Microbial diversity in skin inflammatory diseases

Atopic dermatitis (AD) is an allergic inflammatory disease that is characterized by skin colonization with Staphylococcus aureus and loss of other beneficial commensals, whereas psoriasis exhibits a more complex disease-specific microbiota. The pathophysiologic relevance of this microbial dysbiosis remains unknown. Fyhrquist et al. performed a large-scale comprehensive analysis of the microbiome and associated host transcriptome in healthy volunteers as well as patients with AD and psoriasis. AD was dominated by the presence of S. aureus, which correlated with disease severity, and loss of anaerobic species. In the presence of high levels of S. aureus, host transcriptomic data revealed differentially regulated genes related to skin barrier function, immune activation, and tryptophan metabolism in AD lesional skin. Psoriasis, on the other hand, was associated with multiple species, including Corynebacteria and Finegoldia. These data suggest that Corynebacteria may play a regulatory role that is dampened in disease, but overall, microbe-host associations are less prominent for psoriasis than for AD. These findings shed light on possible disease biomarkers and potential microbial dysbiosis targets for therapy of inflammatory skin diseases. (Nat Commun 10:4703, 2019; https://doi.org/10.1038/s41467-019-12253-y) Selected by J. Gelfand

Tissue-resident sensory systems detect allergens

Alterations in sensitivity to environmental allergens contribute to the type 2 skin disease AD via increased numbers of activated mast cells and eosinophils. Nociceptors that innervate the skin transmit sensations of itch and induce scratching, and they may be involved in AD. Serhan et al. demonstrated that treatment of skin with house dust mites (Dermatophagoides farinae) and bacterial exotoxin from S. aureus induced AD-like skin inflammation. TRPV1⁺ nociceptive neurons also expressed Tac1, which encodes the neuropeptide substance P (SP), and MRGPRB2⁺ mast cells were found in physical clusters in mouse skin. In response to allergen stimulation, TRPV⁺ nociceptors released SP to activate MRGPRB2 on adjacent mast cells, which then degranulated, leading to AD-like skin disease. Taken together, these results suggest that tissue-resident sensory systems detect allergens and promote type 2 immune response—associated allergic skin disease. These findings also have implications for allergic disorders that develop in other sites, such as the upper airways, lungs, and gastrointestinal tract, that also harbor these cell types. (Nat Immunol 20:1435—1443, 2019; https://doi.org/10.1038/s41590-019-0493-z) Selected by D. Kaplan

Human ILC2s provide source of IL-17

Subsets of innate lymphoid cells (ILCs) function in immunity at barrier sites, such as the skin, and display remarkable potential to transdifferentiate from one subset to another. Bernink et al. described a subset of ILC2s that convert to IL-17—producing cells that express c-Kit and the chemokine CCR6 in response to exposure to IL-1β and IL-23, cytokines that are known to stimulate ILC3s. IL-17 production was associated with increased RORγt expression and decreased GATA3 mRNA levels. The cytokine transforming growth factor β was implicated in regulation of the conversion of c-Kit⁺ ILC2s to skin-homing RORγt c-Kit⁺ ILC2s that produce IL-17. Furthermore, IL-4 reversed this conversion, suggesting that this cytokine functions to maintain ILC2 identity. In psoriasis, a shift from ILC2s to ILC3-like cells within lesional skin may contribute to disease pathogenesis, which is characterized by enhanced IL-17—producing ILC3s. (Nat Immunol 20:992—1003, 2019; https://doi.org/10.1038/s41590-019-0423-0) Selected by P. Spuls

Fasting reduces inflammatory activity

Caloric excess is associated with systemic inflammation, whereas hypocaloric diets and fasting are associated with reduced proinflammatory cytokines and improvement in metabolic, autoimmune, and inflammatory diseases. Jordan et al. found that short-term and intermittent fasting reduces the pool of circulating monocytes in both humans and mice. Fasting activated the low-energy sensor AMPK in hepatocytes and suppressed CCL2 production, effectively limiting monocyte egress from the bone marrow to the periphery. Fasting also modified monocyte gene expression to reduce the metabolic activity of these cells. Furthermore, fasting improved chronic inflammatory diseases in an experimental autoimmune encephalomyelitis model but did not adversely affect monocyte function during wound healing or acute inflammatory responses to infection. Modulation of peripheral monocyte levels via short-term fasting or caloric intake decreases inflammation and may therefore offer novel clinical strategies for treatment of patients with autoimmune or inflammatory diseases. (Cell 178:1102–1114.e17, 2019; https://doi.org/10.1016/j.cell.2019.07.050) Selected by I. Brownell

TOX regulates T cell immunity to tumors and chronic infection

In the immunosuppressive environment that results from tumors and chronic infection, T cells become exhausted via mechanisms that involve loss of effector function and memory potential. Recently, two independent reports documented a requirement for the transcription factor TOX in T-cell differentiation under conditions of chronic antigen stimulation, such as tumors and chronic infection. Scott et al. specifically reported that strong expression of TOX in these T cells was associated with upregulation of inhibitory receptors, enrichment of T-cell exhaustion gene programs, and dysfunctional tumor-reactive T cells. Yao et al. showed that progenitor-like CD8⁺ cells exhibit differential transcriptional and epigenetic programs in concert with TOX upregulation in chronic infection models to enable persistence under these conditions. Together, these studies indicate that the TOX-generated dysfunction and exhaustion program is likely adopted to prevent overstimulation of T cells and cell death in the face of chronic antigen stimulation. (Nature 571:270—274, 2019; https://doi.org/10.1038/s41586-019-1324-y; Nat Immunol 20:890—901, 2019; https://doi.org/10.1038/s41590-019-0403-4) Selected by I. Brownell