Brain defenders

CD8$^+$ resident memory T cells (T_{RM} cells) act as a first line of defense in tissues and are able to respond rapidly to pathogens and recruit other immune cells. In the *Journal of Experimental Medicine*, Merkler and colleagues demonstrate the existence of a de facto population of brain-resident T_{RM} cells (bT_{RM} cells) in mice. Intracranial viral infection generates bT_{RM} cells that are located chiefly along barrier surfaces such as the choroid plexus or meninges and less so in the parenchmya itself. These bT_{RM} cells proliferate homeostatically and do not require input from the periphery for their long-term maintenance, nor are peripheral memory T cells needed for the bT_{RM} cells to protect the brain from reinfection. Viral reinfection prompts a rapid response from bT_{RM} cells marked by evidence of degranulation and interferon-γ production. Both perforin and interferon-γ are required for bT_{RM} cell–mediated protection. The brain can therefore harbor T_{RM} cells that act as an effective local barrier to viral reinfection. ***ZF***

***J. Exp. Med.* (4 July 2016) doi:10.1084/jem.20151916**

Meta-inflammation and IRF3

Abundant evidence now connects over-nutrition and obesity to a chronic low-grade inflammatory state manifested not only by cells of the immune system but also, notably, by adipocytes, a process collectively known as 'meta-inflammation'. In *The Journal of Clinical Investigation*, Rosen and colleagues investigate the role of the pro-inflammatory transcription factor IRF3 in meta-inflammation. The abundance of IRF3 is greater in adipose tissue of both obese humans and mice fed a high-fat diet. Similarly, IRF3 activity, as measured by transcription of its target genes, is also greater in mice fed a high-fat diet. IRF3-deficient mice and their adipocytes show improved metabolic parameters, such as diminished insulin resistance, when the mice are fed a high-fat diet. These mice also show greater adaptive thermogenesis, probably a consequence of enhanced browning of their white adipose tissue. IRF3 therefore acts as an adipocyte-intrinsic factor that mediates pro-inflammatory signals and opposes browning. *ZF*

J. Clin. Invest. (11 July 2016) doi:10.1172/JCI86080

Kinase Cdk5 in tumors

Many tumors express the inhibitory molecule PD-L1. In *Science*, Dorand *et al.* show that expression of the serine-threonine kinase Cdk5 enhances the resistance of tumors to immunosurveillance by upregulating PD-L1 expression. Many types of tumors, including medulloblastomas, constitutively express Cdk5. Tumors that lack Cdk5 expression are more sensitive to killing mediated by CD4$^+$ T cells than are Cdk5$^+$ tumors. Cdk5 acts in response to interferon-γ signaling, common in the inflammatory tumor environment, to alter the ratio of the transcription factors IRF1 and IRF2. IRF1 promotes, whereas IRF2 represses, expression of the gene encoding PD-L1. Cdk5 suppresses IRF2 function by regulating phosphorylation of its co-repressor IRF2BP2. These findings support the proposal of a role for Cdk5 in tumor evasion of the immune system. ***LAD***

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

Of mitochondria: part I

The mitochondrial DNA of C57BL/6 (BL/6) mice and NZB/OlaHsd (NZB) mice has a degree of divergence comparable to that of the mitochondrial DNA of Eurasian and African humans. In *Nature*, Enriquez and colleagues show that BL/6^{NZB} mice, which have a BL/6 nuclear genome and NZB mitochondrial DNA, have an extended median lifespan, fewer signs of aging and a lower telomere-length-reduction rate relative to that of BL/6 mice. BL/6^{NZB} mice have higher expression of factors involved in lipid metabolism and lower expression of those factors involved in inflammatory pathways, better preservation of mitochondrial respiration, respiratory complexes and ATP synthesis, and lower old-age production of mitochondrial reactive oxygen species than that of BL/6 mice. 1-year-old BL/6^{NZB} mice have a greater ability to regulate glucose and insulin concentrations during fasting or when fed a high-fat diet. These metabolic 'readouts' correlate with a more active regulation of the mitochondrial proteome and less mitochondrial fragmentation in the heart and liver of BL/6^{NZB} mice relative to that of BL/6 mice. *IV*

Nature (6 July 2016) doi:10.1038/nature18618

Of mitochondria: part II

Mitochondrial fusion and fission are actively regulated during metabolic, differentiation and activation challenges in cells. In *Cell*, Buck *et al.* show that fused mitochondrial networks in memory T cells (T_M cells) are associated with enhanced oxidative phosphorylation, fatty-acid oxidation and memory-like characteristics. Effector T cells (T_E cells) have punctate mitochondria and activate the fission factor Drp1, whereas T_M cells have tubular mitochondria and high expression of the fusion mediators Opa1 and Mfn2. Opa1-deficient naive T cells generate normal T_E cells but markedly impaired T_M cell responses, while enforced mitochondrial fusion in T_E cells increases fatty-acid oxidation, production of interferon-g and TNF, and cell longevity after adoptive transfer of the cells. The mitochondria of T_M cells have tighter cristae in the mitochondrial membrane than those of T_E cells, suggestive of more closely associated electron-transport-chain complexes, which might correlate with more efficient oxidative phosphorylation. ***IV***

***Cell* 166, 63–67 (2016)**

Protecting lymph nodes

Pathogens that enter through the skin barrier can access draining lymph nodes via lymph fluid. In *eLife*, Cyster and colleagues identify a role for a population of non-circulating CCR6$^+$ innate-like lymphocytes that protects the exterior surfaces of lymph nodes against lymph-borne pathogens. This population shows enrichment for Vγ4$^+$ γδ T cells that can rapidly produce interleukin 17 upon bacterial or fungal challenge. The trafficking receptors S1PR1 and CCR6 are both required for proper positioning of these cells in or near the subcapsular sinus, where they can establish contact with subcapsular macrophages. The sialic-acid-binding lectin CD169 is essential for these cellular interactions and for the resistance of Vγ4$^+$ γδ T cells to hydrodynamic lymph fluid flow to maintain their retention on surface of lymph nodes. *LAD*

eLife (3 August 2016) doi:10.7554/eLife.18156