INFLAMMATION

Mapping IL-1 in the brain

Immunity https://doi.org/10.1016/j.immuni.2018.12.012 (2018)

In the central nervous system, the cytokine IL-1 controls sleep regulation, memory consolidation, neurodegeneration and sickness behavior. In *Immunity*, Quan and colleagues use a mouse model that allows the in vivo visualization of cells that express mRNA encoding the IL-1 receptor IL-1R1 (*Il1r1*) and the cell-type-specific re-expression of endogenous IL-1R1 to investigate the effect of IL-1 in the brain. Under physiological conditions, *Il1r1* is expressed in endothelial cells, dentate gyrus neurons and choroid plexus cells and at very low levels in astrocytes but not in microglia or macrophages. After intra-cerebroventricular injection of IL-1β, endothelial IL-1R (eIL-1R1) mediates sickness behavior; eIL-1-R1 and myeloid IL-1R1 inhibit neurogenesis; and ventricular (choroid plexus) IL-1R1 (vIL-1R1) recruits monocytes. vIL-1R1 and eIL-1R1 mediate the infiltration of neutrophils via the ventricular route and vascular route, respectively, and induce activation of microglia, while eIL-1R1 induces the production of inflammatory mediators in microglia. *IV*

https://doi.org/10.1038/s41590-019-0337-x

INFLAMMATION

Amateur phagocytes

Nat. Neurosci. https://doi.org/10.1038/s41593-018-0324-9 (2018)

Clearance of myelin debris at the site of spinal cord injury (SCI) is critical for axon regeneration, remyelination and resolution of inflammation. In *Nature Neuroscience*, Ren and colleagues use mouse models of SCI to show that endothelial cells in the lining of microvessels, which form early in the epicenter of the lesion, engulf and degrade myelin debris. Brain microvascular endothelial cells (BMECs) engulf myelin much more slowly than do macrophages, require opsonization of myelin via immunoglobulin IgG and use the autophagy–lysosomal pathway for the degradation of myelin. Engulfment of myelin increases the expression of genes encoding inflammatory cytokines and chemokines (*Il4*, *Il6*, *Ccl2* and *Nos2*) and those encoding molecules involved in autophagy (*Atg3*, *Atg5* and *Gabarap12*) and downregulates the expression of genes encoding molecules involved in angiogenesis (Notch, adhesion and cell junction). Injection of myelin-fed BMECs at the site of SCI promotes angiogenesis, the recruitment and activation of macrophages and the deposition of collagen I and fibronectin. *IV*

https://doi.org/10.1038/s41590-019-0338-9

REGULATORY T CELLS

Metabolism meets gene regulation

Nature https://doi.org/10.1038/s41586-018-0846-z (2019)

Regulatory T cells (T_{reg} cells) exhibit a cellular metabolism distinct from that of $CD4^+$ effector T cells. In *Nature*, Weinberg et al. show that mitochondrial complex III is required for the suppressive activity of T_{reg} cells. Mice that conditionally lack expression of *Uqcrsf1* or *Uqcrq*, which encode components of mitochondrial complex III, develop a scurfy-like autoimmune phenotype, and their T_{reg} cells fail to suppress effector cells in vitro. Interestingly, expression of the transcription factor Foxp3, cytokine receptor CD25 and immunomodulatory receptors CTLA-4 and GITR is not diminished in T_{reg} cells from mitochondrial complex III–deficient mice, nor is the T_{reg} cellularity of those mice altered relative to that of wild-type mice. Instead, expression of the neuropilin NRP1, inhibitory receptor PD-1, AMP nucleotidase CD73 and checkpoint receptor TIGIT is lower in mitochondrial complex III–deficient T_{reg} cells. Loss of mitochondrial complex III in T_{reg} cells alters cellular NAD^+/NADH ratios and increases cellular levels of succinate and 2-hydroxyglutarate, which are correlated with alterations in DNA-methylation patterns and altered gene expression. These findings suggest that the suppressive activity of T_{reg} cells is more complex than previously thought. *LAD*

https://doi.org/10.1038/s41590-019-0339-8

INFLAMMATORY BOWEL DISEASE

Microbiotal impact

Immunity https://doi.org/10.1016/j.immuni.2018.12.015 (2018)

The host microbiota helps shape the composition of the gut immune system, which in turn can affect disease susceptibility in complex ways. In *Immunity*, Faith and colleagues use fecal microbiota transfer (FMT) from healthy donors and those with inflammatory bowel disease (IBD) into germ-free mice to understand mechanistic changes in the gut immune system. At low resolution, the broad composition of the microbiota from donors with IBD and that from healthy donors looks similar; however, they induce distinct immune cell populations. IBD-derived FMT results in many more cells of the T_H17 and T_H2 helper T cell subsets but fewer regulatory T cells expressing the transcription factor RORγt. Mice that received IBD-derived FMT also exhibit worse transfer-colitis sequelae, with the relative frequency of induction of $ROR\gamma t^+$ regulatory T cells versus that of T_H17 cells being predictive of disease severity. *ZF*

https://doi.org/10.1038/s41590-019-0341-1

STERILE INFLAMMATION

Implant response

Nat. Mater. https://doi.org/10.1038/s41563-018-0271-6 (2018)

Orthopedic implants composed of cobalt-chrome — generally considered biocompatible — can occasionally elicit inflammation and contribute to implant failure. In *Nature Materials*, Gause and colleagues investigate the ability of cobalt-chrome microparticles to initiate inflammation in mouse models. Micrometer-sized microparticles, much like those frequently seen in patients with worn cobalt-chrome implants, induce caspase-1-independent type 2 immunity, with macrophages being central to this response. Mechanistically, this type 2 immunity is driven by the uptake of microparticles by macrophages, which then activates SYK–BTK signaling, macrophage death and release of the cytokine IL-33. Interestingly, this microparticle-triggered type 2 response seems to be initiated by pathways qualitatively distinct from those associated with helminth infection. Failed human implants show a similar macrophage response and type 2 immunity around implants. *ZF*

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