of neutrophils and high levels of alternatively activated macrophages as well as increased angiogenesis at wound sites. Restoration of the skin microbiota deprived germ-free mice of such enhanced wound healing [63]. These conflicting results suggest that the effect of skin commensals in wound healing is complicated and versatile, and recognition of the precise role of defined microorganisms is vital.

As the most abundant symbiotic bacteria, the contribution of *S. epidermidis* to enhanced wound healing has been appreciated (Figure 2a). In the innate arm of the immune system, *S. epidermidis* colonization induces the expression of many antimicrobials, such as AMPs [64, 65] and LTA, which attenuate cutaneous injury-induced TLR-3-mediated inflammation through TLR-2 signaling [1]. *S. epidermidis* activates the keratinocyte aryl hydrocarbon receptor and downstream IL-1α, IL-1β and β-defensin 3 expression [66]. In the adaptive arm, *S. epidermidis*-specific skin Tc17 cells expressed high levels of genes associated with wound healing, including angiogenesis (Csf2, Fgf2, Vegfa, Pdgfb), keratinocyte proliferation (Areg, Fgf2, Fgf16, Fgf18, Tgfb1, furin), chemotaxis (Pdgfb, Csf2, Tgfb1, furin), tissue remodeling (Mmp10, Mmp25) and ECM production (Fgf2, Pdgfb, Tgfb1, furin) [26]. In a mouse wound model, *S. epidermidis*-specific Tc17 cells rapidly accumulated at the wound edge postinjury and promoted faster wound closure compared to wounds associated with an *S. epidermidis* strain incapable of inducing such a cell subset [26]. When exposed to cytokines and alarmins previously shown to be associated with tissue damage, skin-resident *S. epidermidis*-elicited Tc17 cells demonstrate significant plasticity and rapidly release the type 2 cytokines IL-4 and IL-13, which are involved in tissue repair [2]. Furthermore, *S. epidermidis* strains expressing staphylococcal aromatic amino acid decarboxylase (SadA) are able to accelerate wound healing by converting aromatic amino acids into trace amines, which abrogate the cell motility inhibition effect of epinephrine produced by keratinocytes [67]. *S. epidermidis* also secretes a sphingomyelinase that facilitates host production of ceramides to maintain skin barrier integrity and prevent water loss in damaged skin [68].

Probiotics, defined as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' [69], are host-friendly microbes that are able to

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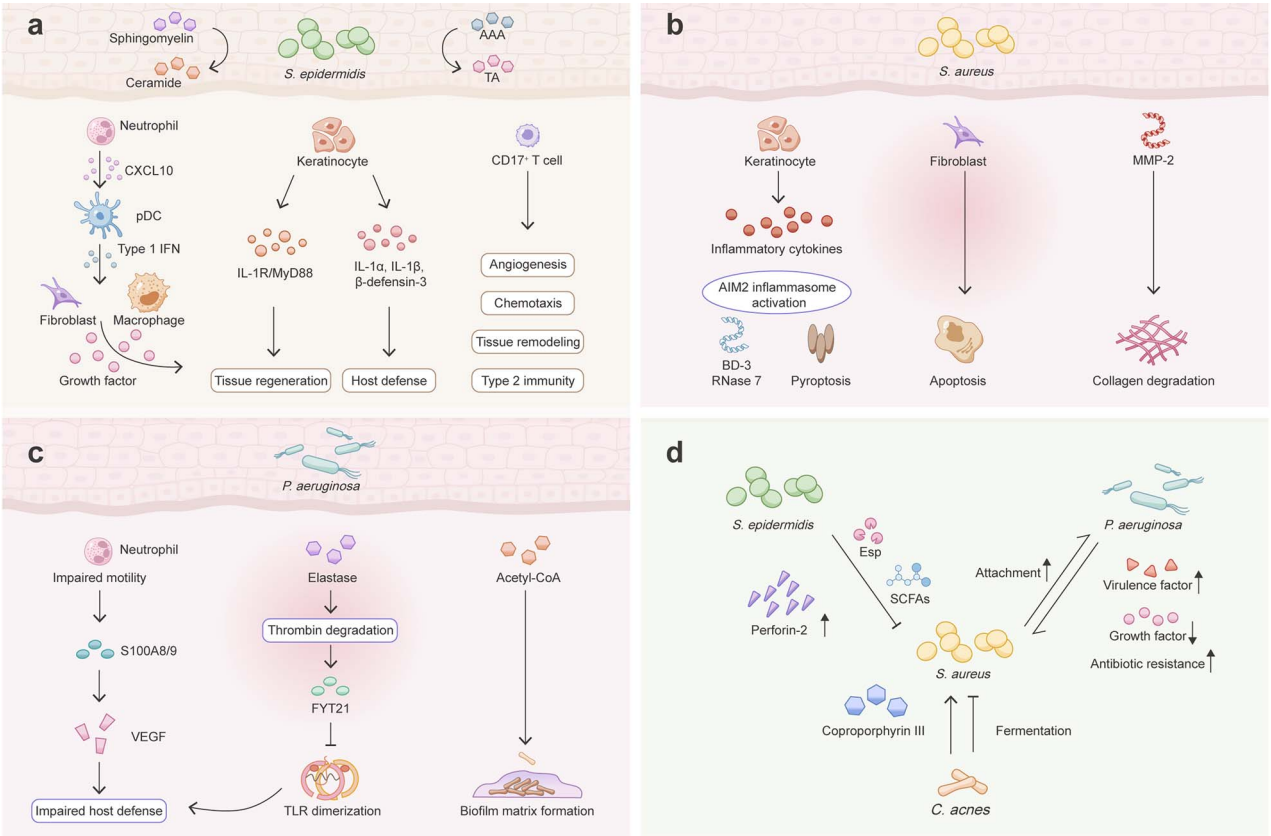

Figure 2. Microbe–host and microbe–microbe interactions in wound healing. (**a**) *S. epidermidis* promotes wound healing by converting AAA into TA and facilitating host ceramide production. *S. epidermidis* mediates neutrophil secretion of CXCL10 to induce pDC production of type 1 interferons, which stimulate growth factor production by fibroblasts and macrophages to promote tissue regeneration. *S. epidermidis* stimulates keratinocyte regeneration through the IL-1R/MyD88 pathway and induces IL-1α, IL-1β and β-defensin-3 production. *S. epidermidis*-specific CD17+ T cells express genes related to multiple facets of wound healing, including angiogenesis, chemotaxis, tissue remodeling and the release of type 2 cytokines. (**b**) *S. aureus* induces an inflammatory phenotype of keratinocytes with inflammatory cytokine production, AIM2 inflammasome activation and AMP (BD-3 and RNase 7) production and causes keratinocyte death. *S. aureus* inhibits fibroblast migration and induces apoptosis. *S. aureus* increases the level of MMP-2, which leads to collagen degradation. (**c**) *P. aeruginosa* impairs neutrophil motility and effector function. *P. aeruginosa*-derived elastase degrades thrombin and releases FYT21, which inhibits TLR dimerization. During the chronic infection phase, *P. aeruginosa* alters metabolic pathways to facilitate biofilm matrix formation. (**d**) *S. epidermidis* inhibits *S. aureus* growth in wounds via the protease Esp and SCFA and upregulates host expression of perforin-2. *S. aureus* promotes *P. aeruginosa* attachment, while *P. aeruginosa* increases the virulence and antibiotic resistance of *S. aureus*. Together, these bacteria reduce the level of growth factors related to regeneration. *C. acnes* either promotes *S. aureus* biofilm formation via coporphyrin III or inhibits its growth through fermentation. *S. epidermidis Staphylococcus epidermidis*, *AAA* aromatic amino acids, *TA* trace amine, *IL-1* interleukin-1, *CXCL10* CXC ligand 10, *pDC* plasmacytoid dendritic cell, *IFN* interferon, *MyD88* myeloid differentiation primary response 88, *S. aureus Staphylococcus aureus*, *MMP-2* matrix metalloproteinase-2, *AIM2* absent in melanoma 2, *BD-3* β-defensin-3, *P. aeruginosa Pseudomonas aeruginosa*, *S100A8/9* S100 calcium binding protein A8–A9 complex, *VEGF* vascular endothelial growth factor, *TLR* toll-like receptor, *acetyl-CoA* acetylcholine A, *SCFA* short-chain fatty acid, *C. acnes Cutibacterium acnes*

restore the body's microbiome balance, such as the perturbed microbiome in the wound bed. *In vitro* studies have demonstrated the ability of *Lactobacilus* spp., mainly *Lactobacillus plantarum*, or their supernatant to promote keratinocyte proliferation and migration [70] and prevent biofilm formation [71–73]. Evidence from animal models also supports the role of probiotics, including *Lactobacilus* spp., *Bifidobacteria*, *kefir* and *Saccharomyces cerevisiae*, in reducing pathogen colonization and biofilm formation, promoting tissue repair, decreasing excessive scarring and lowering the mortality rate of infected wounds [74–81].

The microbiome in chronic wounds

Biofilm formation characterizes chronic wounds Chronic wounds usually occur in elderly individuals with diabetes mellitus, vascular disease and obesity, as well as individuals with compromised immune and nutritional status [82, 83]; furthermore, care for nonhealing wounds leads to high healthcare expenditure [84]. The hallmark of impaired healing wounds is persistent inflammation, with microbial infection being the leading cause. Microbes colonizing the wound exist either as single, planktonic cells or as a complex structure called a biofilm, which consists of polysaccharides, lipids, proteins and nucleic acids and harbors a single species or various types of bacteria and fungi [85]. In contrast to acute wounds, a higher rate of biofilm formation was observed in chronic wounds (60 vs. 6%) by light and scanning electron microscopy techniques [86]. A systemic review and meta-analysis assessing 185 chronic nonhealing wounds reported an average biofilm prevalence of 78.2% [87]. A

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biofilm provides a habitable environment for microbial growth and is far more resistant to antimicrobial agents and host immune defense. It provides a continuous stimulus to the immune system, contributes to local hypoxic niche establishment and impedes the natural process of wound healing [86,88–91]. Even if a biofilm-infected wound is closed, the skin post-closure exhibits compromised epithelial tight-junction function [92] and reduced tensile strength [93]. As a result, the low-quality healed skin is likely to have higher risk of future complications such as wound recidivism.

Bacterial community and clinical relevance in chronic wounds A large-scale retrospective clinical study of 2963 chronic wounds of various etiologies, including 916 venous leg ulcers, 767 decubitus ulcers and 370 nonhealing surgical wounds, revealed a distinct microbial profile compared to that of the surrounding healthy skin, but the composition of microbiota was similar among different types of wounds and was not affected by patient demographics [89]. *Staphylococcus*, *Pseudomonas* and *Corynebacterium* were identified as the most common genera [89], which is well supported by evidence from other studies [83,94–98]. *S. aureus* and *S. epidermidis* were the predominant species, and methicillin-resistant *S. aureus* (MRSA) was identified in 25% of chronic wounds. *Pseudomonas* is not only the most dominant genus in chronic wound polymicrobial biofilms but also the most common microbe seen in single-species biofilms [89]. Although chronic wounds are usually exposed to high levels of oxygenation, deep ulcers and those of a longer duration contain a large number of anaerobic bacteria, including *Anaerococcus*, *Fingelodia*, *Prevotella*, *Preptonipihlus*, *Peptostreptococcus* and *Clostridium* [83, 86, 89, 95, 97]. Importantly, facultative anaerobes, especially *Enterobacter*, were significantly associated with nonhealing wounds [99].

Among all types of chronic wounds, diabetic foot ulcers (DFUs) are the most studied. Using 16S rRNA gene sequencing technology, a reduced microbial diversity [94, 100] and a significantly increased relative abundance of *Staphylococcus* spp. [83, 96, 98, 100] was found in DFUs in contrast to healthy skin. Changes in the skin microbiome likely occur prior to ulcer development or skin infection. Surprisingly, unlike diabetic wounds, the plantar foot of diabetic men showed a higher bacterial diversity and a lower relative abundance of *Staphylococcus* spp. compared to nondiabetic men, but they possessed a higher quantity of more virulent forms of *S. aureus* [101]. Diabetic patients also had a lower relative abundance of *Firmicutes* and a higher abundance of *Actinobacteria* in their feet, but the composition and total bacterial counts were similar in arm samples from the two groups [101]. These observations have been linked to the risk of future DFU development.

When connected to clinical presentation and outcomes, Gardner *et al*. found that a high microbial diversity and an increase in the relative abundance of anaerobic bacteria and gram-negative *Proteobacteria* spp. were associated with deep DFUs and long disease duration, whereas an increase in the relative abundance of *Staphylococcus* spp., mainly *S. aureus*, was found in shallow ulcers and in those with a short disease duration [97]. A longitudinal study further illustrated that rapid and dynamic changes in the skin microbiota were associated with rapid and improved healing of DFUs [98]. This may seem counterintuitive, but microbiota community instability might reflect efficient clearance of wound-colonized bacteria that prevents dominance of the wound bed by a single aggressive bacterial strain. Moreover, systemic antibiotics that destabilize the chronic wound bed microbiome foster wound healing [98]. Using metagenomic shotgun sequencing, Kalan *et al*. discovered two isolates of *S. aureus*, SA10757 and SA7372, that were associated with nonhealing DFUs [83]. These strains harbored multiple antibiotic resistance genes and expressed staphylococcal enterotoxins. Sharp debridement, rather than antibiotics, significantly shifted the wound microbiota by depleting anaerobic bacteria and decreasing the bacterial diversity, which accelerated wound healing [83].

Fungi and viruses in chronic wounds In contrast to bacteria, fewer studies have explored fungal communities in chronic wound healing. Since the foot is colonized by large amounts of fungi, fungal foot infections are common in diabetic patients [102]. Fungi were cultured from 27.2% of the lower-limb wounds of patients with type 2 diabetes [103]. Dowd *et al*. reported a positive rate of 23% fungal colonization in chronic wounds with different etiologies using deep molecular sequencing methods [104]. Of note, fungi were detected in 40.8% of DFUs. Unlike bacteria, fungi are extremely diverse in DFUs. The most abundant fungal members were *Asomycota* (*Cladosporidium herbarum* and *C. albicans*) and *Basidomycota* (*Trichosporon asahii* and *Rodhosporidium diobovatum*) [105]. Interestingly, fungal diversity increased upon the administration of systemic antibiotics and wound deterioration, and polymicrobial biofilms consisting of bacteria and fungi were associated with poor clinical outcomes [105].

Little attention has been given to the virome in wounds due to the difficulty of achieving sufficient sequencing depths, and only the phageome has been investigated. A recent metagenomic study evaluated 20 chronic wound patients with different etiologies, including diabetic, venous, arterial and pressure ulcers, and discovered a virome of greater diversity and containing more pathogen-targeting phages instead of commensal-targeting phages compared to that of healthy skin [106]. In addition, wounds that healed in 6 months were associated with two phage species targeting *Staphylococcus* strains, while unhealed ones were associated with phages targeting *Streptococcus* and putative *Enterobacter* phage spp. [106]. Clearly, further studies are desperately needed to elucidate the make-up of the virome in wounds.

Pathogens hinder wound healing Mechanistic studies further confirmed the pathogenicity of defined microbes in chronic wounds, as was seen in correlative observations. As a

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prevalent pathogen persisting in nonhealing wounds, the role of *S. aureus* in wound healing has been extensively investigated (Figure 2b). Using coculture methods, Kirker *et al*. showed that *S. aureus*-induced biofilms promoted keratinocyte secretion of proinflammatory cytokines, led to keratinocyte death and impaired scratch closure [107]. It also hampered dermal fibroblast migration and resulted in fibroblast apoptosis [108]. In a porcine wound model, *S. aureus*-induced biofilm repressed microRNA (miR)-143, causing upregulation of the expression of the downstream target gene MMP-2. MMP-2 degrades collagen type 1 in granulation tissue and compromises wound healing [93]. Furthermore, reduction in collagen type 1 in the wound bed decreased the tensile strength of the healed skin, predisposing to wound recidivism [93]. *S. aureus* impaired DNA repair mechanisms via induction of miR-15b-5p and led to a sustained inflammatory response and delayed wound closure in DFUs [109]. Intracellular accumulation of *S. aureus* in the epidermis also triggered absent in melanoma 2 (AIM2) inflammasome activation and pyroptosis, which correlated with nonhealing DFUs [110].

The persistence of *S. aureus* in chronic wounds implies its ability to escape host defense, and this has recently been linked to the suppression of perforin-2 expression [110, 111]. Perforin-2, an AMP, is an antibacterial protein expressed by $\gamma\delta$ T cells, keratinocytes, endothelial cells and fibroblasts in human skin [110, 111]. It is released from endosomal vesicles and fuses with bacteria-containing phagosomes to eliminate intracellular bacteria. A keratinocyte cell line overexpressing perforin-2 cleared intracellular *S. aureus* infection more efficiently than control cells [111]. However, perforin-2 expression was inhibited in both hematopoietic cells and skin tissue cells in *S. aureus*-infected human wounds [110, 111]. Using perforin-deficient mice, Tomic-Canic *et al*. showed that MRSA epicutaneously inoculated only translocates to internal organs and leads to death in the absence of perforin-2 expression [112], confirming the importance of perforin-2 in preventing *S. aureus* invasion.

Pseudomonas aeruginosa (*P. aeruginosa*) is an opportunistic gram-negative bacterium implicated in inducing biofilm formation in chronic wounds (Figure 2c). In contrast to *S. aureus,* which usually resides in the superficial layers of wounds, *P. aeruginosa* is localized in deeper tissues of the wound bed [113]. Wound infection with *P. aeruginosa* initiates an immune response characterized by early recruitment of neutrophils to sites of injury and later activation of systemic adaptive immunity [114]. *P. aeruginosa*-induced biofilms impair neutrophil effector function both *in vitro* [115] and *in vivo* in murine wound models [116] and delay wound closure by reducing VEGF and AMP (S100A8/9) levels [116, 117]. In addition, *P. aeruginosa*-derived elastase inhibits host inflammatory responses by digesting thrombin and releasing the C-terminal thrombin-derived peptide FYT21, which prevents TLR dimerization [118]. Compromised host defense against *P. aeruginosa* then leads to the chronicity of *P. aeruginosa* wound infection. Surprisingly, *P. aeruginosa* biofilms were not more virulent than planktonic *P. aeruginosa* in a murine chronic wound model [114].

Metabolome analysis of the log-phase *P. aeruginosa* (PAO1) strain, from colonizing to acute infecting and then to biofilm-infecting full-thickness excision wounds, has unveiled a dynamic regulation of gene expression related to metabolism, especially carbon-utilization pathways, and cell replication [119]. Pathway of 'branched-chain amino acids' was increasingly upregulated along with progression to chronic infection. From earlier to later biofilm infection, pathway associated with 'fatty acid degradation' were upregulated. Both metabolic pathways produce the extracellular polysaccharide acetyl-CoA, a component of the biofilm matrix [119].

Microbial crosstalk in chronic wounds Since most chronic wounds are inhabited by more than one bacterial or fungal species, understanding the dialog between these microorganisms is essential (Figure 2d). As previously mentioned, perforin-2 plays an essential role in combating intracellular *S. aureus* infection and is downregulated in *S. aureus*-infected wounds [110, 111]. *S. epidermidis* aids in host defense against *S. aureus* infection by upregulating perforin-2 expression in $\gamma\delta$ T cells, keratinocytes and fibroblasts [65]. *S. epidermidis* inhibits the formation of *S. aureus*-induced biofilm, destroys *S. aureus*-induced biofilms through the serine protease Esp and eliminates *S. aureus* nasal colonization [120]. Some strains of *S. epidermidis* also limit *S. aureus*-induced neutrophil recruitment and cytokine production [121]. Interestingly, commensal *S. aureus* can suppress pathogenic MRSA growth by several mechanisms; *S. aureus* ferments carbohydrates into short-chain fatty acids, which diffuse into the bacterial cell to reduce the intracellular pH and finally kill MRSA USA300. Antibodies induced upon exposure to commensal *S. aureus* offer protection against pathogenic *S. aureus* infection [122].

Pastar *et al*. evaluated the interaction between the two most common bacteria, *S. aureus* and *P. aeruginosa,* in chronic wounds using a porcine wound model [43]. *P. aeruginosa* diminished MRSA USA300 growth both *in vitro* and *in vivo*, but not vice versa. However, the presence of *P. aeruginosa* promoted MRSA expression of the virulence factors Panton–Valentine leukocidin and α-hemolysin, and coinfection with these bacteria significantly delayed re-epithelialization through suppression of keratinocyte growth factor 1 expression [43]. *In vitro* coculture experiments further demonstrated that *S. aureus* mediated an increase in the attachment of *P. aeruginosa* to human keratinocytes, while *P. aeruginosa* promoted an invasive phenotype in *S. aureus* [123]. *P. aeruginosa* also decreased the sensitivity of *S. aureus* biofilms to vancomycin [124]. Collectively, these results confirm both competitive and reciprocally beneficial interactions between these two bacteria in biofilm formation.

In other cases, *Cutibacterium* spp. can serve as an accomplice to *S. aureus* pathogenicity as coproporphyrin III secreted by *Cutibacterium* spp. induces the formation of *S. aureus*

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biofilms [125]. However, *C. acnes* can also suppress the growth and wound colonization of MRSA USA300 through glycerol fermentation [126]. Coculture of *S. aureus* with another common skin commensal, *Corynebacterium striatum*, induces a broad shift in *S. aureus* gene expression, including the downregulation of quorum sensing genes, which shifts the bacteria toward a commensal phenotype [127]. *Enterococcus faecalis* and *P. aeruginosa* have a synergistic effect on biofilm matrix production [128]. Most current studies regarding microbial crosstalk have been limited to dual-species models, but given that wound biofilms are frequently colonized by multiple microbial species, the development of novel multispecies biofilm models is urgently needed.

The microbiome in scar formation

Excessive ECM deposition by fibroblasts and imbalanced ECM degradation by recruited leukocytes in wound healing leads to scarring/fibrosis, an unintended result of aberrant tissue repair. Persistent pathogen-induced chronic inflammation characterized by massive alternatively activated macrophage (M2) infiltration and a T helper 2 cell (Th2) cytokine response is believed to be the key driver of unrestrained fibrotic responses in the lungs, liver, kidney, spleen, intestines and brain [129]. This is evidenced by the existence of pathogens in fibrotic patients, the successful induction of organ fibrosis by infectious agents using animal models, the exacerbation of fibrosis by infectious agents and the promising effects of antimicrobial treatment on fibrotic diseases [130]. Classic examples of pathogen-induced fibrosis include pulmonary tuberculosis and chronic viral hepatitis. Unfortunately, no specific pathogen has been linked to hypertrophic scars and keloids, although they share a similar dysregulated immune signature (Th2 activation and M2 infiltration) with other fibrotic diseases [131, 132]. Indeed, little is presently known about the role of the microbiome in scar formation, as the main focus of skin microbiome research is skewed toward nonhealing wounds instead of overly healed ones (Figure 3).

The assumption that microbial infection plays a role in scar formation has some theoretical support. First, inflammatory skin diseases explicitly associated with bacteria such as acne and folliculitis and virus vaccine inoculation are common risk factors for keloids. Although the broad spectrum of pathogens capable of inducing keloids indicates that there might not be a single culprit, microbial-induced chronic local inflammation may still be responsible. Therefore, infection-based theories of keloidogenesis are constantly proposed [133, 134]. Second, scarless tissue regeneration is commonly seen in fetuses who live in the sterile environment of the amniotic fluid [135]. The introduction of bacteria into rabbit fetal wounds induces neovascularization and fibroplasia, which are classic features of scar formation in adults [15]. The oral mucosa represents another place where scar-free healing usually occurs. Similar to amniotic fluid, saliva provides a wet and bacteria-inhibiting milieu for wound healing [135].

Supporting this hypothesis, recent studies have shed some light on this area. As previously mentioned, depletion of skin commensals in mice leads to scarless wound healing [63]. Similarly, a hydrogel loaded with growth factors and antimicrobial components to create a sterile, moist microenvironment has been developed to treat skin wounds, and it indeed results in accelerated healing in the absence of scarring [136]. A study group compared the bacteriology of scalp folliculitis with different severities. *S. aureus* infection was detected in acne keloidalis nuchae, while less severe folliculitis was associated with *C. acnes* [137]. In a porcine burn model, infection of burn wounds with *S. aureus* led to delayed re-epithelialization and increased dermal injury and deep scarring [138]. Moreover, TLRs associated with classical viral infection are highly expressed in keloids [139], highlighting the potential involvement of viruses in skin fibrosis. This is intriguing because fibroblasts isolated from other fibrotic tissues showed high levels of TLR activation and subsequent release of profibrotic chemokines [129]. In another skin fibrotic disease, parvovirus B19 persists in systemic sclerosis fibroblasts and is able to stimulate human dermal fibroblast migration and the production of fibrotic cytokine metalloproteases [140]. Whether a similar mechanism exists in hypertrophic scars remains an interesting research question.

Modulating the microbiota following skin injury

Acute wound management There is no doubt that timely empiric use of antibiotics is essential for reducing bacterial load and preventing infection in circumstances such as severe burn injury and trauma. However, currently, topical antibiotics are routinely used for even minor skin injuries by some patients and even physicians. In addition to the development of pharmacologic resistance due to the abuse of antibiotics, new evidence has suggested a counterproductive effect of topical antibiotic use in wound treatment. Contrary to our previous understanding, resident commensal bacteria may promote wound healing, and disruption of the skin microbiota delays tissue regeneration [3, 4]. Therefore, topical prophylactic antibiotic use for acute wounds with no signs of infection should be discarded in future clinical practice.

Chronic wound management Management of chronic wounds requires comprehensive wound assessment and appropriate care. Basic strategies include wound cleansing, debridement, moisture control, nutritional support and microbial regulation, yet the effect is suboptimal. Because chronic wounds are characterized by an altered microbiome with an overgrowth of certain bacteria [83, 98], elimination or destabilization of the existing microbiota is of vital importance. Anti-fungal treatment is also necessary when there is concurrent fungal infection [58]. However, established biofilms are seldom removed via antibiotics alone, which conversely may lead to the selection of more resistant bacterial species. Alternatives or adjuvants to conventional antibiotics in inhibiting bacterial growth are needed (Figure 4).

Sharp debridement is recommended in all diabetic wounds to remove debris and necrotic and infected tissues. This

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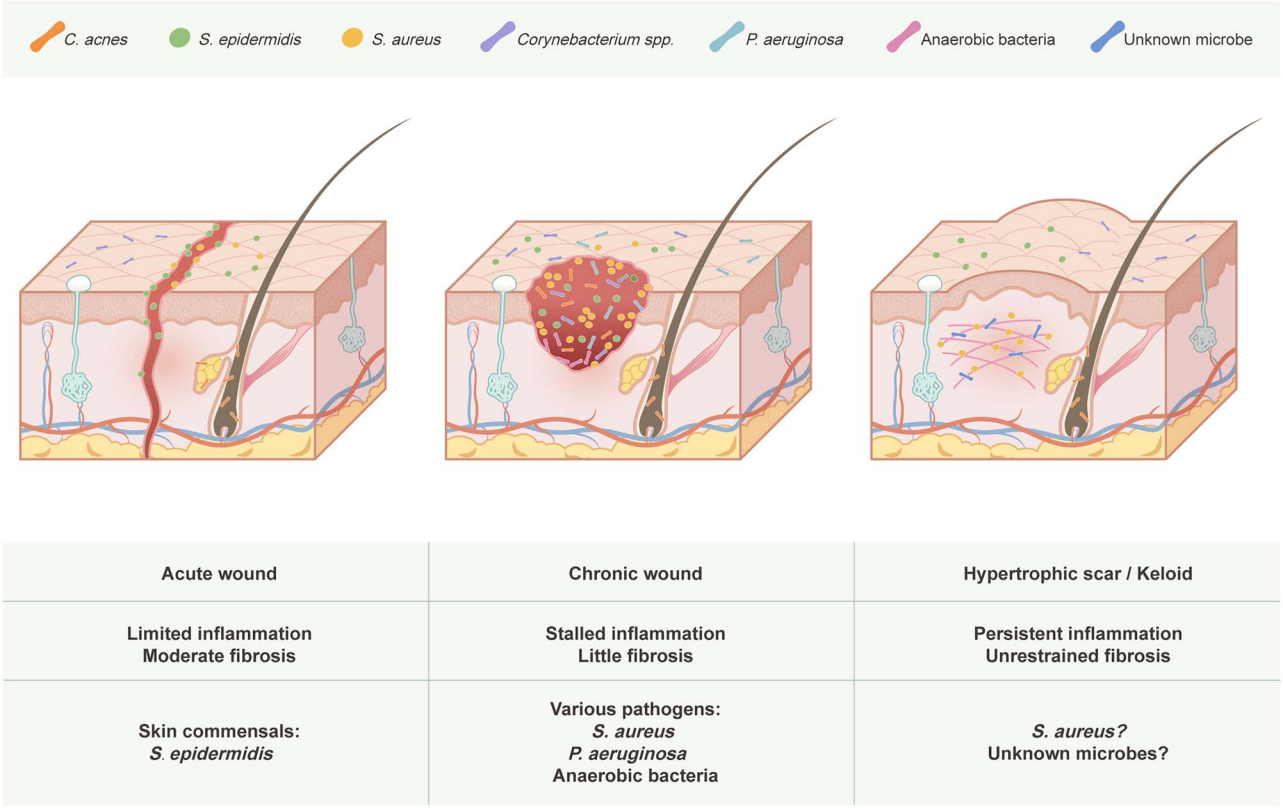

Figure 3. Schematic diagram representing the interplay between the microbiota and different types of skin wounds. Skin commensals interact with host immunity to promote timely healing with normal scarring in acute wounds. Various pathogens form biofilms in chronic wounds and cause a strong inflammatory response, preventing healing from progressing to the next phase. Microbe-induced dermal inflammation might be responsible for inciting an uncontrolled fibrotic response that gives rise to hypertrophic scars and keloids. *C. acnes Cutibacterium acnes, S. epidermidis Staphylococcus epidermidis, S. aureus Staphylococcus aureus, spp.* species, *P. aeruginosa Pseudomonas aeruginosa*

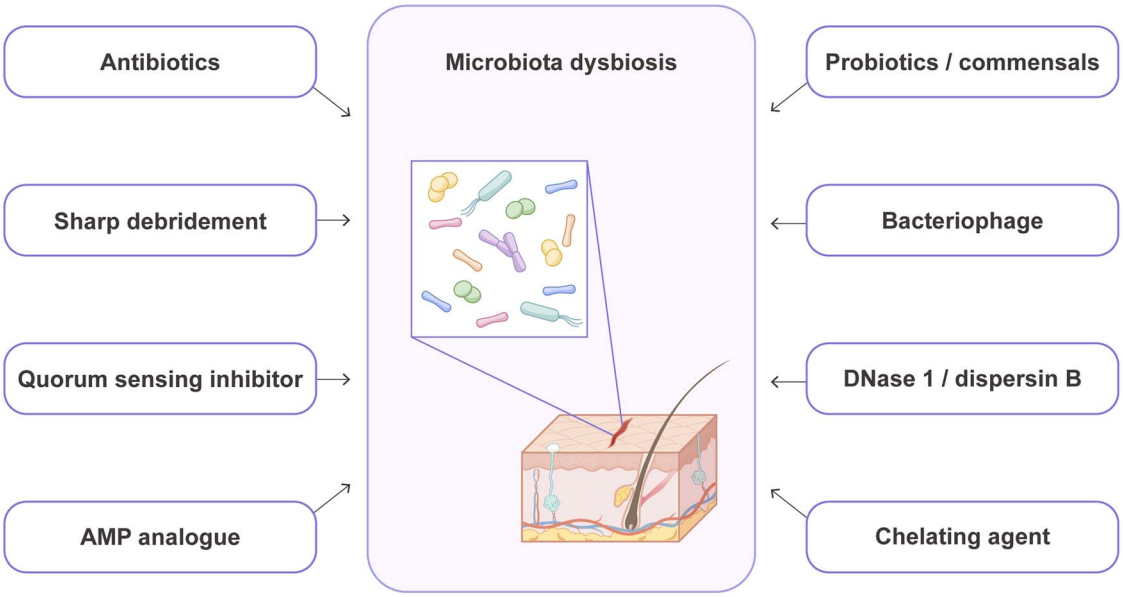

Figure 4. Biocontrol strategies in wound management. *AMP* antimicrobial peptides

procedure aims to induce an acute wound by creating sterile tissue damage and 'reactivating' healing pathways [141]. Sharp debridement is effective in reducing wound microbial diversity and disrupting anaerobic networks and has been linked to more favorable DFU clinical outcomes [83]. Several other approaches have also been developed to induce

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an acute wound healing response. Topical application of pathogen-associated molecular patterns, such as lipopolysaccharide and exopolysaccharide, rescues the wound from stalled status to amplify inflammation and subsequent tissue regeneration [142, 143].

One unique way in which bacterial communities communicate with each other in terms of population density is by quorum sensing, which regulates both biofilm formation and bacterial toxin production. Using murine wound infection models, several studies demonstrated that exposure to quorum sensing inhibitors prevented *Staphylococcus spp*.-induced biofilm formation, decreased bacterial bioburden and restored normal wound healing kinetics [88, 144]. Similarly, a synthetic quorum sensing inhibitor inhibits *P. aeruginosa* virulence factor pyocyanin production and biofilm formation [145]. Quorum sensing inhibitors also increase the susceptibility of bacterial biofilms to antibiotics, resulting in an enhanced therapeutic effect [146].

Engineered synthetic peptides derived from naturally produced AMPs represent another promising approach in inhibiting bacterial biofilms [147]. In addition to their antimicrobial function, AMPs improve the host's immune response by recruiting antigen-presenting cells and enhancing their differentiation, facilitating neutrophil extracellular trap activation, enhancing phagocytosis, inducing proinflammatory cytokines and promoting T-cell polarization [147]. AMPs also accelerate wound healing by modulating the proliferation, migration and activation of keratinocytes and fibroblasts, facilitating re-epithelialization and angiogenesis [148, 149]. Approaches with these molecules are currently under development, and several peptides have entered clinical trials for treating infected burn wounds, DFUs and venous leg ulcers [147].

Correcting dysbiosis via probiotics has demonstrated satisfactory clinical efficacy in treating many intestinal diseases, such as *Clostridium difficile* infection and irritable bowel diseases; however, the same strategy has not been well developed in skin disorders, including wounds. *In vitro* studies have demonstrated the ability of probiotics, mainly *L. plantarum*, or their supernatants to promote keratinocyte proliferation and migration [70] and prevent biofilm formation [71–73]. Evidence from animal models also supports the role of probiotics in reducing pathogen colonization, promoting tissue repair, decreasing excessive scarring and lowering the mortality rate of infected wounds [74–77]. To date, only a few small-scale clinical studies involving burn wounds, chronic venous ulcers and oral wounds have evaluated the impact of the topical use of probiotics on wound healing, yet they have demonstrated promising therapeutic effects [150–153]. Moreover, probiotics can also serve as a drug-delivery system. CXCL12-delivering *Lactobacillus* promoted murine wound healing by inducing the proliferation of TGF-β-producing macrophages [154].

Harnessing the competitive relationship between commensals and pathogens by counteracting pathogens with commensals and their products is a viable option for bacterial control with unexploited potential in infected wound treatment. Accordingly, active colonization/transplantation of commensals with probiotic properties, such as *S. epidermidis* or *C. acnes*, or application of bacterial products such as commensal-derived short-chain fatty acids or proteases might be helpful in combating pathogens in wound infection and thus accelerating healing [3, 155]. This field awaits further investigation and more mechanistic studies evaluating microbe–microbe crosstalk could provide novel insights into microbial control.

Phages are natural enemies of bacteria. They target specific bacterial strains, and once they enter the bacterial host, they inject phage DNA to induce bacterial lysis and interfere with bacterial metabolism [156]. Therefore, they are potentially useful with minimal side-effects in treating wounds of a known pathogen infection. Cocktail therapy containing various phages has been considered a plausible biocontrol strategy for phytobacteria [157]. In a phase 1 trial, injection with phages targeting *P. aeruginosa*, *S. aureus* and *Escherichia coli* was proven to be safe and efficient in treating chronic venous leg ulcers [158].

Apart from eradicating bacteria themselves, disrupting the biofilm matrix that they attach to is another approach for microbial control. Deoxyribonuclease I and dispersin B degrade extracellular DNA (eDNA) and poly-β 1,6-*N*-acetylglucosamine, respectively, which are involved in microbial surface attachment [159, 160]; these agents have been found to be highly effective in inhibiting pathogens and promoting wound healing [161]. Ethylenediaminetetraacetic acid (EDTA) chelates Mg^{2+} and Ca^{2+} from the outer cell wall of gram-negative bacteria and destabilizes the negative charge of lipopolysaccharide [162, 163]. The application of a hydrogel containing EDTA and bacteriocin significantly reduced the bacterial load in a *S. aureus* Xen-31-infected murine model [164].

Reducing scar formation Except for chronic nonhealing wounds, scar-related disfigurement and disability remain major challenges for medicine and cosmetics. Both normal and hypertrophic scars are difficult to treat and even less likely to be prevented. A variety of strategies have been applied in clinical practice, but their effects are still limited. Surgery, usually in combination with postoperative radiation, remains the major approach for reducing scarring; however, this strategy causes secondary trauma to the skin and the cost is high. A less invasive treatment is topical use and intralesional injections of corticosteroids, but it comes with many adverse effects, such as hypopigmentation, dermal atrophy, telangiectasia, widening of the scar and delayed wound healing [165]. Mechanical offloading is another attempt to limit fibrosis after skin injury, as mechanical tension activates many mechanoresponsive signaling pathways to induce inflammation and promote ECM deposition [166], but mechanical offloading is seldom used as a single therapy.

Due to the lack of active infection in most hypertrophic scars, antimicrobial treatment is not routinely used. Whereas

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antibiotics together with other therapies are effective in treating acne, their efficacy in preventing acne-associated keloid formation is largely unknown. Therefore, with its elusive pathogenesis, we are currently in no position to manipulate microbes in scar prevention. Further research characterizing the composition and function of the skin microbiome in hypertrophic scars and keloids would be informative in achieving the ultimate goal of scarless wound healing.

Current status and outlook for future research

Reviewing the past research literature shows that many skin microbes play a dual role in wound healing, depending on the bacterial load, strain-level heterogeneity (strain-level differences in the gene content determine functional differences of the same species) and interaction with other microbes. This is consistent with our new understanding about a microbe's pathogenicity being contextual [167], and understanding factors that foster the transition from commensalism to pathogenicity may be the key to more effective and specific therapeutic approaches. It must be kept in mind that wound healing is an extremely complex process with a series of variables being potential confounding factors. Hence, similar to many other skin disorders, an overly simplified one-to-one mapping of microbes to poor wound healing is inappropriate.

The methodologies used in microbiome research should be prudently evaluated and utilized with caution given their huge impact on results. For example, skin specimens are typically low in bioburden and extremely susceptible to reagent and environmental contamination [168]. While skin swabbing is the most commonly used approach for microbial sampling because it is noninvasive, tissue biopsies are the gold standard to capture the whole microbial population. Therefore, standardized sampling and analysis are required to ensure reproducibility across studies. In addition, differences exist in the healing process of rodents and humans, and most animal wound models illustrate the process of acute wound healing instead of chronic wound healing. Therefore, care must be taken when interpreting the results obtained from descriptive human studies as well as experimental animal studies.

Most wound microbial studies have focused on chronic DFUs, and the bacterial communities in acute wounds, other types of chronic wounds and hypertrophic scars/keloids are only partially understood. With technological progress in profiling fungi, future studies should also encompass these microorganisms considering their potency in inducing cutaneous inflammation and interacting with bacteria via unknown mechanisms. More large-scale longitudinal *in vivo* studies are also desperately needed to elucidate the temporal dynamics of the microbiome in wounds. Follow-up metatranscriptomics studies that identify real-time gene expression profiles may delineate the host–microbiome interaction in wounds more thoroughly. Additionally, to date, our understanding of host–microbe interplay mainly stems from pathogen-induced inflammation and infection. However, a symbiotic relationship uncoupled from inflammation is more common and yet largely underestimated in both healthy and certain disease conditions, including noninfected well-healed wounds. How the immune system coordinates with commensals to establish skin homeostasis and re-establish the balance in wound repair remains an important and fruitful question for future study.

Conclusions

The progress made in identifying skin microbiota using culture-independent methods in the past decade has been remarkable, leading to a more complex and thorough understanding of the association of wound healing with previously unappreciated microbial composition and diversity. Current evidence from germ-free and gnotobiotic animal studies as well as human wound studies indicates that efficient clearance of microbes with high inflammatory potential is detrimental to avoiding a stalled inflammation state and prolonged healing duration, while colonization of moderate nonaggressive commensals may aid rapid healing. Persistent dermal inflammation caused by unknown microbes may underscore the pathogenesis of exaggerated fibroproliferative responses in hypertrophic scars and keloids. These findings have revealed potential biomarkers that are associated with the quality of wound healing and provide the rationale and targets for manipulating the skin microbiome, paving the way for possible satisfactory wound healing induction.

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Authors' contributions

Conceptualization: YY, JH, NY and XW; writing–original draft: YY; writing–review and editing: YY, JH, AZ, NY and XW; visualization: YY and NY; funding acquisition: JH, XL and XW; and supervision: XW

Conflict of interest

None declared.

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