NEUROIMMUNOLOGY

γδ T cells support learning

Sci. Immunol. **4**, eaay5199 (2019)

The brain has long been considered to be a site of immune privilege; however, it is now increasingly appreciated that immune cells can enter the brain at steady state to exert important physiological effects. In *Science Immunology*, Ribot and colleagues find a distinctive population of $V_\gamma6^+$ γδ T cells in the mouse meninges but not in the brain parenchyma. These cells are derived from the fetus, are present perinatally and do not require the presence of microbiota or inflammatory signals for their maintenance in the meninges. Phenotypically, these γδ T cells are the preeminent producers of the cytokine IL-17 within the meninges but almost wholly lack production of the cytokine IFN-γ. Their steady-state production of IL-17 acts on glia — and potentially other cells of the brain parenchyma — to elicit production of the nerve growth factor BDNF. This signaling axis via γδ T cell–produced IL-17 supports synaptic plasticity and short-term spatial memory acquisition. *ZF*

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IMMUNOMETABOLISM

Histone lactylation

Nature **574**, 575–580 (2019)

The production of lactate modulates angiogenesis, hypoxia and immune cell function. In *Nature*, Zhao and colleagues show that lactate drives the lactylation of histone lysine residues and directly modulates gene transcription. In human HeLa cells and mouse bone marrow–derived macrophages (BMDMs), histone lysine lactylation (Kla) is driven by extracellular lactate or glucose-derived intracellular lactate and is increased during hypoxia, which increases glycolysis and the production of lactate. Histone Kla is induced with slower kinetics (24 h) than is histone acetylation (6 h). BMDMs treated with lipopolysaccharide and the cytokine IFN-γ or with Gram-negative bacteria have more H3K18la in the promoters of genes that are activated at later timepoints (24 h) and encode non-inflammatory, homeostatic mediators, such as *Arg1*. LPS- and IFN-γ-polarized BMDMs deficient in the lactate dehydrogenase LDHA have less production of lactate, less global histone Kla and lower expression of *Arg1* than that of wild-type BMDMs, whereas their expression of pro-inflammatory cytokines is normal. In transcription assays, histone lactylation promotes gene transcription similar to histone acetylation. *IV*

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DENDRITIC CELLS

cDC2 subsets

Cell **179**, 846–863.e24 (2019)

Classical dendritic cells are classified as cDC1 and cDC2 on the basis of their function and dependence on transcription factors. In *Cell*, Rudensky and colleagues describe two distinct subsets of cDC2s in mice and humans. Through the use of *Tbx21*$^{RFP\text{-}Cre}$ reporter mice and single-cell RNA sequencing, the authors identify a subpopulation of T-bet$^+$ cDC2s that express a core set of 69 genes, including *Tbx21*, *Dtx1* and *Ccr6*. A distinct subset of T-bet$^-$ cDC2s express *Rorc*, *Tmem176a*, *Tmem176b*, *Clec12a*, *Cx3cr1*, *Cd14*, *Il1a* and *P2rx7*. cDC2s acquire these specific transcriptional profiles in the periphery, probably in response to signals from the tissue microenvironment. The two cDC2 subsets express distinct patterns of genes encoding Toll-like receptors, chemokines and chemokine receptors. T-bet$^-$ cDC2s have a more pro-inflammatory profile, while T-bet$^+$ cDC2s express transcripts encoding molecules involved in tissue repair and have a diminished ability to polarize naive T cells. On the basis of single-cell RNA sequencing of spleen and blood cells, human CD1c^{lo}CLEC10A$^-$CLEC4A^{hi} cDC2s and CD1c$^+$CLEC10A$^+$CLEC4A^{lo} cDC2s are the equivalent of mouse T-bet$^+$ cDC2s (designated 'cDC2A') and T-bet$^-$ cDC2s ('cDC2B'), respectively. *IV*

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MYOCARDIAL INFARCTION

T_{reg} cells mend a broken heart

J. Clin. Invest. **129**, 4922–4936 (2019)

Myocardial infarction (MI) — the leading cause of death in the developed world — has a well-described pathological contribution from inflammation and the innate immune system; however, whether or not adaptive immunity has a predominantly harmful or reparative role is less clear. In *The Journal of Clinical Investigation*, Ramos and colleagues use a cardiac epitope screen in a mouse model of MI to find autoreactive T cells specific for peptides derived from the heart protein MYHCA. Far from being pathogenic, these MYHCA-autoreactive T cells assume a regulatory T cell phenotype, express genes encoding wound-healing molecules and exert a cardioprotective effect. Necropsies of patients who suffered an MI also show an increase in cells expressing the regulatory T cell transcription factor Foxp3. Heart-autoreactive T cells might therefore serve an important role in ameliorating MI — at least in the acute phase of the disease. *ZF*

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MAIT CELLS

Early life encounters

Science **366**, eaax6624 (2019)

Host interactions with commensal microbes at barrier tissues serve a crucial role in sculpting immune system responsiveness and in engendering tolerogenic networks. In *Science*, Constantinides et al. investigate how commensals influence the establishment of mucosal-associated invariant T cells (MAIT cells) in the skin of neonatal mice and how these interactions dictate adult immune responses to cutaneous infection. Surprising variability in the frequency of MAIT cells exists among separately housed mice, but not among their cage mates. MAIT cells must be established by 2–3 weeks of age, and their frequency, which remains fixed throughout life, is dictated by the abundance of riboflavin-producing microbiota during this early time period. Skin MAIT cells become exclusively cytokine IL-17A–producing cells and exhibit a transcriptional program distinct from that of other tissue-resident MAIT cells. After skin infection, MAIT cells respond to local signaling by IL-1 and IL-18, in conjunction with riboflavin-MR1-dependent antigen presentation, and secrete IL-17A and thereby promote wound healing. *LAD*

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