Tim-3 promotes maternal tolerance

Natural killer (NK) cells have a protective role in establishing and maintaining maternal tolerance to a developing fetus. In *Science Signaling*, Li *et al.* show that peripheral NK cells upregulate their expression of the immunoinhibitory molecule Tim-3 during the first trimester of pregnancy and thereby promote maternal–fetal tolerance via interaction with the Tim-3 ligand galectin-9. Tim-3$^+$ NK cells express anti-inflammatory cytokines and are less cytotoxic than Tim-3$^-$ NK cells. NK cells from women who have experienced recurrent miscarriages have lower expression of Tim-3 protein and are more cytotoxic than NK cells obtained during a normal pregnancy. Corresponding differences at the chromatin level and in gene expression are also seen in Tim-3$^+$ and Tim-3$^-$ NK cells. Tim-3$^+$ NK cells also contribute to an increased frequency of induced regulatory T cells dependent on the cytokine TGF-β1, which suggests another mode by which NK cells contribute to maternal–fetal tolerance. ***LAD***

***Sci. Signal.* 10, eaa4323 (26 September 2017)**

CD28 enhances mitochondrial function

Costimulation via the co-receptor CD28 is required for the generation of effective memory T cells. A lack of CD28 signaling during the priming of naive T cells results in anergic T cells that fail to provide protection against subsequent challenge. In *Cell*, Pearce and colleagues reveal that CD28 signals at initial priming lead to metabolic changes that result in the increased mitochondrial morphology, spare respiratory capacity and fatty-acid metabolism necessary for effector memory responses. Mechanistically, CD28 transiently suppresses the metabolic regulator TXNIP, which regulates expression of the microRNA miR-33. In turn, CD28 enhances expression of the miR-33 target *Cpt1a*, which encodes the rate-limiting mitochondrial enzyme carnitine palmitoyltransferase that is necessary for fatty-acid oxidation. Modulation of miR-33 expression during T cell priming is inversely correlated with memory-cell function after recall challenge. The Cpt1a inhibitor etomoxir likewise impairs the CD28-dependent function of memory T cells. Thus, early CD28 signals prepare T cells for subsequent memory responses by enhancing mitochondrial capacity and fatty-acid utilization. *LAD*

Cell (14 September 2017) doi:10.1016/j.cell.2017.08.018

What is the point of the gallbladder?

The lectin and surfactant SP-D is a secreted component of the innate immune system known mainly for its presence and function in the lungs. In the *Proceedings of the National Academy of Sciences USA*, Taniguchi and colleagues find that SP-D is also generated by epithelial cells in the gallbladder, but nowhere else within the digestive system or in the liver. SP-D is secreted into the intestine as a component of bile; once there, it binds particular commensals such as *Lactobacillus* species. Deficiency in SP-D results in dysbiosis, including a reduction in the abundance of *Clostridia* species, which have been linked to the homeostasis of regulatory T cells. SP-D-deficient mice also exhibit worse experimentally induced colitis. The apparently unique production of SP-D within the digestive system has potentially important implications for otherwise routine gallbladder removal (cholecystectomy). ***ZF***

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

Old fat macrophages

Catecholamine signaling is normal in the elderly; however, the catecholamine-induced generation of free fatty acids diminishes with age. In *Nature*, Camell *et al.* show that adipose tissue macrophages regulate the age-dependent decrease in adipocyte lipolysis in mice by lowering the availability of noradrenaline. Aged adipose tissue macrophages inhibit the release of free fatty acids from noradrenaline-stimulated young adipocytes and have high expression of enzymes that regulate catecholamine catabolism, such as monoamine oxidase A, as well as of genes encoding molecules linked to inflammasome activation. Aged *Nlrp3*$^{-/-}$ mice show restoration of expression of factors involved in catecholamine catabolism and in the release of free fatty acids after fasting, which are lower in old wild-type mice than in young wild-type mice. Inhibition of monoamine oxidase A in inflammasome-activated macrophages restores lipolysis in noradrenaline-induced adipocytes *in vitro* and fasting-induced lipolysis in old mice *in vivo*. Macrophages are present in association with sympathetic nerve fibers in the adipose tissue, which suggests that they might regulate the access of adipocytes to noradrenaline. *IV*

Nature (27 September 2017) doi:10.1038/nature23912

Breathe easy with neutrophils

The lungs are continually exposed to harmful pathogens such as *Aspergillus fumigatus*, and prompt clearance of such pathogens with limited inflammation is needed to avoid dangerous aspergillosis or collateral damage from the immune response. In *Science*, Hohl and colleagues demonstrate that myeloid cells in the lungs, such as neutrophils, induce an apoptosis-like process of programmed cell death (PCD) in *A. fumigatus* conidia. This process is dependent on the generation of reactive oxygen species in neutrophils via the NADPH complex. Accordingly, fungi that overexpress the anti-apoptotic protein AfBIR1 are relatively resistant to neutrophil-induced PCD and demonstrate enhanced virulence. This previously unknown PCD-dependent mechanism for the clearance of conidia represents an effective form of lung immunosurveillance that prevents transition of the fungus to its invasive hyphal form; additionally, it suggests a potential target for the pharmacological treatment of fungal infection. ***ZF***

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Neurodegenerative signature

Microglia lose their homeostatic function during neurodegenerative disorders. In *Immunity*, Butovsky and colleagues show that in mouse models of amyotrophic lateral sclerosis, Alzheimer's disease and multiple sclerosis, the neurodegenerative phenotype of microglia is triggered by activation of the receptor TREM2–apolipoprotein E (APOE) pathway. This phenotype is characterized by the suppression of TGF-β-dependent genes encoding homeostatic molecules, such as *Sall1* and *Tgfbr1*, and the upregulation of genes encoding inflammatory molecules, including *Apoe* and *Clec7a*, and is distinct from microglial activation induced by lipopolysaccharide or the cytokine IFN-γ. The expression of APOE and Clec7a increases in microglia situated in close proximity to amyloid-b plaques in humans and mice and is induced by the injection of apoptotic neurons but not by *Escherichia coli* or zymosan. The neurodegenerative phenotype is not induced in *Apoe*$^{-/-}$ or *Trem2*$^{-/-}$ microglia after the phagocytosis of apoptotic neurons, and in contrast to wild-type microglia, *Apoe*$^{-/-}$ microglia from the spinal cord of mice at the peak of experimental autoimmune encephalomyelitis suppress T cell proliferation. As such, APOE might inhibit a tolerogenic phenotype in microglia. *IV*

Immunity **47**, 566–581 (2017)