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Early development of the skin microbiome: Therapeutic opportunities

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Abstract

As human skin hosts a diverse microbiota in health and disease, there is an emerging consensus that dysregulated interactions between host and microbiome may contribute to chronic inflammatory disease of the skin. Neonatal skin is a unique habitat, structurally similar to the adult but with a different profile of metabolic substrates, environmental stressors, and immune activity. The surface is colonized within moments of birth with a bias toward maternal strains. Initial colonists are outcompeted as environmental exposures increase and host skin matures. Nonetheless, early life microbial acquisitions may have long lasting effects on health through modulation of host immunity and competitive interactions between bacteria. Microbial ecology and its influence on health has been of interest to dermatologists for more than 50 years, and an explosion of recent interest in the microbiome has prompted ongoing investigations of several microbial therapeutics for dermatological disease. In this review, we consider how recent insight into the host and microbial factors driving development of the skin microbiome in early life offers new opportunities for therapeutic intervention.

1. Introduction

The complex microbial community that inhabits barrier tissues, called the microbiome, is essential to understanding human health. Resident microbes support many functions of the human body, including metabolism (1), synthesis of vitamins (2), protection against pathogen invasion (3), and immune development (4,5). “Germ-free” gnotobiotic animals, born of sterile parents in a permanently sterile environment, demonstrate numerous physiological derangements and disease susceptibilities not seen in genetically identical animals enveloped by their microbiota (6–8). Thus, microbes found on the healthy host include commensals and symbiotes, colonization with which is mutually beneficial.

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With the follicular surface included, skin is the largest epithelial surface of the human body for interaction with microbes (9). This surface is a dynamic interface rather than an impermeable barrier, as the microbiome extends into the dermis and dermal adipose (10). The skin microbiome is characterized by diversity, skin site specificity, and stability. Human skin is a unique habitat with a microbiota distinct from other primates', showing a greater preponderance of skin specialists and lower diversity overall (11). Nonetheless, healthy skin hosts a diverse microbial community with over 200 genera from 19 different phyla (12–14). Different parts of the body display markedly different microbial communities on the skin (15). Shared features of the skin microbiome between sites reflect shared skin physiology (13,16). For example, *Cutibacterium acnes* (formerly *Propionibacterium acnes*) is a frequent colonist of sebaceous skin, while the harsher environment of dry skin is dominated by staphylococci and streptococci (13,16). Much like a fingerprint, the adult skin microbiome is highly personalized and stable in strain composition over years (16,17).

Cohabitation with trillions of microorganisms is not without risk. Breakdown of the symbiotic relationship has been linked to chronic diseases of the skin, including atopic dermatitis (18) and psoriasis (19), consistent with a role for microbiota in chronic diseases of other organs, such as the lung (20) and the gut (21–25). An enduring question is how and why symbiosis with microbes either fails to develop or devolves into chronic disease.

Microbiologists have long appreciated that the presence of bacteria alone is insufficient to predict illness (26,27). Microscopic observation of abundant colonies of bacteria in skin abscesses (27), acne comedones (28), and eczematous dermatoses (29) led early authors to propose that disease followed from excessive bacterial proliferation. Sabouraud proposed that bacterial overgrowth was prevented in health by constant epithelial desquamation (30), while later authors described the skin as an "acid mantle" inhospitable to bacterial growth due to low pH (31), osmotic stress (32), and desiccation (33). However, by the 1970s, improved culture methods had revealed that acne folliculitis, and its response to treatment, had no association with bacterial burden (34–36). This finding led to the hypothesis that host maturation induced native *C. acnes* toward an inflammatory phenotype, with colonizing strains showing variable propensity for inflammatory conversion (37). A key insight of this hypothesis is that genetic differences between different strains of the same species of bacterium can have drastically different and long-lasting effects on the host.

Interest in the strain specificity of disease has been renewed by increasingly intractable resistance to antimicrobial therapy and the technical ability to examine composition of the whole microbiome at strain-level resolution using metagenomics (38). In the last decade, culture-independent surveys of the indoor environment have revealed myriad commensal and pathogenic strains absent in individual microbiota despite persistent exposure (39–44). These observations suggest that understanding the developmental ecology of the microbiome, such as the host and microbial factors influencing strain acquisition from the environment, may add considerable insight into chronic skin diseases associated with dysbiosis. Therefore, the mechanisms by which infants acquire and retain specific microbes is of great interest. This review will focus on skin microbiome composition in early life and the host and microbial mechanisms governing its strain-specific development.

2. Skin microbiome assembly in early life

The order and timing of colonization events determines how strains subsequently interact with one another, an effect known as priority (45,46). Indeed, in mouse models of enteric disease, prior colonization of a naïve host with a benign strain can limit subsequent engraftment of a pathogenic strain of the same species and prevent mucosal injury (47). Thus, an infant's first microbial encounters may have long-term consequences for microbiome composition and skin health.

The sterility of newborns at birth has been questioned. Several groups have reported bacterial DNA in the placenta, amnion and fetus (48–53), including viable bacteria visualized and cultured from fetal mice during the second trimester (53), while others have failed to find evidence of microbial colonization before birth except in cases of clinically significant infection (54,55). Some authors have proposed that maternal microbiota are selectively transported to the placenta in order to colonize the fetus (48,49). Indeed, in a recent report, human infants were found to have oral and meconium microbiota at the time of Caesarean delivery predicted to originate from the placenta (53).

The most extensive microbial colonization begins at birth. Immediately postpartum, the microbiota is homogeneously distributed across the human body regardless of delivery method or gestational age (56–59). Culture-dependent surveys of the skin within five minutes of vaginal delivery showed that culturable microbiota were overwhelmingly staphylococci (phylum Firmicutes) at every body site, with a minority of diptheroids (phylum Actinobacteria, including cutibacteria and corynebacteria) (59). Neonates born by Caesarean section had no detectable bacteria (59), consistent with a sterile uterine environment. More recent culture-independent surveys of newborn infants showed vaginally delivered neonates were preferentially colonized by vaginal Prevotella and Lactobacillus, while the skin of neonates born by Caesarean section was found to have a diverse community of cutibacteria, corynebacteria, and micrococcae presumably contaminating the operative field from maternal skin (57,60).

The infant's first bath may alter the process of microbiome assembly. The newborn infant is coated with vernix caseosa, an unevenly distributed waxy layer derived from sebaceous glands with a unique profile of lipids, ceramides, and antimicrobial peptides (61). Bathing in the first 24 hours of life is known to disrupt this layer and is no longer recommended due to increased risk of hypothermia (62). Culture-dependent studies have shown that the first bath is also associated with immediate changes in the composition of the microbiome that are not yet fully characterized (63,64). These effects may depend on gestational age, as the distribution of vernix caseosa is different between preterm, term, and post-term infants (65). Moreover, preterm infants admitted to the NICU are more likely to be washed with antimicrobial soap (66).

The long-term consequences of these initial perturbations are not known. The early life microbiome undergoes frequent strain replacements over time (67–69). Thus, the association between birth environment and microbiome fades within weeks to months (56,70,71). In the absence of perturbation, a significant fraction of the skin microbiota of hospitalized

infants at any given time originates from their hospital rooms (72). Bacterial communities at different skin sites begin to diverge into distinct functional communities like those found in the adult as soon as two days after delivery (73). Six weeks after delivery, the skin microbiota of mother and infant are more similar than their microbiota at other body sites, like the gut and oropharynx, which diverge more rapidly (56).

The similarity observed between maternal and infant microbiota may be due to vertical transmission of maternal strains. Maternal microbiota are crucial for developing the microbiome of the skin, as of the gut (74–76). Postnatal vertical transmission of the mother's bacteria may provide early colonists that can reside in the child's gastrointestinal tract and influence its composition for many years while it develops into a distinct community (77). Indeed, maternal strains are more likely to persist in the infant gut than non-maternally acquired strains due to shared environment and common genetic and immunological factors (78,79). This may explain why probiotic supplementation during pregnancy is associated with lower incidence of childhood atopic dermatitis (80), a disease with significant microbial involvement (18). Vertical transmission of strains on the skin has not yet been directly demonstrated, however, and any mechanistic basis for mother-infant strain specificity remains unclear.

Identification of environmental reservoirs of bacteria, their contribution to skin microbiota, and the mechanisms of transmission in early life is currently underway. Initial colonists are those available in the immediate environment, such as the NICU or hospital room (72,81). As a result, seeding of the birthing room with maternal microbiota may be an important determinant of initial bacterial exposure, as the microbiota found throughout an indoor space can match their occupants within hours (41,82). The similarity between mother and infant microbiota decreases over the first year of life (83), suggesting successful invasion of environmental strains. These strains may be dispersed from the skin of close contacts, as has been shown for gut microbiota (46). A significant fraction of bacterial transmission may be indirect. A large study of pediatric patients around the age of 3, their homes, and their household contacts found that frequent handwashing could prevent household colonization of new *S. aureus* strains, while strain transmission within households was associated with high household burden of the strain, as well sharing bedrooms, cosmetics, and bathroom towels (44). This work suggests that microbial transmission can be controlled by modifiable behaviors.

3. Cutaneous determinants of microbial ecology

The restricted composition of the skin microbiome was first attributed to an active "degerming" process of normal skin (30). Growing appreciation of bacterial physiology led to the hypothesis that skin microbiota was constrained by environmental limitations. The epidermis is structurally mature by 34 weeks gestation (84). However, the cutaneous environment of early life differs from the adult by having higher water content, higher pH, fewer lipids, and more rapid epidermal turnover (85). Infant skin has higher water content than the adult within 3 months (86), which change corresponds to eccrine sweat gland maturation (87). This may be significant for microbial colonization, as surface bacteria in the adult experience severe water restriction (33). Humans produce much more sebum

than other mammals, which in part explains the greater abundance of *C. acnes* (88). Secretion is reduced in early life (89), which may explain why children have proportionally fewer corynebacteria and cutibacteria (90). Desquamation, originally proposed as the skin's principal "degerming" mechanism (30), is elevated in infants, as sebum production is inversely related to epidermal turnover (85,86). Melanin production also changes with age due to sun exposure (91). While melanin utilization is widespread among bacteria (92), its role in skin ecology is unknown.

Recent attention has turned to host selection of bacteria through the targeted action of the immune system, including innate cells like keratinocytes. In healthy skin, keratinocytes are the primary source of antimicrobial peptides (AMPs) (93), each AMP with its own antimicrobial profile, including cathelicidins, beta-defensins, and S100A peptides (94). AMP accumulation in epidermal and dermal compartments restricts tissue invasion (95) and peaks in early life. Keratinocytes express microbial pattern recognition receptors and upregulate AMP secretion in response to microbial ligands (96), thus balancing microbial ligand density with AMP secretion. Surprisingly, a population of AMP-secreting keratinocytes were recently shown in the mouse to express the antigen presentation complex MHC class II in response to the barrier-protective cytokine IL-22 (97). These specialized cells are physically associated with cutaneous CD4+ T cells that express IFN-γ after stimulation with commensal antigens (97). IFN-γ signaling induced by commensal microbiota in the murine gut has been shown to inhibit colonization with a pathogenic *Salmonella* strain (98). Similarly, recent work shows that IL-4Rα blockade, which potentiates IFN-γ signaling, is associated with reduced *S. aureus* colonization and increased microbial diversity in adult atopic patients (99), which may in part explain its efficacy in ameliorating the symptoms of atopic dermatitis (100). Whether tonic IFN-γ activity modifies skin ecology to select certain microbiota over others, and whether this selection protects the host or predisposes to disease, remains to be shown.

Skin is also home to innate lymphoid cells (ILCs) and lymphocytes with innate-like functions, including γδ T cells, NKT cells, and mucosal-associated invariant T (MAIT) cells. Skin-resident ILCs, recruited to pilosebaceous units via CCR6, have been described to nurture Gram-positive commensalism in the mouse by expressing TNF receptor ligands that downregulate Notch signaling in sebocytes and restrain antimicrobial fatty acid secretion (101). Interestingly, ILCs in different tissue layers express significantly different genetic programs, indicating selective compartmentalization of immune functions (101). Most human epidermal T cells are γδ T cells (102). These cells may respond to microbial cues (103) and are thought to be important in regulating IGF-1-induced keratinocyte turnover (104,105). NKT cells alter the intestinal microbiome in mouse models (106). In the skin, the NKT cell population expresses a pro-inflammatory phenotype (107) that may, for example, contribute to alopecia areata (108). MAIT cells depend on riboflavin derivatives generated by skin microbiota and do not develop in germ-free animals (109). They have been described to control bacterial translocation (109,110) and direct tissue repair (111–113). As MAIT cell development in mice is restricted to early life (111), dysregulated immune-microbe crosstalk during childhood may predispose an individual to skin dysbiosis throughout life.

Early life is also critical for the development of adaptive lymphocytes. Anti-inflammatory regulatory T cells (Tregs) occur at higher density in neonatal skin of humans and mice, which biases the neonate towards an anti-inflammatory response (114,115). For example, neonatal germ-free mice exposed to *S. epidermidis* develop antigen-specific Tregs that dampen inflammation against this benign commensal later in life (115). Colonization of hair follicles, an important niche for coagulase-negative staphylococci such as *S. epidermidis*, stimulates Treg recruitment to the hair follicles via chemokine CCL20 (116). In the gut, Treg recruitment may promote selective bacterial colonization by facilitating B cell class switch to IgA (117). Indeed, *Bacteroides fragilis* promotes mucosal Treg polarization and invites IgA binding to associate intimately with host epithelium and exclude exogenous competitors (118–120). Like the gut microbiome, the skin microbiome is highly stable after infancy (77,121,122). It is tempting to speculate that skin commensals are similarly adapted to direct host immunity for species- or strain-specific tolerance.

4. Mechanisms of microbial competition

Competition between microbiota for the hospitable early life environment may be especially important in structuring the microbiome to favor long-term skin health (123). Medicinal use of antagonism between bacteria has been discussed by every generation of microbiologists since Louis Pasteur in the 19th century (124–126). Several therapeutic approaches have been identified. In the early 20th century, a Danish physician named Schiotz observed that a young patient with *S. aureus* pharyngitis, mistakenly placed in the diphtheria ward, was resistant to acquiring the disease. Schiotz cultured benign staphylococci from a surgical patient, and reported success in protecting *C. diphtheriae* carriers against diphtheria by spraying the staphylococci culture into the throat (127,128). A number of physicians in the United States reported employing this “overriding” therapy for pediatric diphtheria before widespread use of antitoxin superseded the practice (129–132). Variability in engraftment of *S. aureus* and displacement of *C. diphtheriae* was frequently observed but could not be explained (131). Similarly, the variability of exogenously introduced bacteria in successfully colonizing the enteric niche may explain the frequent failure of oral probiotic therapy in randomized trials (133,134). Recent attempts to displace *S. aureus* in atopic dermatitis patients with daily administration of competing strains of streptococci, coagulase-negative staphylococci and the Gram negative *Roseomonas mucosa* have shown efficacy in limited studies (135,136). Successful niche displacement, as measured by durable colonization of the probiotic strain, may significantly enhance the therapeutic effect.

An alternative approach for the pediatric population is to preempt initial pathogen invasion of the cutaneous niche. In the 1960s, a strain of *S. aureus* defined by phage type 80/81 that resisted existing antibiotics became epidemic to hospital nurseries worldwide (137–139). After identifying a benign *S. aureus* strain 502A common in infants that resisted strain 80/81, Henry Shinefield and colleagues showed that prophylactic inoculation of 502A lowered the rate of strain 80/81 engraftment into the neonatal microbiome and decreased the incidence of staphylococcal disease (140–144). The mechanism of antagonism was never defined, however, and 502A proved susceptible to displacement from environmental strains over time (145).

Increasing awareness of the role of dysbiosis in chronic disease has renewed interest in how such niche competition structures the microbiome. An elaborate system of strain competition among Gram negative bacteria has recently been described involving contact-dependent injection into neighboring bacteria of bacteriocidal toxins through the type VI secretion system (T6SS) (146,147). Effectors are classically paired with immunity proteins to prevent self-intoxication; dozens of such pairings, specific to different strains, have been reported (68). The T6SS is a large protein complex that requires significant metabolic commitment to operate (148). Nonetheless, there appears to be strong evolutionary pressure among enteric commensals to accumulate genetic elements that neutralize T6S toxins (149), indicating their central place in structuring the enteric microbial community.

Many Gram positive bacteria of the skin share a similar type VII secretion system (T7SS). *S. aureus* secretes four ESS proteins through the T7SS, which promote persistent infection in murine hosts (150). While one study reported association between *S. aureus* T7S expression and bacterial antagonism (151), efforts to identify antibacterial activity in analogy to T6S have not been successful (152). A T7SS-dependent system of LXG proteins with bacteriocidal properties, expressed together with an antidote against self-intoxication, was recently described in *Streptococcus intermedius* (153). As in the gut, these proteins could mediate single strain stability by preventing cutaneous engraftment of competing strains. However, the prevalence of T7SS and the specificity of effectors among strains is unknown.

The inhibitory effect of *S. aureus* against corynebacteria like *C. diphtheriae* was attributed to an antibiotic peptide isolated in 1947 (130), one of an enormous class of peptides called bacteriocins first identified in E. coli in the 1920s (154). While bacteriocins have been described in all lineages of prokaryotes (155), Gram positive bacteria show bacteriocin-specific regulation and encode dedicated transport machinery that prevents self-intoxication (156). The toxicity of bacteriocins is generally restricted to other Gram positive bacteria (157), with narrow activity often limited to cells of the same genus, species, or strain, although bacteriocins with broad activity have also been described (158).

Colicin from *E. coli* has been used as a model bacteriocin for investigating microbial community assembly for more than 50 years (159–161). Bacteriocins are predicted to be most relevant for physically structured habitats (162,163), and in models of skin biology their efficacy depends on tissue context and structure (164). A recent survey of human skin identified many novel bacteriocins with activity against *C. acnes*, *S. epidermidis*, and *S. aureus* (165). Success has been reported in using specific bacteriocin-secreting strains *S. epidermidis* and *Streptococcus hominis* to reduce *S. aureus* colonization of the skin in adult atopic dermatitis patients (136). Such antagonistic relationships show strain- and microenvironment-specificity. For example, phenol-soluble modulins secreted by a *Staphylococcus capitis* strain E12 were found to selectively inhibit *C. acnes* proliferation on the skin surface of mice and pigs (166), while a bacteriocin produced by *C. acnes* named cutimycin found widely distributed across individuals was associated with exclusion of *S. epidermidis* from human hair follicles (167). Consistent with their importance in microbial ecology of the skin, like T6SS genes in the gut, bacteriocins are often carried by mobile genetic elements, vary in composition between different strains of the same species, and show extensive history of gene transfer (168). How the sum of these diverse competitive

interactions shapes assembly of a durable and long-lasting skin microbiome in early life remains to be understood.

5. Conclusion

The human microbiome is an attractive therapeutic target in chronic disease. Unlike the genome, it is modifiable. Neonates born by Caesarean section and artificially exposed to vaginal microbiota readily accepted maternal microbes (60). However, artificial inoculation with entire microbial communities carries considerable risks (169). Strain replacement is a superior approach where disease-causing strains, or an inappropriate immune reaction to benign strains, can be identified. Advances in metagenomics and gnotobiotic animals have been used to define minimal consortia of healthy bacteria that resist pathogen invasion of the gut (170). In concert with this approach, benign variants of disease-associated bacteria could be genetically engineered for optimum bacterial antagonism such that engraftment on the skin of the engineered strain would preclude acquisition of pathogenic variants encountered in the environment for durable and long term health. Gaps remain in understanding which strains are beneficial to the skin, from where they originate, the immunological determinants of successful engraftment, and the molecular mechanisms by which successful colonists exclude competitors. The effect on the skin microbiome of existing interventions, such as bathing and formula feeding, is also poorly understood. The developing microbiome is dynamic and vulnerable, and microbial exposures must be carefully curated. As understanding improves, however, early life may offer a rich opportunity for strain-level engineering of the microbiome.

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Impact

- Advancement in understanding molecular mechanisms of bacterial competition opens new avenues of investigation into dermatological disease.
- Primary development of the skin microbiome is determined by immunological features of the cutaneous habitat.
- Understanding coordinated microbial and immunological development in the pediatric patient requires a multidisciplinary synthesis of primary literature.