

T<sub>RM</sub> CELLS

Tissue adaptation

Science <https://doi.org/10.1126/science.aat6280> (2018)

Commensals and commensal-reactive lymphocytes coexist at barrier tissues. In *Science*, Belkaid and colleagues show that skin-resident commensal-specific T cells express a type 17 program associated with a poised type 2 program. *Staphylococcus epidermis*-colonized mice develop long-lived, tissue-resident, *S. epidermis*-specific CD8<sup>+</sup> memory T cells. *S. epidermis*-elicited RORγt<sup>+</sup>CD4<sup>+</sup> T<sub>H</sub>17 cells and RORγt<sup>+</sup>CD8<sup>+</sup> Tc17 cells produce the type 2 cytokines IL-5 and IL-13 after intradermal injection of chitin, sand fly bites or skin-specific deletion of regulatory T cells. During homeostasis, *S. epidermis*-specific Tc17 cells co-express the transcription factors RORγt and GATA-3 and express a broad GATA-3-dependent type 2 transcriptome (*Il5*, *Il13* and *Ccr8*, but not *Il10* or *Il4*), without protein translation. Exposure to IL-18 in the context of TCR stimulation triggers production of IL-5 and IL-13 in *S. epidermis*-specific Tc17 cells and T<sub>H</sub>17 cells, regardless of whether they expressed IL-17A previously or not. These results highlight the plasticity and adaptability of tissue-resident commensal-specific T cells. IV

<https://doi.org/10.1038/s41590-018-0306-9>

INHIBITORY RECEPTORS

New ligand for LAG-3

Cell <https://doi.org/10.1016/j.cell.2018.11.010> (2018)

MHC class II is considered the canonical ligand for the inhibitory receptor LAG-3.

In *Cell*, Chen and colleagues identify the fibrinogen family protein FGL1 as a major ligand for LAG-3. The FGL1–LAG-3 interaction is conserved in human and mouse, is specific to FGL1, involves the fibrinogen-like domain of FGL1 and the D1–D2 domain of LAG-3 and is independent of MHC class II. *Fgl1*<sup>-/-</sup> mice develop spontaneous autoimmunity with age. Similar to *Lag3*<sup>-/-</sup> mice, *Fgl1*<sup>-/-</sup> mice control the growth of inoculated tumors better than wild-type mice do, in a manner dependent on CD8<sup>+</sup> T cells and CD4<sup>+</sup> T cells. Antibodies to LAG-3 are not protective against tumors in the *Fgl1*<sup>-/-</sup> mice. *FGL1* mRNA, which is normally expressed only in liver and pancreas, is upregulated in a variety of human solid tumors, and high expression of FGL1 in the plasma of patients with melanoma or lung cancer is associated with decreased survival in response to therapy with antibody to PD-1. These results indicate that the FGL1–LAG-3 interaction represents a mechanism of tumor evasion. IV

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IMMUNOMETABOLISM

Suppressing alarmins

Nat. Metab. <https://doi.org/10.1038/s42255-018-0001-z> (2018)

Increasing evidence shows that the immune system senses diet-derived signals that then influence metabolic responses. In *Nature Metabolism*, Fishman and colleagues report a link between nutrient-induced glucose-

dependent insulinotropic polypeptide (GIP) signaling and the suppression of myeloid cell inflammatory responses. Mice that lack expression of the GIP receptor specifically in myeloid cells exhibit excessive weight gain, impaired glucose tolerance and dysregulation of cold-induced adaptive thermogenesis when fed a high-fat diet. Lack of the GIP receptor leads to increased expression of the alarmin S100A8 by fat-resident myeloid cells. This scenario leads to greater myelopoiesis, neutrophilia and recruitment of myeloid cells to fat depots than that of wild-type mice. This phenotype is ‘rescued’ by deficiency in S100A9, which stabilizes S100A8 protein and hence leads to functional double deficiency in the alarmins. The findings show a role for GIP signaling in myeloid cells in the maintenance of insulin sensitivity and thermogenesis in adipose tissues. LAD

<https://doi.org/10.1038/s41590-018-0308-7>

VACCINE RESPONSES

Vaccine sex differences

Proc. Natl. Acad. Sci. USA <https://doi.org/10.1073/pnas.1805268115> (2018)

Immune responses can be strongly influenced by biological sex; however, this is rarely considered as a variable in vaccine responses. Klein and colleagues, in the *Proceedings of the National Academy of Sciences*, use a mouse model of influenza virus challenge and vaccination to systematically compare responses in males and females. Female mice show more-robust humoral and cellular immunity than that of male mice after infection with influenza virus, although vaccination serves to protect both sexes equivalently. Passive transfer of serum, however, demonstrates that antibodies in female mice mediate more-potent protection. B cells from female mice have higher expression of TLR7, and knockout of this receptor impairs their more-potent antibody response. Therefore, TLR7 might, at least in part, underpin sex differences in vaccine efficacy. ZF

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ANTI-VIRAL IMMUNITY

Regulating MAVS

Cell Host Microbe **24**, 776–790 & 791–803 (2018)

Cytosolic RNA viruses are detected by the intracellular sensors RIG-I or MDA5, which both signal via the mitochondrial anti-viral signaling protein MAVS to initiate anti-viral immunity by inducing type I interferons and interferon-response gene expression. Two reports in *Cell Host & Microbe* identify distinct modes of post-translation regulation of MAVS. Li et al. show that MAVS is modified on Ser366 by O-linked-β-N-acetylglucosamine after viral infection. Such modification is required for K63-linked poly-ubiquitination and optimal activation of downstream TBK and NF-κB signaling pathways. Dai et al. show that the poly-ubiquitination of MAVS is negatively regulated by the host scaffold protein FAF1 through competition with the E3 ligase TRIM31. FAF1 is inactivated by phosphorylation by the kinase IKKε to derepress MAVS. Both pathways suggest that the poly-ubiquitination of MAVS is tightly regulated to prevent spurious or prolonged inflammatory responses. LAD

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