Interactions between members of the microbiota both shape the resident microbial community and prevent colonization by pathogenic bacteria in a process termed 'colonization resistance' (Ref. 68). However, in certain contexts, bacteria that are ordinarily beneficial to their hosts can become pathogenic. Many common skin diseases are associated with changes in the microbiota, termed dysbiosis69. This dysbiosis is often driven by common commensal species, as described below for acne, eczema and chronic wounds. Both rare and common skin disorders are thought to have underlying contributions both from individual species and from alterations to the microbial community. Additional longitudinal clinical studies may elucidate a mechanistic link between fungal species and dandruff or toenail infections and between viruses and warts.

Microorganisms associated with common acne. The prevalent teenage condition acne vulgaris is a chronic inflammatory skin condition that is associated with the bacterium P. acnes70, the most abundant organism in the microbiota of healthy adults18,71. At a functional level, gene expression profiles of P. acnes are distinct between individuals with acne and individuals without acne72. The observation that almost all adults are colonized with P. acnes but only a minority have acne highlights the importance of studying diseases in the broader context of host genetics, immune or barrier defects, the microbiome and the environment. For example, increased sebum secretion is associated with the pathophysiology of acne, as secretion rates correlate with the severity of clinical symptoms73. In a study using fluorescent microscopy to visualize P. acnes in follicles of skin biopsy samples, acne development was substantially associated with the presence of P. acnes in follicles and its formation of biofilms74. At the clade level, P. acnes belonging to the type 1A 1 phylogroup have been consistently associated with acne across studies utilizing distinct sampling and analysis methods71,75,76,77. Strains within the type 1A 1 phylogroup have increased inflammatory potential based on the presence of putative virulence factors that affect bacterial adhesion and host immune responses78.

Historically, vitamin B 12 supplementation has been associated with acne in a subset of individuals79,80,81,82,83. Recently, this has been linked to supplemental vitamin B 12 repressing vitamin B 12 biosynthesis in P. acnes, which subsequently increases the production of porphyrins that can induce skin inflammation and acne development72. Interestingly, acne-associated P. acnes strains were found to produce substantially higher levels of porphyrins84.

Staphylococcus aureus and atopic dermatitis. Atopic dermatitis (also known as eczema) is a chronic, relapsing inflammatory disease with multiple contributing factors, including epidermal barrier impairment, immune cell activation and alterations in the community of associated skin microorganisms. Atopic dermatitis susceptibility has been associated with mutations in over 30 host gene loci, including the gene encoding skin barrier protein filaggrin85 and genes linked to the immune system86. In addition to S. aureus, which is commonly cultured from the skin of individuals with atopic dermatitis87, there are additional factors that support the hypothesis that microbiota have an influential role in disease pathogenesis. Atopic dermatitis is clinically

treated with emollients that promote barrier integrity and immunosuppressive medications, such as steroids88. In cases where there is an infection or disease persistence, antimicrobial approaches (for example, antibiotics and dilute bleach baths) may be used, and their success has been shown to correlate with decreases in the relative abundance of S. aureus4; however, their overall effectiveness is uncertain89. As described above, much research is aimed to develop novel therapies specific to anti-S. aureus to replace the more broad-spectrum antimicrobials that are currently used.

In longitudinal studies of paediatric individuals with atopic dermatitis, 16S rRNA and whole genome sequencing of clinical samples showed that the relative abundance of Staphylococcus spp., particularly S. aureus and S. epidermidis, increased in the flare (episodic exacerbation) versus the post-flare state and that the relative abundance of staphylococci correlated with more severe disease at flare4,90. At the strain level, individuals with atopic dermatitis were found to be colonized with heterogeneous communities of S. epidermidis, and those with more severe disease were colonized with dominant S. aureus strains90. The correlation of S. aureus with atopic dermatitis during active disease exacerbation is well documented. However, the functional role of staphylococci in driving the atopic dermatitis disease state is poorly understood. Longitudinal sampling at more frequent intervals before a flare is still needed to identify whether increased staphylococci levels precede clinical symptoms, which would support the notion that staphylococci contribute to the initial onset of inflammation rather than bloom as a consequence of it. This warrants further investigation, as preliminary studies found a greater abundance of Staphylococcus spp. at 2 months in infants who did not develop atopic dermatitis by age 1 than in those who did develop atopic dermatitis by age 1. This suggests that Staphylococcus spp. exposure at an early age is helpful for proper education of the immune system91.

Another genome sequencing study compared the unaffected skin of adults with atopic dermatitis with that of a control cohort and identified an enrichment of Streptococcus spp. and Gemella spp. and a depletion of Dermacoccus spp. in individuals prone to atopic dermatitis92. At a functional level, the study showed that the microbiome of these individuals is primed to generate excess ammonia, providing an explanation for the high pH levels that are observed during atopic dermatitis flares92.

The decreased diversity of the skin microbiome in individuals with atopic dermatitis has been linked to a reduction in

environmental biodiversity in the areas surrounding their homes93. In one study, healthy individuals had greater diversity of gammaproteobacteria in their skin, the presence of which correlated with greater IL-10 expression in blood93. A follow-up study using in vitro and in vivo animal experiments showed that the gammaproteobacteria genus Acinetobacter could induce strong T helper 1 (T H 1) and anti-inflammatory immune responses that were protective against allergic inflammation94. In a study that examined the microbiome of unaffected skin of individuals with ichthyosis vulgaris and a filaggrin deficiency, there was an under-representation of Gram-positive anaerobic cocci compared with their presence in healthy controls, indicating that a defective stratum corneum is sufficient to alter the skin microbiome and may drive the dysbiosis that is associated with eczema95.

Owing to the association of S. aureus with atopic dermatitis, other skin diseases and bloodstream infections, many studies have focused on interactions between S. aureus, its toxins and the immune system. For example, S. aureus Î´-toxin induces the degranulation of mast cells, which promotes both innate and adaptive type two immune responses96. S. aureus Î±-toxin can also induce IL-1Î² production from monocytes, which may consequently promote a T H 17 response, or from CD4+ T cells making the cytokine IL-17 (Ref. 97). By contrast, when exposed to S. aureus-derived cell wall component lipoteichoic acid, T cells neither proliferated nor produced cytokines98, indicating that S. aureus products can activate the immune system and also temporarily paralyse it. In addition to targeting immune cells, S. aureus has also been shown to trigger adipocytes to rapidly proliferate and to produce increased levels of the antimicrobial peptide cathelicidin as a host defence mechanism99. These examples demonstrate the many ways that S. aureus could initiate or exacerbate skin disorders in the broader context of barrier defects or altered immunity. In fact, it has been demonstrated that in the context of barrier defects, S. aureus is able to traverse the epidermis into the dermis, where it encounters immune cells and triggers the expression of the inflammatory cytokines IL-4, IL-13 and IL-22 and thymic stromal lymphopoietin100. Notably, the ability of S. aureus to trigger the cutaneous immune response can be strain-dependent90, highlighting the importance of evaluating a phenotype across isolates of a species. Although many of these experiments were performed in murine models, they are relevant to humans, as many of the pathways underlying inflammation and immunity in murine skin appear relevant in human infection and disease. Additional examples of interactions between skin microorganisms and immune cells are discussed in Box 2.

Although the inflammatory potential of S. aureus has been demonstrated and dysbiosis is common to many skin diseases, it is still unknown whether these changes are a consequence of the disease state or whether S. aureus contributes to the initiation of the disease. Experiments with mouse models that are genetically and physically challenged to produce skin barrier or immunological defects have been used to determine the contribution of the microbiota to skin disease.

For example, mice deficient in disintegrin and metalloproteinase domain-containing protein 17 (ADAM17) developed eczematous dermatitis as a consequence of microbial dysbiosis101. Alterations in cutaneous microbial communities, characterized by an overgrowth of Corynebacterium mastitidis, Corynebacterium bovis and S. aureus, preceded the development of features of atopic dermatitis. Targeted antibiotic treatment of these animals was sufficient to reverse the dysbiosis and eliminate skin inflammation, thus demonstrating a causal link between skin barrier alterations, dermatitis and the microbiome.

Skin microbiome of individuals with primary immunodeficiency. While several studies have investigated how microorganisms educate the immune system, the study of individuals with primary immunodeficiency (PID) provides an opportunity to understand the role of immunity in determining the structure of microbial communities. Underlying the rationale for these investigations are the common cutaneous manifestations of individuals with PID, particularly the eczematous features. To study this, skin microbiota samples were taken from individuals with rare monogenic PIDs, hyper immunoglobulin E (IgE) syndrome, Wiskottâ€“Aldrich syndrome and dedicator of cytokinesis 8 syndrome. Despite distinct underlying mutations, all diseases are characterized by eczematous-like skin disease, reduced T and B cells, variable eosinophilia and elevated IgE levels102. Although overall similar in the types of bacteria that colonize the skin of healthy individuals, the skin of individuals with PID is more ecologically permissive with decreased temporal stability102. Despite individuals with PID being colonized with opportunistic fungi (for example, Candida spp. and Aspergillus spp.) and bacteria (for example, Serratia marcescens), which are typically absent in controls, these microorganisms still belong to phyla that are commonly associated with the skin. This suggests that organisms outside of these primary phyla are unable to stably survive in the nutrient-poor environments of the skin. In a separate study of individuals with PID caused by mutations in signal transducer and activator of transcription 1 (STAT1) or STAT3, the skin was colonized with more Gram-negative bacteria, particularly Acinetobacter spp., and there was a reduction in Corynebacterium spp. colonization compared with the levels in healthy controls103. To identify possible alterations in the viral communities, shotgun metagenomic sequencing of samples from these individuals is needed; these studies are clinically relevant, as some individuals with PID commonly suffer from viral skin infections104.

Microorganisms in chronic wound infections. In addition to classical skin diseases, microorganisms that colonize the skin have also been shown to affect the healing of chronic wounds prevalent in populations that are elderly or have diabetes or obesity. For example, the role of microorganisms has been well studied in the case of diabetic foot ulcers (DFUs). It is estimated that over 50% of DFUs are infected105. DFUs are a common result of diabetes-induced neuropathy and will occur in 15â€“25% of individuals with diabetes106, with 15.6% requiring amputation107. A 16S rRNA sequencing

survey found that bacterial communities colonizing neuropathic DFUs were associated with clinical features108. For example, shallow ulcers and those of short duration were associated with greater abundances of Staphylococcus spp., particularly S. aureus, whereas deeper ulcers and those of longer duration had greater microbial diversity and a higher relative abundance of anaerobic bacteria and Gram-negative Proteobacteria spp.108. In addition, poor control of blood glucose was associated with greater Staphylococcus spp. and Streptococcus spp. colonization108.

In a longitudinal survey of microorganisms associated with DFUs, 16S rRNA sequencing of the wound revealed that bacterial community instability was associated with faster healing and more positive clinical outcomes109. This observation is counterintuitive, as many studies of other body sites have associated disease with bacterial community instability4,110. However, in the context of a wound, microbial instability could result in effective clearance of wound bacteria by the immune system. In addition to bacteria, the fungal community was also explored in the same cohort with amplicon sequencing of the ITS1 region111. Fungi were identified in 80% of the 100 DFUs analysed, with Cladosporium herbarum and Candida albicans identified as the most abundant species. In chronic wounds with poor clinical outcomes fungal diversity was increased and polymicrobial biofilms of fungi and bacteria were commonly found111.

Reference

[Lab 257: The Disturbing Story of the Government's Secret Germ Laboratory]

[Creating a Caring Science Curriculum, Second Edition: A Relational Emancipatory Pedagogy for Nursing]