Modulation of CD46 in T cells

The complement regulator CD46 has multiple functions, including modulating the effect of T cells on interleukin 10 (IL-10)-producing Tr1 regulatory T cells. In *Science Signaling*, Astier and colleagues show that signaling via the T cell antigen receptor (TCR) alters the O-glycosylation patterns of CD46 to induce its ectodomain shedding and liberation of cytoplasmic domains that influence downstream effector functions. Healthy human T cells undergo loss of CD46 O-linked modifications and secrete IL-10, but T cells from patients with relapsing-remitting multiple sclerosis do not undergo similar processing of CD46 and fail to generate Tr1 cells. The authors speculate that O-glycosylation regulates the accessibility of CD46 to the matrix metalloproteinases needed to liberate its ectodomain. What remains unknown is how TCR signaling leads to changes in *de novo* glycosylation and how this is altered in patients with autoimmunity. ***LAD***

***Sci. Signal.* 10, eaah6163 (24 October 2017)**

Interferons control fungus

Type III interferons trigger antiviral responses and transcriptionally overlap type I interferons but differ mainly in their compartmentalized effects on mucosal epithelia. In *Science Immunology*, Rivera and colleagues demonstrate an essential role for type III interferons in the control of *Aspergillus fumigatus*, a pathogenic fungus. Infection with *A. fumigatus* triggers rapid release of type I interferons, chiefly from pulmonary CCR2$^+$ monocytes. The type I interferons thus generated drive the production of type III interferons from both hematopoietic sources and non-hematopoietic sources. Type III interferons then act directly on neutrophils to activate their antifungal responses. The classic role of type III interferons on the epithelium does not seem to be essential for this response. These findings demonstrate an unexpected target cell and role for type III interferons and furthermore suggest new options for the treatment of fungal infection. *ZF*

Sci. Immunol. (6 October 2017) doi:10.1126/sciimmunol.aan5357

Gut clues to MS

Infection and alterations in the intestinal microbiota are often associated with multiple sclerosis (MS). In the *Proceedings of the National Academy of Sciences USA*, Ito and colleagues generate a humanized mouse with transgenic expression of a TCR from a patient with MS to assess the influence of age and the gut microbiota on experimental autoimmune encephalitis (EAE), the mouse counterpart of MS. A subset of these transgenic mice spontaneously develop EAE in an age-dependent way, with young adult mice being the most vulnerable, whereas disease fails to manifest in mice over 18 weeks of age. The microbiota is also relevant, as mice treated with antibiotics are protected and alterations in the frequency of particular gut bacteria species (dysbiosis) leads to a greater abundance of complement C3 in the periphery and precedes disease onset. The concentration of feces-associated immunoglobulin M (a proxy of gut inflammation) is also a useful predictor of EAE development. ***ZF***

***Proc. Natl. Acad. Sci. USA* (16 October 2017) doi:10.1073/pnas.1615715114**

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Tumor control

How immunological checkpoint blockade modulates tumor evolution during therapy is poorly understood. In *Cell*, Chan and colleagues perform whole-exome, transcriptome and TCR sequencing in 68 patients with advanced melanoma before and after therapy with antibody to the costimulatory molecule PD-1. Responders show a decrease in mutation and neoantigen load 4 weeks after initiation of therapy, whereas no single gene mutation is associated with response or resistance to therapy. Genomic contraction in responders is associated with enrichment for genes encoding molecules linked to signaling through PD-1, TCR, interferon-γ and IL-2 and the downregulation of tumor-growth pathways, such as cell-cycle regulation, mitotic division and translation. More immune-system-related genes are selectively upregulated in responders than in non-responders. Only the responders show a linear correlation between the number of expanded T cell clones and the number of neoantigens that become undetectable after therapy, which suggests that T cell clonal expansion modulates the genetic profile of the tumor and that T cells are effective in eliminating tumor cells expressing immunogenic neoantigens. *IV*

Cell (12 October 2017) doi:10.1016/j.cell.2017.09.028

Epithelial stem cell memory

How epithelial stem cells (EpSCs) that reside in the basal layer of the skin epithelium respond to inflammatory stimuli remains unclear. In *Nature*, Fuchs and colleagues show that skin EpSCs maintain prolonged memory of acute inflammation to induce rapid responses after subsequent tissue damage. Mice previously exposed to various inflammatory stimuli, such as imiquimod, abrasion wounding or *Candida* infection, heal wounds 2.5 times faster than do naive mice, even 180 days later. Inflammation-exposed skin shows proliferation rates similar to those of naive skin but accelerated re-epithelialization, a process still observed in mice deficient in the recombinase component RAG-2 or mice depleted of macrophages. At 30 days after exposure to imiquimod, EpSCs show greater chromatin accessibility in genes encoding molecules associated with inflammation, interleukin signaling, oxidative stress response and proliferation, relative to that of naive EpSCs. Those genes represent 50% of the genes upregulated 12 hours after secondary injury. Enhanced skin repair is lost in inflammation-exposed mice deficient in the AIM2 inflammasome or the IL-1 receptor IL-1R1, which indicates AIM2 and IL-1β are central regulators of EpSC memory. ***IV***

***Nature* 550, 475–480 (2017)**

Inflammatory lipids

CD14 acts as a co-factor for the Toll-like receptor TLR4 to activate inflammatory responses to lipopolysaccharides. In *Immunity*, Zanoni *et al.* report that CD14 recognizes host-derived inflammatory lipids composed of oxidized phosphrylcholine derivatives released from dying cells. Such recognition triggers transient down-regulation of CD14 from the cell surface and cytosolic caspase-11-dependent activation of the inflammasome, independently of TLR4 responses. Exposure to oxidized phosphrylcholine components, specifically 1-palmitoyl-2-glutaryl-*sn*-glycero-3-phosphocholine and 1-palmitoyl-2-(5'-oxo-valeroyl)*sn*-glycero-3-phosphocholine, leads to hyperactivation of dendritic cells and macrophages and prolonged release of IL-1 without triggering cell death via pyroptosis. Hence, exposure to these sterile damage-associated molecular patterns leads to chronic inflammation *in vivo*. *LAD*

Immunity **47**, 697–709 (2017)