NLRP3 lights a flame in the eyes

Age-related macular degeneration (AMD), a leading cause of blindness in the developed world, is characterized by the degeneration of retinal pigment epithelial (RPE) cells. In *Cell*, Ambati and colleagues identify a key role for activation of the NLRP3 inflammasome in the RPE cell death seen in AMD. They find that *Alu* RNA, an abundant noncoding retrotransposon-derived RNA species, triggers RPE cell death but is not recognized by any conventional sensors of nucleic acid, such as the various TLRs, RIG-I or Mda5. Furthermore, loss of the RNase Dicer1 results in the accumulation of *Alu* RNA in RPE cells and RPE cell death. This death seems to be unrelated to pyroptosis but requires NLRP3, caspase-1 and interleukin 18 (IL-18), and, notably, RPE cells from patients with AMD have higher expression of these inflammasome components. Dicer1 therefore seems to have a role independent of microRNA processing by preventing the accumulation of NLRP3 inflammasome–stimulatory *Alu* RNA. ***ZF***

***Cell* (11 May 2012) doi:10.1016/j.cell.2012.03.036**

Building high affinity

The B cell antigen receptor (BCR) promotes the selective survival or population expansion of germinal-center (GC) B cells of higher affinity, but how this occurs is unclear. In *Science*, Shlomchik and colleagues show that proliferating GC B cells are refractory to BCR signaling because of enhanced phosphatase activity. GC B cells have less phosphorylation of the proximal tyrosine kinases Syk and BLNK than do non-GC or naive B cells. This is due to greater activation of the tyrosine phosphatases SHIP-1 and SHP-1, which also show enhanced association with the BCR at steady state and after activation. The diminished signaling ability of GC B cells suggests that the GC BCR may favor antigen presentation over signaling and that the survival advantage of cells with high-affinity BCRs is due to more effective capture of antigen, followed by more efficient competition for T cell–dependent signals. *IV*

Science (3 May 2012) doi:10.1126/science.1213368

cDC-specific transcription factor

Humans and mice have a variety of professional antigen-presenting cells. Bone marrow–derived myeloid precursors produce heterogeneous populations that arise under homeostatic settings or are induced by inflammation, yet distinguishing classical dendritic cells (cDCs) from monocytes, macrophages and plasmacytoid DCs remains problematic, as these all express the DC marker CD11c. In the *Journal of Experimental Medicine*, two reports by Nussenzweig and Murphy and their colleagues identify Zbtb46 (BTBD4 in humans) as a zinc-finger transcription factor expressed in pre-cDCs and cDCs but not in plasmacytoid DCs or cells of other myeloid lineages. Zbtb46 itself is not needed for the generation of cDCs, but it represses the expression of receptors for growth factors for alternative myeloid lineages. Conditional depletion of Zbtb46$^+$ cells identifies a central role for cDCs in eliciting T helper type 1 responses, but immunity to tumors or *Toxoplasma* is impaired only partially. Zbtb46 thus serves as a specific marker for distinguishing cDCs and their functional activities. ***LAD***

***J. Exp. Med.* (21 May 2012) doi:10.1084/jem.20112675 & doi:10.1084/jem. 20120030**

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

Reporter effects

The *Foxp3*^{tm2Ayr} (*Foxp3*^{gfp}) reporter mouse, which expresses enhanced green fluorescent protein (GFP) fused to the amino-terminal region of the transcription factor Foxp3, is widely used to track regulatory T cells (T_{reg} cells) *in vivo*. In *Immunity*, Bettini *et al.* and Darce *et al.* report that the chimeric Foxp3-GFP protein has altered functions relative to those of native Foxp3, with consequences for the differentiation, genomic signature and regulatory function of T_{reg} cells and the onset of autoimmunity in various mouse models. Darce *et al.* report less pathology in the K/BxN mouse model of arthritis, whereas Bettini *et al.* report considerably accelerated diabetes in *Foxp3*^{gfp} mice on the NOD (nonobese diabetic) background. Defective association of Foxp3-GFP with Eos, Tip60 and HDAC7, proteins known to bind to the amino terminus of Foxp3, may explain the T_{reg} cell insufficiency and enhanced diabetes of *Foxp3*^{gfp} NOD mice. The greater efficiency of *Foxp3*^{gfp} T_{reg} cells in blocking differentiation into the T_H17 subset of helper T cells may explain the amelioration of arthritis in *Foxp3*^{gfp} K/BxN mice. Thus, the molecular substrate of T_{reg} cell effector functions varies depending on the physiological context. *IV*

Immunity **36**, 717–730 & 731–741 (2012)

A new cellular player in asthma

IL-25 is a cytokine with considerable T helper type 2 response–promoting properties and is therefore important in the etiology of asthma. In *Nature Medicine*, Lukacs and colleagues identify a previously unknown IL-25-responsive cell in the lungs that seems to be key in driving disease in a steroid-resistant model of asthma. IL-25 is the main cytokine released in the lungs after sensitization of mice with cockroach allergen. Sensitization also results in the appearance of a non–B cell, non–T cell granulocytic population that expresses the IL-17RB receptor for IL-25. In response to IL-25, these 'T2M' cells become major producers of IL-4 and IL-13, two cytokines critical for the asthma phenotype. The adoptive transfer of T2M cells into otherwise asthma-resistant *Il17rb*$^{-/-}$ host mice demonstrates that these cells are sufficient to induce disease. This population also seems to be relevant to humans, as the peripheral blood of patients with asthma has a greater abundance of T2M-analogous cells. ***ZF***

***Nat. Med.* (29 April 2012) doi:10.1038/nm.2735**

PPAR-γ in fat T_{reg} cells

Visceral adipose tissues (VATs) have a distinct subset of T_{reg} cells. In *Nature*, Mathis and colleagues show that the transcription factor PPAR-γ is required for the unique gene-expression profile and functions of VAT T_{reg} cells relative to those of lymph node T_{reg} cells. Retroviral expression of PPAR-γ1 or PPAR-γ2 with Foxp3 recapitulates much of the VAT T_{reg} cell expression profile, which differs from that induced by Foxp3 alone and includes upregulation of genes encoding molecules linked to lipid metabolism; however, PPAR-γ1 has additional inhibitory functions not seen with PPAR-γ2. *Pparg*$^{f/f}$ × *Foxp3*-Cre mice, which experience conditional loss of PPAR-γ, have fewer VAT T_{reg} cells and have altered leukocyte populations in visceral fat. These mice likewise develop metabolic syndrome. PPAR-γ expression by fat T_{reg} cells is necessary for the effective restoration of insulin sensitivity by thiazolidinedione, a drug used for the treatment of type II diabetes. These findings suggest that tissue-specific T_{reg} cells manifest distinct functions. *LAD*

Nature (16 May 2012) doi:10.1038/nature11132