THE GUT EPITHELIUM

Villus regional heterogeneity

Cell https://doi.org/10.1016/j.cell.2018.08.063 (2018)

The position of enterocytes along the villus correlates with their age, exposure to morphogen gradients and hypoxia. In *Cell*, Moor et al. analyze the transcriptome of microdissected epithelial samples spanning the length of a villus in the mouse jejunum to establish a panel of landmark genes, which they then use to map enterocytes, analyzed by single-cell RNA sequencing, in the geography of the villus. The data reveal the regional and functional heterogeneity of enterocytes in the villus. The biosynthetic capacity of enterocytes decreases gradually as they migrate toward the top. Cells at the bottom, just above the crypt intestinal stem cell niche, express genes encoding antimicrobial molecules, such as *Reg3g* and *Lypd8*. The middle shows enrichment for transporters for amino acids and carbohydrates, while the upper part of the villus shows enrichment for cholesterol transporters. The cells at the tip express an immunomodulatory program, including the ectonucleosidase CD73, and genes encoding molecules involved in the organization of tight junctions. This pattern of expression is confirmed by proteomics analysis. *IV*

https://doi.org/10.1038/s41590-018-0266-0

INNATE IMMUNITY

Rules of engagement

Nature https://doi.org/10.1038/s41586-018-0657-2 (2018)

The innate immune response is the first line of defense against pathogens. In *Nature*, Hagai et al. use bulk and single-cell transcriptomics analysis of fibroblasts and bone marrow–derived mononuclear phagocytes (from humans, mice and several other mammals) stimulated with the double-stranded RNA poly(I:C) or lipopolysaccharide, respectively, to map the architecture of the innate immune response. The most divergent genes in both fibroblasts and phagocytes have promoter architectures with high sequence conservation, enrichment for TATA boxes and depletion of CpG islands. Cytokines, chemokines and their receptors diverge more than do chromatin modulators, transcription factor or kinases. Genes that are highly divergent between species are also more variable in expression across individual cells within a species, with only a small subset of responding cells expressing various cytokines. Transcriptionally divergent genes are evolutionarily younger and encode proteins with fewer interactions with other proteins. Viruses target conserved modulators of the immune response. *IV*

https://doi.org/10.1038/s41590-018-0267-z

INFLAMMASOMES & CHOLESTEROL

Metabolic crosstalk

Immunity https://doi.org/10.1016/j.immuni.2018.08.021 (2018)

Multiple agonists trigger activation of the NLRP3 inflammasome and subsequent caspase-1-dependent maturation and release of the cytokine IL-1β. In *Immunity*, Guo et al. show that the initiation of cholesterol biosynthesis also activates NLRP3. The transcription factor SREBP2 regulates the expression of genes that encode cholesterol-biosynthetic enzymes; however, membrane-tethered SREBP2 is regulated by SCAP, a proteolytic adaptor that resides in the endoplasmic reticulum. Activation of NLRP3 induces endoplasmic reticulum–to–Golgi translocation of the SREBP2–SCAP complex, which leads to the activation of SREBP2. Reciprocally, depletion of cholesterol, which activates the biosynthetic pathway, also leads to the activation of NLRP3. Notably, NLRP3 requires interaction with SCAP via its NACHT domain to promote translocation of NLRP3 to the Golgi for full activation. Thus, activation of the NLRP3 inflammasome is closely attuned to cellular cholesterol sensing and regulatory feedback pathways through interactions with SCAP. *LAD*

https://doi.org/10.1038/s41590-018-0268-y

NEUROIMMUNOLOGY

Microglial activity in brain injury

PLoS Biol. https://doi.org/10.1371/journal.pbio.2005264 (2018)

Spinal cord injury (SCI) triggers an influx of monocyte-derived macrophages (MDMs) into the central nervous system. In *PLoS Biology*, David and colleagues use a mouse model of SCI to show that MDMs enter the central nervous system within 3–5 days and form close interactions with resident microglia. This interaction reduces microglial phagocytic activity and inflammatory pathways. The ability of MDMs to ameliorate the activation of microglia is dependent on their production of prostaglandin E_2, which acts directly on the microglia. Preventing the infiltration of MDMs into the central nervous system impairs functional recovery after SCI. Recruited MDMs therefore seem to modulate the functions of microglia, preventing their chronic activation and aiding recovery after injury. *ZF*

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MUCOSAL IMMUNOLOGY

T_{reg} cell tune-up

Sci. Immunol. https://doi.org/10.1126/sciimmunol.aat6975 (2018)

The microbiota exerts profound effects on the development and responses of the gut immune system. In *Science Immunology*, Im and colleagues screen many microbiotal strains for their ability to generate regulatory T cells (T_{reg} cells) de novo. One strain of *Bifidobacterium bifidum* strongly induces T_{reg} cells mainly in the colon lamina propria. Mechanistically, a neutral polysaccharide extract (CSGG) of *B. bifidum* converts dendritic cells into a regulatory form, largely by binding and signaling via the receptor TLR2. These regulatory dendritic cells then use the immunomodulatory cytokine TGF-β to convert conventional T cells into T_{reg} cells that are able to suppress a model of colitis. These findings shed light on the mechanism by which the microbiota can modulate gut immune responses. *ZF*

https://doi.org/10.1038/s41590-018-0271-3