Fatty acid regulation of T_H17 cells

Regulatory T cells and effector T cells (such as those of the T_H17 subset of helper T cells) have distinct metabolic requirements for their development and proliferation, with the former reliant on fatty acid oxidation and the latter reliant on glycolysis. In *Nature Medicine*, Sparwasser and colleagues describe a soil bacterium–derived compound, SorA, that skews the development of both human T cells and mouse T cells toward regulatory T cells at the expense of T_H17 cells. SorA inhibits ACC1, an enzyme involved in fatty acid metabolism, by blocking its phosphorylation. T_H17 cells from mice with conditional deletion of the gene encoding ACC1 or treated with SorA show impaired glycolysis and glutaminolysis. Accordingly, mice with conditional deletion or treated with an inhibitor show greatly ameliorated experimental autoimmune encephalitis. SorA is therefore an effective anti-glycolytic drug, and targeting ACC1 may represent a fruitful strategy for controlling autoinflammatory and autoimmune diseases. ***ZF***

***Nat. Med.* (5 October 2014) doi:10.1038/nm.3704**

Neurotrophic receptors in HSCs

Increasing evidence supports the idea that the nervous system communicates with and influences responses of the immune system. In *Nature*, Fonseca-Pereira *et al.* show that hematopoietic stem cells (HSCs) express the tyrosine receptor kinase RET, which signals in response to neurotrophic factors of the GDNF family. HSCs lacking RET have diminished fitness and are unable to reconstitute hematopoiesis in irradiated recipients. GDNF-RET signaling induces expression of the prosurvival molecules Bcl-2 and Bcl-2L1 dependent on the mitogen-activated protein kinase p38. Overexpression of either molecule can 'rescue' RET deficiency in HSCs. Moreover, treatment of wild-type HSCs with GDNF improves their transplantation efficiency, probably by enhancing their survival. These findings suggest that neuronal communication within the bone marrow stem cell niche might contribute the regulation of HSC fitness and response to physiological stress. *LAD*

Nature **514**, 98–101 (2014)

Computational toolbox

Flow and mass cytometry techniques have enabled simultaneous single-cell analysis of millions of cells with heterogeneity in multiple parameters. In *Science*, Pe'er and Nolan and their colleagues describe a 'computational toolbox' that can provide robust statistical analysis of such high-dimensional data sets. They have developed a visualization tool, DREVI, and a versatile metric, DREMI, that are able to quantify the strength of directional relationships in signaling cascades in heterogeneous cell populations. They illustrate their computational methods by comparing dynamic changes in the phosphorylation status of the invariant signaling protein CD3z, adaptor SLP-76, kinase Erk and ribosomal protein S6 that occur after engagement of the T cell antigen receptor. Because multiple cell types, such as naive T cells and effector memory T cells, can be analyzed simultaneously in the same sample, changes in the activity of signaling pathways can be observed. Such tools can thus provide new understanding about how even subtle changes can lead to profound differences in cellular responses. ***LAD***

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

IL-37 as an adaptive dampener

IL-37 is a cytokine of the interleukin 1 (IL-1) family with potent anti-inflammatory effects on innate immunity. In the *Proceedings of the National Academy Sciences*, Fujita and colleagues use a contact hypersensitivity model with the hapten DNFB to demonstrate that IL-37 is also able to dampen adaptive immunity. Although functional IL-37 is not expressed by mice, human IL-37 expressed trangenically is effective. Mice with trangenic expression of human IL-37 do not express the protein constitutively but upregulate expression locally in the skin after application of DNFB, and such mice prove resistant to the subsequent induction of contact hypersensitivity. The number, migration and phagocytosis of dendritic cells (DCs) in the skin of these mice are all normal; however, bone marrow–derived DCs from these mice have poor antigen-presenting ability. The impaired function of these DCs is probably due to their lower expression of major histocompatibility complex class II and the costimulatory receptor CD40 and production of inflammatory cytokines, as well as an increase in anti-inflammatory IL-10. *ZF*

Proc. Natl. Acad. Sci. USA (7 October 2014) doi:10.1073/pnas.1416714111

T_H1 identity

Bcl-3 is an inhibitor of transcription factor NF-κB (IκB) family protein that associates with DNA-bound homodimers of the NF-κB subunits p50 and p52 and can either promote NF-κB-dependent gene expression or inhibit it. In *Immunity*, Siebenlist and colleagues show that Bcl-3 serves as a regulator of the T_H1 lineage identity by preventing conversion into T_H17 cells. In a model of colitis in mice deficient in recombination-activating gene 1 (*Rag1*$^{-/-}$ mice), transferred *Bcl3*$^{-/-}$ CD4$^+$ T cells do not induce inflammation. Naive *Bcl3*$^{-/-}$ CD4$^+$ T cells differentiate normally into T_H1 cells *in vitro* and *in vivo*, but trace experiments with interferon-γ (IFN-γ) tagged with yellow fluorescent protein show that they gradually and cell-autonomously convert into IFN-γ$^+$IL-17$^+$ T cells and later into IL-17$^+$ T cells in the mesenteric lymph nodes of *Rag1*$^{-/-}$ hosts after transfer. The process is dependent on microbiota, stimulation via the T cell antigen receptor and IL-23. In T_H1 cells, Bcl-3 associates with the NF-κB subunits c-Rel and p50 in the promoter of the gene encoding the transcription factor RORγt. Expression of RORγt is higher in Bcl-3-deficient T_H1 cells, which is sufficient to induce conversion into T_H17 cells. ***IV***

***Immunity* 41, 555–566 (2014)**

Inflammation super-enhancers

The transcription transactivator BRD4 recruits transcription-elongation factors to active genes and is known to interact with the NF-κB subunit p65 following p65 acetylation induced by lipopoysaccharide or tumor-necrosis factor (TNF). In *Molecular Cell*, Plutzky and colleagues show that activation of endothelial cells induced by TNF or stimulation of macrophages with lipopolysaccharide leads to redistribution of BRD4 enrichment from basal cellular regulatory elements known as 'super-enhancers' to newly induced and cell-specific inflammatory super-enhancers marked by histone acetylation, enrichment of p65 binding, recruitment of RNA polymerase II and transcriptional activation. Inhibition of BRD4 has a minimal effect on the activation-induced recruitment of p65 and aceylation at these sites but impairs the RNA polymerase II–dependent induction and elongation of transcription. *In vivo*, inhibition of BRD4 diminishes the adhesion of leukocytes to TNF-activated endothelium and the accumulation of macrophages in atherosclerotic plaques, which highlights the importance of this terminal step in the functionality of super-enhancers during inflammation. *IV*

Mol. Cell **56**, 219–231 (2014)