“Wildlings” reflect human microbiota and immune response

Although laboratory mice have enabled important immunological advances, divergent microbiota often contribute to variable results at different institutions and limit translational relevance. Rosshart and colleagues implanted C57BL/6 embryos into wild mice to generate a wild mouse microbial genome on an isogenic laboratory strain background. The microbiome of these “wildlings” resembled wild mice at barrier sites in the gut, skin, and vagina and was stable for generations. These “natural” microbiota were resilient to antibiotic and microbiological challenge. Furthermore, the immune phenotype of these wildlings reflected that of wild mice in the blood and spleen. Treatment of wildlings and laboratory mice with immunotherapeutics (CD28SA and anti–tumor necrosis factor-α) that were successful in preclinical trials but not in human trials revealed that the wildlings better phenocopied human immune responses, suggesting that resident microbiota influence immune responses and that adoption of this wildling model may enhance study reproducibility and the translational relevance of animal research. (Science 365:eeaw4361; 2019; https://doi.org/10.1126/scienceaaw4361) Selected by I. Brownell

Checkpoint inhibitors expand novel T-cell clonotypes

Inhibitory checkpoint receptor blockade therapies, including anti–PD-1 antibodies, have become a mainstay of cancer treatment. T-cell responses in the setting of such blockade have not been well characterized. In experiments involving single-cell profiling of clinical tumor biopsies, T-cell receptor clonotype analysis, and small conditional RNA sequencing phenotype assessment, Yost and colleagues reported clonal expansion of CD8+ T cells in response to PD-1 blockade in patients with advanced basal cell carcinomas. Expanded T cells expressed tumor specificity markers, including CD39 and CD103, as well as markers of chronic T-cell activation and exhaustion. The expanded clones were derived from a distinct repertoire of novel clonotypes that were not previously detectable in tumors and did not result from re-invigoration of pre-existing tumor infiltrating lymphocytes in response to checkpoint blockade. Although this study did not identify the source of these novel T-cell clones, the findings are important for the design of next-generation checkpoint blockade immunotherapies. (Nat Med. 25:1251-1259, 2019; https://doi.org/10.1038/s41591-019-0522-3) Selected by I. Brownell

CGRP shapes ILC responses in neuroimmune cell units

Innate lymphoid cells (ILCs) are conditioned to respond to tissue-specific microenvironmental signals, and neural regulation of local immune responses at barrier sites has been reported. Nagashima and colleagues examined the transcriptional profiles of lung lymphocytes during helminth infection, revealing a type 2 immune response and subsets of ILCs (ILC2s) that express IL-5 versus IL-13. α-Calcitonin gene-related peptide (αCGRP) is induced in these ILC2s, and this neuropeptide antagonized the effects of the NMU neuropeptide and the alarmin IL-33 while promoting IL-5 production by ILC2s. CGRP also suppressed type 2 immune responses following treatment with IL-33 or helminth infection. Mechanistically, these studies indicated that CGRP suppresses lymphocyte proliferation via generation of cAMP. Although previous studies have demonstrated both context-dependent pro- and anti-inflammatory effects in the lung by CGRP, this neuropeptide constrains the magnitude of innate type 2 immune responses during helminth infection, indicating that CGRP may serve as a useful therapeutic target in type 2 inflammatory diseases. (Immunity, 2019; https://doi.org/10.1016/j.immuni.2019.06.009) Selected by I. Brownell

Neurons activate anticipatory immunity in the skin

TRPV1+ sensory afferent neurons in skin respond to a variety of stimuli and are required for type 17 innate immune responses against some pathogens. Cohen and colleagues generated mice that express optogenetic-stimulated TRPV1+ sensory afferent neurons and found that activation of these neurons induced type 17 inflammation and augmented host defense via a mechanism that is dependent on vesicle fusion in the nerve terminal, the neuropeptide CGRP, and IL-17A. Moreover, optogenetic activation of TRPV1+ neurons induced a nerve reflex arc that transmitted the activation to adjacent areas, extending the early type 17 cytokine release and enhanced host defense beyond the site of stimulation. Furthermore, following stimulation with Candida albicans, TRPV1+ neuron activation stimulated not only host defense at the site of stimulation but also anticipatory immunity at adjacent unstimulated sites in the skin. Although these studies focused on host defense, similar type 17 inflammatory processes contribute to pathogenesis in skin diseases such as psoriasis, suggesting that these findings may be informative for investigations of these diseases and potential treatment strategies. (Cell 178:919-932, 2019; https://doi.org/10.1016/j.cell.2019.06.022) Selected by C. Niessen

Long-term 3D epidermal organoid cultures

Epidermal stem cell culture is useful not only for investigation of skin pathologies but also for therapy of burns and chronic wounds. To date, most culture methods are characterized by either spontaneous immortalization, limited differentiation capacity, requirement for feeder cells or serum, or derivation only from neonatal skin. Recently, Boonekamp and colleagues established a long-term murine epidermal three-dimensional (3D) organoid culture system that yields genetically stable cultures from adult mouse skin. These organoids, which are independent of feeder cells and serum, require high extracellular calcium concentrations, induction of cAMP, activation of extracellular signal–regulated kinase/mitogen-activated protein kinase via fibroblast growth factor, stabilization of Wnt/β-catenin signaling via R-spondin, and bone morphogenetic protein inhibition. Epidermal organoids can be maintained for at least 6 months without losing their clonogenic potential or differentiation ability, and molecular profiling indicated that they exhibit a signature resembling that of the interfollicular epidermis. It is anticipated that 3D epidermal organoid cultures will prove useful for studies of adult epidermal homeostasis as well as skin diseases, including cancer. (PNAS 116:14630-14638, 2019; https://doi.org/10.1073/pnas.1715272116) Selected by I. Brownell