MicroRNA and T_{reg} cells

MicroRNAs are important controllers of T cell homeostasis and function, including immunohomeostasis mediated by regulatory T cells (T_{reg} cells). Rudensky and colleagues in *Cell* show that the microRNA miR-146a has a critical role in maintaining T_{reg} cell suppression. T_{reg} cells have higher expression of miR-146a, and mice deficient in miR-146a develop a severe lymphoproliferative syndrome even though they have more T_{reg} cells. However, *in vitro*, miR-146a-deficient T_{reg} cells demonstrate essentially intact suppressive function with one exception: they are poor at suppressing IFN-γ production by target cells. Moreover, miR-146a-deficient T_{reg} cells themselves have a propensity to express IFN-γ. Blockade and knockout studies confirm that the *in vivo* pathology of the miR-146a-deficient mice can be attributed to dysregulated production of IFN-γ. They find that miR-146a regulates the important IFN-γ transcription factor STAT1 in T_{reg} cells, but how this regulates IFN-γ extrinsic to T_{reg} cells remains to be determined. *ZF*

***Cell* 142, 914–929 (2010)**

Resting BCRs

How BCR complexes remain silent on resting B cells and how they are activated by ligands is poorly understood. The assumption at present is that resting B cells express monomeric, signaling-inert BCRs that are activated by clustering. In *Nature*, Yang and Reth use a quantitative bifluorescence complementation assay to show that in the absence of antigen, BCRs have an intrinsic ability to form oligomers on the surface of cells. Mutant molecules lacking conserved hydrophilic residues in the transmembrane region of the IgD heavy chains are defective in BCR oligomerization, but not BCR assembly, and are more readily phosphorylated and internalized. The authors propose a model in which most BCRs on resting cells form closed autoinhibited oligomers, whereas a few active monomers may provide tonic survival signals. Polyvalent antigens can create clusters of signaling-active monomers by keeping BCR complexes apart. *IV*

Nature **467**, 465–469 (2010)

Innate-like $CD8^+$ T cells

$CD8^+$ T cells with innate-like features, including rapid production of IFN-γ and IL-4, arise in mice lacking the Tec family kinases Itk and Rlk. In *Immunity*, Kee and colleagues report that *i*NKT cells that arise in the thymus induce this unconventional subset of $CD8^+$ T cells. Mice lacking the E2 transcriptional antagonist Id3 have a phenotype similar to that of Itk- or Rlk-deficient mice, including more innate-like $CD8^+$ thymocytes and *i*NKT cells. The requirement for interaction between the adaptor SAP and its receptor SLAM, previously suggested to positively select the innate $CD8^+$ thymocytes, is indirect for the generation of *i*NKT cells, as the *Id3*$^{-/-}$ $CD8^+$ cells still require presentation of conventional MHC class I on thymic stromal cells. Instead, IL-4 produced by the thymic *i*NKT cells contributes to the increased generation of innate-like $CD8^+$ T cells. The function of this unusual subset requires further study. *LAD*

***Immunity* 33, 203–215 (2010)**

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

CAR-JAMs activate DETCs

Dendritic epidermal γδ T cells (DETCs) reside in the skin, where they contribute to antimicrobial protection and wound healing, but how these DETCs are activated remains unknown. In *Science*, Havran and Wilson and their colleagues show that DETC activation occurs via the γδ TCR and costimulation provided by the junctional adhesion molecule–like protein JAML. Keratinocytes express the virus receptor CAR, which is the ligand for JAML. Epidermal wounding elicits upregulation of CAR expression. Structural analysis shows the CAR-JAML ectodomain interface is extremely hydrophilic and highly conserved. CAR-JAML interaction causes the JAML dimerization or clustering necessary for the recruitment of phosphatidylinositol-3-OH kinase to the JAML intracellular domain. Ligation of JAML by CAR activates that kinase and the downstream kinases Akt and Jnk, triggering DETC proliferation and cytokine production. Thus, JAML functions analogously to CD28 in αβ T cells. The identity of the ligands recognized by the γδ TCRs expressed on DETCs remains unknown. *LAD*

Science **329**, 1205–1210 & 1210–1214 (2010)

First on site

Histone demethylases are chromatin-modifying enzymes required for methylation removal and chromatin opening at specific promoters, but the mechanistic basis of their recruitment to particular gene loci remains poorly understood. In *Molecular Cell*, Saccani and colleagues show that Aof1, a demethylase of Lys9 on histone H3, is targeted to inducible promoters in a stimulus-dependent manner and then initiates a feed-forward circuit that allows transcriptional activation. In dendritic cells and macrophages stimulated with lipopolysaccharide, Aof1 interacts with NF-κB c-Rel subunits that associate weakly with lipopolysaccharide-inducible promoters, such as *Il12b* and *Mdc*. Aof1 binding initiates promoter demethylation and enables enhanced recruitment of NF-κB transcription factors, which can drive transcription. How c-Rel subunits can associate with these promoters in unstimulated cells, as well as the mechanism by which lipopolysaccharide stimulation triggers Aof1–c-Rel interactions, remain unclear. *IV*

***Mol. Cell* 39, 750–760 (2010)**

Feeling the anti-inflammatory burn

Obesity is associated with resistance to leptin and insulin as well as a generalized proinflammatory status. In *PLoS Biology*, Carvalheira and colleagues make a direct link between exercise and the anti-inflammatory effects of hypothalamic IL-10. The hypothalamus senses the body's nutritional status and is responsible for the control of food intake and energy expenditure. Exercise in obese rats results in higher concentrations of IL-6 and IL-10 in the hypothalamus, which is associated with suppression of hyperphagia. Blockade with antibodies or administration of cytokines confirms that IL-6 and IL-10 are responsible for the beneficial effects on feeding behavior. Furthermore, IL-10 suppresses the canonical transcription factor NF-κB inflammatory pathway in the thalamus, and this is critical for restoring sensitivity to leptin and insulin and normalization of feeding behavior in obese rats. Therefore, exercise not only has the beneficial effect of greater energy expenditure but also has a directly anti-inflammatory effect on the hypothalamus, which suppresses hyperphagia. *ZF*

PLoS Biol **8**, 1-20 (2010)