Generating CD4+CD8αα+ IELs

CD4+CD8αα+ double-positive intraepithelial lymphocytes (DP IELs) serve regulatory roles in the small intestine. In *Science*, Cervantes-Barragan *et al.* show that the commensal *Lactobacillus reuteri* can induce the generation of DP IELs in C57BL/6 mice. *L. reuteri* is found in mice from Charles River Laboratories but not in those from Jackson Laboratories. *L. reuteri* metabolizes tryptophan to indole-3-lactic acid, which is a ligand for the transcription factor Ahr. The generation of DP IELs requires Ahr to act in conjunction with cytokine TGF-β signaling to downregulate expression of the transcriptional regulator ThPOK in CD4+ T cells, which derepresses expression of *Cd8a*. The presence of this lactobacillus plus a tryptophan-rich diet might therefore be beneficial in patients with irritable bowel disease. ***LAD***

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Distinct Zika responses

Two lineages of Zika virus exist, African and Asian; the latter is responsible for the present epidemic of mosquito-spread infections. In *Nature Microbiology*, Foo *et al.* assess the immune responses elicited by *in vitro* infection of human blood cells with Zika virus. Clinical isolates from both lineages infect CD14+ monocytes and 'preferentially' expand the non-classical $CD14^{lo}CD16^{+}$ cell subset. While the African Zika viruses induce expression of interferon-β and the chemokine CXCL10 and other 'M1 macrophage–like' expression patterns, the Asian Zika viruses induce interleukin 10 and an 'M2 macrophage–like' expression pattern. Such monocyte shifts and gene expression are further enhanced in monocytes obtained from pregnant women during their first trimester. Notably, Asian Zika viruses, but not African Zika viruses, induce expression of fibronectin-1 and the metallopeptidase ADAMTS14, both of which have been previously associated with pregnancy complications. *LAD*

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Regulatory ILCs

Innate lymphoid cells (ILCs) regulate homeostasis and protective immunity in the intestine. In *Cell*, Fan and colleagues identify a population of intestinal regulatory ILCs that expands after pathogenic stimulation and inhibits innate immune responses. Lin− CD45+CD127+IL-10+ cells in the lamina propria and epithelium of the small intestine of mice and humans have an expression and transcriptional profile characteristic of ILCs (*Il10*, *Il7r*, *Il2ra*, *Id2* and *Ly6a*) do not express genes encoding markers specific for the ILC1, ILC2 and ILC3 subsets (*Rorc*, *Tbx21*, *Gata3*) or regulatory T cells (*Foxp3* and *Cd4*) and specifically express the transcription factor Id3 and the cytokine receptors TGF-βR and IL-2R. They develop from $\alpha_4\beta_7{}^{+}Id2^{hi}$ progenitor cells that generate all lymphoid-tissue–inducer cells and ILCs and are the only ILC subset affected by deletion of Id3. Regulatory ILCs reach peak population expansion in *Rag1*$^{-/-}$ mice on day 8 after treatment with inflammatory stimuli and produce TGF-β1 (which is required for their proliferation and survival in an autocrine manner) and IL-10 (which suppresses the activation of ILC1 and ILC3 cells). Regulatory T cells have no substantial inhibitory effect on ILC activation, which indicates that regulatory ILCs are essential in resolving innate intestinal inflammation. ***IV***

***Cell* (24 August 2017) doi:10.1016/j.cell.2017.07.027**

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

CMTM6 controls PD-L1

The checkpoint ligand PD-L1 expressed by tumor cells inhibits the effector functions of CD8+ T cells. In *Nature*, Burr *et al.* and Mezzadra *et al.* identify the previously uncharacterized transmembrane protein CMTM6 as a critical regulator of the cell-surface expression of PD-L1 in cancer cells and myeloid cells in mice and humans. CMTM6 associates with both constitutive PD-L1 and interferon-γ-induced PD-L1 at the plasma membrane and in recycling endosomes. Depletion of CMTM6 does not affect transcription of the gene encoding PD-L1 or trafficking of PD-L1 from the endoplasmic reticulum to the cell surface but stabilizes cell-surface PD-L1 by preventing its lysosome-mediated degradation, possibly by preventing its ubiquitination. Depletion of CMTM6 enhances T cell activation and the anti-tumor response *in vitro* and in mouse melanoma models. CMTM6 shows specificity for PD-L1 and does not effect the expression of major histocompatibility complex class I or PD-L2. In addition, CMTM4 interacts with PD-L1 and restores PD-L1 expression in CMTM6-deficient melanoma cells, but other CMTM proteins do not. *IV*

Nature (16 August 2017) doi:10.1038/nature23643 and doi:10.1038/nature23669

Blood T_{FR} cells

Follicular regulatory T cells (T_{FR} cells) are a subset of T_{reg} cells that are specialized in the control of germinal-center (GC) and antibody responses. In *Science Immunology*, Graca and colleagues investigate the origin and function of the little-known blood counterpart of GC-resident T_{FR} cells. They find that in blood from human donors, there are more T_{FR} cells, defined as CXCR5+FOXP3+, in those with Sjögren syndrome or after vaccination against seasonal influenza virus, and that these cells correlate with antibody production. Much like conventional T_{reg} cells, blood T_{FR} cells can suppress T cell responses *in vitro*, but unlike GC T_{FR} cells, they do not seem to specialize in the suppression of antibody responses. Furthermore, unlike other T_{reg} cell populations, they have a predominantly naive phenotype. Developmentally, blood T_{FR} cells are generated in secondary lymphoid tissue from GC precursor cells but exit into the blood before differentiating into fully functional T_{FR} cells. ***ZF***

***Sci. Immunol.* (11 August 2017) doi:10.1126/sciimmunol.aan1487**

Testicular macrophage origin

The testes contain two populations of tissue macrophages, interstitial and peritubular; among other functions, they are involved in maintaining immunological privilege, but their developmental relationships are unknown. In the *Journal of Experimental Medicine*, Sieweke and colleagues observe that beyond the histological localization and morphology of these cells, the markers CD64 and MHC class II can be used to reliably distinguish interstitial macrophages from peritubular macrophages. Expression analysis shows that both populations have an anti-inflammatory tissue-macrophage-like signature, with slow turnover and a long lifespan. However, fate-mapping and adoptive-transfer approaches show that the two populations are developmentally distinct: interstitial macrophages are initially entirely embryonically derived, whereas peritubular macrophages appear only postnatally and are bone marrow derived. As the *in situ* self-renewal ability of interstitial macrophages diminishes post-natally, there is a degree of input from bone marrow precursor cells, which gives them a mixed origin. *ZF*

J. Exp. Med. (7 August 2017) doi:10.1084/jem.20170829