Acute Itch Flares Are Dependent on a Basophil-Neuronal Circuit

Patients with atopic dermatitis (AD) experience acute itch in addition to chronic itch. The mechanisms underlying acute itch flares remain poorly understood. Leveraging the observation that patients with AD exhibit acute itch flares in association with the presence of allergen-specific IgE, Wang et al. (2021) developed a murine model of AD-like disease in which itch flares are induced by allergen exposure. In these mice, IgE-dependent acute itch flares were independent of mast cells, but basophils were both necessary and sufficient for itch-induced scratching after allergen exposure. Basophils directly interacted with sensory neurons in the skin and secreted leukotriene C4, which bound to a receptor (CysLTR2) on the sensory neurons to invoke acute itch. The observation that leukotriene C4 activated NP3 sensory neurons, which express the IL-31 receptor, suggests that therapies targeting the IL-31 pathway may attenuate itch flares in diseases such as AD. (Cell 184:422–40.e17, 2021; https://doi.org/10.1016/j.cell.2020.12.033) Selected by M. Udey

Human Skin Cell Atlas

Reynolds et al. (2021) developed a comprehensive atlas of human skin cells from early prenatal stages (7–10 weeks of gestation), adults, and patients with AD or psoriasis to detail the changes that take place in the skin during development and immune-mediated inflammatory diseases. Single-cell RNA sequencing, in concert with FACS, identified a total of 34 cell states among these samples. These studies revealed that innate lymphocytes and macrophages predominate in early fetal skin, whereas keratinocytes with differentiation potential, endothelial cells that contributed to postcapillary venules, and migratory dendritic cells were predominant in adult samples. Clonally expanded disease-associated T lymphocytes characterized AD and psoriasis samples. Furthermore, cellular programs inherent to development, involving prenatal vascular endothelial cells and macrophages, were identified in cell states from inflammatory skin diseases. These findings provide a new perspective on the pathogenesis of inflammatory diseases and may ultimately inform the development of novel therapeutics for AD and psoriasis. (Science 371:364, 2021; https://doi.org/10.1126/science.aba6500) Selected by T. Schwarz

A Reference Map for Human Cells

In October 2016, an international group of scientists and researchers launched a collaborative initiative to generate a Human Cell Atlas that would provide a collection of reference maps that would describe the molecular state of cells in healthy tissues and disease. Utilizing increasingly available high-throughput technologies, including single-cell RNA sequencing and in situ examination of genes and proteins at the subcellular level as well as refined computational methods that will support this initiative, the researchers proposed large-scale efforts from the broad scientific community with an approach similar to that of the Human Genome Project. This catalog of cells would define all human cells on the basis of their stable properties, transient features, locations, and relative abundances. The final output of such a project will serve as the foundation for understanding human cellular development and homeostasis and for diagnosing, monitoring, and treating disease. (Elife 6:e27041, 2017; https://doi.org/10.7554/eLife.27041) Selected by D. Kelsell

Deciphering Macrophage Dysfunction in Diabetic Wound Repair

Diabetic wounds are characterized by impaired healing owing in part to reduced resolution of monocyte- and/or macrophage-driven inflammation and a lack of transition of macrophages from an inflammatory state to a reparative state. Davis et al. (2020) reported that persistent elevation of cyclooxygenase 2 (COX2) and prostaglandin E2 (PGE2) in macrophages occurs during this macrophage transition in diabetic wounds. Levels of COX2 and PGE2 are increased in wound macrophages through TGFβ1-mediated upregulation of miR29b, which destabilizes DNA methylase 3a and/or b, results in hypomethylation of the COX2 gene, and induces the production of COX2. This epigenetic regulation of COX2, in turn, increases PGE2 levels in macrophages in diabetic wounds, leading to inflammatory cytokine production as well as impaired macrophage phagocytosis and pathogen-killing ability. Pharmacologic inhibition of the COX2/PGE2 pathway altered macrophage phenotype and improved diabetic wound healing in mice, supporting a further examination of this strategy to facilitate wound healing in patients with diabetes who exhibit chronically delayed wound healing. (JCI Insight 5:e138443, 2020; https://doi.org/10.1172/jci.insight.138443) Selected by M. Tomic-Canic

Immunological Memory Extends to Myeloid Cells

Although immunological memory, which involves T and B cells as well as innate myeloid and lymphoid cells, is useful in host protection against pathogens, this phenomenon can also be detrimental in cases of organ transplant survival. Dai et al. (2020) investigated whether innate myeloid cells acquire memory to previous antigenic exposure using allogeneic bone marrow plug grafts in mice. These studies revealed that host monocytes acquired specific memory to previously encountered alloantigens by binding to nonself major histocompatibility complex (MHC) molecules. The MHC I–binding paired Ig-like receptors (PIRs) on monocytes were upregulated on alloantigen stimulation, and the blockade of these receptors inhibited monocyte memory and diminished the killing of allogeneic targets after alloimmunization in a mouse model. Additional studies indicated that PIR-A is required for monocyte and macrophage immunological memory and allograft rejection, whereas PIR-B mitigates such rejection. The determination that PIRs mediate monocyte and macrophage MHC I allorecognition and memory to previously encountered antigens and lead to allograft rejection may inform strategies to improve organ transplant survival in patients. (Science 368:1122–7, 2020; https://doi.org/10.1126/science.aax4040) Selected by I. Brownell