TISSUE RESIDENCY

Maturation programs

Immunity **52**, 295–312.e11 (2020)

The molecular programs that drive the differentiation of regulatory T (T_{reg}) cells into tissue resident cells remain unclear. In *Immunity*, Delacher et al. describe how Klrg1$^+$ST2$^+$ T_{reg} cells, a population of tissue resident T_{reg} cells present in all non-lymphoid tissues, sequentially differentiate from spleen T_{reg} progenitors. On the basis of ATAC-seq data, Klrg1$^+$ST2$^+$ T_{reg} cells from skin, colon and lung are distinct from tissue conventional T cells and lymph node T_{reg} cells. On the basis of the expression of the transcription factor Nfil3, which is part of a 'core' chromatin accessibility signature in Klrg1$^+$ST2$^+$ T_{reg} cells, as well as single-cell RNA-seq data, TCR analysis and analysis of postnatal tissue seeding, the authors infer a sequential differentiation of spleen Klrg1$^-$ *Nfil3*$^+$ cells into lymph node Klrg1$^+$*Nfil3*$^+$ T_{reg} cells and then into Klrg1$^+$ST2$^+$ T_{reg} cells in tissues. Klrg1$^-$*Batf*$^{-/-}$ precursors do not differentiate into Klrg1$^+$ST2$^+$ T_{reg} cells, indicating that the transcription factor Batf enables the development of mature T_{reg} cells in the tissues. *IV*

https://doi.org/10.1038/s41590-020-0655-z

IMMUNE SIGNATURES

Predicting responses

Nat. Med. https://doi.org/10.1038/s41591-020-0769-8 (2020)

Individual responses to vaccination can vary widely, making it difficult to predict whether someone will mount a robust antibody response or a poor response. In *Nature Medicine*, Tsang and colleagues identify a prevaccination blood transcriptional signature (TGSig) that can predict 'high' and 'low' responders. TGSig is stably expressed at baseline in healthy individuals. Interestingly, for a subset of patients with systemic lupus erythematosus (SLE), whose disease is correlated with plasmablast frequency, this same TGSig expressed during periods of disease quiescence is predictive of flare intensity. Single-cell CITE-seq (cellular indexing of transcriptomes and epitopes by sequencing) analysis revealed that plasmacytoid dendritic cells, rather than B cells, are primarily responsible for the differences observed in gene expression that define the blood TGSig. Accordingly, type I interferon expression by plasmacytoid dendritic cells is linked to elevated activation of B and T cells, consistent with the higher immune response seen in healthy individuals and the more severe flares in the SLE cohort. *LAD*

https://doi.org/10.1038/s41590-020-0656-y

INNATE IMMUNITY

Sirtuin regulation of NLRP3

Cell Metab. **31**, 580–591 (2020)

Age-associated chronic inflammation has been dubbed 'inflammaging' and is linked to persistent activation of the NLRP3 inflammasome. In *Cell Metabolism*, He et al. show that NLRP3 is post-translationally modified by acetylation of conserved lysines located within the pyrin domain. Acetylated NLRP3 assembles more readily into active inflammasomes. The deacetylase SIRT2 negatively regulates NLRP3 activation. Accordingly, loss of SIRT2 enhances NLRP3–caspase 1 activation of proinflammatory interleukin (IL)-1β and IL-18. Expression of *Sirt2* decreases in macrophages from older mice as compared to young mice, a finding correlated with increased NLRP3 and IL-1β activation. Older mice, especially SIRT2-deficient mice, have decreased glucose tolerance and insulin resistance — hallmarks of metabolic syndrome. These findings suggest that some effects of inflammaging are due to decreased SIRT2-mediated control of NLRP3 activation. *LAD*

https://doi.org/10.1038/s41590-020-0657-x

MYCOBACTERIUM INFECTION

An unwelcome boost

Elife **9**, e52668 (2020)

Attempts to enhance immune responses to *Mycobacterium tuberculosis* (Mtb) infection can, paradoxically, worsen infection and lead to active tuberculosis. In *eLife*, Elkington and colleagues investigate the mechanism of disease enhancement by using an in vitro microsphere model of Mtb infection. Both granulomas from patients and microsphere models show expression of the checkpoint pathway molecules PD-1, PD-L1 and PD-L2, and their expression is enhanced by hypoxia. Checkpoint blockade increases proinflammatory cytokine expression in the microspheres, with TNF in particular seeming to enhance Mtb growth. These findings suggest thwat, while certain inflammatory cytokines are necessary to combat Mtb effectively, their overproduction, such as that elicited by checkpoint blockade, may result in unintended and harmful consequences. *ZF*

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CHRONIC INFECTIONS

Immunity remodeled

Proc. Natl Acad. Sci. USA https://doi.org/10.1073/pnas.1913776117 (2020)

Many pathogens can infect the thymus and thereby potentially disrupt the education and development of thymocytes. In the *Proceedings of the National Academy of Sciences of the USA*, Brooks and colleagues use a chronic lymphocytic choriomeningitis virus (LCMV) model to investigate the long-term consequences of infection on the T cell compartment. Following infection, LCMV is readily detectable in the thymus, primarily infecting hematopoietic cells and especially medullary dendritic cells. LCMV infection results in involution of the thymus and a dramatic reduction in double-positive thymocytes. This thymic disruption and the loss of thymocytes are dependent on the recruitment of LCMV-specific CD8$^+$ T cells and a largely T cell–intrinsic interferon-α–STAT2 signaling pathway. Surprisingly, the continued presence of LCMV in the thymus doesn't result in negative selection of LCMV-specific thymocytes; rather, there appears to be a compensatory reduction in negative selection, allowing rescue of these useful clones, but at the cost of the escape of potentially hazardous autoreactive T cells. *ZF*

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