Early development of the skin microbiome: Therapeutic opportunities

Benjamin W. Casterline1,*, Amy S. Paller2
1The University of Chicago Pritzker School of Medicine, Chicago, Illinois.
2Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

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.
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 micrococcace 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.

Acknowledgments

Statement of financial support: BWC is supported by the National Institute of Allergy and Infectious Diseases (5 F30 AI126791).

References

1. Goodman AL, Gordon JI. Our unindicted coconspirators: human metabolism from a microbial perspective. Cell Metab 2010;12:111–6. [PubMed: 20674856]
2. Degnan PH, Taga ME, Goodman AL. Vitamin B12 as a modulator of gut microbial ecology. Cell Metab 2014;20:769–78. [PubMed: 25440056]
3. Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. Nat Rev Immunol 2013;13:790–801. [PubMed: 24096337]
4. Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome and the immune system. Nature 2011;474:327–36. [PubMed: 21677749]
5. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. Nature 2016;535:65–74. [PubMed: 27383981]
6. Belkaid Y, Naik S. Compartmentalized and systemic control of tissue immunity by commensals. Nat Immunol 2013;14:646–53. [PubMed: 23778791]
7. Gordon HA, Pesti L. The gnotobiotic animal as a tool in the study of host microbial relationships. Bacteriol Rev 1971;35:390–429. [PubMed: 4945725]
8. Naik S, et al. Compartmentalized control of skin immunity by resident commensals. Science 2012;337:1115–9. [PubMed: 22837383]
9. Gallo RL. Human Skin Is the Largest Epithelial Surface for Interaction with Microbes. J Invest Dermatol 2017;137:1213–4. [PubMed: 28395897]
10. Nakatsuji T, et al. The microbiome extends to subepidermal compartments of normal skin. Nat Commun 2013;4:1431. [PubMed: 23385576]

11. Ross AA, Müller KM, Weese JS, Neufeld JD. Comprehensive skin microbiome analysis reveals the uniqueness of human skin and evidence for phylosymbiosis within the class Mammalia. Proc Natl Acad Sci U S A 2018;115:E5786–95. [PubMed: 29871947]

12. Grice EA, et al. A diversity profile of the human skin microbiota. Genome Res 2008;18:1043–50. [PubMed: 18502944]

13. Grice EA, et al. Topographical and Temporal Diversity of the Human Skin Microbiome. Science 2009;324:1190–2. [PubMed: 19478181]

14. Kong HH, Segre JA. The Molecular Revolution in Cutaneous Biology: Investigating the Skin Microbiome. J Invest Dermatol 2017;137:e119–22. [PubMed: 28411842]

15. Costello EK, et al. Bacterial community variation in human body habitats across space and time. Science 2009;326:1694–7. [PubMed: 19892944]

16. Oh J, et al. Biogeography and individuality shape function in the human skin metagenome. Nature 2014;514:59–64. [PubMed: 25279917]

17. Oh J, et al. Temporal Stability of the Human Skin Microbiome. Cell 2016;165:854–66. [PubMed: 27153496]

18. Paller AS, et al. The microbiome in patients with atopic dermatitis. J Allergy Clin Immunol 2019;143:26–35. [PubMed: 30476499]

19. Fyhrquist N, et al. Microbe-host interplay in atopic dermatitis and psoriasis. Nat Commun 2019;10:4703. [PubMed: 31619666]

20. Stokholm J, et al. Maturation of the gut microbiome and risk of asthma in childhood. Nat Commun 2018;9:141. [PubMed: 29321519]

21. Morgan XC, et al. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biol 2012;13:R79. [PubMed: 23013615]

22. Parekh PJ, Balart LA, Johnson DA. The Influence of the Gut Microbiome on Obesity, Metabolic Syndrome and Gastrointestinal Disease. Clin Transl Gastroenterol 2015;6:e91. [PubMed: 26087059]

23. Kostic AD, et al. Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res 2012;22:292–8. [PubMed: 22009990]

24. Vogtmann E, et al. Colorectal Cancer and the Human Gut Microbiome: Reproducibility with Whole-Genome Shotgun Sequencing. PLoS One 2016;11:e0155362. [PubMed: 27171425]

25. Zeller G, et al. Potential of fecal microbiota for early-stage detection of colorectal cancer. Mol Syst Biol 2014;10:766. [PubMed: 25432777]

26. Koch R Ueber den augenblicklichen Stand der bakteriologischen Choleradiagnose. Z Für Hyg Infekt 1893;14:319–38.

27. Ogston A Report upon Micro-Organisms in Surgical Diseases. Br Med J 1881;1:369.b2–375.

28. Whitfield A, Sabouraud R, MacKenna RW. Discussion On Acne And Seborrhoea, Their Causation And Treatment. Br Med J 1912;2:286–9.

29. Sabouraud Dr., et al. A Discussion On The Role Of Cocci In The Pathology Of The Skin. Br Med J 1901;2:794–7.

30. Marples RR, Richardson JF, Newton FE. Staphylococci as part of the normal flora of human skin. Soc Appl Bacteriol Symp Ser 1990;19:935–99S. [PubMed: 2119070]

31. Schade H, Marchionini A. Der Säuremantel der Haut (Nach Gaskettenmessungen). Klin Wochenschr 1928;7:12–4.

32. Pillsbury DM, Rebell G. The bacterial flora of the skin: factors influencing the growth of resident and transient organisms. J Invest Dermatol 1952;18:173–86. [PubMed: 14908192]

33. Marples RR. The effect of hydration on the bacterial flora of the skin. In: Maibach HI, Hildick-Smith G, editors. Skin Bacteria and their Role in Infection. New York: McGrawHill; 1965. p. 3341.

34. Cunliffe WJ, et al. Tetracycline and acne vulgaris: a clinical and laboratory investigation. Br Med J 1973;4:332–5. [PubMed: 4271323]
35. Holland KT, Cunliffe WJ, Roberts CD. Acne vulgaris: an investigation into the number of anaerobic diphtheroids and members of the Micrococcaceae in normal and acne skin. Br J Dermatol 1977;96:623–6. [PubMed: 141301]

36. Puhvel SM, Amirian DA. Bacterial flora of comedones. Br J Dermatol 1979;101:543–8. [PubMed: 160242]

37. Holland KT, Ingham E, Cunliffe WJ. A review, the microbiology of acne. J Appl Bacteriol 1981;51:195–215. [PubMed: 6457823]

38. Planet PJ, Parker D, Ruff NL, Shinefield HR. Revisiting Bacterial Interference in the Age of Methicillin-resistant Staphylococcus aureus: Insights Into Staphylococcus aureus Carriage, Pathogenicity and Potential Control. Pediatr Infect Dis J 2019;38:958–66. [PubMed: 31274832]

39. Gibbons SM, et al. Ecological succession and viability of human-associated microbiota on restroom surfaces. Appl Environ Microbiol 2015;81:765–73. [PubMed: 25398865]

40. Hogan PG, et al. Interplay of personal, pet, and environmental colonization in households affected by community-associated methicillin-resistant Staphylococcus aureus. J Infect 2019;78:200–7. [PubMed: 30503843]

41. Lax S, et al. Longitudinal analysis of microbial interaction between humans and the indoor environment. Science 2014;345:1048–52. [PubMed: 25170151]

42. Miller M, et al. Staphylococcus aureus in the community: colonization versus infection. PloS One 2009;4:e6708. [PubMed: 19693269]

43. Mork RL, et al. Comprehensive modeling reveals proximity, seasonality, and hygiene practices as key determinants of MRSA colonization in exposed households. Pediatr Res 2018;84:668–76. [PubMed: 30135590]

44. Mork RL, et al. Longitudinal, strain-specific Staphylococcus aureus introduction and transmission events in households of children with community-associated methicillin-resistant S aureus skin and soft tissue infection: a prospective cohort study. Lancet Infect Dis 2019;

45. Fukami T Historical Contingency in Community Assembly: Integrating Niches, Species Pools, and Priority Effects. Annu Rev Ecol Evol Syst 2015;46:1–23.

46. Sprockett D, Fukami T, Relman DA. Role of priority effects in the early-life assembly of the gut microbiota. Nat Rev Gastroenterol Hepatol 2018;15:197–205. [PubMed: 29362469]

47. Hecht AL, et al. Strain competition restricts colonization of an enteric pathogen and prevents colitis. EMBO Rep 2016;17:1281–91. [PubMed: 27432285]

48. Aagaard K, et al. The placenta harbors a unique microbiome. Sci Transl Med 2014;6:237ra65.

49. Collado MC, Rautava S, Aakko J, Isolauri E, Salminen S. Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. Sci Rep 2016;6:23129. [PubMed: 27001291]

50. Perez-Muñoz ME, Arrieta M-C, Ramer-Tait AE, Walter J. A critical assessment of the “sterile womb” and “in utero colonization” hypotheses: implications for research on the pioneer infant microbiome. Microbiome 2017;5:48. [PubMed: 28454555]

51. Rodríguez JM, et al. The composition of the gut microbiota throughout life, with an emphasis on early life. Microb Ecol Health Dis [Internet] 2015 [cited 2018 Sep 2];26. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4315782/

52. Tapiainen T, et al. Maternal influence on the fetal microbiome in a population-based study of the first-pass meconium. Pediatr Res 2018;

53. Younge N, et al. Fetal exposure to the maternal microbiota in humans and mice. JCI Insight 2019;4.

54. de Goffau MC, et al. Human placenta has no microbiome but can contain potential pathogens. Nature 2019;572:329–34. [PubMed: 31367035]

55. Theis KR, et al. Does the human placenta delivered at term have a microbiota? Results of cultivation, quantitative real-time PCR, 16S rRNA gene sequencing, and metagenomics. Am J Obstet Gynecol 2019;220:267.e1–267.e9. [PubMed: 30832984]

56. Chu DM, et al. Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery. Nat Med 2017;23:314–26. [PubMed: 28112736]
57. Dominguez-Bello MG, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 2010;107:11971–5. [PubMed: 20566857]

58. Olm MR, et al. Identical bacterial populations colonize premature infant gut, skin, and oral microbiomes and exhibit different in situ growth rates. Genome Res 2017;27:601–12. [PubMed: 28073918]

59. Sarkany I, Gaylarde CC. Skin flora of the newborn. Lancet Lond Engl 1967;1:589–90.

60. Dominguez-Bello MG, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. Nat Med 2016;22:250–3. [PubMed: 26828196]

61. Nishijima K, Yoneda M, Hirai T, Takakuwa K, Enomoto T. Biology of the vernix caseosa: A review. J Obstet Gynaecol Res 2019;45:2145–9. [PubMed: 31507021]

62. Bergström A, Byaruhanga R, Okong P. The impact of newborn bathing on the prevalence of neonatal hypothermia in Uganda: a randomized, controlled trial. Acta Paediatr Oslo Nor 2005;94:1462–7.

63. Sarkany I, Gaylarde CC. Bacterial colonisation of the skin of the newborn. J Pathol Bacteriol 1968;95:115–22. [PubMed: 4966873]

64. Medves JM, O’Brien B. Does bathing newborns remove potentially harmful pathogens from the skin? Birth Berkeley Calif 2001;28:161–5.

65. Visscher MO, et al. Vernix caseosa in neonatal adaptation. J Perinatol Off J Calif Perinat Assoc 2005;25:440–6.

66. Lund C Bathing and Beyond: Current Bathing Controversies for Newborn Infants. Adv Neonatal Care Off J Natl Assoc Neonatal Nurses 2016;16 Suppl 5S:S13–20.

67. Lozupone CA, Stombaugh JI, Gordon JJ, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature 2012;489:220–30. [PubMed: 22972295]

68. Verster AJ, et al. The Landscape of Type VI Secretion across Human Gut Microbiomes Reveals Its Role in Community Composition. Cell Host Microbe 2017;22:411–419.e4. [PubMed: 28910638]

69. Yatsunenko T, et al. Human gut microbiome viewed across age and geography. Nature 2012;486:222–7. [PubMed: 22699611]

70. Capone KA, Dowd SE, Stamatas GN, Nikolovski J. Diversity of the human skin microbiome early in life. J Invest Dermatol 2011;131:2026–32. [PubMed: 21697884]

71. Costello EK, Carlisle EM, Bik EM, Morowitz MJ, Relman DA. Microbiome assembly across multiple body sites in low-birthweight infants. mBio 2013;4:e00782–00713. [PubMed: 24169577]

72. Youngs NE, Araújo-Pérez F, Brandon D, Seed PC. Early-life skin microbiota in hospitalized preterm and full-term infants. Microbiome 2018;6:98. [PubMed: 29855335]

73. Kennedy EA, et al. Skin microbiome before development of atopic dermatitis: Early colonization with commensal staphylococci at 2 months is associated with a lower risk of atopic dermatitis at 1 year. J Allergy Clin Immunol 2017;139:166–72. [PubMed: 27609659]

74. Asnicar F, et al. Studying Vertical Microbiome Transmission from Mothers to Infants by Strain-Level Metagenomic Profiling. mSystems 2017;2.

75. Korpela K, et al. Selective maternal seeding and environment shape the human gut microbiome. Genome Res 2018;28:561–8. [PubMed: 29496731]

76. Zhu T, et al. Age and Mothers: Potent Influences of Children’s Skin Microbiota. J Invest Dermatol 2019;139:2497–2505.e6. [PubMed: 31420081]

77. Faith JJ, et al. The long-term stability of the human gut microbiota. Science 2013;341:1237439. [PubMed: 23828941]

78. Ferretti P, et al. Mother-to-Infant Microbial Transmission from Different Body Sites Shapes the Developing Infant Gut Microbiome. Cell Host Microbe 2018;24:133–145.e5. [PubMed: 30001516]

79. Yassour M, et al. Strain-Level Analysis of Mother-to-Child Bacterial Transmission during the First Few Months of Life. Cell Host Microbe 2018;24:146–154.e4. [PubMed: 30001517]

80. Doerge K, et al. Impact of maternal supplementation with probiotics during pregnancy on atopic eczema in childhood--a meta-analysis. Br J Nutr 2012;107:1–6. [PubMed: 21787448]
81. Shin H, et al. The first microbial environment of infants born by C-section: the operating room microbes. Microbiome 2015;3:59. [PubMed: 26620712]
82. Lax S, et al. Colonization and Succession of Hospital-Associated Microbiota. Sci Transl Med 2017 9(391):eaah6500 [PubMed: 28539477]
83. Gaitanis G, et al. Variation of cultured skin microbiota in mothers and their infants during the first year postpartum. Pediatr Dermatol 2019;36:460–5. [PubMed: 31025407]
84. Evans NJ, Rutter N. Development of the epidermis in the newborn. Biol Neonate 1986;49:74–80. [PubMed: 3697429]
85. Oranges T, Dini V, Romanelli M. Skin Physiology of the Neonate and Infant: Clinical implications. Adv Wound Care 2015;4:587–95.
86. Hoeger PH, Enzmann CC. Skin physiology of the neonate and young infant: a prospective study of functional skin parameters during early infancy. Pediatr Dermatol 2002;19:256–62. [PubMed: 12047648]
87. Saijo S, Tagami H. Dry skin of newborn infants: functional analysis of the stratum corneum. Pediatr Dermatol 1991;8:155–9. [PubMed: 1923986]
88. Webster GF, Ruggieri MR, McGinley KJ. Correlation of Propionibacterium acnes populations with the presence of triglycerides on nonhuman skin. Appl Environ Microbiol 1981;41:1269–70. [PubMed: 7259157]
89. Agache P, Blanc D, Barrand C, Laurent R. Sebum levels during the first year of life. Br J Dermatol 1980;103:643–9. [PubMed: 7459260]
90. Oh J, Conlan S, Polley EC, Segre JA, Kong HH. Shifts in human skin and nares microbiota of healthy children and adults. Genome Med 2012;4:77. [PubMed: 23050952]
91. Mack MC, et al. Development of solar UVR-related pigmentation begins as early as the first summer of life. J Invest Dermatol 2010;130:2335–8. [PubMed: 20428184]
92. Nosanchuk JD, Casadevall A. Impact of Melanin on Microbial Virulence and Clinical Resistance to Antimicrobial Compounds. Antimicrob Agents Chemother 2006;50:3519–28. [PubMed: 17065617]
93. Gallo RL, Nakatsuji T. Microbial symbiosis with the innate immune defense system of the skin. J Invest Dermatol 2011;131:1974–80. [PubMed: 21697881]
94. Lai Y, Gallo RL. AMPed up immunity: how antimicrobial peptides have multiple roles in immune defense. Trends Immunol 2009;30:131–41. [PubMed: 19217824]
95. Gläser R, et al. Antimicrobial psoriasin (S100A7) protects human skin from Escherichia coli infection. Nat Immunol 2005;6:57–64. [PubMed: 15568027]
96. Schaubert J, et al. Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. J Clin Invest 2007;117:803–11. [PubMed: 17290304]
97. Tamoutounour S, et al. Keratinocyte-intrinsic MHCII expression controls microbiota-induced Th1 cell responses. Proc Natl Acad Sci U S A 2019;116:23643–52. [PubMed: 31672911]
98. Thiemann S, et al. Enhancement of IFNγ Production by Distinct Commensals Ameliorates Salmonella-Induced Disease. Cell Host Microbe 2017;21:682–694.e5. [PubMed: 28618267]
99. Callewaert C, et al. IL-4Rα Blockade by Dupilumab Decreases Staphylococcus aureus Colonization and Increases Microbial Diversity in Atopic Dermatitis. J Invest Dermatol 2020;140:191–202.e7. [PubMed: 3125032]
100. Simpson EL, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med 2016;375:2335–48. [PubMed: 27690741]
101. Kobayashi T, et al. Homeostatic Control of Sebaceous Glands by Innate Lymphoid Cells Regulates Commensal Bacteria Equilibrium. Cell 2019;176:982–997.e16. [PubMed: 30712873]
102. Davey MS, et al. Clonal selection in the human V61 T cell repertoire indicates γδ TCR-dependent adaptive immune surveillance. Nat Commun 2017;8:14760. [PubMed: 28248310]
103. Kabelitz D. Function and specificity of human gamma/delta-positive T cells. Crit Rev Immunol 1992;11:281–303. [PubMed: 1379436]
104. Sharp LL, Jameson JM, Cauvi G, Havran WL. Dendritic epidermal T cells regulate skin homeostasis through local production of insulin-like growth factor 1. Nat Immunol 2005;6:73–9. [PubMed: 15592472]
105. Toulon A, et al. A role for human skin-resident T cells in wound healing. J Exp Med 2009;206:743–50. [PubMed: 19307328]

106. Selvanantham T, et al. NKT Cell-Deficient Mice Harbor an Altered Microbiota That Fuels Intestinal Inflammation during Chemically Induced Colitis. J Immunol Baltim Md 1950 2016;197:4464–72.

107. Doisne J-M, et al. Skin and peripheral lymph node invariant NKT cells are mainly retinoic acid receptor-related orphan receptor (gamma)t+ and respond preferentially under inflammatory conditions. J Immunol Baltim Md 1950 2009;183:2142–9.

108. Ito T, et al. Maintenance of hair follicle immune privilege is linked to prevention of NK cell attack. J Invest Dermatol 2008;128:1196–206. [PubMed: 18160967]

109. Gold MC, et al. Human thymic MR1-restricted MAIT cells are innate pathogen-reactive effectors that adapt following thymic egress. Mucosal Immunol 2013;6:35–44. [PubMed: 22692454]

110. Le Bourhis L, et al. Antimicrobial activity of mucosal-associated invariant T cells. Nat Immunol 2010;11:701–8. [PubMed: 20581831]

111. Constantinides MG, et al. MAIT cells are imprinted by the microbiota in early life and promote tissue repair. Science 2019;366.

112. Hinks TSC, et al. Activation and In Vivo Evolution of the MAIT Cell Transcriptome in Mice and Humans Reveals Tissue Repair Functionality. Cell Rep 2019;28:3249–3262.e5. [PubMed: 3153045]

113. Leng T, et al. TCR and Inflammatory Signals Tune Human MAIT Cells to Exert Specific Tissue Repair and Effector Functions. Cell Rep 2019;28:3077–3091.e5. [PubMed: 3153032]

114. Cordoro KM, et al. Skin-infiltrating, interleukin-22-producing T cells differentiate pediatric psoriasis from adult psoriasis. J Am Acad Dermatol 2017;77:417–24. [PubMed: 28624119]

115. Scharschmidt TC, et al. A Wave of Regulatory T Cells into Neonatal Skin Mediates Tolerance to Commensal Microbes. Immunity 2015;43:1011–21. [PubMed: 26588783]

116. Scharschmidt TC, et al. Commensal Microbes and Hair Follicle Morphogenesis Cooperatively Drive Treg Migration into Neonatal Skin. Cell Host Microbe 2017;21:467–477.e5. [PubMed: 28343820]

117. Russler-Germain EV, Rengaraj S, Hsieh C-S. Antigen-Specific Regulatory T Cell Responses to Intestinal Microbiota. Mucosal Immunol 2017;10:1375–86. [PubMed: 28766556]

118. Donaldson GP, et al. Gut microbiota utilize immunoglobulin A for mucosal colonization. Science 2018;360:795–800. [PubMed: 29724905]

119. Lee SM, et al. Bacterial colonization factors control specificity and stability of the gut microbiota. Nature 2013;501:426–9. [PubMed: 23955152]

120. Mazmanian SK, Liu CH, Trizianos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell 2005;122:107–18. [PubMed: 1609137]

121. Mehta RS, et al. Stability of the human faecal microbiome in a cohort of adult men. Nat Microbiol 2018;3:347–55. [PubMed: 29335554]

122. Truong DT, Tett A, Pasolli E, Huttenhower C, Segata N. Microbial strain-level population structure and genetic diversity from metagenomes. Genome Res 2017;27:626–38. [PubMed: 28167665]

123. Torow N, Hornef MW. The Neonatal Window of Opportunity: Setting the Stage for LifeLong Host-Microbial Interaction and Immune Homeostasis. J Immunol Baltim Md 1950 2017;198:557–63.

124. Florey HW. The use of micro-organisms for therapeutic purposes. Yale J Biol Med 1946;19:101–17. [PubMed: 20275724]

125. Henderson DW. Bacterial interference. Bacteriol Rev 1960;24:167–76. [PubMed: 14400978]

126. Sprunt K, Redman W. Evidence suggesting importance of role of interbacterial inhibition in maintaining balance of normal flora. Ann Intern Med 1968;68:579–90. [PubMed: 4966900]

127. Schiotz A Uskadeliggorelse af infektionsbaerere ved difteri. Ugeskr Læg 1909;71:1382–4.

128. Books Received. J Am Med Assoc 1910;LIV:422–422.

129. Albert H The treatment of diphtheria carriers. J Am Med Assoc 1913;61:1027–31.
130. Jennings MA, Sharp AE. Antibacterial activity of the Staphylococcus. Nature 1947;159:133. [PubMed: 20281240]

131. Lorenz WF, Ravenel MP. The treatment of diphtheria-carriers by overriding with Staphylococcus aureus. J Am Med Assoc 1912;LIX:690–3.

132. Womer WA. Results of staphylococcus spray treatment in forty-two cases of diphtheria carriers. J Am Med Assoc 1913;61:2293–4.

133. Panigrahi P, et al. Long-term colonization of a Lactobacillus plantarum symbiotic preparation in the neonatal gut. J Pediatr Gastroenterol Nutr 2008;47:45–53. [PubMed: 18607268]

134. Panigrahi P, et al. A randomized symbiotic trial to prevent sepsis among infants in rural India. Nature 2017;548:407–12. [PubMed: 28813414]

135. Myles IA, et al. First-in-human topical microbiome transplantation with Roseomonas mucosa for atopic dermatitis. JCI Insight 2018;3.

136. Nakatsuji T, et al. Antimicrobials from human skin commensal bacteria protect against Staphylococcus aureus and are deficient in atopic dermatitis. Sci Transl Med 2017;9.

137. Blair JE, Carr M. Staphylococci in hospital-acquired infections; types encountered in the United States. J Am Med Assoc 1958;166:1192–6. [PubMed: 13513341]

138. Blair JE, Carr M. Distribution of Phage Groups of Staphylococcus aureus in the Years 1927 through 1947. Science 1960;132:1247–8. [PubMed: 17801672]

139. Rountree PM, Freeman BM. Infections caused by a particular phage type of Staphylococcus aureus. Med J Aust 1955;42:157–61.

140. Boris M, et al. Bacterial interference: its effect on nursery-acquired infection with Staphylococcus aureus. IV. The Louisiana epidemic. Am J Dis Child 1960 1963;105:674–82.

141. Shinefield HR, Ribble JC, Boris M, Eichenwald HF. Bacterial interference: its effect on nursery-acquired infection with Staphylococcus aureus. I. Preliminary observations on artificial colonization of newborns. Am J Dis Child 1960 1963;105:646–54.

142. Shinefield HR, Sutherland JM, Ribble JC, Eichenwald HF. Bacterial interference: its effect on nursery-acquired infection with Staphylococcus aureus. II. The Ohio epidemic. Am J Dis Child 1960 1963;105:655–62.

143. Shinefield HR, Boris M, Ribble JC, Cale EF, Eichenwald HF. Bacterial interference: its effect on nursery-acquired infection with Staphylococcus aureus. III. The Georgia epidemic. Am J Dis Child 1960 1963;105:663–73.

144. Shinefield HR, Ribble JC, Eichenwald HF, Boris M, Sutherland JM. Bacterial interference: its effect on nursery-acquired infection with Staphylococcus aureus. V. An analysis and interpretation. Am J Dis Child 1960 1963;105:683–8.

145. Light IJ, Sutherland JM, Schott JE. Control of a Staphylococcal Outbreak in a Nursery: Use of Bacterial Interference. JAMA 1965;193:699–704. [PubMed: 14328467]

146. Russell AB, et al. Type VI secretion delivers bacteriolytic effectors to target cells. Nature 2011;475:343–7. [PubMed: 21776080]

147. Russell AB, et al. A type VI secretion-related pathway in Bacteroidetes mediates interbacterial antagonism. Cell Host Microbe 2014;16:227–36. [PubMed: 25070807]

148. Wexler AG, et al. Human symbionts inject and neutralize antibacterial toxins to persist in the gut. Proc Natl Acad Sci U S A 2016;113:3639–44. [PubMed: 26957597]

149. Ross BD, et al. Human gut bacteria contain acquired interbacterial defence systems. Nature 2019;575:224–8. [PubMed: 31666699]

150. Burts ML, DeDent AC, Missiakas DM. EsaC substrate for the ESAT-6 secretion pathway and its role in persistent infections of Staphylococcus aureus. Mol Microbiol 2008;69:736–46. [PubMed: 18554323]

151. Christensen GJM, et al. Antagonism between Staphylococcus epidermidis and Propionibacterium acnes and its genomic basis. BMC Genomics 2016;17:152. [PubMed: 26924200]

152. Ohr RJ, Anderson M, Shi M, Schneewind O, Missiakas D. EssD, a Nuclease Effector of the Staphylococcus aureus ESS Pathway. J Bacteriol 2017;199.

153. Whitney JC, et al. A broadly distributed toxin family mediates contact-dependent antagonism between gram-positive bacteria. eLife 2017;6.
154. Gillor O, Etzion A, Riley MA. The dual role of bacteriocins as anti- and probiotics. Appl Microbiol Biotechnol 2008;81:591–606. [PubMed: 18853155]

155. Klaenhammer TR. Bacteriocins of lactic acid bacteria. Biochimie 1988;70:337–49. [PubMed: 3139051]

156. Nes IF, et al. Biosynthesis of bacteriocins in lactic acid bacteria. Antonie van Leeuwenhoek 1996;70:113–28. [PubMed: 8879403]

157. Riley MA, Wertz JE. Bacteriocin diversity: ecological and evolutionary perspectives. Biochimie 2002;84:357–64. [PubMed: 12423779]

158. Mota-Meira M, LaPointe G, Lacroix C, Lavoie MC. MICs of mutacin B-Ny266, nisin A, vancomycin, and oxacillin against bacterial pathogens. Antimicrob Agents Chemother 2000;44:24–9. [PubMed: 10602718]

159. Ikari NS, Kenton DM, Young VM. Interaction in the germfree mouse intestine of colicinogenic and colicin-sensitive microorganisms. Proc Soc Exp Biol Med Soc Exp Biol Med N Y N 1969;130:1280–4.

160. Riley MA, Gordon DM. The ecological role of bacteriocins in bacterial competition. Trends Microbiol 1999;7:129–33. [PubMed: 10203843]

161. Sassone-Corsi M, Nuccio S-P, Liu H, et al. Microcins mediate competition among Enterobacteriaceae in the inflamed gut. Nature 2016;540:280–3. [PubMed: 27798599]

162. Chao L, Levin BR. Structured habitats and the evolution of anticompetitor toxins in bacteria. Proc Natl Acad Sci U S A 1981;78:6324–8. [PubMed: 7031647]

163. Durrett R, Levin S. Allelopathy in Spatially Distributed Populations. J Theor Biol 1997;185:165–71. [PubMed: 9344720]

164. Noble WC, Willie JA. Interactions between antibiotic-producing and non-producing staphylococci in skin surface and sub-surface models. Br J Exp Pathol 1980;61:339–43. [PubMed: 7426387]

165. O’Sullivan JN, Rea MC, O’Connor PM, Hill C, Ross RP. Human skin microbiota is a rich source of bacteriocin-producing staphylococci that kill human pathogens. FEMS Microbiol Ecol 2019;95.

166. O’Neill AM, et al. Identification of a Human Skin Commensal Bacterium that Selectively Kills Cutibacterium acnes. J Invest Dermatol 2020;

167. Claesen J, et al. Cutibacterium acnes antibiotic production shapes niche competition in the human skin microbiome. bioRxiv 2019;594010.

168. Janek D, Zipperer A, Kulik A, Krismer B, Peschel A. High Frequency and Diversity of Antimicrobial Activities Produced by Nasal Staphylococcus Strains against Bacterial Competitors. PLoS Pathog 2016;12:e1005812. [PubMed: 27490492]

169. DeFilipp Z, et al. Drug-Resistant E. coli Bacteremia Transmitted by Fecal Microbiota Transplant. N Engl J Med 2019;381:2043–50. [PubMed: 31665575]

170. Sorbara MT, Pamer EG. Interbacterial mechanisms of colonization resistance and the strategies pathogens use to overcome them. Mucosal Immunol 2019;12:1–9. [PubMed: 29988120]
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.