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#### REVIEW

# Dialogue between skin microbiota and immunity

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Human skin, the body's largest organ, functions as a physical barrier to bar the entry of foreign pathogens, while concomitantly providing a home to myriad commensals. Over a human's life span, keratinized skin cells, immune cells, and microbes all interact to integrate the processes of maintaining skin's physical and immune barrier under homeostatic healthy conditions and also under multiple stresses, such as wounding or infection. In this Review, we explore the intricate interactions of microbes and immune cells on the skin surface and within associated appendages to regulate this orchestrated maturation in the context of both host physiological changes and environmental challenges.

**M**ulticellular organisms exist as meta-organisms composed of both the macroscopic host and symbiotic commensal microbiota. Compartmentalized barrier tissues such as the skin are a complex composite of microbes and host structural, hormonal, nervous, and immunological networks. The development of defined arms of the immune system, particularly adaptive immunity, has coincided with the acquisition of complex microbiota, suggesting that a large fraction of this host complexity has evolved to maintain this symbiotic relationship. In turn, microbiota can regulate multiple aspects of the immune system. However, this alliance may also come at a price when extrinsic and intrinsic factors, such as diet, indoor heating, and use of antibiotics, change rapidly. Profound changes in the microbiota and as a direct result, the immune system, are now believed to contribute to the dramatic and rapid increase in chronic inflammatory and autoimmune disorders seen in high-income countries. Indeed, while each inflammatory disease is associated with specific genetic and biological mechanisms, many inflammatory diseases are also associated with shifts in the resident microbiota from a “healthy” to a “diseased” state. These diseases can therefore be viewed as dysbiotic host-microbial metaorganismal states.

#### Skin microbial diversity and plasticity

The skin is home to a myriad of microbial communities residing on the tissue surface, as well as in associated appendages, such as hair follicles and sebaceous glands (1–3). Skin is a stratified, cornified epithelium of basal stem cells that undergo a 4-week process of terminal differentia-

tion to become enucleated cross-linked sacs of proteins cemented together by extruded lipids (4, 5). Across the 1.8 m<sup>2</sup> of skin surface, 1 million bacteria reside per square centimeter for a total of over 10<sup>10</sup> bacterial cells covering a human (6). However, the skin's surface is quite diverse, consisting of different microenvironments with distinct pH, temperature, moisture, sebum content, and topography (1). These niche-specific physiologic differences influence the resident bacteria (2, 3) and fungi (7); oily surfaces like the forehead support lipid-loving bacteria that differ from dry, low-biomass sites like the forearm (Fig. 1).

Surveys of discrete skin sites, selected for predilection to microbial infections, demonstrated that skin physiology (moist, dry, or sebaceous) is the organizing principle of bacterial communities. Sebaceous sites are dominated by lipophilic *Propionibacterium* species, while humidity-loving *Staphylococcus* and *Corynebacterium* species are abundant in moist areas. Fungi of the genus *Malassezia* dominate core-body and arm sites, while foot sites, which are major sites of fungal infection, are colonized by a more diverse combination of *Malassezia*, *Aspergillus*, *Cryptococcus*, *Rhodotorula*, *Epicoccum*, and others (7) (Fig. 1).

The vast majority of the human-associated microbes reside within the rich gut milieu. By contrast, the skin habitat is less hospitable and nutrient poor (8) (Table 1 and Fig. 2). The skin surface is cool, acidic, desiccated, and bathed in sweat with only sebum and skin stratum corneum peptides and lipids as nutrients. Moreover, sweat is salt-laden and replete with antibacterial molecules, such as free fatty acids and antimicrobial peptides (AMPs), natural antibiotics that represent an evolutionarily ancient arm of protective responses (8). Yet humans and their commensal microbial communities have coevolved to provide mutual benefit. Some strains of the predominant skin symbiotic *Staphylococcus* are tolerant of high salt and may even utilize the urea present in sweat as a nutrient (9). Sebaceous glands secrete lipid-rich sebum, a hydrophobic coating that protects and lubricates hair and skin.

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Although sebum generally serves as an antibacterial coating, *Propionibacterium acnes* hydrolyzes triglycerides present in sebum, releases free fatty acids that promote bacterial adherence, and then colonizes sebaceous units (10). Many *Malassezia* and *Corynebacterium* species do not produce their own lipids and must obtain them from their environment, which makes them well-suited to reside on skin whose most abundant resource is the lipid-rich content of sebum and skin stratum corneum.

The gut microbiota eventually converge toward an adultlike profile during the first years of life with dramatic transient shifts, presumably when a new microbe is ingested or other normal developmental processes (11, 12). For the skin, one might imagine shifts associated with the exploration of new environments through crawling, walking, and increased socialization. Examination of a birth cohort's skin microbial succession awaits further study. Major shifts are occurring during the first few years of human life, which is also the time when the immune system is maturing and being educated. Gut communities are perturbed by antibiotics, after which the individual may return to their previous state or a "new normal" (13, 14). Skin bacterial communities, however, go through a major shift with sexual maturation and the transition through puberty (Table 1). The skin microbiome of young children and adolescent/postadolescent individuals clustered into two distinct groups. *Streptococcus*, *Betaproteobacteria*, and *Gamma-proteobacteria* dominated the microbial commu-

nities of children (15). In contrast, postadolescent young adults had few to none of these taxa; their microbiomes were dominated instead by lipophilic bacteria, including *Propionibacterium* and *Corynebacterium*. Subsets within the larger immune system of skin are functionally distinct in younger individuals and may permit the colonization and growth of a wider range of bacteria, consistent with the higher community-wide diversity observed in younger children.

Very recent work has moved beyond amplicon-based studies to direct sequencing of all microbial DNA (shotgun metagenomics) to analyze more fully the functional and taxonomic landscape of the human skin microbiome as shaped by the local biogeography (16). This inclusive, relational analysis of the bacterial, fungal, and viral communities showed not only site specificity but also unique individual signatures. Similar to results from amplicon studies, shotgun metagenomics confirmed that microbial communities were shaped primarily by the microenvironment in which differential abundance of taxa such as *P. acnes*, commensal staphylococci, and *Corynebacterium* contributed most significantly to variation both between and within individuals. However, with more genomic information, relationships between different microbial communities were apparent. For example, Fungi, primarily *Malassezia*, represented a small fraction of the community, except near the ears and forehead, which had a higher fungal presence. The feet had low fungal relative abundance (<1%) despite high diversity observed in amplicon-based studies (7) (Fig. 1).

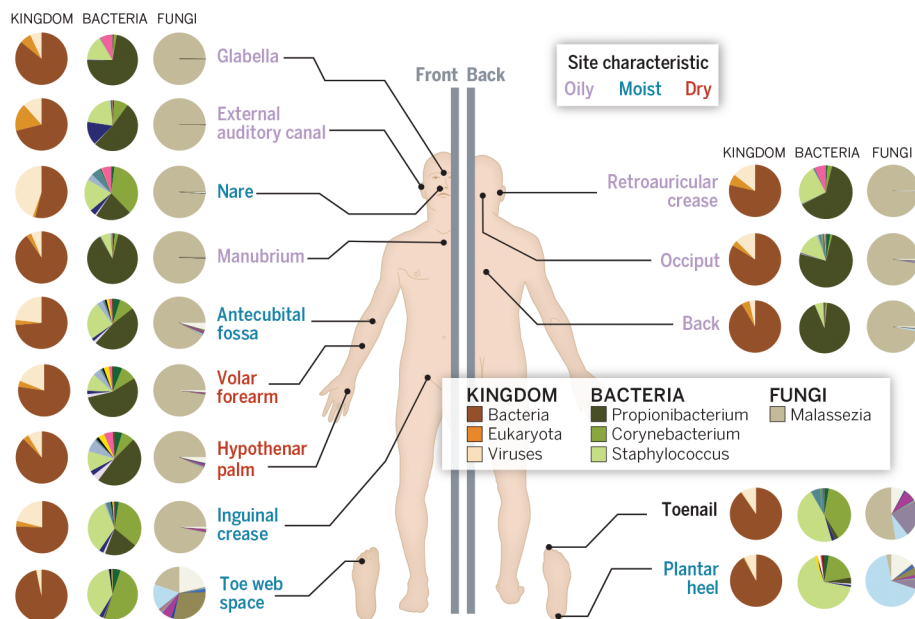
Shotgun metagenomic sequencing now empowers studies of interkingdom interactions (e.g., bacterial-fungal) to explore how these relationships exacerbate disease severity or facilitate a transition between opportunism and pathogenicity (17). Moreover, shotgun metagenomic sequencing demonstrates the extensive strain-level diversity for dominant skin bacterial species, suggesting that both the individual and the microenvironment differentially shape subspecies variation. While *P. acnes* strains were more individual-specific, *S. epidermidis* strains were significantly more site-specific with diminished interindividual variation. Strains of species may vary dramatically in their genome content, their ability to perform critical microbial functions, and their relationship with the immune system. For example, the variable component of the genome of *S. epidermidis* was enriched in genes encoding functions such as repair, transcriptional regulators, and defense mechanisms, all gene pools that one could imagine impact intermicrobial and microbial-host interactions (18).

With increasing concerns of antibiotic-resistant microorganisms, shotgun metagenomics also empowers an exploration of the reservoir of antibiotic resistance genes in the skin. Although skin is physically compartmentalized from other body sites, cross-inoculation remains a risk factor. For example, the nares can harbor methicillin-resistant *Staphylococcus aureus* (MRSA), which causes skin and soft-tissue infections (19). Antibiotic resistance potential is host- and site-specific, such as multi-antimicrobial extrusion efflux pump genes found only on specific healthy individuals, whereas lincosamide resistance genes were found across multiple individuals, specifically on the three foot sites examined (16). While resistance activity may differ in vivo, these studies point to the pervasive antimicrobial resistance potential encoded in healthy humans.

The extent to which the human host benefits from resident microbes remains under investigation. For example, the commensal skin bacterium *S. epidermidis* was shown to inhibit both nares colonization and biofilm formation by *S. aureus*. A subset of *S. epidermidis* expresses the *Esp* gene, which can synergize with a human-expressed AMP to interfere with *S. aureus* colonization (20). Meanwhile, MRSA colonization may have been enhanced when the now dominant USA300 strain acquired the arginine catabolic mobile element horizontally from *S. epidermidis* (21). Although better described for gut microbiota, skin microbiota are likely to compete for resources with pathogenic microbes for defined metabolites in a process referred to as colonization resistance (Table 1) (22–24). Commensals can also promote the establishment of an environment hostile to pathogen establishment by affecting the local pH (25).

### Skin microbiota–immunity dialog

The skin is equipped with a highly sophisticated system of immune surveillance that results from the combined action of a rich network of epithelial



**Fig. 1. Skin shotgun metagenomics defines relative abundance of viral, bacterial, and fungal components of the microbial community.** Sites represent three microenvironments: sebaceous (blue), dry (red), and moist (green). Toenail (black) is a site that does not fall under these major microenvironments and is treated separately. Pie charts represent consensus relative abundance of the different categories kingdom, bacteria, and fungi. For bacteria and fungi, major taxa colors are identified in the legend. Relative proportion of minor taxa are colored to represent relative proportion.

cells, lymphocytes, and antigen-presenting cells that populate the epidermis and the dermis (26). When operating optimally, the skin immune system interweaves the innate and adaptive arms of immunity in a dialogue that selects, calibrates, and terminates responses in the most appropriate manner. One of these fundamental processes involves tissue repair, a response that can be controlled by defined components of the skin microbiota. Acute skin damage releases ligands that activate keratinocytes and trigger the release of inflammatory mediators (27). In these settings, a defined product of *S. epidermidis*, lipoteichoic acid, can mitigate inflammation and promote wound healing through its capacity to bind to the innate immune receptor, Toll-like receptor (TLR) 2 (27).

In contrast to the known role of the gut microbiota in the control of the development of gut-associated lymphoid structures, skin commensals are not required for the seeding of immune cells and overall organization of the tissue (Table 1) (28, 29). However, skin-resident microbes do control the expression of various innate immune factors, including AMPs (9). Epithelial

cell AMPs belong to multiple protein families, which in the skin are dominated by cathelicidins and  $\beta$ -defensins (9). These molecules can rapidly kill or inactivate a diverse range of skin pathogens, including Gram-negative and Gram-positive bacteria, fungi, viruses, and parasites (30). Whereas some of these molecules are constitutively expressed, the expression of others is controlled by defined members of the microbiota such as *Propionibacterium* species (31, 32). How AMPs, and more particularly the ones induced by the microbiota, shape microbial communities remains unclear, but this dialogue is likely to play a fundamental role in the skin microbial ecology.

The skin microbiota also promotes the expression of other potent and highly conserved pathways of host defense. For instances, skin-resident microbes can increase expression of components of the complement system. This system is composed of a large number of proteins that react with one another to opsonize pathogens and induce inflammatory responses that promote clearance of pathogens. In mice raised in the absence of live microbes (germ-

free), impaired expression of the complement component C5aR results in decreased expression of antimicrobial peptides and proinflammatory factors, alterations that are associated with dysbiosis of skin-resident microbes (33). The skin microbiota also controls the level of expression of interleukin-1 (IL-1), a cytokine involved in the initiation and amplification of immune responses (28). Of note, AMPs, the complement system, and IL-1 all represent ancient arms of the innate immune system, suggesting that these pathways may have arisen as early mediators of host skin-commensal interaction.

### Control of adaptive immunity by skin commensals

A downstream consequence of the effect of the skin microbiota on innate immunity is enhanced activation of lymphocytes both at steady state and during infection and an overall increase of adaptive immunity (28). As such, the skin microbiota acts as an endogenous adjuvant of the skin immune system. Skin commensals modulate the function of local T cells through their capacity to tune the local innate immune milieu and in particular IL-1 production (28). This action of skin commensals results in increased potential for the production of cytokines involved in both host defense and inflammatory diseases such as IL-17A and interferon- $\gamma$  (IFN- $\gamma$ ) by dermal T cells. The skin flora controls immune homeostasis and responses to infection in an autonomous manner and independently of the gut flora (28), suggesting that under steady-state conditions or in the context of local inflammation, each barrier site is likely to be controlled independently of other commensal niches. Furthermore, commensals may have evolved to specifically control the immunological network associated with their ecological niches. 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 inflammatory responses.

Because of the extraordinary pressure exerted by the microbiota on the immune system, the highest number of immune cells in the body is at sites colonized by commensals. In particular, the healthy human skin harbors ~20 billion effector lymphocytes, making it one of the largest reservoirs of memory T cells in the body (34). We speculate that a large fraction of tissue-resident lymphocytes may recognize skin microbiota-derived antigens. Indeed, recent observations reveal that, in the gastrointestinal tract, a large fraction of T helper 17 (T<sub>H</sub>17) cells are specific for commensals (35–37). In an analogous manner, IL-17 produced by skin commensal-specific T cells could reinforce skin immunity through its action on keratinocytes' antimicrobial function. In support of this, mice lacking adaptive immunity fail to efficiently contain their skin microbiota, leading to microbial dissemination to the regional lymph node (38). Collectively, these results reveal that through their capacity to promote various aspects of innate and adaptive

**Table 1. Comparison of skin and gut microbial communities and effect on the immune system.**

	Gut	Skin
Density	10 <sup>12</sup> /g of intestinal matter	10 <sup>6</sup> /cm <sup>2</sup>
Diversity	Bacteria dominant 7–8 phyla of bacteria ~100 species/individual Fungi and virus (non-phage) rare	Bacteria dominant 7–8 phyla of bacteria ~40 species/individual Up to 10% fungi and 40% viral/phage colonization
Niche	Mucus Epithelial surfaces Crypts	Stratum corneum (surface) Appendages (sebaceous glands, hair follicle, sweat glands)
Community establishment	Early life	Early life Puberty
Nutrients	Rich Dietary (sugars, proteins, lipids) Bacterial metabolic products Mucus	Poor Sweat Sebum Stratum corneum (peptides, lipids)
Effect on the immune system	Secondary lymphoid structure development Adjuvant effect (innate immune activation) Regulation Functional Tuning Colonization resistance	Functional tuning Colonization resistance
Range of the effect	Local Systemic (e.g. arteries, bone marrow)	Local ?



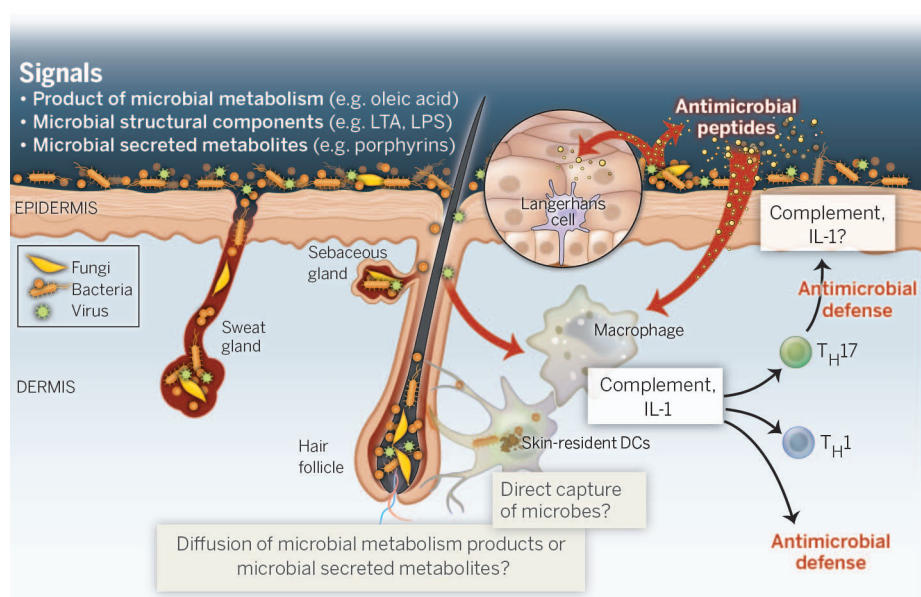
responses, the skin microbiota not only limit pathogenic microbial invasion but also reinforce its own stability and containment.

In the gastrointestinal tract, defined microbes and products of microbial metabolism can promote immune homeostasis by controlling the induction, function, and homeostasis of the regulatory immune network (29). Albeit less documented in the skin, a few examples suggest that this may be also true for environmental microbiota that can interface with the skin. For instance, epicutaneous exposure to a lysate of *Vitreoscilla filiformis*, a Gram-negative bacterium originally found in thermal spa water, can promote the induction of tissue-resident regulatory T cells and inhibit T cell proliferation during cutaneous inflammation in mice (39, 40). Thus, the immune landscape of the skin may not be under the sole control of its resident microbes—transient partners may also play an important role in setting the skin threshold of activation.

How skin commensal products or antigens are recognized by the immune system and the cellular mediators involved in this dialogue remain largely unknown. We could speculate that analogous to the gastrointestinal tract (41), tissue-resident dendritic cells, surrounding the rich commensal communities associated with appendages such as the hair follicle, may be able to directly capture microbes or microbial products. Further, microbial secreted metabolites or their downstream products may be able to diffuse from these niches and be captured or sensed by neighboring cells (Fig. 2).

### Immune regulation of microbiota in human primary immunodeficiency patients

Although landmark studies have shown that microbiota activate and educate host immunity, how the immune system shapes microbial communities and contributes to disease is less-well characterized. An open question is the extent to which symbiotic bacteria are selected for mutualistic interactions with the human host based on the limited ecological niches of human tissues versus a more active modulation of microbial communities by the immune system. Studying primary immunodeficiency (PID) patients provides a unique perspective on the degree to which altered immunity may influence the human microbiome and how, in turn, microbiota may interact with the host to develop disease. Skin of PID patients displayed increased ecological permissiveness with decreased site specificity and temporal stability, and colonization with microbial species not observed in controls, such as *Clostridium* species and *Serratia marcescens* (42). The overarching theme of increased ecological permissiveness in PID skin was counterbalanced by the maintenance of a phylum barrier in which colonization remained restricted to the typical human-associated phyla. Extending these studies into mouse models of immune deficiency could begin to tease apart the functional role of immunity in shaping microbial communities



**Fig. 2. Cross-talk between the microbiota and the skin immune system.** Microorganisms (virus, fungi, bacteria) cover the skin surface and reside in appendages (hair follicle, sebaceous glands, and sweat glands). These microbes can directly produce antimicrobial peptides and control the production of antimicrobial peptides by keratinocytes, as well as the production of cardinal mediators of immunity such as complement and IL-1. These molecules can directly or indirectly enhance skin immunity by promoting cytokine production, enhancing cell microbicidal function, and promoting the recruitment of effector cells. Enhanced production of IL-17 by the microbiota may promote keratinocyte effector function against invading microbes. Skin-resident microbes may exert their function via the release of defined products or metabolites and/or could be directly captured by skin-resident dendritic cells (DCs).

under homeostatic conditions and the stress of infection.

### Potential association of the microbiota with skin inflammatory disorders

Common skin disorders such as psoriasis, atopic dermatitis, and acne have all been associated with dysbiosis of the skin flora (43). While understanding the initiating event is crucial to early disease diagnosis and molecular interventions, breaking the escalating danger signals that cycle between skin microbial, structural, and immunologic cells can also provide clinical benefit. Atopic dermatitis (AD; commonly known as eczema) has long been associated with *S. aureus* skin colonization or infection and is typically managed with regimens that include antimicrobial therapies. However, the role of microbial communities in the pathogenesis of AD is incompletely characterized. A longitudinal study of microbial diversity of AD showed that the proportion of *Staphylococcus* and in particular *S. aureus* was greater during disease flares (episodic exacerbation) and correlated with worsened disease severity (44). However, the clinical effectiveness of AD treatments does not rely on the total elimination of *S. aureus*, suggesting that therapeutic modalities may act to recalibrate the diversity of the skin microbiome. AD patients using no treatment during flares ex-

hibited markedly reduced bacterial diversity on affected sites, leading to the hypothesis that lesional skin requires continued intensive treatment to sufficiently reduce the inflammatory response. Increases in diversity associated with AD treatments may be due to therapies that preferentially kill *S. aureus*, promote growth of microbes that control *S. aureus* predominance, or reduce bacterial biomass, followed by rapid repopulation with a diverse community.

The prevalence of AD has more than doubled in industrialized countries with no clear cause (45, 46) and at a high cost (47). More than half of children with moderate to severe AD develop hay fever and/or asthma, atopic disorders associated with substantial morbidity and rare mortality, a phenomena called the “atopic march.” Mutations in *FLG*, the gene encoding the skin barrier protein filaggrin, are associated with AD, particularly in patients who subsequently develop asthma or hay fever (48). Since *FLG* is not expressed in nasal or lung epithelia, this genetic association suggests that skin microbial exposure sets the stage for other atopic disorders later in life. A question of active investigation is whether, in the context of inflammation, the skin microbiota could act distally and prime the subsequent immune response observed in lungs and nasal passages. Such an effect could be mediated by diffusion of microbial products or metabolites or through direct means, whereby

skin microbes may be seeding lung and nasal epithelium. These types of distal effects of the gut microbial communities on atherosclerosis and hematopoiesis have been some of the most intriguing recent findings in the field (49, 50).

Lesional psoriasis is a chronic T cell-mediated skin disease affecting ~1 to 3% of the U.S. and European populations (51). Notably, lesional skin from plaque psoriatic patients is more diverse, enriched in *Streptococcus* spp. with reduced *P. acnes* (52). Although most studies have focused on the common psoriasis vulgaris, only the subtype of guttate psoriasis has been associated with a microbial streptococcal infections (53).

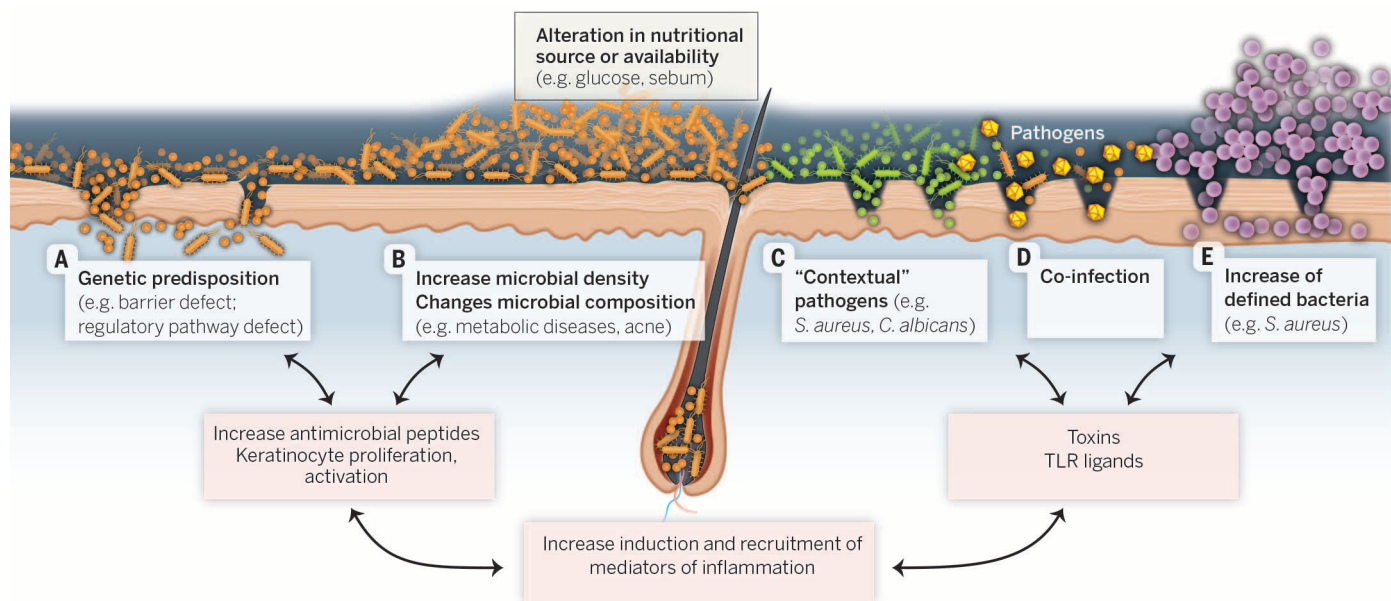
The classic feature of teenage acne vulgaris is sebaceous hyperplasia and lipid release into the follicular lumen, which leads to a clogged pore (54). This process results in follicular wall rupture, triggering neutrophil influx and pustule formation, a process that is further amplified by the capacity of *P. acnes* to activate keratinocytes (55). However, the confounding issue of assigning a causative role to *P. acnes* in disease initiation is that *P. acnes* predominates on both normal and disease-associated skin (56, 57). Genomic comparison of *P. acnes* strains explored whether there might be functional differences of *P. acnes* in functioning as a commensal in healthy skin and as a pathogen in diseases (57, 58). However, elucidation will require longitudinal studies to track adolescents transitioning through puberty and functional studies performed in animal models.

As previously discussed, the skin microbiota can promote responses (IL-1, IL-17A, comple-

ment) that play an important role in host defense but also contribute to the etiologies of various inflammatory disorders. For instance, the IL-1 pathway that is promoted by skin-resident commensals is also linked to a multitude of chronic inflammatory disorders, including psoriasis and other cutaneous disorders (59). Psoriatic plaques are also characterized by marked infiltration of activated T cells, producing inflammatory cytokines and in particular cytokines of the IL-17 family such as IL-17A that have been recently associated with the pathogenesis of the disease (60, 61). Some of the pathogenic role of IL-17A results from its capacity to amplify various inflammatory pathways in the skin, leading to keratinocyte hyperproliferation and lesion formation in psoriasis (62, 63). Additionally, in the context of inflammation, changes in barrier permeability and enhanced contact with commensals could further promote the local inflammatory process. Given the capacity of the microbiota to control both innate and adaptive immunity, resident microbes are likely primary drivers and amplifiers of skin pathologies (Fig. 3).

Whether alterations of the microbial composition described in various disease states are the results of inflammation rather than the cause remains difficult to evaluate. Furthermore, an important point to consider when exploring the potential role of the microbiota in inflammation is that pathogenicity is, in most cases, a contextual state. Indeed, the capacity of a given microbe to trigger or promote disease is highly dependent on the state of activation of the host,

the host's genetic predisposition, the localization of the particular microbe, or the coexistence of other microbial members (64) (Fig. 3). Thus, the culprit microbe may remain elusive in most cases. Nonetheless, we could envision several mechanisms by which microbes or microbial communities could contribute to the initiation or amplification of skin pathologies (Fig. 3). For instance, local expansion of defined commensals with enhanced inflammatory potential could trigger disease states in susceptible individuals. For example, colonization of the skin with *S. aureus* triggers local allergic responses by releasing  $\delta$ -toxin, which directly induces the degranulation of dermal mast cells and in turn promotes both innate and adaptive type 2 immune responses (65). In addition to the relative enrichment of defined microbes, increase in microbial load itself may be sufficient to trigger aberrant production of AMPs and keratinocyte proliferation, or as previously discussed, promote the local production of inflammatory mediators. Increased bacterial density can be observed in the context of chronic diabetic wounds in a murine model of type 2 diabetes where nonhealing wounds are associated with increased abundance of *Staphylococcus* spp. (66). Thus, in the context of defined metabolic diseases, altered nutrient availability and sustained inflammatory states could contribute to the emergence and dominance of bacteria that either qualitatively or quantitatively alter the local inflammatory milieu and promote local pathologies. All of these effects could be amplified in the context of altered barrier integrity mediated



**Fig. 3. Potential mechanisms by which the skin microbiota may initiate or amplify skin disorders.** (A) Enhanced sensing or translocation of the microbiota can be mediated by host genetic predispositions (e.g., filaggrin, IL-23, IL-10 mutation). (B) Metabolic diseases (e.g., diabetes) associated with alteration of nutrients could lead to enhanced microbial density and dysbiosis. (C) In the context of barrier breach, normal constituents of the microbiota could act as pathogens. (D) In the context

of infection, skin microbes may contribute to inflammation and tissue damage. (E) Microbes with inflammatory potential may dominate, an event that can also be promoted by antibiotic treatment or environmental alterations. In most settings, combinations of the various scenarios are likely required to trigger pathologies. In turn, enhanced inflammation can alter microbial communities, a process that can further amplify tissue damage.

by inflammation and/or genetic predisposition (Fig. 3).

### Future therapeutic potential to modulate skin immunologic and microbial constituency

Although the relationships between microbiota, host, and disease are complex, investigators have long relied upon Koch's postulates to impute causation between microorganism and disease. However, the requirement that disease-causing microorganisms uniformly recapitulate disease in healthy individuals was compromised when Koch discovered asymptomatic carriers of *Vibrio cholera* and *Salmonella typhi*, revealing the important distinction between apparent colonization and infection (67). Potential pathogenicity of bacteria that colonize humans is likely influenced by host immunologic factors and the native microbial community. This paradigm requires that diseases with microbial involvement must be investigated within the context of their microbial community, host factors, and immunity.

Longitudinal plasticity of the microbial and immunologic communities is one of the great complications of this research, but also one of the greatest potential benefits for designing probiotic or prebiotic therapies. Studies of metabolic capacity, pathogenicity islands, and virulence genes in disease states, with our catalog from healthy skin, will uncover biomarkers associated with transmission, recurrence, and severity of disease. Finally, characterization and tracking of surprisingly pervasive antibiotic resistance elements will remain clinically relevant, as skin sites can serve as a taxonomic and genetic reservoir for pathogens. We envision a new therapeutic landscape leveraging unique metagenomic profiles with tailored clinical interventions that reshape our microbial communities. Notably, because of the scarcity of nutrients available for the skin microbiota, the opportunity for prebiotic-based therapy in this tissue may be unmatched. In these arid conditions, subtle alterations in defined nutrient availability may have a dramatic impact on the skin microbiota composition and when rationally designed could provide a powerful advantage for microbes endowed with regulatory or protective properties. While humans typically use creams to moisturize their skin and improve barrier function, this product is also fertilizing the microbial garden. As such, topical products could be designed to specifically shape microbial communities.

Finally, the capacity of skin-resident and potentially transient partners to modulate local immunity could be harnessed. One major impediment in the development of vaccine adjuvants for clinical use is associated unacceptable amounts of inflammation. As previously discussed, the skin microbiota is likely to have coevolved with its host to finely tune the unique requirements of this tissue. Consequently, these microbes may release or engage highly adapted tissue-specific adjuvants. A search for these products and mechanisms associated

with the stimulatory effect of the microbiota may allow development of a novel class of adjuvants capable of boosting local immunity while preserving tissue homeostasis. Further, as our arsenal of antimicrobial weapons falls short in the battle against multidrug-resistant pathogens, perhaps therapeutics derived from microorganisms themselves offer promise as viable alternatives.

### Conclusions

While we can now imagine how to characterize the language encoded by the representative cell types, how is context encoded into the language spoken by the microbes and immune cells? A classic feature of dermatologic disorders of microbial etiology is their manifestation at stereotypical sites and at different times of human development such as AD in the bend of the elbow during early childhood, acne on forehead and back during puberty, and psoriasis on the outer elbow with onset in the second or third decade of life. While long appreciated that the rolls of skin of a baby's neck are quite different from the oily forehead of a teenager, only the last few years of research have begun to tease out the specificity of the microbial and immunologic cells that inhabit these very specific skin niches.

Language differs from communication in that language is deeply entrenched in human culture. Humans acquire language through social interaction in early childhood, and children generally speak fluently when they are about 3 years old. However, specificity and fine-tuning of language continue throughout life with specialization. By analogy, microbial communities acquired at birth are very dynamic for early years of life, and immune cells mature during postnatal development. Just as children begin to appreciate the context of their words on the playground versus the dinner table, immune-microbe interactions are context dependent. In addition to its strictly communicative uses, language also has many social and cultural uses, such as signifying group identity, and social stratification. Analogously, studies are just beginning to explore how cohabitation or early microbial exposures may link humans across space and time.

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