TUMOR IMMUNOLOGY

Regnase-1 in the TME

Nature **576**, 471–476 (2019)

Activated T cells often become less functional in the tumor microenvironment or during chronic infection. In *Nature*, Chi and colleagues describe an unbiased CRISPR-Cas9 screen in CD8$^+$ T cells that identifies Regnase-1 as a negative regulator of T cell function within the tumor environment. Regnase-1-null CD8$^+$ T cells persist longer in tumors, exhibit enhanced mitochondrial spare respiratory capacity and increased oxidative phosphorylation, and express more effector molecules as compared to wild-type cells. Tumor-bearing mice receiving Regnase-1-null CD8$^+$ T cells also survive longer. The authors also identify mRNAs encoding the transcription factor BATF as a major target of Regnase-1, as deletion of *Batf* abolished the enhanced antitumor activity of Regnase-1-null CD8$^+$ T cells. These findings reveal Regnase-1 as a regulator of cytotoxic T cell function within the tumor microenvironment. *LAD*

https://doi.org/10.1038/s41590-020-0591-y

NEUROIMMUNOLOGY

Nociceptors in antimicrobial defense

Cell https://doi.org/10.1016/j.cell.2019.11.014 (2019)

Nociceptors are sensory neurons that detect harmful stimuli. In *Cell*, Chiu and colleagues show that TRPV1$^+$ nociceptors in the dorsal root ganglia protect mice against infection with *Salmonella enterica* serovar Typhimurium (ST). Deletion of TRPV1$^+$ neurons in mice reduces the abundance of segmentous filamentous bacteria (SFB) embedded in the epithelium of the ileum Peyer's patches (PP). The density of Peyer's patches M cells, which are used as entry points by ST for systemic dissemination, is higher in TRPV1$^+$ neuron-depleted mice. Transplantation of SFB or depletion of M cells reduces the ST burden in TRPV1$^+$ neuron-depleted mice. Mice deficient for CGRP, a neuropeptide produced by dorsal root ganglia neurons in culture in response to ST, have more M cells, reduced SFBs and increased ST loads compared to wild-type mice. Immune and epithelial parameters are normal in TRPV1$^+$ neuron-depleted mice, indicating that nociceptors modulate host susceptibility to ST through regulating M cells and SFB homeostasis. *IV*

https://doi.org/10.1038/s41590-019-0586-8

TYPE 1 DIABETES

The benefits of exhaustion

J. Clin. Invest. https://doi.org/10.1172/JCI126595 (2019)

The rate of loss of beta cells in type 1 diabetes (T1D) can be highly variable between patients. In the *Journal of Clinical Investigation*, Long and colleagues use mass cytometry to deep-phenotype islet-specific CD8$^+$ T cells from patients with T1D and healthy controls in order to understand whether these cells — which are known drivers of T1D — influence the rate of loss of residual beta cell mass. Patients with T1D were stratified into 'slow' or 'rapid' progressors depending on the rate of C-peptide loss. Interestingly, slow and rapid progressors and even healthy controls showed equivalent frequencies of islet-reactive CD8$^+$ T cells in peripheral blood; however, the phenotype of the CD8$^+$ T cells clearly differed. Specifically, slow progressors' cells showed an exhausted phenotype and were poorly responsive in vitro, whereas rapid progressors' CD8$^+$ T cells had an activated phenotype. CD8$^+$ T cell phenotype may thus represent a useful biomarker to predict the progression of T1D. *ZF*

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TISSUE HOMEOSTASIS

Protective ILC1s

Immunity https://doi.org/10.1016/j.immuni.2019.11.004 (2019)

ILC1s are the dominant subset of innate lymphoid cells (ILCs) in the liver. In *Immunity*, Nabekura et al. show that acute liver injury triggered by injection with carbon tetrachloride (CCl_4) activates ILC1s to produce the cytokine interferon-γ (IFN-γ), which in turn promotes the survival of hepatocytes. NK1.1$^+$DX5$^-$CD49a$^+$CD200R$^+$ ILC1s, but not NK1.1$^+$DX5$^+$CD49a$^-$CD200R$^-$ natural killer (NK) cells, NKT cells, αβ T cells, γδ T cells or MAIT (mucosa-associated invariant T) cells, make IFN-γ, and depletion of liver ILC1s or deletion of *Ifng* increases the amount of alanine aminotransferase in the serum—a measure of liver injury—after injection of CCl_4 or acetaminophen. Production of IFN-γ in ILC1s is dependent on the expression of the NK receptor DNAM-1 (CD226) on these cells, is induced by the cytokine IL-12 and extracellular ATP and, in turn, upregulates the expression of the prosurvival molecules Bcl2 and Bcl-x_L in hepatocytes. Transferred ILC1s protect *Rag2*$^{-/-}$*Il2r*$^{-/-}$ mice from CCl_4-induced liver injury, indicating that ILC1s are necessary and sufficient in this context. *IV*

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INNATE IMMUNITY

Nuclear ignorance

Elife **8**, e47491 (2019)

Cyclic GMP-AMP synthase (cGAS) is an innate immune sensor that detects double-stranded DNA (dsDNA), which activates the STING pathway to elicit type I interferon production. It is widely assumed that cGAS is localized to the cytoplasm, thereby averting activation of host nuclear DNA. In *eLife*, Volkman et al. show that, contrary to this assumption, the vast majority of cellular cGAS resides in the nucleus, where it is tightly tethered to nuclear chromatin fractions. Addition of exogenous dsDNA does not induce cGAS cytosolic translocation. Nuclear tethering of cGAS is distinct from its dsDNA binding and self-dimerization, which activates its nucleotidyltransferase catalytic core. However, the authors identify several conserved positively charged amino acids that, when mutated, disrupt cGAS tethering in the nucleus and lead to constitutive activation. These findings explain previous confounding studies showing that cGAS recognizes viral pathogens that replicate in the nucleus, but they also reveal that regulation of cGAS activation is more complicated. *LAD*

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