

REGULATORY T CELLS
Mst kinase roles

Immunity <https://doi.org/10.1016/j.immuni.2018.10.010> (2018)

Regulatory T cells (T_{reg} cells) require the cytokine IL-2 for their suppressive activity, yet T_{reg} cells are adapted to low concentrations of IL-2, which has prompted questions about how efficient use of IL-2 is achieved. In *Immunity*, Chi and colleagues show that T_{reg} cells utilize the Hippo signal-transduction pathway to amplify IL-2-mediated activation of the transcription factor STAT5. Kinase-inhibitor screens identify roles for the Hippo kinases Mst1 and Mst2 in T_{reg} cells. Mice with T_{reg} cell-specific loss of Mst1-Mst2 exhibit a scurfy-like autoimmune phenotype and die prematurely. Loss of Mst kinases impairs T_{reg} cell lineage stability and survival in response to IL-2. Mechanistically, Mst1 interacts with the actin cytoskeleton regulators DOCK8, LRCH and Rac1, which regulate T cell mobility. Consistent with that finding, Mst kinase-deficient T_{reg} cells display defective homing and positioning within lymphoid organs, in addition to defective activation of phosphorylated STAT5 that compromises their suppressor function. LAD

<https://doi.org/10.1038/s41590-018-0284-y>

GENE THERAPY
Cas9-directed immunity

Nat. Med. <https://doi.org/10.1038/s41591-018-0204-6> (2018)

The CRISPR-Cas9 nuclease system holds great promise for therapeutic

manipulation of the genome, but neutralizing immunity to this bacteria-derived product could severely limit its utility in vivo. In *Nature Medicine*, Schmueck-Henneresse and colleagues investigate whether the normal human population has pre-existing T cell immunity to the Cas9 component derived from *Streptococcus pyogenes* (SpCas9), a bacterium that causes common childhood infections. Both CD4⁺ effector T cells and CD8⁺ effector T cells respond to Cas9 in almost all donors assessed. In addition, responses to SpCas9 orthologs derived from *Acidaminococcus* and *Staphylococcus* are detected. Regulatory T cells also respond to SpCas9, which suggests that although pre-existing T cell immunity to Cas9 is prevalent in the human population, it might be mitigated by regulatory T cell-mediated suppression. ZF

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NEUROIMMUNOLOGY
Blood-brain barrier integrity

Proc. Natl. Acad. Sci. USA <https://doi.org/10.1073/pnas.1808609115> (2018)

Aging is associated with progressive systemic increases in inflammation that can contribute to neurodegeneration. In the *Proceedings of the National Academy of Sciences*, Mucke and colleagues use a mouse model to investigate the choroid plexus (CP), a major gateway that regulates entry of cells of the immune

system into the brain. They observe that expression of the anti-aging protein Klotho decreases in the CP of aged mice. Experimental depletion of Klotho specifically in the CP results in increased inflammatory signatures in the CP, infiltration by macrophages and enhanced microglial activation in the brain in response to lipopolysaccharide challenge. In vitro modeling shows that Klotho regulates inflammation by cooperating with signaling via the fibroblast growth factor FGF23 to reduce activation of the NLRP3 inflammasome. High levels of Klotho in the CP might therefore enhance blood-brain barrier integrity. ZF

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GUT EPITHELIUM
Stem cell-immune cell cross-talk

Cell <https://doi.org/10.1016/j.cell.2018.10.008> (2018)

The gut epithelium constantly regenerates through the rapid proliferation and differentiation of intestinal stem cells (ISCs). In *Cell*, Biton et al. identify two subpopulations of proliferative Lgr5⁺ ISCs that express major histocompatibility class II (MHCII), process extracellular antigens and activate naive T cells. In intestinal organoid cultures, the addition of regulatory T cells or the anti-inflammatory cytokine IL-10 leads to the expansion of ISC populations; addition of the T_H1 subset of helper T cells or the cytokine IFN- γ induces the differentiation of ISCs into Paneth cells; and the addition of T_H2 cells or the cytokine IL-13 induces the differentiation of ISCs into tuft cells. In mice, infection with *Salmonella enterica* or *Heligmosomoides polygyrus* increases the frequency of MHCII⁺ ISCs and the number of Paneth cells or tuft cells, respectively. Mice that lack expression of MHCII on Lgr5⁺ ISCs or T cell-deficient mice have an increased number of ISCs. Regulatory T cell-deficient mice have a lower frequency of quiescent Lgr5⁺ ISCs, an increased frequency of MHCII⁺ ISCs and increased proliferation and differentiation of ISCs into Paneth and tuft cells. IV

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ANTIGEN PRESENTATION
cDC1 cross-priming

Science **362**, 694–699 (2018)

Cross-presentation of exogenous particulate antigen is essential for the priming of CD8⁺ T cells and effective adaptive immunity to viruses and tumors. In *Science*, Theisen et al. identify a new player, the BEACH domain-containing protein WDFY4, that is expressed in CD8 α ⁺XCR1⁺ classical dendritic cells (cDC1s) and is necessary for their cross-presentation function. Although WDFY4-deficient mice develop cDC1s normally and can mount protective interleukin 12-dependent responses to *Toxoplasma gondii*, these mice fail to efficiently cross-present antigen for priming CD8⁺ T cells after viral or tumor challenge. WDFY4 localizes near the cytoplasmic face of the plasma membrane, co-localizing with clathrin- and Rab11-containing vesicles. Protein co-immunoprecipitation assays suggest specific interaction between WDFY4 and the chaperone protein HSP90. The specific role of WDFY4 in cross-presentation remains to be delineated, but its identification provides a hook by which to investigate phagosomal antigen-processing pathways. LAD

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