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INVITED REVIEW

The microbiome in wound repair and tissue fibrosis

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Abstract

Bacterial colonization occurs in all wounds, chronic or acute, and the break in epithelium integrity that defines a wound impairs the forces that shape and constrain the microbiome at that site. This review highlights the interactions between bacterial communities in the wound and the ultimate resolution of the wound or development of fibrotic lesions. Chronic wounds support complex microbial communities comprising a wide variety of bacterial phyla, genera, and species, including some fastidious anaerobic bacteria not identified using culture-based methods. Thus, the complexity of bacterial communities in wounds has historically been underestimated. There are a number of intriguing possibilities to explain these results that may also provide novel insights into changes and adaptation of bacterial metabolic networks in inflamed and wounded mucosa, including the critical role of biofilm formation. It is well accepted that the heightened state of activation of host cells in a wound that is driven by the microbiota can certainly lead to detrimental effects on wound regeneration, but the microbiota of the wound may also have beneficial effects on wound healing. Studies in experimental systems have clearly demonstrated a beneficial effect for members of the gut microbiota on regulation of systemic inflammation, which could also impact wound healing at sites outside the gastrointestinal tract. The utilization of culture-independent microbiology to characterize the microbiome of wounds and surrounding mucosa has raised many intriguing questions regarding previously held notions about the cause and effect relationships between bacterial colonization and wound repair and mechanisms involved in this symbiotic relationship.

Keywords: bacteria; inflammation; skin; gastrointestinal tract

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Introduction

The host microbiome is the entire collection of microorganisms that inhabit a host. This includes bacteria, archaea, fungi, parasites, viruses, and phages. In this review, we will focus almost extensively on the bacterial microbiome. This subset of the microbiome is almost exclusively restricted to mucosal sites during health, ie the surfaces of the body that are exposed to the outside world. This includes the skin, gastrointestinal tract, upper airways, oral cavity, and reproductive tract. However, despite being exposed to the outside world, the mucosal surfaces exert selective pressures on the composition of the bacterial microbiome. For example, while over 20 bacterial phyla have been reported for their growth on plant surfaces, only nine have been identified in the human gut [1,2].

In the context of this review article, a wound will be defined as a physical break in epithelium integrity and the subsequent host response to repair this break. Such a break in epithelium integrity impairs the forces that shape and constrain the microbiome at that site. Epithelium destruction will result in reduced production of mucus or lipids, alter anti-microbial peptide expression, and activate inflammatory cascades. Mucosal surfaces are exposed to the environment; thus, wounds also offer an opportunity for non-indigenous microbes to colonize the site, as well as altering the forces that balance indigenous microbial colonization (Table 1).

The initiation of wound repair normally begins very quickly after damage and involves well-integrated iterative steps in tissue regeneration that include the following [3–5]:

- clotting and coagulation
- secretion of extracellular signal molecules; eg cytokines, chemokines, growth factors, and eicosanoids
- leukocyte recruitment and formation of granulation tissue
- fibroblast activation and proliferation
- formation of new basement membrane and other extracellular matrix

Table 1. Wound microbiome bacterial species with known associations in wound repair

Summary of studies of bacteria associated with wounds	Association
Streptococcus spp.	Higher incidence in chronic diabetic wounds
Staphylococcus aureus, *Staphylococcus epidermidis*	Higher incidence in chronic diabetic wounds Colonization can impair the wound healing process Readily cultured from wounds
Enterococcus spp.	Higher incidence in chronic diabetic wounds
Peptostreptococcus spp.	Higher incidence in chronic diabetic wounds
Bacteroides spp.	Higher incidence in chronic diabetic wounds
Prevotella spp.	Higher incidence in chronic diabetic wounds
Pseudomonas aeruginosa	Higher incidence in chronic diabetic woundsInoculation into germ-free mouse wounds leads to accelerated wound repair (re-epithelialization, epidermal cell proliferation, and neo-vascularization) Readily cultured from wounds
Lactobacillus spp.	Induces ERK phosphorylation in the GI tract, which could regulate cell migration and epithelium restitution during wound repair
Lactobacillus reuteri strain RC-14	Can inhibit colonization of other species (ie *Staphylococcus aureus*) in a strain-specific manner
Escherichia coli	Outgrowth in the GI tract can occur in environments of increased inflammation due to epithelial damageReadily cultured from wounds
Klebsiella pneumoniae	Outgrowth in the GI tract can occur in environments of increased inflammation due to epithelial damageNecessary to induce transmissible spontaneous colitis in mice
Proteus mirabilis	Necessary to induce transmissible spontaneous colitis in mice
Corynebacteria spp.	Readily cultured from wounds
Propionbacteria spp.	Readily cultured from wounds, but in lesser levels than that found in healthy skin
Neisseria spp.	Fastidious and anaerobic bacteria commonly found in wounds
Campylobacteria spp.	Fastidious and anaerobic bacteria commonly found in wounds
Clostridiaceae	Fastidious and anaerobic bacteria commonly found in wounds

This table highlights microbes with known associations to wound healing that are discussed in this review.ERK = extracellular signal-regulated kinases; GI = gastrointestinal.

- new blood vessel growth
- remodelling to restore normal tissue architecture.

The balance between extracellular matrix formation and degradation is a key step during the normal wound-healing process and combined with a balance between proliferation and apoptosis of fibroblasts, is a major step in determining whether injured tissues return to their pre-injury state or develop fibrosis. A recent review by Meneghin and Hogaboam [3] provides an excellent overview on the role of infectious agents including bacteria, viruses, fungi, and multicellular parasites in cellular activation and the promotion of fibrosis (including examples in pulmonary, cardiovascular, integumentary, and alimentary systems). This review will focus on our current understanding of the role of the bacterial microbiome in mucosal wound repair pathology.

What is the bacterial microbiome and where is it found in the body?

Bacteria outnumber host cells by 10 : 1 and the metagenome of the bacterial microbiome is 100 times larger in size than the host genome [6]. Culture-independent methods have revealed a much greater diversity within the bacterial communities on the mucosa than previously identified by traditional culture-based methods [2,6]. The four most dominant phyla in the human body are the Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. However, the relative distributions of these four phyla differ vastly between body sites. For example, Firmicutes and Bacteroidetes are the most abundant members in the gastrointestinal tract [2,6], while Proteobacteria and Actinobacteria dominate the skin [1] and Proteobacteria appear to be significant members of the airways [7–11]. Furthermore, the density of the indigenous microbiota differs along the mucosa, with the highest concentration and diversity being found in the large intestine.

Metabolic, immunological, secretory, and structural forces shape the bacterial communities of the mucosa [1,2,6,12] (summarized in Figure 1). Diet and nutrient availability are two major factors that modulate bacterial growth. Polymicrobial communities naturally form complex, three-dimensional aggregates called biofilms, which create metabolic webs of agonistic and antagonistic relationships among its membership [13,14]. Host defence/immunity also plays an important role in creating specific niches for bacterial colonization through the production of anti-microbial peptides, secretory immunoglobulins, and bactericidal effector mechanisms activated through mucosal damage [12]. Other secretory mechanisms important in modulating bacterial community structure include the production of mucus, surfactants, and specific lipids. All of these forces are in play on the smooth and involuted mucosal surfaces that are also subject to one or more of the following structural forces, depending on the body site: physical abrasion; peristaltic movement of solids and liquid; ciliary movement of mucus; epithelium stretch; and gradients of pH, temperature, and/or oxygen concentration.

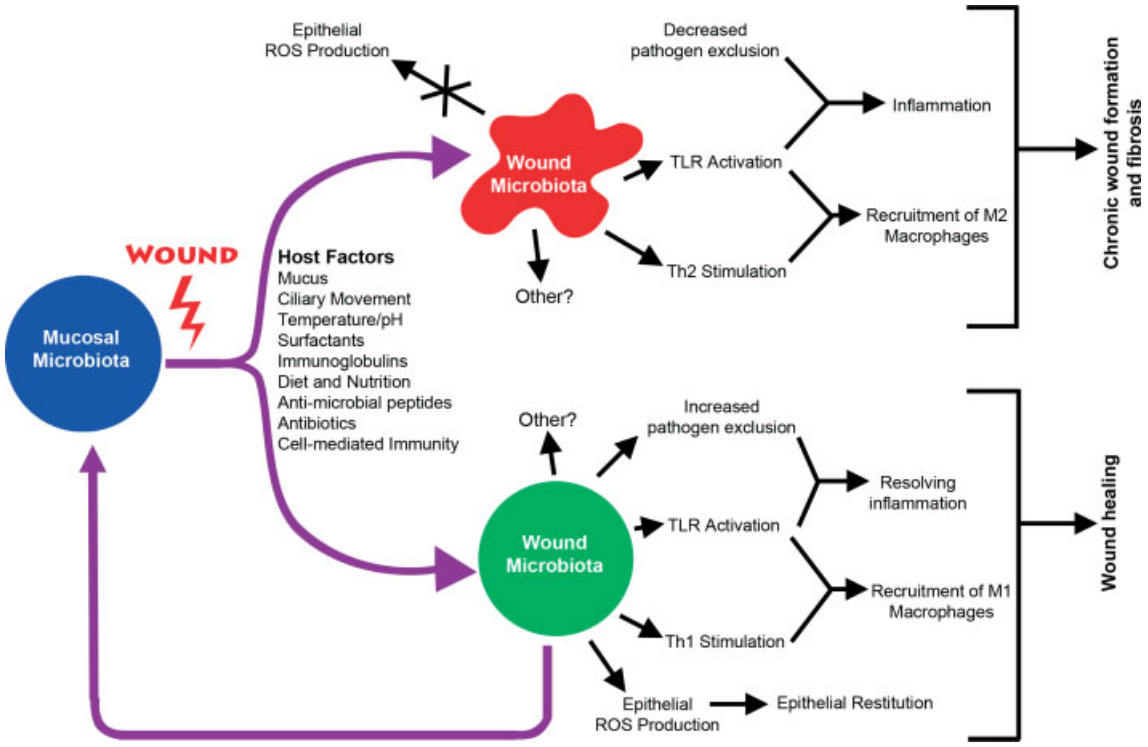

Figure 1. Summary of the mechanisms involved in modulating the bacterial microbiome of wounds and the effects of different wound microbiomes on the inflammatory and healing process. Specific details of the processes outlined in this figure are described in the text. ROS = reactive oxygen species; TLR = toll-like receptor.

How do you analyse the microbiome?

The adaptation of recently developed, high-throughput molecular approaches to culture-independent microbiology, such as 16S rRNA gene-based pyrosequencing, is beginning to provide new insight into identifying and understanding the role of bacterial communities in the processes of wound repair, chronic wound formation, and fibrosis. Of note are the recent numerous reports that chronic wounds support complex microbial communities consisting of a wide variety of bacterial phyla, genera, and species, including some fastidious anaerobic bacteria not identified using culture-based methods [15–18]. The key limitation of culture-based methodologies is the inability to routinely grow out these fastidious and/or currently 'unculturable' organisms. Estimates are that more than 60% of bacterial species in the human microbiome have not been able to be cultured and a majority of the remaining bacteria have complex and dynamic growth requirements, rendering them difficult to reproducibly isolate [19]. Most commonly, culture-independent techniques are based on PCR amplification of the 16S rRNA gene. This gene is relatively small (approximately 1.5 kbp), highly conserved, not subject to natural selection pressures, and transmitted vertically without lateral gene transfer. It possesses nine hypervariable regions (V1–9) in which the vast majority of evolutionary changes have occurred, rendering this single gene useful for taxonomic identification [20]. Databases are available that encompass more than 500 000 16S rRNA sequences from a range of phylotypically diverse bacteria. Conserved sequence stretches within the 16S rRNA gene allow for the design of broad bacterial kingdom-specific primers, which can be used to create amplicons of individual 16S rRNA genes derived from a mixed bacterial population. High-throughput sequencing of these 16S rRNA gene amplicon libraries is possible, with the most powerful being 454-pyrosequencing, due to sequence read lengths of over 400 bp (sufficient to cover at least two adjacent 16S rRNA hypervariable regions) and output of greater than 10^6 high-quality sequence reads [21–23], permitting a rapid robust sampling of microbial communities [24–28].

What is the microbiome in sites of acute resolving, acute non-resolving, and chronic (non-resolving) wounds?

Bacterial colonization occurs in all wounds, chronic or acute. One area of active investigation is understanding the correlation between different microbial communities in the wound and the ultimate repair of the wound (versus the development of chronic wounds and/or fibrotic lesions). Chronic wounds often contain higher levels of culturable bacteria compared with healing wounds, and experimental colonization of wounds can delay healing [29,30]. Bacterial colonization of wounds is polymicrobial [15–17,31,32] and in the form of a biofilm [32–34]. Antibiotics typically do not sterilize wounds (even broad spectrum antibiotics) because

bacterial cells in biofilms have increased resistance to biocides [35]. However, antibiotics can shift the growth balance in bacterial community composition, preventing pathogenic bacterial colonization that can lead to enhanced tissue damage and/or systemic dissemination of pathogenic bacteria. Despite this, published research does not support a positive effect of antibiotic therapy for chronic wound healing [36]. Antibiotic use for chronic wounds is often associated with selection for more resistant bacterial species. Many *Pseudomonas* species are extremely adept at adapting to antibiotic pressure, and certain antibiotics appear to actually induce the formation of pseudomonal biofilms, perhaps accounting for the increased colonization of chronic wounds by *Pseudomonadaceae* [15,37].

A number of groups have used culture-independent methods to analyse bacterial wound communities and, collectively, these groups have reported the following observations about the microbiota of wounds [15–18,31,32]. First, the number and proportion of bacterial species can range greatly between individual wounds. Second, bacterial diversity as determined by culture-based methods is significantly lower than that obtained through 16S rRNA gene-based amplicon pyrosequencing. Thus, the complexity of bacterial communities in wounds has historically been underestimated. Commonly isolated organisms include *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* (although *Propionibacterium* species are typically found at lower levels in wounds compared with healthy skin). Notable on the list of wound bacteria are the fastidious and/or anaerobic organisms *Neisseriaceae, Campylobacteriaceae, and Clostridiaceae*. Proteobacteria are commonly identified in wounds and largely belong to the *Pseudomonadaceae, Enterobacteriaceae, Oxalobacteraceae, and Neisseriaceae* families. Additional work needs to be done to identify many of these non-culturable organisms at the species level. Third, the microbiota can differ between different wounds, while bacterial communities at different sites within an individual wound are significantly more similar to each other than to those from different wounds [17,38]. Finally, the reliability of both culture- and non-culture-based analysis depends heavily on the sampling method used. For example, certain sampling techniques will not detect anaerobic bacteria, which are common in chronic wounds [39]. Therefore, when studying the human microbiome, important controls need to be in place to guarantee that the chosen sampling techniques are as unbiased and comprehensive as possible.

Diabetic wounds are well documented to display defects in the steps involved in normal wound healing, resulting in chronic wounds. Colonization of diabetic versus non-diabetic wounds is also markedly different, including an increased incidence of colonization by *Streptococcus* or *Staphylococcus* in diabetic wounds [17]. Other commonly cultured bacteria from non-healing diabetic wounds include *Staphylococcus aureus*, *S. epidermidis*, *Pseudomonas aeruginosa*, *Enterococcus* spp., *Peptostreptococcus* spp., *Bacteroides* spp., and *Prevotella* spp. [40–42]. Colonization of wounds by *Staphylococcus* likely impairs wound healing, as supported by both clinical associative data and experimental animal models, including reports that colonization of wounds in mice can prevent re-growth of the epithelium and the aberrant inflammatory response in the skin of diabetic db/db mice promotes colonization by *Staphylococcus* [40,43–47].

Surprisingly, many of these studies are finding readily-culturable bacteria by culture-independent methods that are otherwise not being identified by traditional culture-based methods [15–17,31,32]. Cultivation relies heavily on selective media and can mask the presence of less numerous organisms. However, beyond the obvious devil's advocate answer that these bacteria are actually dead (which evidence from a variety of sources is rendering unlikely), there are a number of intriguing possibilities to explain these results that may also provide novel insights into changes and adaptation of bacterial metabolic networks in inflamed and wounded mucosa. Within biofilms, the precipitous oxygen gradients that form microaerophilic and anaerobic regions, combined with increased gene flow among biofilm members, lead to metabolic alteration of bacterial cells [48,49]. Species known to readily grow on standard laboratory media will no longer exhibit typical phenotypes, sometimes leading to non-culturability. This phenomenon has been heavily researched in *Pseudomonadaceae* biofilms. For example, *Pseudomonas* species isolated from clinical chronic biofilms will commonly exhibit a loss of motility [50], amino acid auxotrophy [51], lack of type III secretion and siderophore production [52], and a long list of other loss-of-function mutations [53]. There is also a robust line of investigation in understanding the mechanisms that regulate the viable-but-not-culturable (VBNC) state, where bacteria cease to multiply but remain metabolically active [54], and this may be relevant to the lifestyle of wound bacteria.

In microbial communities, both bacterial competition and cooperation will have an impact on the pathophysiology of the host. One example of cooperation that leads to increased virulence involves siderophore-producing bacteria, such as *P. aeruginosa*, that are able to 'share' the production of iron-scavenging siderophores with non-siderophore producers [55]. A heterogeneous population of siderophore producers and non-siderophore-producing bacteria can lead to higher levels of bacterial growth. The evolution of such iron 'cheats' occurs more readily in low-iron conditions, revealing how the host environment shapes such microbial cooperation [56]. It should be noted that sequestration of free iron is a major mechanism of innate immunity [57,58]. However, inter-species bacterial competition also plays a role in mixed bacterial populations. For example, *P. aeruginosa* can lyse other bacterial species, such as *S. aureus*, and utilize the bacterial lysate as a source of free iron, thereby increasing

its ability to colonize under iron-limited conditions of the host [59,60].

As an additional illustration of potential bacteria–bacteria antagonism in a wound, it has been demonstrated that *Lactobacillus reuteri* strain RC-14 can inhibit *Staphylococcus aureus* infection in a rat surgical-implant model [61]. In this study, a small sterile piece of silicone was inserted subcutaneously and inoculated with *L. reuteri* and/or *S. aureus*. The surgical incisions were then sutured and abscess formation was followed. Implantation of lactobacillus alone did not induce any abscess formation and the addition of the lactobacilli prevented abscess formation induced by *S. aureus*. This was not true for all the lactobacillus strains tested, suggesting a strain-specific mechanism, which may involve a secreted cell-signalling molecule [62]. Many other examples exist in the literature of competing bacteria interfering with quorum-sensing pathways, bacteriocin production, and virulence factor production. It remains to be determined whether such mechanisms shape the bacterial microbiome of wounds.

What is the effect of changing the localized microbiome on wound repair?

Microbial colonization or infection is hypothesized to play an important role in driving chronic inflammation, chronic wounds, and the development of fibrosis [3,5,63] (summarized in Figure 1). Pulmonary tuberculosis is one example of a chronic disease that is characterized by bacterially-induced chronic fibrosis. In this disease, there are significant numbers of activated M2 macrophages and fibroblasts in *Mycobacterium tuberculosis*-containing granulomas [64]. These macrophages express TLRs that when activated with the appropriate bacterial PAMPs stimulate T cells to produce cytokines and chemokines that promote a fibrotic response. Activated M2 macrophages are also found at sites of wound repair in chronic non-resolving wounds; thus, it seems likely that the microbial populations that colonize these wounds can significantly influence the activation and signal production by these macrophages (reviewed in refs 3 and 5). In addition to leukocytes, myofibroblasts also express many TLRs, including TLRs 2–7. Stimulation of these TLRs can lead to the production of chemokines and cytokines, including CXC chemokine ligand 8 (CXCL8/IL-8), which has neutrophil chemotactic activity as well as being a pro-angiogenesis molecule. Bacterial CpG stimulation of TLR9 can also drive interstitial fibrotic pathways. Primary fibroblasts from sites of inflammation have also been demonstrated to release large amounts of other CXC and CC chemokines including CCL5, CCL8, and CXCL6. Thus, stimulation of TLRs by PAMPs released by the microbiota of wounds may play a role in maintaining leukocytes and myofibroblasts in a heightened state of activation.

The heightened state of activation of host cells in a wound that is driven by the microbiota can certainly lead to detrimental effects on wound regeneration, but the microbiota of the wounds may also have beneficial effects on wound healing. For example, wound healing following surgical skin incision and suture was followed in germ-free and conventionalized mice [65]. The conventional mice showed greater tensile strength of the wound initially, including higher hydroxyproline concentration in the surrounding tissue, than the germ-free mice. In another study, of dermal wounding in rats, inoculation of wound sites with *P. aeroginosa* PA01 accelerated re-epithelialization, epidermal cell proliferation, and neo-vascularization, as well as the local infiltration of neutrophils and TNF production [66]. Treatment of these rats with antibodies against neutrophils or TNF caused a significant reduction in the wound healing response. Other experimental studies have demonstrated a similar positive effect of low-level wound colonization, even by potentially pathogenic microbes, depending on the level of colonization and type of wound [67–69]. While these examples suggest local benefits of the microbiota on wound healing, other studies in experimental systems have clearly demonstrated a beneficial effect for members of the gut microbiota on regulation of systemic inflammation [70,71], which could impact wound healing at sites outside the gut.

Could changes in the gastrointestinal microbiome affect local epithelium repair?

The gastrointestinal (GI) epithelium is constantly undergoing wounding and repair. The process of repairing small gaps, ie a few individual epithelial cells, within the epithelial layer of the GI tract is known as epithelial restitution [72]. This process involves a highly localized response in the adjacent epithelium, while losses of larger contiguous epithelium regions (> 10 cells) stimulate a more robust repair response, analogous to skin wound repair, and involve cell types present in the lamina propria, including leukocytes, fibroblasts, and subepithelial myofibroblasts.

The mechanisms by which the resident microbiota influences restitution and the wound repair response of the GI epithelium are areas of active investigation [73]. Gastrointestinal restitution is modulated by numerous host factors; however, the indigenous microbiota also plays a role (positive and/or negative) in modulating the GI restitution response, such as through the production of short-chain fatty acids and modification of bile acids. Epithelial cells of the GI tract express multiple TLRs on both their basolateral and their apical surfaces, as well as intracellular TLRs that recognize bacterial PAMPs. The requirement for TLR-mediated signalling in the GI repair response is illustrated in a study of DSS-induced colitis [74]. In this study, acute

GI epithelial damage and inflammation were aggravated in TLR2−/−, TLR4−/−, and MyD88−/− mice, confirming the key role of microorganisms and microbial products in GI repair.

Epithelial restitution requires active cell migration, a process dependent on a constant turnover of focal cell–matrix adhesions (FAs). In a recent study, it was demonstrated that enteric resident bacteria can potentiate epithelial restitution via the generation of reactive oxygen species (ROS) in epithelial cells, which in turn mediates inactivation of focal adhesion kinase phosphatases [75]. ROS generation induced oxidation of target cysteines in the redox-sensitive tyrosine phosphatases LMW-PTP and SHP-2, which in turn resulted in increased phosphorylation of focal adhesion kinase (FAK), a key protein regulating the turnover of FAs. Phosphorylation of FAK substrate proteins, focal adhesion formation, and cell migration were all significantly enhanced by bacterial contact in both *in vitro* and *in vivo* models of wound closure.

Microbiota–host epithelial cell interactions can also modulate β-catenin signalling, a key component in regulating epithelial cell proliferation [76]. Enteric bacteria can inhibit the NF-κB pathway through the blockade of IκB-α ubiquitination, a process catalysed by the E3-SCF(β-TrCP) ubiquitin ligase. The activity of this ubiquitin ligase is regulated via covalent modification of the Cullin-1 subunit by the ubiquitin-like protein NEDD8, and it is reported that the interaction of viable indigenous bacteria with mammalian intestinal epithelial cells can result in rapid and reversible generation of ROS in epithelial cells that modulate neddylation of Cullin-1 and suppression of the NF-κB pathway [77]. The short-chain fatty acid and bacterial fermentation product butyrate has also been shown to influence epithelial signalling via ROS-mediated changes in Cullin-1 neddylation [78]. Treatment of human intestinal epithelia *in vitro* and human tissue *ex vivo* with butyrate can cause a loss of neddylated Cul-1 and modulate the ubiquitination and degradation of a target of the E3-SCF(β-TrCP) ubiquitin ligase, the NF-κB inhibitor IκB-α.

A number of indigenous bacterial species have also been demonstrated to induce ERK phosphorylation without stimulating pro-inflammatory phospho-IκB or pro-apoptotic phospho-c-Jun NH_2-terminal kinase [79]. Of interest was the observation that *Lactobacillus* species have very potent activity. Whole bacterial cell signalling has also been recapitulated in experimental studies of epithelial cells using the bacterial peptide *N*-formyl-Met-Leu-Phe (N-fMLP) through the formyl peptide receptors (FPRs). This induction of extracellular signal-regulated kinase pathway signalling occurred via FPR-dependent redox modulation of dual specific phosphatase 3 [80]. The indigenous microbiota could initiate ERK signalling through rapid FPR-dependent ROS generation and subsequent modulation of MAP kinase phosphatase redox status. Epithelial ROS generation induced by *Lactobacillus rhamnosus* GG and N-fMLP could be abolished in the presence of selective inhibitors for G protein-coupled signalling and FPR ligand interaction. Inhibitors of ROS generation could attenuate microbiota-induced ERK signalling, implicating ROS generation in ERK pathway activation. Altogether, the studies described in the last few paragraphs raise the possibility that normal members of the bacterial microbiome stimulate the generation of ROS in intestinal epithelial cells through FPR-mediated signalling that modulates the ERK pathway, which in turn regulates epithelial cell migration and epithelium restitution.

The indigenous microbiota can also promote wound pathology. For example, indomethacin-induced gastric ulceration in rats is dependent on the presence of a microbiota [81]. Treatment of rats with indomethacin also changes their microbiome [82], implicating a relationship between mucosal inflammation and microbiome community structure. This concept is supported by other studies of gastrointestinal inflammation in which mucosal inflammation and epithelium damage drive changes in the indigenous microbiota, resulting in the outgrowth of γ-proteobacteria, such as *E. coli* and *Klebsiella pneumoniae* [83,84]. In a model of transmissible spontaneous colitis in mice, the transmissible bacterial community required the presence of *K. pneumoniae* and *P. mirabilis* in that community for mucosal inflammation [85]. Outgrowth of γ-proteobacteria in the GI microbiota appears to be a general ecological phenomenon of a disturbed microbiome [86]. Thus, wounded epithelium appears to provide a selective niche for chronic colonization by γ-proteobacteria, as well as other bacteria in a polymicrobial biofilm [32–34], which in turn may drive inflammatory and fibrogenic processes that are detrimental to controlled wound repair and tissue regeneration.

Conclusion

The utilization of culture-independent microbiology to characterize the microbiome of wounds and surrounding mucosa has raised many intriguing questions regarding previously held notions about the cause and effect relationships and mechanisms involved. Microbial colonization or infection is hypothesized to play an important role in driving chronic inflammation and the development of fibrosis, while inflammation itself can alter microbial colonization. Percival *et al*. have recently discussed two possible hypotheses to explain the role of bacteria in non-healing chronic wounds [87]. In both of these hypotheses, wounds naturally have bacterial biofilms that form and only when the environmental balance within the wound's microbiota changes (due to alterations in host immune response, local pH, temperature, wound dressings, anti-microbial treatment, etc.) do these biofilms lead to infection. The first of these hypotheses is the 'specific bacterial hypothesis', which states that only a few select species of bacteria break away from the polymicrobial biofilms,

cause infection, and lead to delayed wound healing. The second, 'non-specific bacterial' or 'community' hypothesis, states that it is the overall composition of the biofilms that creates a pathogenic bacterial community and leads to infection and delays in wound healing [87].

Examples of areas of active investigation into the role of the microbiome in wound repair in the lungs include diseases such as interstitial pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and asthma [9–11,88]. In the gastrointestinal tract, normal members of the microbiota, especially lactobacilli and butyrate-producing bacteria, promote epithelial repair. Are there also locally resident bacteria that promote wound repair in the skin and lungs? What about sterile sites, such as the heart or liver? Could there be effects of the mucosal microbiome on wound repair of these non-mucosal sites? The study of the microbiome as a metabolically active 'organ' [89–92], which can have local and systemic effects on wound repair and fibrosis, has only just begun.

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Author contribution statement

Both authors contributed to the intellectual concepts and writing of this manuscript.

Abbreviations

FAK, focal adhesion kinase; FAs, focal cell–matrix adhesions; FPR, formyl peptide receptor; ROS, reactive oxygen species.

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