Learning during inflammation

Infection and inflammation are frequently associated with impairment in learning and memory, but the mechanistic basis of this effect is unclear. In *Nature Medicine*, Yang and colleagues use systemic exposure of mice to the synthetic RNA duplex poly(I:C) to simulate a viral infection and assess its effect on learning tasks. Poly(I:C) substantially impairs learning in a manner dependent on the cytokine TNF. Bone-marrow chimeras or selective-depletion approaches show that monocytes and macrophages present outside the central nervous system, not microglia that reside in the central nervous system, are the key source of the TNF responsible for impairing learning. At the cellular level, learning is known to be influenced by spine remodeling on neuronal dendrites. In a reporter mouse in which they can track changes in spine remodeling, the authors observe greater alterations after exposure to poly(I:C). ***ZF***

Nat. Med. **(15 May 2017)** doi:10.1038/nm.4340

Highly localized memory

Pneumonia is caused by pathobionts present in the respiratory tract, such as *Streptococcus pneumoniae*. In *Mucosal Immunology*, Mizgerd and colleagues show that resistance to pneumonia is provided by highly localized resident memory T cells (T_{RM} cells). The authors use a heterotypic stimulation model whereby mice primed via the lungs with one strain of *S. pneumoniae* are protected from infection by a different serotype. Protection is dependent on IL-17$^+$ T_{RM} cells present in the lung parenchyma, probably through their recruitment of neutrophils. Generalized, nonspecific stimulation of innate cells and new recruitment of T cells from outside the lungs seem to be dispensable for this protection. However, protection is compartmentalized, with the T_{RM} cells remaining local in the site of their generation. Thus, T_{RM} cells raised in one lung lobe offer no protection to the opposite lobe. *ZF*

Mucosal Immunol. (17 May 2017) doi:10.1038/mi.2017.43

Tissue-specific amplifiers

Type 2–mediated activation of macrophages is required for tissue defense and homeostasis. In *Science*, Minutti *et al.* show that local amplifiers enhance interleukin 4 (IL-4)-dependent activation and proliferation of macrophages in a tissue-specific manner. Sp-A, the main component of pulmonary surfactant, enhances the IL-4-induced proliferation of alveolar macrophages, and Sp-A-deficient mice infected with *Nippostrongylus brasiliensis* have less proliferation of alveolar macrophages, worm clearance and tissue healing than that of wild-type mice. C1q, a soluble defense collagen related to Sp-A, enhances the IL-4-induced proliferation of peritoneal macrophages, and C1q-deficient mice have less type 2 macrophage–dependent fibrosis after peritoneal dialysis and less liver repair after infection with *Listeria monocytogenes* than wild-type mice. Both proteins are induced by IL-4, trigger the cell-surface localization of and signal through the unconventional myosin Myo18A but show alveolar or peritoneal macrophage specificity. Such specificity might depend on the expression of co-receptors for Myo18A. ***IV***

Science **(11 May 2017)** doi:10.1126/science.aaj2067

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

Regulating hair growth

Human and mouse skin contains many tissue-resident regulatory T cells (T_{reg} cells) that localize mostly around the hair follicles. In *Cell*, Ali *et al.* show that T_{reg} cells enhance the activation and differentiation of hair-follicle stem cells (HFSCs) and hair growth. In mice, the abundance and activation of T_{reg} cells increase during the telogen (quiescent) stage of the hair follicle cycle compared with the anagen (proliferation) stage. Depletion of T_{reg} cells results in slower hair regeneration and attenuates the telogen-to-anagen transition and the proliferation of bulge HFSCs after depilation or during normal growing cycles, without affecting their steady-state numbers or inducing an inflammatory environment. T_{reg} cells in the skin have higher expression of the Notch1 ligand Jagged1 than that of T_{reg} cells in the draining lymph nodes, and depletion of T_{reg} cells changes the Notch-dependent transcriptional signature in HFSCs. T_{reg} cell enhancement is known to promote hair regeneration in patients with alopecia areata. *IV*

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IL-22 in Peyer's patches

IL-22 contributes to barrier protection by eliciting the production of mucus and antimicrobial peptides and assisting in wound healing. However, excessive IL-22 signaling can be deleterious. In the *Journal of Experimental Medicine*, Jinnohara *et al.* show that IL-22BP, a soluble IL-22 receptor and inhibitor of IL-22, is expressed exclusively by CD11b$^+$CD8α$^-$ dendritic cells in the subepithelial dome of Peyer's patches. Loss of IL-22BP leads to increased IL-22–STAT3 signaling and subsequent increased mucus production and fucosylation of intestinal epithelial cells, as well as increased production of antimicrobial peptides. This leads to diminished uptake of luminal antigens and decreased antigen presentation within the Peyer's patches. However, IL-22BP-deficient mice do not show substantial changes in the production of immunoglobulin A or alterations in microbial composition. Whether loss of IL-22BP results in altered immune responses to gut pathogens remains unclear. ***LAD***

J. Exp. Med. **(16 May 2017)** doi:10.1084/jem.20160770

Epigenetic changes in TILs

Tumor-infiltrating lymphocytes (TILs) can become functionally disabled within the tumor environment. In *Nature*, Schietinger and colleagues assess the epigenetic changes that manifest after inactivation of TILs. Through the use of an inducible liver-cancer model and infusion of tumor-specific CD8$^+$ T cells, they identify two waves of chromatin remodeling that occur in the TILs between day 5 and day 7 (stage 1) and after day 14 (stage 2). These chromatin changes include increased accessibility of sites recognized by the transcription factor NFATc1 and decreased accessibility of sites recognized by TCF1, which leads to the concordant upregulation of inhibitory molecules such as CTLA-4, PD-1 and LAG3 and downregulation of the effector molecules TNF and IFN-γ. This epigenetic reprogramming is reversible in cells at stage 1 but becomes a fixed dysfunctional state in cells at stage 2, and these states can be phenotypically distinguished by the expression of CD5, CD38 and CD101. Human CD8$^+$ TILs can also be distinguished phenotypically and epigenetically by those markers, which might be used as surrogates to determine patients' responses to immunotherapy. *LAD*

Nature (17 May 2017) doi:10.1038/nature22367