REVIEW

# Microbiota and maintenance of skin barrier function

Tamia A. Harris-Tryon[1] and Elizabeth A. Grice[2]

**Human skin forms a protective barrier against the external environment and is our first line of defense against toxic, solar, and pathogenic insults. Our skin also defines our outward appearance, protects our internal tissues and organs, acts as a sensory interface, and prevents dehydration. Crucial to the skin's barrier function is the colonizing microbiota, which provides protection against pathogens, tunes immune responses, and fortifies the epithelium. Here we highlight recent advances in our understanding of how the microbiota mediates multiple facets of skin barrier function. We discuss recent insights into pathological host–microbiota interactions and implications for disorders of the skin and distant organs. Finally, we examine how microbiota-based mechanisms can be targeted to prevent or manage skin disorders and impaired wound healing.**

Humans live in partnership with their microbiota, complex communities of bacteria, fungi, and viruses that inhabit the body's surfaces. These relationships have been forged and challenged over millions of years of coevolution. Thus, it is unsurprising that our microbial cohabitants are major participants in shaping and maintaining essential physiological processes. As our outermost barrier against the external environment, the skin is colonized by a distinctive commensal microbiota that stimulates and educates defense and immune responses, contributes to proper differentiation and epithelialization, and even provides direct defense against pathogenic microorganisms.

In this Review, we examine our current understanding of the skin's microbial ecology and highlight recent insights into the microbiota's role in shaping and fortifying the barrier function of the skin. We also consider pathological microbe–host interactions and their role in skin disease and disruptions to other organ systems. Finally, we consider how these interactions could be leveraged to prevent or treat skin disease and impaired wound healing.

## Microbial ecology of the human skin

Human skin, with its hypersaline and acidic environment and low nutrient availability, is distinct from other mucosa and epithelia. Both culture-based approaches and metagenomic profiling strategies of increasing resolution demonstrate that the human skin microbiota comprises a restricted set of bacterial, fungal, and viral inhabitants (*1*–*3*). Within the skin, bacteria predominantly belong to three phyla, Actinobacteria, Firmicutes, and Proteobacteria, with associated bacteriophages further modulating bacterial community dynamics and virulence. Eukaryotic viruses are also present, although generally in lower numbers. The skin also houses eukaryotic organisms, but these are less abundant than bacteria. *Malassezia* species, for example, predominate among fungal communities throughout adult human skin (Fig. 1), and the eight-legged arachnid genus *Demodex* resides within the hair follicle. Initial colonization of neonatal skin is suspected to occur during delivery. In infants born vaginally, *Lactobacillus*, *Prevotella*, or *Sneathia* species are transferred to the skin during passage through the cervix and vagina. These species disappear by 6 weeks of age, when the microbiota begins to develop a more skin-like profile enriched with *Staphylococcus* and *Corynebacterium* species. In infants born by cesarian section, *Staphylococcus*, *Corynebacterium*, and *Cutibacterium* species predominate, without a preceding vaginal signature (*4*).

One of the major drivers of the skin's microbial ecology is the pilosebaceous unit, a skin appendage that contains the hair follicle and its associated sebaceous gland. Sebaceous glands excrete a waxy, oily substance called sebum that emolliates the skin and selects for microbial species that metabolize the nutrients it contains. The pilosebaceous unit is also hypoxic, providing an ideal environment for the facultative anaerobe *Cutibacterium acnes*, which dominates this niche. Other signature bacteria of the skin surface include the coagulase-negative staphylococci (CoNS) species, such as *Staphylococcus epidermidis*, which are equipped to adhere and persist on human skin and tolerate the conditions. Skin sites with higher moisture and occlusion (e.g., the groin, axilla, and umbilicus) are enriched by *Corynebacterium* species that can be lipid-dependent and slow-growing in culture (Fig. 1).

The skin microbiota experiences a major shift at puberty when sex hormones drive maturation of the sebaceous gland and initiate sebum production. The introduction of lipid-rich sebum drives expansion of lipophilic *C. acnes* and *Malassezia* spp. on the skin surface, which correlates with serum sex hormone concentrations (*5*). Outside of puberty, the strains of bacteria and fungi colonizing the skin remain relatively stable within an individual over time (*2*). This stability is remarkable given the continuous disturbances imposed by lifestyle, the environment, and other host-specific factors, including constant shedding of terminally differentiated keratinocytes (squames) and secretions of sweat and sebum (Fig. 1). *C. acnes* and the pilosebaceous unit are likely major stabilizers of this effect in the human skin microbiome. The spatial architecture and hypoxic

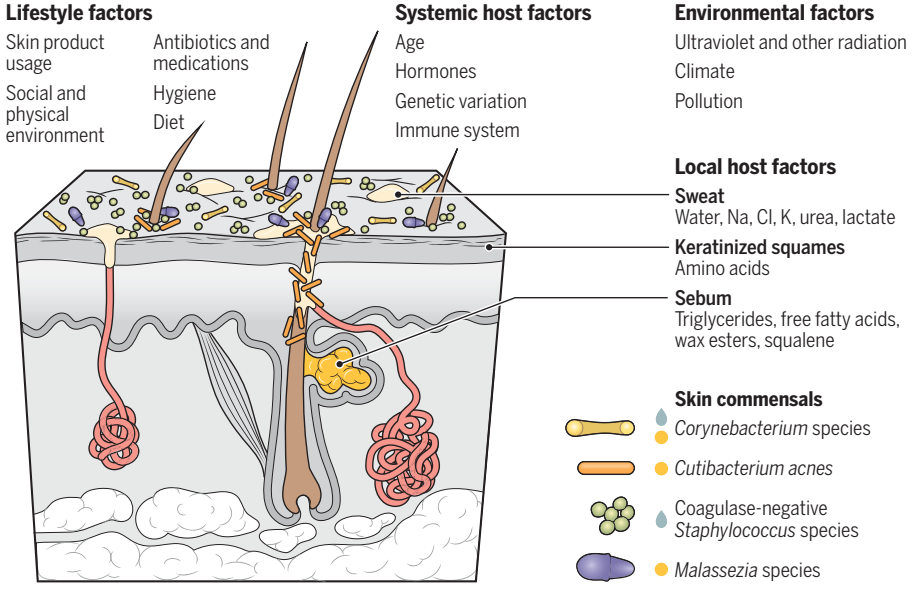


ILLUSTRATION: KELLIE HOLOSKI/*SCIENCE*

**Fig. 1. Factors that influence the microbial colonization of skin.** Local, systemic, environmental, and lifestyle factors together contribute to colonization and stability of the skin microbiome. Pictured are common human skin commensals. Hydrophilic and lipophilic microbes are indicated with a water droplet (blue) and oil droplet (yellow), respectively.

[1]Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, USA. [2]Departments of Dermatology and Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.
**Email: tamia.harris-tryon@utsouthwestern.edu (T.A.H.-T.); egrice@pennmedicine.upenn.edu (E.A.G.)**

conditions of the pilosebaceous unit impose a bottleneck on *C. acnes*, allowing early colonizing strains of *C. acnes* to predominate a given follicle with limited competition (*6*). Although pulse disturbance experiments with topical antiseptics displace sensitive lower-abundance taxa, *C. acnes* remains during community recovery (*7*). By contrast, longer disruptions to the microbiota through the use of systemic antibiotics impose long-lasting effects at the community level and drive selection for antibiotic-resistant staphylococci. Systemic antibiotics also increase gene mobilization among the microbiome, which is indicative of a stress response (*8*).

## Microbes fortify multiple facets of the skin barrier

The skin is a formidable structure composed of a stratified, cornified epithelium of keratinocytes, which undergo terminal differentiation. These physical structures are further fortified by chemical and immunological features that enhance the barrier. The skin microbiota affects all aspects of the skin barrier, while also directly interacting with commensal and pathogenic microbes encountered at the surface (Fig. 2). We next discuss how microbes interact with the skin barrier's microbial, chemical, and innate and adaptive immune components.

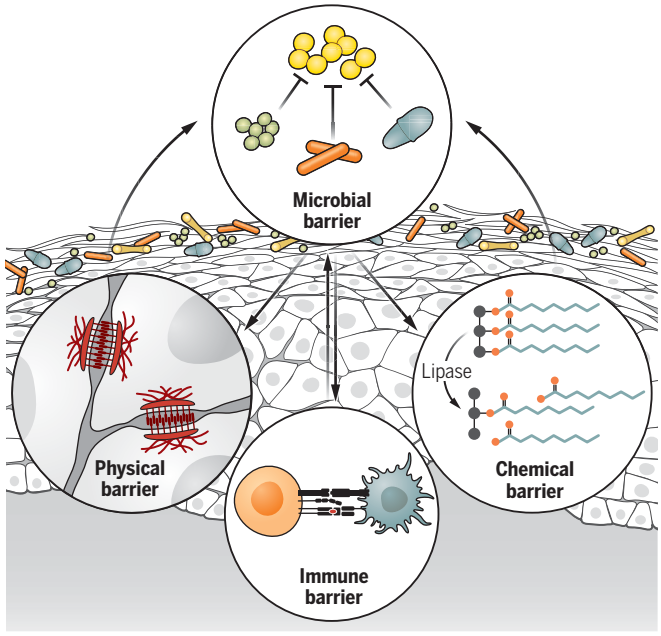


**Fig. 2. The skin microbiota mediates multiple levels of barrier function.** Skin microbes form the first barrier against the environment through various mechanisms of colonization resistance, including resource exclusion, direct inhibition, and/or interference. The skin microbiota also contributes to the differentiation and epithelialization of the physical skin barrier. Microbes boost the chemical barrier of the skin by producing lipases that digest sebum triglycerides to free fatty acids, which amplify the acidity of skin and restrict colonization by transient and pathogenic species. Finally, microbes stimulate innate and adaptive immune defenses such as release of antimicrobial peptides, induction of neonatal tolerance, and development of protective immunity.

### *Microbial barrier*

The skin microbiota itself is a barrier against invasion, colonization, and infection by foreign and pathogenic microbes. Living in polymicrobial communities, skin microbes vie for resources and have evolved mechanisms to directly antagonize their rivals. Multiple CoNS species, such as *Staphylococcus hominis*, produce antibiotics with unique chemistry and potent inhibitory activity against the major skin pathogen *Staphylococcus aureus* (*9*). Other species such as *Staphylococcus capitis* antagonize *S. aureus* through interference with the accessory gene regulator (agr) quorum sensing pathways, which are required for *S. aureus* virulence (*10*, *11*). Notably, many of these antagonistic mechanisms synergize with host antimicrobial responses. For example, lugdunin, a peptide antibiotic produced by *Staphylococcus lugdunensis*, induces keratinocytes to produce the antimicrobial peptide LL-37 and neutrophil chemoattractant CXCL8 through the Toll-like receptor–myeloid differentiation primary response protein 88 (TLR–MyD88) pathway (*12*). Competitive mechanisms are not limited to CoNS species in the skin microbiota. *C. acnes* competes to maintain its niche in the human pilosebaceous unit, with specific strains producing a thiopeptide antibiotic, cutimycin, that limits *S. aureus* colonization (*13*). How these individual interactions coalesce in a community setting and how this affects the community structure and function remain unclear.

### *Physical barrier*

Keratinocytes undergo a program of tightly regulated terminal differentiation to form the stratum corneum, a process that also can be mediated by the microbiota. Self-renewing basal keratinocytes exit the cell cycle and acquire the machinery (e.g., intermediate filaments and lipid granules) that together form the "bricks and mortar" of the permeability barrier. This barrier also directly interfaces with the microbiota, resident or transient, and is subject to microbial regulation. The microbiota is required for normal skin barrier structure and function in mice and promotes differentiation and epithelial integrity through signaling of the keratinocyte aryl hydrocarbon receptor (AHR) (*14*). Skin bacteria also secrete sphingomyelinases that process lamellar lipids into ceramides (*15*), a critical component of the stratum corneum.

### *Chemical barrier*

In addition to the physical distance from the environment provided by the corneocytes, keratinocytes, and skin lipids, the acidic skin surface creates a chemical environment that restricts bacterial colonization. Both *C. acnes* and *Corynebacterium* spp. secrete lipases that hydrolyze free fatty acids from triglycerides in sebum (*16*, *17*). Free fatty acids further augment skin immunity by directly inhibiting bacteria and by stimulating the expression of human β-defensin 2 (hBD-2) (*18*). *C. acnes* also binds directly to free fatty acids, suggesting that the availability of free fatty acids facilitates the colonization of *C. acnes*.

### *Innate immune barrier*

The microbiota is intimately associated with the skin epithelium, and the host and microbe have the capacity for cross-talk. Microbes can stimulate a range of innate immune responses that often depend on the metabolic and inflammatory contexts. For example, filamentous and yeast forms of *Candida albicans* stimulate distinct immune responses in the skin (*19*). Similarly, the T cell response to *S. epidermidis* in skin requires the expression of specific glycans on the bacterial surface that interact with C-type lectins on host innate immune cells (*20*). Oxygen availability can also affect host–microbial interactions at the skin surface. The microaerophilic bacterium *C. acnes* ferments the glycerol backbone of triglyceride and generates short-chain fatty acids (SCFAs). In turn, SCFAs inhibit histone deacetylases (HDACs), which can act as epigenetic regulators of the immune system (*21*). Unlike in the gastrointestinal tract, where SCFAs have anti-inflammatory effects on gut immunity, SCFAs have proinflammatory effects in the skin. By means of keratinocytes, *C. acnes*–derived SCFAs inhibit HDAC8 and HDAC9 and stimulate inflammation through TLR signaling (*22*). In the sebaceous gland, SCFAs derived from *C. acnes* fermentation augment inflammation through the activation of the free fatty acid receptor (*23*). Thus, a microbe's metabolic and inflammatory context can result in distinct types of immune responses.

Skin microbes further bolster skin immunity by stimulating the production of host-derived antimicrobial peptides and proteins (AMPs), which act as natural antibiotics. The expression of the AMP LL-37, a fragment of the protein cathelicidin, increases in response to activation of TLR signaling initiated by microbial signals (*24*). In addition to the cathelicidin family of AMPs, the skin also generates members of the

β-defensin family with bactericidal action against *Escherichia coli* and *S. aureus* strains. The sebaceous gland responds to Gram-negative lipopolysaccharide by generating the small proline-rich proteins SPRR1 and SPRR2, which directly disrupt negatively charged bacterial membranes (*25*). The skin also produces numerous cationic intrinsically disordered proteins with broad antimicrobial activity (*26*). These AMPs act in concert to provide the skin with a range of antimicrobial defenses against the microbes encountered in the environment.

The skin microbiota also helps coordinate innate immune responses during wound repair. Similar to observations made in the lung and gut, the commensal microbiota in the skin elicits a type I interferon (IFN) response during this process (*27*). In response to microbial stimuli, neutrophils express CXCL10, which recruits activated plasmacytoid dendritic cells (pDCs) to sites of injury. pDCs generate type I IFNs, which accelerate wound repair through stimulation of fibroblast and macrophage growth factor responses. Indeed, the recruitment of antigen-presenting cells to the skin is microbiota-dependent (*28*). Similarly, microbes enhance skin regeneration in wound repair and hair follicle neogenesis through a process that requires interleukin-1 receptor (IL-1R)–MYD88 signaling (*29*).

### *Adaptive immune barrier*

The skin is home to a diverse repertoire of adaptive immune cells, among them vast pools of resident memory T cells poised to respond to various environmental stimuli, including pathogenic and commensal microbes. In early infancy, exposure to the skin commensal *S. epidermidis* mediates the influx of regulatory T cells ($T_{regs}$) into the skin (*30*). This wave of $T_{reg}$ migration occurs concurrently with hair follicle development and requires the production of chemokines generated by the hair follicle keratinocytes (*30*, *31*). $T_{regs}$, along with many other immune cell subsets in the skin, ultimately reside adjacent to the hair follicle, with specificity to the microbial antigens detected during this developmental window.

In a parallel process, mucosal-associated invariant T (MAIT) cells are acquired in infancy during a similar time-restricted developmental window. MAIT cells are absent in germ-free mice, and their development requires vitamin B2 metabolites that are only produced by bacteria and fungi, not mammalian cells. In the thymus, exposure to 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil, a bacterial metabolite of vitamin B2 trafficked to the thymus from mucosal sites, mediates MAIT cell expansion and targeting to the skin and mucosal sites (*32*, *33*). Microbial cell surface molecules can also act as signals to the host. Most species of *Corynebacterium* contain mycolic acid in their cell envelope. Mycolic acid from *Corynebacterium* species can promote γδ T cell accumulation in an IL-23–dependent manner under steady state. However, this interaction is context-dependent, as a high-fat diet instead promotes cutaneous inflammation (*17*). Thus, the inflammatory milieu present at the time of microbial exposure affects the immune response within the skin. Taken together, these findings highlight the key role that microbes play in the recruitment and stimulation of immune cells in the skin.

## Pathological microbial–host interactions and skin disorders

From an ecological standpoint, microbial communities are inevitably destined to change in structure and function when their niche is disrupted. As such, an altered skin microbiome is more often the rule than the exception in skin disease. Shifts in resource availability and, in some cases, complete devastation of their habitat are factors that drive the depletion of normal skin residents in favor of opportunists. Owing to the tight interconnectivity of the microbiota with its host, it is difficult to distinguish between "the chicken and the egg" in the absence of experimental approaches that rely on cultured isolates in experimental model systems. Whether causative or a consequence, altered microbial communities can mediate tissue damage and/or inflammation across a variety of skin disorders.

*S. aureus* is a frequent opportunist of the skin and overwhelms the commensal microbiota in barrier disorders such as atopic dermatitis (AD) and skin wounds (*34*–*36*). In the setting of disease, *S. aureus* can evade the host immune response to establish chronic infection. Moreover, *S. aureus* and some CoNS species produce proteases and other factors that further damage the barrier and drive pathological inflammatory responses (*11*, *37*). In addition to direct damage, *S. aureus* interferes with adaptive immune responses by producing alpha toxins that trigger IL-1R–mediated inflammation and prevent the accumulation of *S. aureus*–specific $T_{regs}$ and the development of tolerance to *S. aureus* later in life (*38*).

In AD and other dysbiotic contexts where an opportunist overtakes the ecosystem, there is a depletion of the commensal microbes and their mediators that previously supported the skin's barrier defenses. For example, tryptophan metabolites are reduced in AD skin. When these metabolites are therapeutically administered, inflammation in mouse models of AD is attenuated by AHR (*39*). Coal tar, one of the oldest therapies for AD, can activate the AHR in the skin to drive differentiation programs, AMP expression, and normalization of the microbiome (*40*). Dysregulation of tryptophan catabolism by the microbiota may also contribute to hidradenitis suppurativa (HS), a condition characterized clinically by festering wounds of the armpits and groin whose pathogenesis is poorly understood. HS lesions are also deficient in AHR activation, which coincides with a depletion of tryptophan-metabolizing microbiota (*41*). Thus, microbial metabolites produced by skin commensals are depleted during disease states, which may maintain and exacerbate inflammation and barrier disruption.

A dysregulated or dysfunctional immune system also has impacts on the skin microbiota, which can further exacerbate disease. *S. aureus* and *S. epidermidis*, for example, are more abundant and cause greater amounts of skin damage in Netherton syndrome patients, who have a genetic defect in the skin protease inhibitor lymphoepithelial Kazal-type–related protease inhibitor 1 (LEKTI-1) (*42*). Skin infections and shifts in skin colonization can also occur in humans with primary immunodeficiency disorders. For example, in patients with dedicator of cytokinesis protein 8 (DOCK8) deficiency, the cutaneous virome is enriched with a diversity of eukaryotic viruses, including human papilloma viruses (*43*). Genetic deletion studies in murine models further highlight the key role that the immune system plays in restricting the microbiota. Mice devoid of type 2 innate lymphoid cells (ILC2s) have enlarged sebaceous glands and generate greater amounts of antimicrobial lipids that restrict colonization of Gram-positive commensals (*44*). By contrast, mice lacking T cells and epidermal expression of the transcription factor JunB are unable to control *S. aureus* inflammation at the skin surface and recapitulate several aspects of atopic inflammation (*45*).

As shotgun metagenomics and culture-based investigations have advanced, it is becoming clear that strain-level variations of human skin commensals and pathogens also have an impact on disease pathogenesis. Specific strains of *S. aureus* correlate with disease severity and clinical outcomes in different contexts (*34*, *36*). Acneic skin is colonized with *C. acnes* strains that inherently produce greater amounts of the proinflammatory metabolite porphyrin compared with *C. acnes* strains recovered from healthy skin (*46*). Moreover, porphyrin production by *C. acnes* is under the control of vitamin B12. A vitamin B12 supplementation study in humans showed increased porphyrin production leading to acne development (*47*). This is a potential molecular mechanism that may explain how the same species of bacteria can both cause disease and reside as a member of the healthy skin microbiota. A challenge going forward will be to identify specific markers of virulence within bacterial strains that can inform management strategies for problematic microbial burdens.

Another advantage of culture-independent approaches is that they have greatly facilitated the identification of fastidious anaerobic microbiota in skin disease and wounds. In chronic wounds and HS, mixed communities of Gram-positive anaerobic bacteria can inhabit deeper tissues of the skin (*48*). Although the skin commensal *C. acnes* may be found in some abundance in these mixed communities, other players,

such as *Anaerococcus* spp., *Porphyromonas* spp., *Finegoldia* spp., *Veillonella* spp., and *Peptostreptococcus* spp., are more common. In chronic wounds, the persistence of anaerobic communities after debridement is associated with poor wound outcomes (*36*, *49*). The challenges of isolation and study of anaerobes, especially in mixed communities, are limiting factors in advancing our understanding of their role in skin disorders such as HS and chronic wounds.

Psoriasis is another common inflammatory skin disease. In contrast to AD and other barrier disorders, alterations to the skin microbiota in psoriasis are more subtle, less consistent across studies, and are more weakly associated with disease (*35*, *50*, *51*). Thus, there is currently limited evidence that the skin microbiota drives psoriasis pathogenesis. However, in a psoriasis mouse model, *C. albicans* exposure augmented T helper 17 cell immunity with increased infiltration of and IL-17 production by αβ T cells sensitized by *Candida* (*52*). Microbial–host interactions at other mucosal sites are hypothesized to contribute to psoriasis as well, as discussed in the next section.

### Systemic roles for the skin microbiome

There is increasing evidence that skin damage and sensitization can affect other barrier sites, such as the intestine and the lung (Fig. 3). For example, superficial skin damage causes keratinocytes to release IL-33 systemically. In synergy with IL-25, IL-33 triggers the activation of ILC2s in the intestine to generate IL-4. This, in turn, stimulates the expansion of mast cells in the intestine, where they are poised to respond to food allergens and mediate anaphylaxis (*53*). Wounding of the skin also augments intestinal inflammation in dextran sodium sulfate–induced colitis mouse models, which mimic inflammatory bowel disease. Cross-talk between the skin and gut depends on the production of hyaluronan fragments generated in the dermis during injury that stimulate intestinal fibroblasts to differentiate into proinflammatory adipocytes through a process called reactive adipogenesis. These reactive adipocytes propagate gut inflammation through the production of AMPs and other inflammatory mediators (*54*).

Skin sensitization also affects the lungs. Epidemiological evidence demonstrates that many patients progress through an "atopic march," first presenting with the skin barrier condition AD and subsequently developing allergic rhinitis, food allergies, and asthma (*55*). Epicutaneous exposure to *S. aureus* stimulates keratinocytes to produce IL-36, which amplifies serum immunoglobulin E (IgE) levels. Mice lacking the IL-36 receptor do not develop elevated IgE in response to *S. aureus* and are also protected from allergen-specific lung inflammation (*56*). These findings provide evidence for skin exposure to microbial pathogens as an initiating event in systemic inflammation. However, it is notable that the skin has the capacity to control and restrict commensal responses independently of other mucosal sites through a sophisticated network of immune strategies (*57*). More work is needed to uncover the many ways that these regulatory mechanisms, which contribute to sustained compartmentalization, malfunction in disease.

The gut microbiome can also affect skin inflammation. For example, type 3 inflammation in a mouse psoriasis model is dampened in germ-free mice, which lack a microbiome (*58*). Moreover, mice that are sensitized to allergens in the intestine through oral administration develop antigen-specific T cells in the skin after epicutaneous challenge with the same antigen (*59*). In both cases, activation of the intestinal immune networks affects the amplitude of the inflammatory signals in the skin. Thus, alterations in the gut microbiome may affect skin immunity, although clear targets for therapeutic avenues to influence skin disease through modulation of the intestinal microbes remain undefined. What has been shown is that the dietary impacts on the gut microbiome, especially dietary fiber, have meaningful effects on systemic immunity (*60*). Cutaneous innate immune responses are also linked to the gut, where adequate expression of AMPs that protect against bacterial skin infection is dependent on dietary vitamin A (*61*). Together, these findings strengthen our molecular understanding of the importance of diet in the development of host immunity.

An emerging area of investigation is the interface between skin microbiota and the neuroimmune axis. Bacteria can directly activate sensory neurons in the skin and cause pain through the production of pore-forming toxins (*62*). As in interactions with other aspects of the host, variation at the strain level drives variable responses, depending on the presence of specialized toxins and quorum sensing systems. Sensory neurons in the skin are also directly activated by the fungal pathogen *C. albicans*, and stimulation is required for γδ T cell immunity to control cutaneous candidiasis through release of neuropeptide CGRP (*63*). By contrast, the pathogen *Streptococcus pyogenes*, which causes necrotizing fasciitis, directly activates nociceptor neurons by secreting streptolysin S, which in turn promotes neuropeptide CGRP release and inhibits killing of *S. pyogenes*. In this context, CGRP antagonism prevents necrotizing infection (*64*). Although these studies have focused on skin pathogens in neuroimmune interactions, how skin commensals, at the community level, contribute to our sensory perceptions under homeostatic conditions remains under investigation.

### Outlook and conclusions

The application of molecular, culture-independent techniques to survey microbial communities has reinvigorated the study of skin microbiota and its role in dermatological health

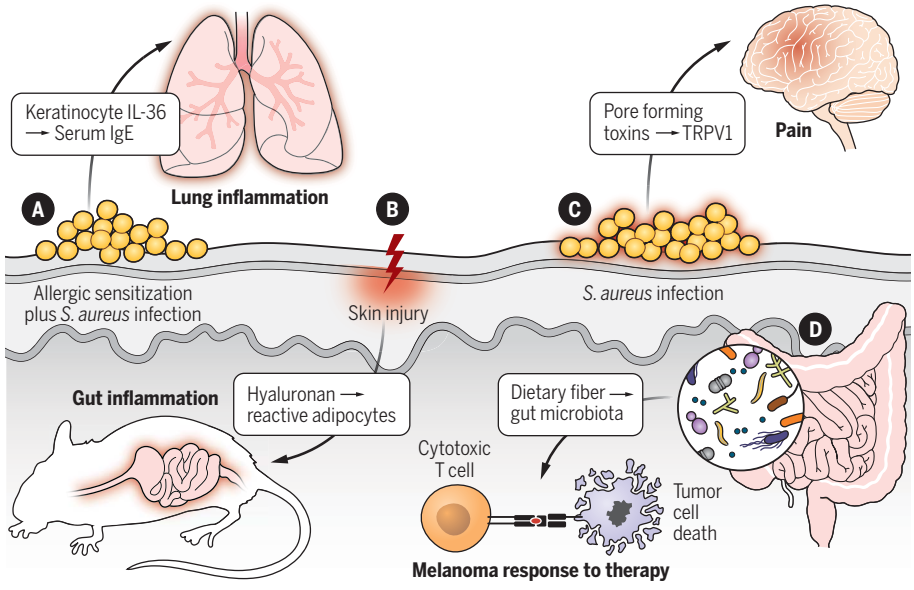


**Fig. 3. Skin cross-talk with other organ systems is mediated by the microbiota.** Emerging evidence highlights the role of skin cross-talk with distant organ systems, which is driven by host–microbiota interactions. Depicted are four examples of cross-talk between skin and other organ systems. (**A**) Allergic sensitization of skin, together with *S. aureus* infection, results in IL-36–dependent lung inflammation, suggesting a potential mechanism for the "atopic march." (**B**) Skin injury releases hyaluronan fragments systemically, which drives reactive adipogenesis, gut inflammation, and dysbiosis in murine models. (**C**) During infection, *S. aureus* releases pore-forming toxins that are implicated in directly activating nociceptors and causing pain. TRPV1, transient receptor potential cation channel subfamily V member 1. (**D**) The gut microbiome and dietary fiber contribute to melanoma response to immune checkpoint therapy, driving cytotoxic T cell accumulation and killing of tumor cells.

ILLUSTRATION: KELLIE HOLOSKI/*SCIENCE*

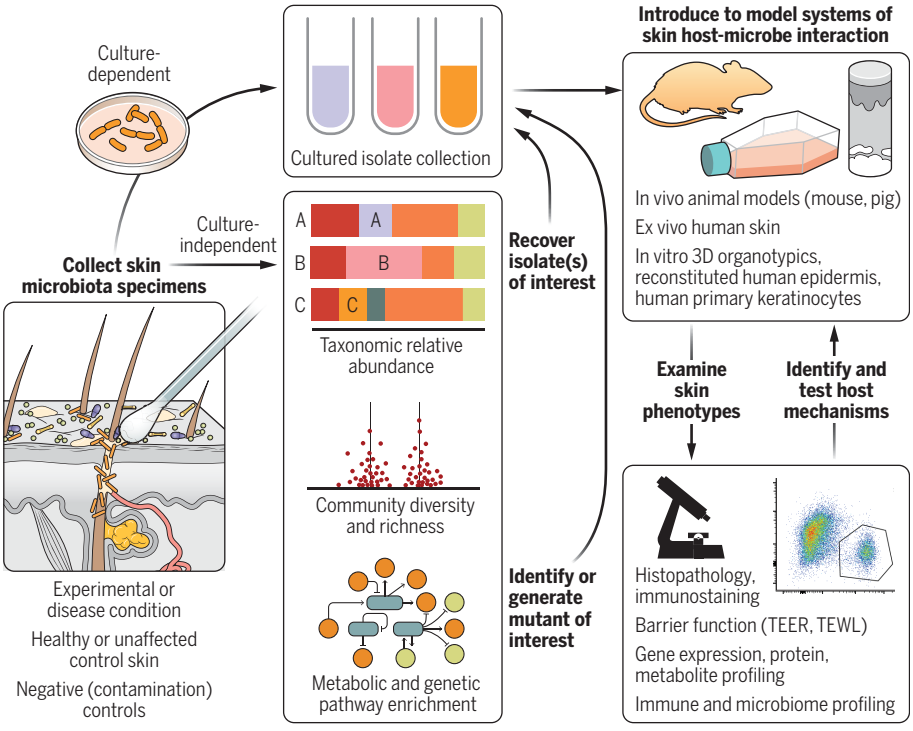


**Fig. 4. Framework for examining functional and mechanistic attributes of the skin microbiota.** Illustrated is an example pipeline for using skin microbiome profiles to inform functional and mechanistic investigations. Applying a combination of culture-independent and culture-dependent approaches allows examination of specific microbes or consortia in the context of skin model systems. Furthermore, shotgun metagenomic sequencing can inform which metabolic or genetic pathways to target in the microbiota, which then can be functionally interrogated by examining mutants for these pathways. Deep phenotyping of skin or skin models colonized or associated with clinical isolates, mutants, and/or consortia facilitates hypothesis generation regarding host interactive pathways, which then can be tested in this pipeline. TEER, transepithelial electrical resistance; TEWL, transepidermal water loss.

and disease. Interpreting results from skin microbiota surveys, such as 16*S* rRNA gene sequencing or shotgun metagenomics, and using these data to guide a deeper understanding of functional and mechanistic attributes of the microbiota remains a challenge for the field. We posit that application of both culture-independent and culture-dependent approaches, within an ecological framework of community-wide interactions, can advance our understanding of homeostatic and pathological mechanisms at the host–microbiota interface (Fig. 4). Skin microbiome surveys can reveal the composition and diversity of the community and be combined with culture-based approaches to identify isolates or target the isolation of community members. These isolates can then be used individually or in combination to test their effects on the skin in vivo with model organisms, in vitro using human skin cells and constructs, or ex vivo using human skin explants. In this framework, shotgun metagenomics of ample read depths can be a useful approach for strain-level characterization of the community or can identify functional genetic pathways that are enriched within a sample. Genetic deletion of these pathways or genes can then be targeted in clinical isolates or obtained from collections of laboratory isolates, to test the role of these pathways in driving skin phenotypes. Deep-skin phenotyping, for example, using unbiased assays to measure gene expression can further define how the host responds to the skin microbiota.

Therapeutic advancement based on the skin microbiome will rely on such approaches to identify candidates for either enhancement or depletion in the community. Bacteriotherapy, or transplantation of live, defined bacteria, is currently under development for the treatment of AD using a strain of *S. hominis* that was isolated from healthy human skin and inhibits *S. aureus* (*9*). Phase 1 trials in *S. aureus*–positive AD patients ($n$ = 54) indicate the safety of *S. hominis A9* and demonstrate a reduction of *S. aureus* colonization, although overall clinical severity of disease was not significantly affected (*65*). Moreover, a placebo-controlled trial using lysates of the Gram-negative *Vitreoscilla filiformis* has proven beneficial through the stimulation of IL-10–producing dendritic cells within the skin (*66*). Screening strategies may also be tailored to identify microbes that activate or repress host pathways of interest. The "Flowers' Flora" consortium, for example, was developed by screening human skin commensals for AHR activation in keratinocytes (*14*). Colonization with this consortium improved barrier function in germ-free mice and reduced disease severity in murine models of AD. The Gram-negative *Roseomonas mucosa*, isolated from healthy human skin, was once explored for the treatment of AD, but clinical trials were ultimately discontinued owing to failure to meet end points (*67*). Other microbiota-based therapeutic approaches are less developed in the skin but could include phage-directed therapies to target pathogens, engineering commensals to express molecules of benefit, and/or prebiotic approaches to modify the habitat and thus the microbiota (*68*).

Although microbes have tremendous therapeutic potential, an ecological perspective of community-level interactions between host and microbes is needed to inform efforts to manipulate the microbiome. Selection of a consortium with desired functional attributes is only the first step, as major obstacles to the delivery and stable engraftment of transplanted communities remain. The host and the endogenous microbiota have powerful effects on the establishment, persistence, growth, and long-term impact of a transplanted community and are likely factors that influence the engraftment of a transplant (*69*). Spatial architecture of the pilosebaceous unit likely limits the complete removal of skin microbes, even with topical treatments meant to sterilize skin. These protected structures may serve as reservoirs to "reseed" the skin microbiome following disturbance. Additionally, it is now apparent that skin microbes are highly specialized to their niches, reflecting millions of years of adaptation to human skin, and not only interact with the local tissue microenvironment but drive signals at distant organs as well. Unsurprisingly, disrupting microbe–host relationships in the skin has consequences on organ structure and function. Introducing a new member to the community undoubtedly triggers responses from both host and microbial cells. Understanding how skin microbial communities interact with the host and each other is crucial to inform transplantation strategies and all types of microbial-based therapeutics that target this interface for the prevention and treatment of skin disorders.

## REFERENCES AND NOTES

1. G. D. Hannigan *et al.*, *mBio* **6**, e01578-15 (2015).
2. J. Oh *et al.*, Temporal stability of the human skin microbiome. *Cell* **165**, 854–866 (2016).
3. S. Saheb Kashaf *et al.*, *Nat. Microbiol.* **7**, 169–179 (2022).
4. D. M. Chu *et al.*, *Nat. Med.* **23**, 314–326 (2017).
5. J. Park *et al.*, *J. Invest. Dermatol.* **142**, 212–219 (2022).
6. A. Conwill *et al.*, *Cell Host Microbe* **30**, 171–182.e7 (2022).
7. A. J. SanMiguel *et al.*, *J. Invest. Dermatol.* **138**, 2234–2243 (2018).
8. J.-H. Jo *et al.*, *Sci. Transl. Med.* **13**, eabd8077 (2021).
9. T. Nakatsuji *et al.*, *Sci. Transl. Med.* **9**, eaah4680 (2017).
10. A. E. Paharik *et al.*, *Cell Host Microbe* **22**, 746–756.e5 (2017).
11. M. R. Williams *et al.*, *Sci. Transl. Med.* **11**, eaat8329 (2019).
12. K. Bitschar *et al.*, *Nat. Commun.* **10**, 2730 (2019).
13. J. Claesen *et al.*, *Sci. Transl. Med.* **12**, eaay5445 (2020).

ILLUSTRATION: KELLIE HOLOSKI/*SCIENCE*

14. A. Uberoi *et al*., *Cell Host Microbe* **29**, 1235–1248.e8 (2021).
15. Y. Zheng *et al*., *Cell Host Microbe* **30**, 301–313.e9 (2022).
16. L. Bomar, S. D. Brugger, B. H. Yost, S. S. Davies, K. P. Lemon, *mBio* **7**, e01725–e15 (2016).
17. V. K. Ridaura *et al*., *J. Exp. Med.* **215**, 785–799 (2018).
18. T. Nakatsuji *et al*., *J. Invest. Dermatol.* **130**, 985–994 (2010).
19. S. W. Kashem *et al*., *Immunity* **42**, 356–366 (2015).
20. Y. E. Chen *et al*., bioRxiv 664656 [Preprint] (2019). https://doi.org/10.1101/664656.
21. P. V. Chang, L. Hao, S. Offermanns, R. Medzhitov, *Proc. Natl. Acad. Sci. U.S.A.* **111**, 2247–2252 (2014).
22. J. A. Sanford *et al*., *Sci. Immunol.* **1**, eaah4609 (2016).
23. J. A. Sanford, A. M. O'Neill, C. C. Zouboulis, R. L. Gallo, *J. Immunol.* **202**, 1767–1776 (2019).
24. Y. Lai *et al*., *J. Invest. Dermatol.* **130**, 2211–2221 (2010).
25. C. Zhang *et al*., *eLife* **11**, e76729 (2022).
26. T. Latendorf *et al*., *Sci. Rep.* **9**, 3331 (2019).
27. J. Di Domizio *et al*., *Nat. Immunol.* **21**, 1034–1045 (2020).
28. N. D. Ubags *et al*., *J. Allergy Clin. Immunol.* **147**, 1049–1062.e7 (2021).
29. G. Wang *et al*., *Cell Host Microbe* **29**, 777–791.e6 (2021).
30. T. C. Scharschmidt *et al*., *Immunity* **43**, 1011–1021 (2015).
31. T. C. Scharschmidt *et al*., *Cell Host Microbe* **21**, 467–477.e5 (2017).
32. M. G. Constantinides *et al*., *Science* **366**, eaax6624 (2019).
33. F. Legoux *et al*., *Science* **366**, 494–499 (2019).
34. A. L. Byrd *et al*., *Sci. Transl. Med.* **9**, eaal4651 (2017).
35. N. Fyhrquist *et al*., *Nat. Commun.* **10**, 4703 (2019).
36. L. R. Kalan *et al*., *Cell Host Microbe* **25**, 641–655.e5 (2019).
37. L. Cau *et al*., *J. Allergy Clin. Immunol.* **147**, 955–966.e16 (2021).
38. J. M. Leech *et al*., *Cell Host Microbe* **26**, 795–809.e5 (2019).
39. J. Yu *et al*., *J. Allergy Clin. Immunol.* **143**, 2108–2119.e12 (2019).
40. J. P. H. Smits *et al*., *J. Invest. Dermatol.* **140**, 415–424.e10 (2020).
41. L. Guenin-Macé *et al*., *JCI Insight* **5**, e140598 (2020).
42. M. R. Williams *et al*., *Cell Rep.* **30**, 2923–2933.e7 (2020).
43. O. Tirosh *et al*., *Nat. Med.* **24**, 1815–1821 (2018).
44. T. Kobayashi *et al*., *Cell* **176**, 982–997.e16 (2019).
45. Ö. Uluçkan *et al*., *Cell Rep.* **29**, 844–859.e3 (2019).
46. T. Johnson, D. Kang, E. Barnard, H. Li, *MSphere* **1**, e00023-15 (2016).
47. D. Kang, B. Shi, M. C. Erfe, N. Craft, H. Li, *Sci. Transl. Med.* **7**, 293ra103 (2015).
48. S. C. Williams, J. W. Frew, J. G. Krueger, *Exp. Dermatol.* **30**, 1388–1397 (2021).
49. S. Verbanic, Y. Shen, J. Lee, J. M. Deacon, I. A. Chen, *NPJ Biofilms Microbiomes* **6**, 21 (2020).
50. H.-W. Chang *et al*., *Microbiome* **6**, 154 (2018).
51. M. A. Loesche *et al*., *J. Invest. Dermatol.* **138**, 1973–1981 (2018).
52. C. Hurabielle *et al*., *Proc. Natl. Acad. Sci. U.S.A.* **117**, 16465–16474 (2020).
53. J.-M. Leyva-Castillo *et al*., *Immunity* **50**, 1262–1275.e4 (2019).
54. T. Dokoshi *et al*., *J. Clin. Invest.* **131**, e147614 (2021).
55. A. S. Paller, J. M. Spergel, P. Mina-Osorio, A. D. Irvine, *J. Allergy Clin. Immunol.* **143**, 46–55 (2019).
56. G. J. Patrick *et al*., *J. Clin. Invest.* **131**, e143334 (2021).
57. S. Naik *et al*., *Science* **337**, 1115–1119 (2012).
58. Z. Zákostelská *et al*., *PLOS ONE* **11**, e0159539 (2016).
59. M. K. Oyoshi *et al*., *J. Clin. Invest.* **121**, 2210–2220 (2011).
60. C. N. Spencer *et al*., *Science* **374**, 1632–1640 (2021).
61. T. A. Harris *et al*., *Cell Host Microbe* **25**, 777–788.e8 (2019).
62. K. J. Blake *et al*., *Nat. Commun.* **9**, 37 (2018).
63. S. W. Kashem *et al*., *Immunity* **43**, 515–526 (2015).
64. F. A. Pinho-Ribeiro *et al*., *Cell* **173**, 1083–1097.e22 (2018).
65. T. Nakatsuji *et al*., *Nat. Med.* **27**, 700–709 (2021).
66. T. Volz *et al*., *J. Invest. Dermatol.* **134**, 96–104 (2014).
67. I. A. Myles *et al*., *Sci. Transl. Med.* **12**, eaaz8631 (2020).
68. M. T. Sorbara, E. G. Pamer, *Nat. Rev. Microbiol.* (2022).
69. J. Walter, M. X. Maldonado-Gómez, I. Martínez, *Curr. Opin. Biotechnol.* **49**, 129–139 (2018).

## ACKNOWLEDGMENTS

We thank the members of the Grice lab and the Harris-Tryon lab for their underlying contributions. **Funding:** This work was supported by National Institutes of Health grants R01NR015639 and R01AI143790 (E.A.G.) and K08AR076459 (T.A.H.-T.), a Linda Pechenik Montague Investigator Award (E.A.G.), a Burroughs Wellcome Fund PATH Award (E.A.G.), a Burroughs Wellcome Fund CAMS Award (T.A.H.-T.), a Dermatology Foundation Sun Pharma Research Award (E.A.G.), and a Robert Wood Johnson Foundation Harold Amos Award (T.A.H.-T.). **Competing interests:** The authors declare that they have no competing interests. 

Submitted 28 February 2022; accepted 26 April 2022
10.1126/science.abo0693

# Microbiota and maintenance of skin barrier function

Tamia A. Harris-TryonElizabeth A. Grice

*Science*, 376 (6596), • DOI: 10.1126/science.abo0693