HHS Public Access

Author manuscript

Nature. Author manuscript; available in PMC 2018 August 03.

Published in final edited form as:

Nature. 2018 January 24; 553(7689): 427–436. doi:10.1038/nature25177.

Skin microbiota–host interactions

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Abstract

The skin is a complex and dynamic ecosystem that is inhabited by bacteria, archaea, fungi and viruses. These microbes—collectively referred to as the skin microbiota—are fundamental to skin physiology and immunity. Interactions between skin microbes and the host can fall anywhere along the continuum between mutualism and pathogenicity. In this Review, we highlight how host–microbe interactions depend heavily on context, including the state of immune activation, host genetic predisposition, barrier status, microbe localization, and microbe–microbe interactions. We focus on how context shapes the complex dialogue between skin microbes and the host, and the consequences of this dialogue for health and disease.

The skin's outermost aspect consists of a lipid- and protein-laden cornified layer dotted with hair follicles and glands that secrete lipids, antimicrobial peptides, enzymes, salts, and many other compounds (Fig. 1a). Whereas the skin surface is an acidic, high-salt, dessicated, aerobic environment, the invaginations that form folliculo-sebaceous units are comparatively anaerobic and even more lipid-rich[7,8] (Fig. 1b). The skin surface and follicles are physically and chemically distinct from another microbe-rich barrier site: the small and large intestines. The intestine is moist, polysaccharide-rich, neutral in pH, and full of diverse carbon and nitrogen sources[9–11]. Additionally, in contrast to the hair follicle, deeper aspects of intestinal crypts that are closer to the epithelium become more aerobic while the lumen is more anaerobic[12,13]. The skin, on the other hand, is replete in diverse and unusual lipids not found elsewhere in the body[14,15] (Fig. 2). Some of these lipids, such as sapienic acid, can have antimicrobial activities[16], while others, such as triglycerides, can be metabolized by

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Author Contributions Y.E.C., M.A.F. and Y.B. conceptualized the article structure, content, and figures, and wrote and edited the manuscript and figures.

The authors declare no competing financial interests.

Readers are welcome to comment on the online version of the paper.

microbes[17] into free fatty acids and di- and monoglycerides that can be bioactive against other microbes or stimulatory to host cells[18].

Across skin regions, the density and variety of glands and hair follicles vary considerably, creating a complex physical and chemical landscape of geographically distinct niches for bacterial growth. For example, *Cutibacterium* (formerly *Propionibacterium*)[19] and *Staphylococcus* species dominate sebaceous areas (such as the face and torso), while *Corynebacterium, Staphylococcus*, and beta-Proteobacteria are found in moist areas (such as the armpits and the elbow and knee creases)[20].

In broad terms, the chemistry of a skin niche drives its microbiome composition, but unknown microbial and host factors contribute to important species- and strain-level differences in composition. For some species, such as *Cutibacterium acnes*[19], the same strain tends to colonize multiple body sites of the same individual; others, such as *Staphylococcus epidermidis*, differ among body sites of an individual (but tend to be similar in, for example, the axillae of different individuals)[21]. Most metagenomic cataloguing of the human microbiome has focused on species composition. However, recent work demonstrates that, even within the same species, different strains can differ markedly in their effects on the host[22]. Strain-level differences have been largely unexplored and remain a frontier for studies of the skin microbiota.

The process of skin microbiota assembly begins during birth and proceeds primarily according to body site over several weeks[23]. The microbiota shifts notably during puberty, with increased predominance of *Corynebacterium* and *Cutibacterium* (formerly *Propionibacterium*) and decreased abundance of Firmicutes (including *Staphylococcus* and *Streptococcus* species)[24]. In adulthood, despite the skin's continuous exposure to the environment, the microbial composition remains surprisingly stable over time[25]. This suggests that stabilizing, mutually beneficial interactions exist among commensal microbes and between microbes and the host.

The composition of the skin microbiome can shift markedly during inflammation[26]. It is not yet understood how pathogens and skin inflammation contribute to a vicious cycle, how homeostasis is re-established, or how pathogens interact with the existing commensal population. The critical role of context to the outcome of a microbe–host interaction animates this review. For example, pathogens such as *Staphylococcus aureus* often colonize the skin asymptomatically, whereas mutualists such as *S. epidermidis* can at times promote disease[27,28]. In this Review, we highlight recent work demonstrating that host–microbe interactions fall along a continuum in which pure pathogenicity and mutualism are at extreme ends, and are rarely useful descriptors. We discuss the importance of context—genetic predisposition, the level of host immune activation, the physical and chemical landscape of the niche, and mitigating or activating microbe–microbe interactions—to the outcome of a host–microbe interaction, and consider how colonization extends from the skin's surface into the follicles and even into subcutaneous tissues.

Host–mutualist interactions

Most microbes living on the skin behave as commensal or mutualistic under steady-state conditions. In contrast to the gut of germ-free mice, which shows grossly altered lymphoid organ development, the skin of germ-free mice does not show marked morphological defects[29,30]. Nonetheless, skin-resident microbes play important roles in the maturation and homeostasis of cutaneous immunity. The skin microbiota modulate the expression of various innate factors, including interleukin 1a (IL-1α)[29]; components of complement[31]; and antimicrobial peptides (AMPs), which are produced by keratinocytes and sebocytes (Fig. 1a). Skin-derived AMPs constitute a diverse array of protein families, but cathelicidins and β-defensins predominate. Although some AMPs are constitutively expressed, others can be stimulated by specific members of the microbiota such as *Cutibacterium*[5,32] or produced by microbes themselves (including *Cutibacterium* thiopeptides[33] and *S. epidermidis* AMPs[34,35]). It is not yet known how the combination of microbiota-induced and microbiota-produced AMPs shape microbial communities, but this multidirectional signalling is likely to play an important role in the ecology of skin microbial communities.

One major genus of skin-resident bacteria is *Corynebacterium*, members of which are present at all body sites and dominate in moist sites. Interestingly, corynebacteria share many microbiological features with the closely related mycobacteria, but these two genera interact very differently with the host. It remains a challenge to understand how the immune system distinguishes between bacteria with such similar surface and cellular structures (Fig. 3), and to determine which factors unique to *Corynebacterium* might be responsible for its commensalism. These questions will help to define the molecular-level differences between mutualism and pathogenicity, and explain how commensal bacteria ‘educate’ the cutaneous immune system.

Corynebacterium minutissimum (erythrasma) and *Corynebacterium tenuis* (trichomycosis axillaris) have been associated with superficial skin pathology, but most *Corynebacterium* species present in surveys of the skin microbiome do not cause any known disease. Corynebacteria and mycobacteria share the unusual feature among Gram-positive bacteria of having an outer membrane, analogous to that of Gram-negative bacteria (Fig. 3). This outer membrane consists of an outer lipid bilayer of long α-branched fatty acids called mycolic acids, which envelop (and are covalently linked to) the meshwork of peptidoglycan underneath. The *Corynebacterium* cell wall features additional lipoglycans termed lipomannans and lipoarabinomannans, which are anchored to the plasma membrane and have long oligosaccharide chains that emanate from the cell surface. Lipomannans and lipoarabinomannans are ligands for host glycan receptors such as Toll-like receptors (TLRs) and C-type lectin receptors, driving either pro- or anti-inflammatory responses depending on their structure and the immunological context in which they are sensed[36–42]. In mycobacteria, lipomannans and lipoarabinomannans play important roles in immune recognition and evasion[43]. It remains to be determined whether similar structures in corynebacteria engage cutaneous immune cells, and whether immune recognition of corynebacteria may protect against future mycobacterial infections.

In addition to microbe–host interactions, many reports have suggested that microbe–microbe interactions also impact human health. For example, a common skin resident, *Corynebacterium accolens*, was recently shown to inhibit the growth of *Streptococcus pneumonia*e, a common respiratory tract pathogen[44]. The active principle of this interaction is an essential corynebacterial lipase that hydrolyses triolein to release oleic acid, which inhibits pneumococcal growth[44]. Another common skin resident, *Corynebacterium striatum*, shifts the global transcriptional program of co-cultured *S. aureus* in a way that suppresses virulence-related genes and stimulates genes assocated with commensalism[28]. These data suggest that the role of skin-resident microbes goes beyond competitive exclusion; these microbes are likely to engage in a web of microbe–microbe interactions that help to tune the behaviour of their co-residents in subtle and context-specific ways.

Another dominant group of skin colonists are the coagulase-negative *Staphylococcus* species, the most prominent of which is *S. epidermidis*. Although *S. epidermidis* can be an opportunisitic pathogen in the context of primary or iatrogenic immunosuppression, it functions predominantly as a mutualist. Skin-resident *Staphylococcus* species engage in microbe–microbe interactions that are beneficial to the host. For example, *S. epidermidis* and *Staphylococcus hominis* have been shown to secrete antimicrobial peptides that kill *S. aureus,* and transplantation of these species onto the skin of patients with atopic dermatitis led to decreased colonization by *S. aureus*[35].

Recent studies of *S. epidermidis* provided the first evidence that skin-resident bacteria are not just passive residents; they actively engage host immunity through an intact skin barrier, and activate specific immune cell populations in a species- and strain-dependent manner[29,45]. For instance, some strains of *S. epidermidis* induce activation of *S. epidermidis*-specific IL-17^{+}CD8^{+} T cells that protect against cutaneous infections by inducing keratinocytes to produce AMPs, a phenomenon called heterologous protection[45]. In addition to their protective role, these commensal-specific T cells also promote wound repair[46]. Of interest, *S. epidermidis* can elicit T cell responses restricted to non-classical major histocompatibility complex (MHC) class I molecules[46]. Thus, non-classical MHC class I molecules, an evolutionarily ancient arm of the immune system, may play an important role in promoting homeostatic immunity to the microbiota. These data show that skin-resident bacteria can have myriad effects on the host; in addition to promoting immune barrier responses, commensal–immune interactions can also affect epithelial biology. The effects of commensal–immune interactions on many other cutaneous processes, including adnexal development, tumorigenesis, ageing, and sensory nerve function, remain to be determined. Additionally, whether immune responses against the skin microbiota also influence microbiota composition or function remains unexplored. In most settings, the skin flora controls skin immunity in an autonomous manner and independently of the gut flora[29]. This compartmentalization and specialization of responses may have evolved as a mechanism to constrain the adjuvant properties of commensals and unwanted consequences associated with systemic increases in inflammatory responses.

Notably, adaptive responses to members of the skin community develop in the absence of inflammation[45], in contrast to the response to invading pathogens. This process, termed ‘homeostatic immunity’, may be induced (at least in part) by the endogenous network of

skin-resident antigen-presenting cells[45]. Under steady-state conditions, the skin is populated by highly diverse T cells[47]. Thus, because of the extraordinary number of potential antigens expressed by the microbiota, a substantial fraction of these skin-resident T cells are expected to be microbiota-specific. As a result, primary exposure to a pathogen in the skin or exposure during an injury is likely to occur in the context of a much broader recall response against diverse microbial antigens. The consequences of this phenomenon for tissue responses remain unclear.

Although B cell dynamics in the skin and the role of antibodies in controlling skin microbes are not well understood, it is known that IgA is secreted on the skin surface by eccrine and sebaceous glands[48,49]. In the gut, IgA has substantial effects on microbiota composition[50–52] through a process that involves coating commensal bacteria[53]; in turn, commensal microbes are essential to development of this antibody response[54,55] and may protect against autoimmunity[56]. Skin commensals are also likely to affect the B cell repertoire, but the extent of this interaction and its effects on the microbiota are not yet known.

In light of the finding that *S. epidermidis* potently and specifically activates a unique branch of adaptive immunity, one major challenge is to dissect mechanistically how specific host cells and receptors recognize molecular features of *S. epidermidis*. Staphylococci produce a variety of immune modulatory molecules, such as teichoic acids, capsular polysaccharides[57,58], and dipeptide aldehydes[59,60]. Just as *Corynebacterium* and *Mycobacterium* share features but can be distinguished by the host, *S. epidermidis* shares many of these molecular features with the contextual pathogen *S. aureus*. Further studies of how, at the molecular level, *S. aureus* differs from *S. epidermidis* will help us understand how these two important human skin residents are distinguished by the immune system, and will highlight key host targets for more effective and specific therapeutic approaches.

Microbial sensing by the immune system is also likely to be controlled by the developmental stage of the host. Although little is understood about the factors that regulate the acquisition of skin microbes at birth, regulatory T cells, which are highly enriched in the skin tissue, have been proposed to control early dialogue with the microbiota. Indeed, colonization of mouse skin with *S. epidermidis* early in life (but not later) induces tolerance to the same microbe in adulthood[61] and promotes accumulation of *S. epidermidis*-specific regulatory T cells in neonatal skin[62].

As well as modulating immune cells, *S. epidermidis* and other commensals promote epithelial integrity, especially during tissue repair. For example, an *S. epidermidis* cell wall component mitigates inflammation by binding to TLR2, limiting tissue damage and promoting wound healing[63]. Other commensal microbiota are also likely to contribute to wound healing, which is a dynamic process associated with global shifts in the skin microbiome; wound bed microbiomes that fail to shift are associated with chronic ulcers[64,65]. Within chronic wounds, fungi and bacteria form mixed biofilms and certain fungal taxa, such as the phylum *Ascomycota*, are predictive of wounds that take more than eight weeks to heal. The fungal mycobiome and its interactions with commensal bacteria may therefore be important contributors to chronic wounds, via mechanisms that have not been explored[64,65].

The skin microbiota are likely to affect many immune-related and immune-independent properties of epithelial health that are not yet appreciated. In the skin, epithelial homeostasis is a constant, active, and energy-intensive process that involves the secretion of complex lipids for signalling and barrier purposes[2,66], maintenance of tight junctions[67,68] and production of a lipid–protein coat to prevent trans-epidermal water loss[69,70], repair of UV-mediated and oxidative damage to epithelial cells to prevent malignant transformation[71,72], and constant remediation of accidental trauma (for example, scrapes, cuts, and nicks). Any disruption of even a small component of these complex processes can result in extreme phenotypes, such as ichthyoses, blistering disorders, progerias, and diffuse fibrosis[69,73,74]. How the skin community contributes to these processes remains to be addressed.

Host–pathogen interactions

Microbe–host interactions that drive (or result from) infectious processes have historically received the most investigative attention. A canonical host–pathogen interaction in the skin involves a one-to-one mapping of microbe to disease and an easily identified phenotype of inflammation. Most of what is known about the skin immune system has been discovered by studying interactions of this sort, highlighting the utility of this simplistic paradigm and foreshadowing its limitations. As we will discuss, most microbe–host interactions on the skin are more nuanced; a threshold example is the observation that traditional pathogens often reside on the skin surface in an asymptomatic manner.

In terms of cost and prevalence, one of the most important pathogens of the skin is *S. aureus*. Although more than 30% of healthy individuals are colonized asymptomatically by *S. aureus*[75,76], it can cause a wide spectrum of infections: some are limited to a single hair follicle (furuncle), others involve subcutaneous tissues (cellulitis), and the most serious feature potentially fatal penetration into any organ in the body, including bone (osteomyelitis), bloodstream (bacterial sepsis), and heart valves (bacterial endocarditis). *S. aureus* has also been implicated in the pathogenesis of chronic diseases such as atopic dermatitis[22,77–79], and more recently in systemic lupus erythematosus with renal and skin involvement[80].

S. aureus is a versatile pathogen with a broad array of virulence factors[81,82], including neutrophil-killing toxins[83], chemotaxis inhibitors[84], anti-phagocytic and anti-killing surface molecules[57,85–88], superantigens, and immune evasion proteins[89,90]. In patients with atopic dermatitis, *S. aureus* isolates grow as biofilms on the skin and produce proteases that degrade host AMPs, such as cathelicidin LL-37[91]. The host has evolved mechanisms to ward off invasion by *S. aureus* at every level of the skin and subcutaneous tissue. In addition to a diverse arsenal of AMPs covering the epidermis, there is also evidence that adipose tissue under the dermis contributes to the innate immune response. Following breach of the skin barrier and subsequent *S. aureus* infection, local pre-adipocytes proliferate rapidly, expanding the subdermal fat layer and increasing production of the AMP cathelicidin[92].

Although some virulence and immune evasion elements are conserved across all species of *S. aureus,* there are important strain-level differences. For example, the arginine catabolic mobile element contributes to the ability of USA300, a methicillin-resistant *S. aureus* strain,

to thrive in the acidic environment of human skin and resist host polyamines, helping to explain this strain's prevalence in skin and soft tissue infections[93,94]. Recent work has also shown that certain strains of *S. aureus* are not only associated with more severe atopic dermatitis, but are also sufficient to induce skin inflammation in mice independent of host genetic predisposition[22]. This work revealed that the most common method of describing microbiome composition, with genus- or species-level data, fails to resolve important functional differences among strains, which can result from modest gene gain or loss events or even differences in gene expression among strains.

Another prominent genus of skin pathogens is *Mycobacterium*, a Gram-positive rod within the phylum *Actinobacteria*. Mycobacteria are a diverse genus of organisms that includes the causative agents of tuberculosis (*Mycobacterium tuberculosis*) and leprosy (*Mycobacterium leprae*), and other species that cause infections at surgical sites or sites of accidental trauma (for example, *Mycobacterium kansasii*, *Mycobacterium chelonae*, and *Mycobacterium marinum*). *M. tuberculosis*, which generally causes pulmonary or systemic infections, is well known; however, skin and soft tissue infections caused by other *Mycobacterium* species are increasing in prevalence in developed countries[95] and continue to be serious problems in developing countries[96]. We highlight mycobacteria because they generate an especially broad spectrum of pathologies, from acute systemic illness to skin manifestations to inert granulomas that persist throughout the lifetime of a host. In addition, mycobacteria are closely related to skin-resident corynebacteria but have very different effects on the host. The similarities and differences between *Mycobacterium* and *Corynebacterium* will probably yield insights into a broad swath of fundamentally important host–microbiota interactions.

M. tuberculosis is one of the most successful pathogens on the planet: it colonizes one-quarter of the world's population (1.7 billion people) in the form of a latent infection[97], with the World Health Organization estimating that 10.4 million new infections occurred in 2015[98]. Among humans who are latent carriers of *M. tuberculosis*, only 10% will suffer reactivation into active tuberculosis during their lifetime[99]. A related pathogen, *M. leprae*, also causes a wide range of diseases, including diverse skin manifestations that can involve the nerves, liver, and bones[100,101]. The time period between *M. leprae* inoculation and clinical manifestation of infection is typically 2–12 years and can be up to a few decades; during this time, the bacterium handily evades host immunity. It is particularly notable that the majority of humans who harbour *M. tuberculosis* and *M. leprae* neither display obvious pathology nor die from their infection. This suggests that we have much to discover about the mechanisms of long-term immune evasion, and that the traditional definition of 'colonist' may need to expand to include an organism such as *M. tuberculosis*, which on the one hand is a pathogen that kills more than a million people each year[102], and on the other hand lives asymptomatically in billions of people and results in the death of only a small percentage of its hosts.

One recently discovered mechanism of mycobacterial host evasion involves the nervous system. *Mycobacterium ulcerans* causes the Buruli ulcer, a progressive, necrotic ulcer that is the third most common mycobacterial disease worldwide[103]. The Buruli ulcer is painless, which contributes to delays in treatment and therefore increases the requirement for more

drastic interventions at later infectious stages, when the only available treatment is surgical resection. *M. ulcerans* produces a polyketide toxin, mycolactone, that is essential for virulence. Recent work has shown that mycolactone induces analgesia via the angiotensin II receptor, COX-1, and prostaglandin E_2, ultimately resulting in activation of TRAAK potassium channels and cell hyperpolarization[104]. Not only does this work provide possible avenues to therapeutic biomimetics for pain relief and to the development of therapies against *M. ulcerans*, but it also demonstrates a novel mode of pathogen–host interaction in which the peripheral nervous system is targeted directly.

Involvement of the peripheral nervous system may be more general and integral to skin immunity than has been previously recognized. *Candida albicans*, a fungal pathogen, also triggers sensory neurons directly; these neurons then stimulate host immunity and activate protective IL-17-producing dermal T cells[105]. *S. aureus* also activates cutaneous neurons directly via *N*-formylated peptides and the pore-forming toxin α-haemolysin, inducing pain and neuropeptide-mediated induction of vasodilation and inflammation[106]. More recently, a direct mechanistic link between neurons and immune cells has been discovered. For instance, in the gut, mucosal neurons were found to produce a neuropeptide, neuromedin U (NMU), that binds an NMU receptor on group 2 innate lymphoid cells (ILC2s) and triggers a protective immune response[107]. Direct microbiota–nervous system interactions appear to be a broader phenomenon than was previously appreciated, with examples emerging in other body sites; in a recent case, a microbiota-derived metabolite (isovaleric acid) was shown to trigger a receptor enriched in enterchromaffin cells, resulting in the basolateral release of serotonin, which stimulated sub-epithelial enteric nervous system afferents[108].

As well as evading immunity so that an infection can establish, mycobacteria can also persist for decades inside granulomas, which are organized aggregates of macrophages. Bacteria living within a granuloma, in equilibrium with the host, can be considered a form of tissue colonization. In the gut, for example, certain subsets of commensal bacteria intracellularly colonize $CD11c^+$ dendritic cells in healthy mice and promote innate lymphoid cell responses that prevent systemic dissemination of these bacteria, as well as IL-10 production that protects against intestinal inflammation and damage[109,110]. These data demonstrate that commensal colonists can reside not only on the surface of the host, but also within host cells and tissues, and that these bacteria can elicit a balance of immune-reactive and immunosuppressive responses in the host. For mycobacteria, granulomas may seed the infection of new macrophages, leading to dissemination[111]. However, in 80–90% of healthy patients with latent tuberculosis, reactivation does not occur during the lifetime of the host[112]. In these patients, *M. tuberculosis* persists within macrophages, using a variety of strategies including efflux pumps that promote drug tolerance[113–115], increased cell wall biosynthesis[116], and global transcriptional changes to survive in anaerobic conditions[117–119]. Within a single host, granulomas can resolve variably: some become sterile, others harbour latent bacteria, and some allow bacteria to escape[120] in a manner that does not depend on host or bacterial genetic features. Therefore, even for an individual pathogen within a single host, it is not yet understood how the specifics of context affect the outcome of a microbe–host encounter.

As well as bacterial pathogens, there are numerous viral and fungal pathogens of the skin. Some viruses, such as human papillomaviruses and herpesviruses, can cause acute pathology but generally persist in a latent manner for a lifetime. Other viruses, such as the orthopoxvirus vaccinia virus, are cleared after epicutaneous infection. Although our current understanding of these viruses encompasses only their pathogenic behaviour, analyses of the double-stranded DNA virome have shown that papillomaviruses and poxviruses can also colonize hosts asymptomatically[21,121]. Even in the 'simple' case of vaccinia virus, intravital multiphoton microscopy has shown a complex spatial orchestration of immune events; although viral infection occurs in keratinocytes, responding $CD8^+$ T cells do not target the infected keratinocytes but rather innate immune cells[122]. Counterintuitively, high local production of the anti-inflammatory cytokine IL-10 helps to limit vaccinia replication and dissemination[123].

An immune cell population that has received attention for its ability to promote memory responses to viruses (and, potentially, other members of the microbiota) is resident memory T (T_{RM}) cells—a population of lymphocytes that occupies tissues without recirculating[124]. While most studies have focused on virally induced $CD8^+$ T_{RM} cells, $CD4^+$ T_{RM} cells (or at least cells with a resident phenotype) have also been shown to accumulate in the skin in response to a large array of infections. Notable differences in anatomical localization exist for memory $CD4^+$ and $CD8^+$ T cells, with $CD4^+$ T cells maintained primarily within the dermis and $CD8^+$ T cells within the epidermal compartment[125]. Given that herpesviruses, papillomaviruses and polyomaviruses that infect epithelial cells generate a high burden of chronic skin disease and, in some cases, aggressive skin cancers, there is an urgent need to better understand how these infections are contained by or escape cutaneous immunity.

Contextual pathogenicity

Traditionally, the term 'pathobiont' has been applied to organisms that have the potential to cause disease but often colonize a host without inducing pathology. Two prominent gut pathobionts are segmented filamentous bacterium (SFB), which stimulates T helper 17 (T_H17) cells in the mouse gut to confer protection against pathogens but can also induce severe colitis; and *Helicobacter pylori*, which colonizes half of the human population, but in a small percentage can cause peptic ulcer disease and potentiate gastric adenocarcinoma[126–129]. However, in more extreme contexts of host predisposition, many other microbial species have the potential to cause diease. Patients with primary immunodeficiency (PID), for example, develop chronic, severe skin infections, many of them induced by normal constituents of the microbiota or environmental microbes[130].

Transitioning from commensalism (for example, on the skin surface or in a follicle) to pathogenicity (for example, in the bloodstream) is a complex and potentially costly process for the microbe. The skin is an imposing physical barrier, and even if it is breached, the microbe must fend off numerous layers of innate responses, including AMPs, proteases, and reactive oxygen species. In addition, would-be pathogens need to induce the expression of genes that enable adhesion, invasion, and immune evasion (that is, virulence factors). As a result, most commensal microbes coexist peacefully with their host, and will exhibit pathogenic potential only in specific settings. Conversely, microbes that are traditionally

considered pathogens do not indiscriminately display aggressive behaviour. As discussed above, the term pathogen does not encompass the range of phenotypes displayed by *S. aureus* or *M. tuberculosis*. Viewed in this light, the term pathobiont becomes unhelpfully broad. Therefore, we suggest that the concept of a continuum of contextual pathogenicity and mutualism may be more useful (Fig. 4). In this section, we discuss examples of microbes that might traditionally be referred to as pathobionts: those that represent the middle of the spectrum between aggressive and mutualistic behaviour.

One example is *C. acnes*, which has been implicated in acne[131–133] and hidradenitis suppurativa[134]. However, the contribution of *C. acnes* to the pathogenesis of acne is unclear[131]. On the one hand, *C. acnes* produces coproporphyrin III, which has been shown to induce the formation of *S. aureus* biofilms[135]—generally seen as a negative consequence for the host. On the other hand, *C. acnes* has also been shown to ferment glycerol into short-chain fatty acids, which suppress the growth of virulent methicillin-resistant *S. aureus* USA300[136]. These data suggest that rich networks of microbe–microbe interactions may govern host inflammation and disease in a strain- and context-dependent manner.

A similar range of harmful and beneficial effects have been demonstrated for other microbes. Herpesviruses are frequent pathogens of the skin, with notable examples including chickenpox (varicella zoster virus) and recurrent labial ulcers (HSV1 and HSV2); however, after the acute infection has resolved, herpesviruses persist within the host as dormant, latent viruses for the host's lifetime. In mice, this herpesvirus latency has been shown to stimulate the immune system in a way that is protective against bacterial pathogens for months[137,138]. As noted above, *H. pylori* colonizes the stomach and can cause ulcers and promote gastric cancer. However, it has long evolved to live within human hosts, and is also thought to protect against tuberculosis[139] and allergic diseases such as childhood asthma[140].

Although *S. epidermidis* is generally beneficial to the host, it is also a leading cause of death in premature infants and nosocomial infections[27,141]. Conversely, *Mycobacterium* species such as *M. leprae* and *M. tuberculosis* are known for their ability to cause serious systemic illness but can persist subclinically inside a granuloma for the lifetime of a host. To generalize, all microbes that reside on or inside a host fall along a spectrum, with some displaying almost no aggressive behaviour and others displaying primarily virulent, invasive phenotypes. The majority of skin residents probably lie somewhere in the middle of the spectrum, and an important challenge in future work will be to better understand which host and environmental factors govern a microbe's switch between passive and aggressive behaviours.

Discussion

The examples discussed herein illustrate that a scheme in which skin-resident microbes are classified as 'full-time' pathogens, mutualists or pathobionts may need to be updated to include the effects of context (Fig. 4). Future work will need to investigate the context-dependent behaviour of resident microbes—how microbe–microbe interactions, host–microbe interactions, and strain-specific differences may govern a microbe's tendency towards cooperation or aggression.

As we learn more about how commensal bacterial strains activate specific immune cell populations, we may be able to harness this specificity by engineering microbes to deliver cytokines, small molecules, or vaccines to specific, activated immune cell populations across an intact skin barrier. A clearer understanding of the dense network of microbe–microbe interactions will also allow us to provide more targeted therapies for dysbiosis, which has been implicated in atopic dermatitis but is also being explored as a pathogenic contributor to many other skin diseases, including psoriasis, hidradenitis suppurativa, and lupus erythematosus. In the gut, using microbes to correct dysbiosis has been successful in the case of faecal transplants for *Clostridium difficile* infections[142], and more recently in the use of a *Lactobacillus plantarum* synbiotic to prevent neonatal sepsis[143]. Similar live microbial therapies for the skin have not yet been developed. However, harnessing the immunomodulatory[45] or antimicrobial properties of skin commensal bacteria[144] has great potential. Furthermore, because of the unique chemical milieu of the skin (Fig. 2), local alterations in defined nutrients may have a marked impact on the composition or function of skin microbiota and—when rationally designed—could promote the expansion of microbes endowed with regulatory or protective properties.

Another important category of microbe–host interactions that has not been well explored consists of distant effects between microbes at one site, for example in the gut, and host responses at another site, such as the skin. Recently, immune checkpoint blockade has achieved unprecedented success in the treatment of multiple skin cancers that were previously associated with high rates of mortality, including metastatic melanoma, squamous cell carcinoma, and Merkel cell carcinoma[145–148]. Although these are cutaneous cancers, commensal gut bacteria have been implicated in the efficacy of anti-tumour immunotherapies at distant sites[149,150]. Conversely, how skin-resident microbes influence immune responses systemically or at distant sites is an important area for further research. Processes that were previously thought to involve skin-limited inflammation, such as plaque psoriasis, have now been linked to an increase in systemic inflammatory co-morbidities, such as atheroscle-rotic cardiovascular disease[151–154]. Indeed, many types of immune cell are known to traffic in and out of skin during both homeostasis and inflammation[155–157]. These observations suggest that the effects of the skin microbiota on the immune system may have wide-ranging systemic sequelae that are ripe for exploration in the near future.

These findings add another layer of complexity to microbe–host interactions, suggesting that research should not only focus on interactions within the local microenvironment but also encompass trafficking of microbiota-educated immune cell populations, or microbial products and metabolites, to other body sites upon stimulation by microbes at diverse barrier sites.

Acknowledgments

We apologize for not having cited all papers relevant to this expanding field of research (in particular, older literature) because of space constraints and editorial limits. This work was supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases (Y.B.), DP1 DK113598 (M.A.F.), R01 DK110174 (M.A.F.), an HHMI-Simons Faculty Scholars Award (M.A.F.), a Fellowship for Science and Engineering from the David and Lucile Packard Foundation (M.A.F.), a Burroughs Wellcome Investigators in the Pathogenesis of Infectious Disease Award (M.A.F.) and the Dermatology Foundation (Y.E.C.).

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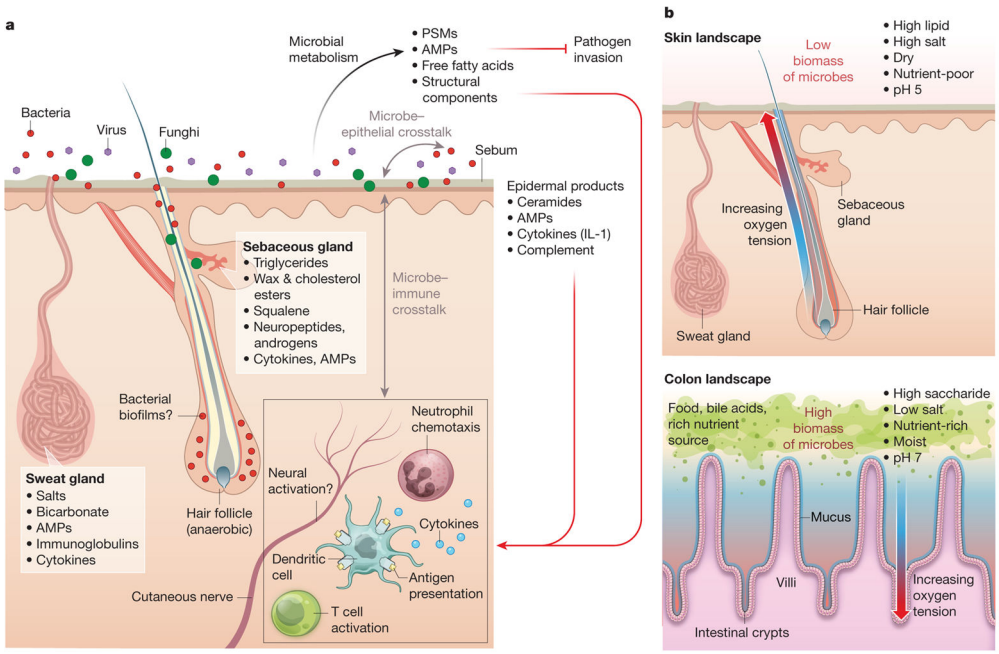

Figure 1. Crosstalk between skin microbiota and the host

a, Diverse microbes (viruses, fungi and bacteria) cover the skin surface and associated structures (hair follicles, sebaceous glands and sweat glands), possibly forming biofilms at some sites. These microbes metabolize host proteins and lipids and produce bioactive molecules, such as free fatty acids, AMPs, phenol-soluble modulins (PSMs), cell wall components, and antibiotics[158,159]. These products act on other microbes to inhibit pathogen invasion, on the host epithelium to stimulate keratinocyte-derived immune mediators such as complement and IL-1, and on immune cells in the epidermis and dermis. In turn, host products and immune cell activity influence microbial composition on the skin. **b**, The skin differs from the gut in its physical and chemical properties. The skin is a dry, acidic, lipid-rich, high-salt environment without exogenous nutrient sources, and therefore has low microbial biomass. By contrast, the gut is moist and has abundant nutrients and a thick layer of mucin[9,159], enabling it to support much greater microbial biomass. While hair follicles become more anaerobic deeper into the follicle, crypts become more aerobic closer to the epithelium[7,11]. In addition, material within crypts regularly exchanges with material in the gut lumen, owing to peristalsis, whereas hair follicles have narrow openings filled with sebum and keratinocytic debris, making them more isolated.

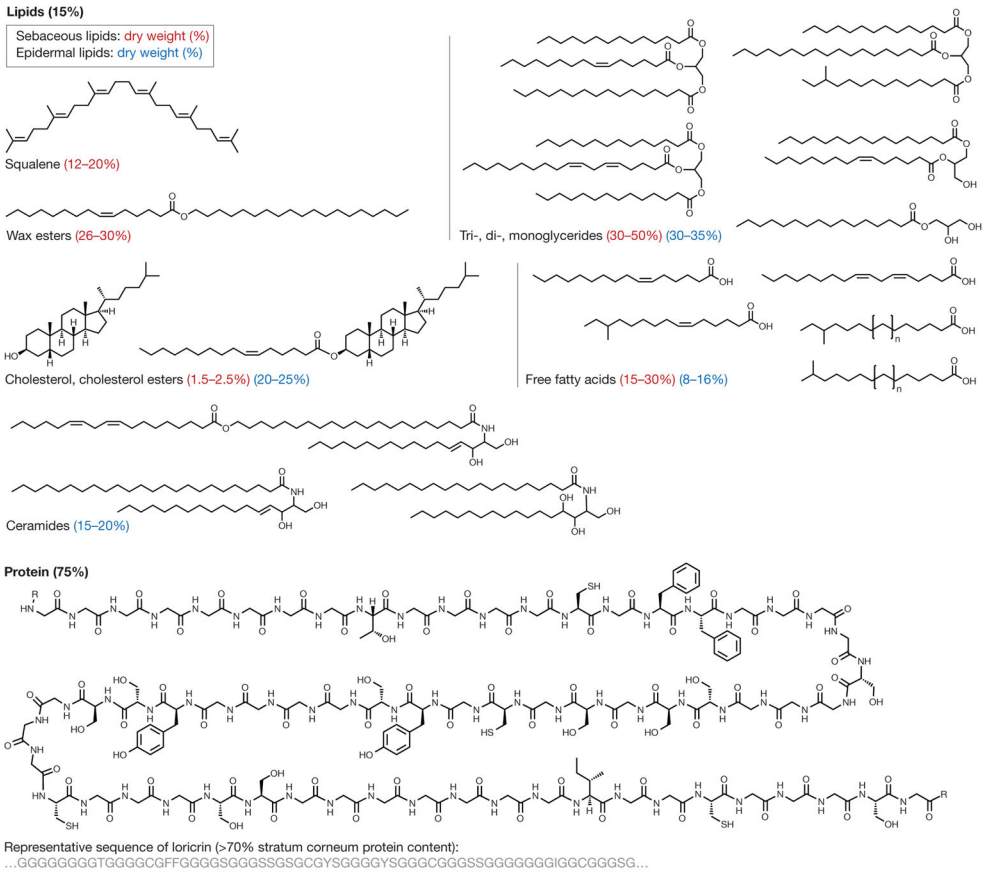

Figure 2. Chemistry of the skin

The skin surface consists of a highly organized basketweave structure of keratinocytic proteins and lipids, which are produced by keratinocytes (epidermal lipids) and sebaceous glands (sebaceous lipids)[160]. Ceramides are unique to epidermal origin, whereas squalene and wax esters are unique to sebaceous origin, with variable composition under endocrine control[14]. Other dominant skin lipids are cholesterol, triglycerides and free fatty acids (which are often microbial products). Some lipids, such as sphingosine and free fatty acids, demonstrate antimicrobial activity against bacteria, fungi, and viruses[66] and may have immunomodulatory effects[144]. Of keratinocytic proteins, more than 70% of the dry protein weight consists of loricrin, a glycine-rich protein that is thought to have important barrier properties[160].

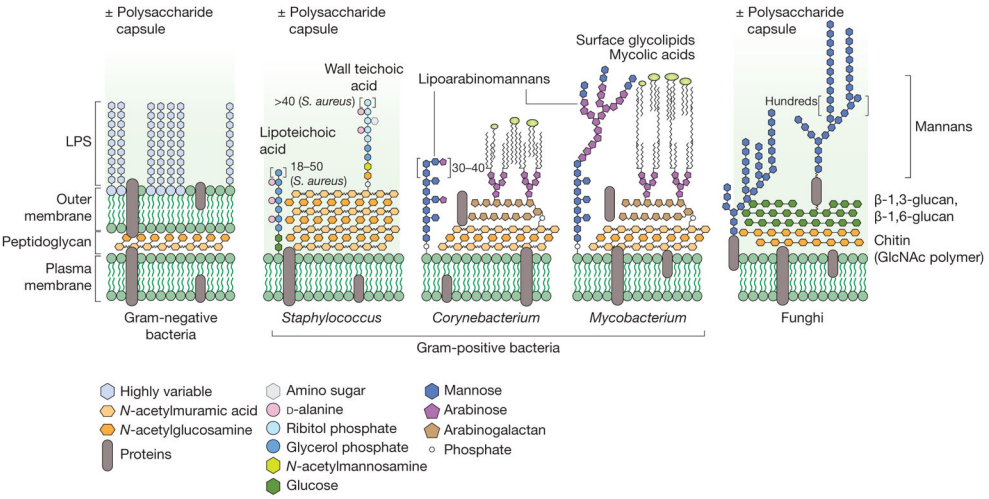

Figure 3. Chemistry of microbial surfaces

Bacteria and fungi have diverse cell envelopes loaded with immunogenic molecules. Gram-negative bacteria (left) have two lipid bilayers separated by a peptidoglycan cell wall. The outer leaflet of the outer membrane is studded with an immunogenic lipoglycan called lipopolysaccharide (LPS), which has a lipid anchor and highly variable polysaccharide region called the O-antigen. In *Escherichia coli*, for example, 184 different O-antigen structures are known[161]. Gram-positive bacteria (middle) lack an outer lipid bilayer but have a thicker peptidoglycan cell wall. *Staphylococcus* species have wall-bound and membrane-anchored teichoic acids, which are analogous to Gram-negative LPS, with a host-facing strain-specific branched polysaccharide. *Corynebacterium* and *Mycobacterium* species also have complex lipoglycans, called lipoarabinomannans. They also have a unique lipid outer layer made up of cell-wall-bound mycolic acids and other noncovalently bound glycolipids. Like Gram-positive bacteria, fungi (right) have only one lipid bilayer membrane. This is covered by a cell wall usually consisting of chitin and a β-D-glucan mesh. The outer layer of the fungal cell wall often contains heavily mannosylated proteins and sometimes a capsule of various polysaccharides. GlcNAc, *N*-acetylglucosamine.

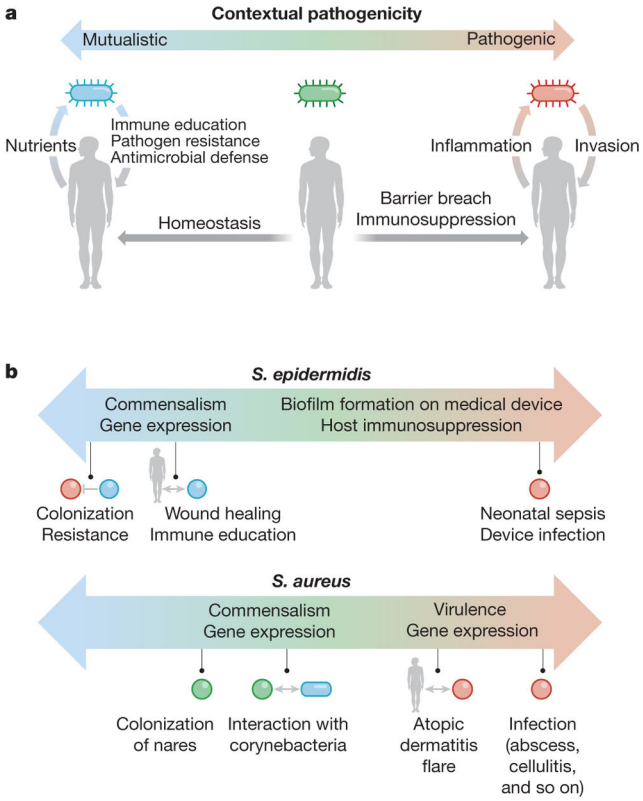

Figure 4. Contextual pathogenicity

a, Microbes exhibit contextual pathogenicity along a spectrum. Host factors such as barrier breaches and immunosuppression bias microbes towards pathogenic behaviour, whereas homeostatic conditions bias them towards mutualistic behaviour. On the microbial side, virulence gene expression and microbe–microbe interactions can also push microbial behaviour to be mutualistic or pathogenic. In a mutualistic host–microbe relationship, the host provides nutrients, while the microbe promotes epithelial and immune homeostasis as well as pathogen resistance through microbial products and occupation of metabolic niches. In a pathogenic relationship, the microbe invades past the epithelium, causing inflammation, and sometimes also benefiting from a host inflammatory response. **b**, Both *S. epidermidis* and *S. aureus* are examples of contextual pathogenicity; *S. epidermidis* is biased towards mutualistic behaviour whereas *S. aureus* displays more pathogenic character.