A sirtuin switch in the brain

Microglia are brain-resident phagocytes with proinflammatory properties and can serve important roles in various neuropathologies. In the *EMBO Journal*, Outeiro and colleagues investigate whether the NAD$^+$-dependent deacetylase SIRT2 regulates the inflammatory activity of mouse microglia. Intracranial injection of lipopolysaccharide activates microglia, and this is exaggerated after deletion of *Sirt2*. *In vitro* culture of microglia cell lines stimulated with lipopolysaccharide (and to some extent, with other ligands of Toll-like receptors) shows that knockdown of *Sirt2* enhances the secretion of inflammatory cytokines and release of reactive oxygen and nitrogen species. Cells in which *Sirt2* is knocked down also maintain acetylation of the transcription factor NF-κB, which probably accounts for the enhanced transcription of genes encoding inflammatory molecules. Finally, activated microglia in which *Sirt2* is knocked down also trigger the death of cocultured primary neurons. Therefore, SIRT2 expressed by microglia seems to be an important anti-inflammatory switch, and defects in its function could contribute to certain diseases of the central nervous system. ***ZF***

***EMBO J.* (6 September 2013) doi:10.1038/emboj.2013.200**

Restricting HIV-1

Mammalian cells contain intrinsic factors, such as APOBEC3, SAMHD1 and TRIM5-α, that restrict pathogenic infection with HIV-1. In *Nature*, Malim and colleagues identify MX2 as another potent inhibitor of such infection , which is induced by interferon-α signaling. MX2, a GTPase known to accumulate at the cytoplasmic face of nuclear pores, may block nuclear uptake of viral replication complexes or decrease their stability. MX2 has high selectivity for primate lentiviruses, and its ability to inhibit HIV-1 replication is dependent on the presence of the viral capsid protein and partially dependent on its GTP-binding domain. MX1, the protein most closely related to MX2, inhibits a variety of RNA and DNA viruses, including influenza A virus, but has no effect on HIV-1. The mechanism by which MX2 interferes with infection by HIV-1 remains unclear. *IV*

Nature (18 September 2013) doi:10.1038/nature12542

Peripheral Aire

Extrathymic cells that express the transcriptional regulator Aire (eTACs) have been described, but their role in immunotolerance is unclear. In *Immunity*, Anderson and colleagues show that eTACs are radioresistant, bone marrow–derived MHCII^{hi}CD80^{lo}CD86^{lo}EpCAM^{hi}CD45^{lo} antigen-presenting cells (APCs) present in the secondary lymphoid organs of mice and humans. eTACs interact with CD4$^+$ T cells and induce immunotolerance via functional inactivation of interacting T cells and independently of the induction of regulatory T cells. T cells tolerized by eTACs have impaired TCR signaling, probably as a result of engagement of the TCR in the absence of effective costimulation. These findings show that Aire expression can induce tolerance in peripheral lymphoid organs. ***IV***

***Immunity* 39, 560–572 (2013)**

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

Lck availability

Restriction by major histocompatibility complex (MHC) molecules is essential for T cell function, but how this is enforced in the thymus is unclear. In *Cell*, Singer and colleagues use a mutant form of the kinase Lck (Lck^{mut}Tg) that is expressed in normal amounts but cannot associate with either the CD4 or the CD8 coreceptor. T cells in Lck^{mut}Tg mice can still be selected; however, this occurs in an Lck-dependent but MHC-independent manner. Instead, these cells must be selected on the poliovirus receptor CD155, which is expressed widely in the thymus, but why this particular molecule and not something else is required remains unclear. The germline-encoded complementarity-determining regions CDR1 and CDR2 of the T cell antigen receptor (TCR) are thought to impose recognition of MHC. However, mutation of the genes encoding those regions also ablates recognition of CD155 by the TCR, which suggests that these regions serve a more general structural role, rather than specifically directing the recognition of the TCR to MHC. *ZF*

Cell **154**, 1326–1341 (2013)

Dysfunctional T cells

Contracted T cell repertoires are found in patients with rheumatoid arthritis (RA), an autoimmune disease linked to HLA class II. In *The Journal of Experimental Medicine*, Yang *et al.* identify defects in glucose metabolism in naive and memory CD4$^+$ T cells from patients with RA. RA-associated T cells have lower expression of PFKFB3, a bifunctional enzyme required for commitment to glycolytic metabolism. As a result, those T cells divert glucose to the pentose phosphate pathway, produce less ATP and are more prone to undergo apoptosis than are T cells from healthy people. A lower abundance of PFKFB3 also leads to a decrease in autophagy, which deprives cells of macromolecule reuse. Notably, T cells from patients with systemic lupus erythematosus do not have the same defect, as their T cells have higher expression of PFKFB3. Thus, T cells from patients with RA have intrinsic metabolic defects, but why these cells have lower expression of PFKFB3 remains unknown. ***LAD***

***J. Exp. Med.* 210, 2119–2134 (2013)**

Tolerogenic MUC2

MUC2 is a mucin glycoprotein secreted by globlet cells. In *Science*, Cerutti and colleagues show how MUC2 directly promotes tolerance in the small intestine, which has a porous mucous layer. MUC2 is recognized by a receptor complex of galectin 3, the C-type lectin dectin-1 and the inhibitory receptor FcγRIIB on the surface of dendritic cells. Activation of this receptor complex by MUC2 induces the stabilization and nuclear translocation of the transcription factor β-catenin, which interferes with the expression of proinflammatory cytokines. Similarly, activation of dectin-1 and FcγRIIB by MUC2 triggers expression of interleukin 10 and transforming growth factor-β1. Thus, MUC2 contributes to both barrier protection in the large intestine and induction of a tolerizing environment in the small intestine. *LAD*

Science (26 September 2013) doi:10.1126/science.1237910