Retroviral PAMP sensor

Retroviruses such as human immunodeficiency virus (HIV) can infect dendritic cells, but cellular innate immune responses limit their productive replicative capacity. In *Cell*, Yoh *et al.* identify the polyglutamine-binding protein PQBP1 as a cytosolic sensor of retroviral cDNA intermediates. HIV infection of primary human dendritic cells is detected by PQBP1, which can interact directly with an early intermediate form of HIV cDNA. PQBP1 acts upstream of the DNA sensor cGAS to activate the transcription factor IRF3. This recognition of viral cDNA triggers dendritic cell expression of type I interferons and upregulation of interferon-response genes. How PQBP1 distinguishes HIV cDNA from other forms of cytosolic nucleic acids remains unknown. ***LAD***

***Cell* 161, 1293–1305 (2015)**

Inflammatory ripples

Interleukin 17 (IL-17)-producing γδ T cells (γδT17 cells) are present in the skin and contribute to the pathogenesis of psoriasis. In the *Proceedings of the National Academy of Sciences*, Cyster and colleagues use a mouse model of stimulating γδT17 cells to gauge their contribution to skin memory responses. Stimulation of skin with the stimulatory ligand imiquimod activates γδT17 cells in skin-draining lymph nodes. Subsequent rechallenge of the skin with imiquimod then rapidly triggers the migration of γδT17 cells to not only inflammed skin but also distal healthy skin, where they can remain for several months. Previously primed skin γδT17 cells show accelerated memory-like responses and recruit neutrophils via their IL-17 production. These more robust recall responses may be dependent at least in part on heightened sensitivity to IL-1. These findings suggest a mechanism by which memory γδT17 cells can 'ripple out' to healthy skin regions and propagate inflammation in conditions such as psoriasis. *ZF*

Proc. Natl. Acad. Sci. USA (15 June 2015) doi:10.1073/pnas.1508990112

Natural resistance

Unlike humans, adult mice with intact microbiota are resistant to gastrointestinal colonization with *Candida albicans*. In *Nature Medicine*, Koh and colleagues demonstrate that in mice, commensal anaerobic bacteria are critical for maintaining resistance to colonization with *C. albicans*. Treatment with penicillin, which depletes an aerobic bacteria, particularly Bacteriodetes and clostridial Firmicutes, induces colonization with *C. albicans* in adult mice. Recolonization with individual anaerobes (*Blautia producta* or *Bacteroides thetaiotamicron*) is sufficient to induce resistance to *C. albicans*, but recolonization with *Bacteroides fragilis* or *Lactobacillus* species is not. Colonization with *Bacteroides thetaiotaomicron* or *Brachycybe producta* increases expression of the transcription factor HIF-1α and the antimicrobial peptide CRAMP (an ortholog of human LL-37, known to have anti–*C. albicans* activity) in the mouse colon. HIF-1α and CRAMP are required for resistance to *C. albicans* in antibiotic-treated mice but not in untreated mice, which suggests redundant immunological pathways of resistance. ***IV***

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Written by Laurie A. Dempsey, Zoltan Fehervari & Ioana Visan

T_H1 complementation

The activation of complement proteins is an ancient form of soluble innate recognition and immunological defense against foreign invaders. In *Immunity*, Kolev *et al.* describe a role for the recognition of complement by $CD4^+$ T helper type 1 (T_H1) cells. Human $CD4^+$ T cells express the complement regulator CD46, which recognizes the complement component C3b and can transmit signals via its cytoplasmic Cyt1 domain. Stimulation via the T cell antigen receptor (TCR) triggers expression of C3, which undergoes proteolytic cleavage to produce C3b and provide an autocrine stimulus for CD46 in T_H1 cells. Stimulation via the TCR plus CD46 *in vitro* leads to increased metabolic responses, including upregulation of both glycolysis and oxidative phosphorylation, increased activation of the metabolic checkpoint kinase mTORC1 and increased expression of interferon-γ and IL-10. It remains unclear whether such responses require prior stimulation to generate memory T cells or whether signaling via costimulatory molecules, such as via CD28 or CTLA-4, interfere with CD46-dependent signaling pathways. Mechanistic details of these signaling cascades await future studies. *LAD*

Immunity **42**, 1033–1047 (2015)

Harmine-izing immunity

Careful control of the differentiation of regulatory T cells (T_{reg} cells) and the T_H17 subset of helper T cells is required for balanced homeostatic and proinflammatory immune responses. In *eLife*, Xavier and colleagues use a chemical screen of more than 3,000 small molecule compounds to identify enhancers of T_{reg} cell differentiation. One compound, the alkaloid harmine, enhances the *in vitro* and *in vivo* differentiation of T_{reg} cells while at the same time impeding T_H17 differentiation. Harmine alone is insufficient to generate T_{reg} cells but instead seems to enhance signaling via transforming growth factor-β, known to be essential for the differentiation of this cell population. Harmine does not seem to act via any previously described pathway important for T_{reg} cells; instead, it inhibits the kinase DYRK1A, and this action is essential for its T_{reg} cell–enhancing effects. Precisely how DYRK1A controls the differentiation of T_{reg} cells and T_H17 cells remains to be determined. ***ZF***

***eLife* (22 May 2015) doi:10.7554/eLife.05920**

Thymoproteasome bias

Optimal positive selection of $CD8^+$ T cells requires the expression of β5t-containing thymoproteosome (tCP) in cortical thymic epithelial cells. In *Nature Communications*, Murata and colleagues show that the thymoproteasome produces unique cleavage motifs in the digested peptides, which leads to a major histocompatibility complex (MHC) class I–associated peptide repertoire with enrichment for low-affinity TCR ligands. Using mass spectrometry to sequence the peptides generated *in vitro* by isolated tCPs and the MHC class I–binding peptides in tCP-expressing mouse embryonic fibroblasts, the authors show that tCPs generate an MHC class I–binding peptide repertoire distinct from the immunoproteasomes. Although high-affinity peptides are also produced, the tCP-generated repertoire shows enrichment for peptides with low affinity for a wide range of TCRs, which, in fetal thymic organ culture, favors the positive selection of $CD8^+$ single-positive thymocytes. In contrast, immunoproteasomes produce peptide with highly diverse TCR affinities. *IV*

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