Eosinophils have the healing touch

Muscle injury results in the regeneration of functional tissue from stem cells (satellite cells), which are in turn supported by trophic factors released by fibroadipogenic stem cells. In *Cell*, Chawla and colleagues demonstrate that eosinophils have a key role in muscle regeneration. With a cardiotoxin model of muscle injury, the authors find that the injury site is rapidly infiltrated by eosinophils that express the type II cytokines IL-4 and IL-13. Mice deficient in those cytokines or that lack eosinophils show impaired muscle regeneration. Signaling via IL-4 to fibroadipogenic stem cells, but not to myocyte precursors, not only triggers their proliferation but also blocks their differentiation into adipocytes, which prevents the accumulation of fatty tissue. IL-4-activated fibroadipogenic stem cells are also very efficient in clearing necrotic cell debris, a critical step in regeneration and a process normally ascribed to macrophages. The coordinated action of eosinophils with fibroadipogenic stem cells is therefore required for the effective regeneration of injured muscle. ***ZF***

***Cell* 153, 376–388 (2013)**

Cytokines 'instruct' HSCs

Whether long-term hematopoietic stem cells (HSCs) receive direct signals from cytokines to make lineage-differentiation 'decisions' is unclear. In *Nature*, Sieweke and colleagues show that the cytokine M-CSF, which is released during infection and inflammation, directly induces the myeloid fate regulator PU.1 in mouse HSCs and thus has an 'instructive' role that is independent of selective survival or proliferation. Video imaging of HSCs from PU.1-*GFP* reporter mice shows induction of PU.1 expression in single, previously PU.1$^-$ cells, whereas single-cell gene expression analysis shows that M-CSF-induced PU.1$^+$ HSCs assume a myeloid-cell identity that leads to myeloid-fate differentiation *in vitro* and *in vivo*. PU.1 is induced in HSCs before cell division and confers no proliferation or survival advantage. These results show that stress-induced cytokines are direct 'instructors' of HSC fate. *IV*

Nature (10 April 2013) doi:10.1038/nature12026

Agonist selection

How TCR signaling strength and duration regulate distinct T cell lineages remains unclear. In *Immunity*, Oh-hora *et al.* show that store-operated Ca^{2+} entry dependent on the Ca^{2+} sensor Stim contributes to the negative selection of conventional TCRαβ T cells and is specifically required for the development of agonist-selected T cells, such as regulatory T cells, invariant natural killer T cells and TCRαβ CD8αα$^+$ intestinal intraepithelial cells. Depletion of Ca^{2+} in the endoplasmic reticulum triggers the Stim-controlled store-operated Ca^{2+} entry to sustain a high concentration of intracellular Ca^{2+} and activate the transcription factor NFAT. Ablation of Stim diminishes expression of the NFAT target genes *Egr2* and *Egr3* and impairs the upregulation of CD122 expression in invariant natural killer T cells and TCRαβ CD8αα$^+$ intraepithelial cells and of CD25 expression in regulatory T cells. These results suggest that store-operated Ca^{2+} entry controls the IL-2- and IL-15-driven expansion of agonist-selected precursors for these T cell subsets. ***IV***

***Immunity* (14 March 2013) doi:10.1016/j.immuni.2013.02.008**

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

Epidermal Blimp-1

Blimp-1 (encoded by *Prdm1*) is a transcriptional repressor expressed by certain cells of the immune system, but its role beyond those cells is not well understood. In the *Proceedings of the National Academy of Sciences*, Lin and colleagues use mice with conditional knockout of *Prdm1* in keratinocytes ('CKO mice') to show that it also has skin-intrinsic roles in immune responses. CKO mice develop spontaneous skin inflammation in the neck and enlarged skin-draining lymph nodes, as well as more sytemic effects, including increased immunoglobulins and more peripheral neutrophilia. CKO keratinocytes also have higher expression of cytokines, particularly those involved in the recruitment and growth of macrophages and neutrophils, such as G-CSF. Mechanistically, Blimp-1 seems to negatively regulate G-CSF through repression of the transactivators encoded by *Fos* and *Fosl1*. In addition to spontaneous skin inflammation in the neck, CKO mice also have enhanced responses in induced models of skin inflammation elsewhere on the body. Certain forms of human eczematous skin also seem to be associated with a lower abundance of Blimp-1. *ZF*

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Pellino-1 in microglia

The activation of microglial cells contributes to the pathogenesis of experimental autoimmune encephalomyelitis, the mouse model of multiple sclerosis. In *Nature Medicine*, Xiao *et al.* show that expression of the E3 ubiquitin ligase Pellino-1 (Peli1) in microglia contributes to the severity of experimental autoimmune encephalomyelitis. Peli1 is activated downstream of the Toll-like receptor–adaptor MyD88 pathway in microglia. Pel1 activates the Lys48-linked ubiquitin ligase cIAP that targets the ubiquitin ligase TRAF3 for destruction and thereby relieves TRAF3-mediated inhibition of mitogen-activated protein kinase signaling pathways. That leads to higher expression of chemokines and proinflammatory cytokines in activated microglia. Peli1-deficient microglia do not activate those pathways, and fewer inflammatory cells and lymphocytes infiltrate the central nervous system. Whether similar Peli1-dependent signaling cascades operate in human microglial cells remains unknown, but if such pathways are conserved, targeting Peli1 might be beneficial in treating multiple sclerosis. ***LAD***

***Nat. Med.* (21 April 2013) doi:10.1038/nm.3111**

Bacterial evasion

Porphyromonas gingivalis infects gingival epithelial cells and is a chief agent causing periodontal disease in humans. In *PLoS Pathogens*, Takeuchi *et al.* identify SerB, a serine phosphatase produced by *P. gingivalis*, as a virulence factor that suppresses host innate immune defenses in gingival tissues. SerB acts by dephosphorylating Ser536 of the p65 subunit of the transcription factor NF-κB, which diminishes the nuclear translocation and activity of NF-κB. That SerB-mediated inhibition blunts the production of IL-8 by epithelial cells. This evasion strategy results in less recruitment of neutrophils into the gingival tissue than would otherwise combat bacterial infection. *P. gingivalis* that lack SerB are unable to inhibit NF-κB activity. Thus, *P. gingivalis* disarms host innate immune responses by inhibiting a central transcription factor responsible for mounting such responses. *LAD*

PLoS Pathog. (18 April 2013) doi:10.1371/journal.ppat.1003326