Plasma cell checkpoint

Roughly half of mature B cells have biallelic rearrangements of immunoglobulin-encoding loci in which one allele encodes a nonfunctional protein due to frameshift mutations. Aberrantly rearranged alleles encoding the immunoglobulin-κ light chain can nevertheless generate truncated proteins via alternative RNA splicing. In *The Journal of Experimental Medicine*, Srour *et al.* reveal a previously unknown checkpoint in plasma cells that eliminates biallelically rearranged cells expressing truncated κ-chains. Premature termination codons within the variable ($V_κ$) exon can promote exon skipping, with transcripts retaining only the leader and constant regions. While mature and germinal center B cells tolerate expression of the κ-chains lacking V domains that arise from skipping of the $V_κ$ exon, plasma cells show heightened endoplasmic reticulum stress when such truncated proteins are expressed and undergo rapid apoptosis, despite their expression of a second, functional allele. This checkpoint probably operates to eliminate those plasma cells bearing frameshift mutations as a result of somatic hypermutation. ***LAD***

***J. Exp. Med.* 213, 109–122 (2016)**

ILC3 aggression

Type 3 innate lymphoid cells (ILC3 cells) have been linked to driving colitis. In *eLife*, Powrie and colleagues offer insight into how the otherwise small population of gut-resident ILC3 cells can exert a disproportionate influence on the immunopathology of colitis. Using two different experimental models of colitis, as well as data from patients with colitis, the authors show that ILC3 cells are important producers of the proinflammatory cytokine GM-CSF. This cytokine serves to recruit inflammatory monocytes, which are critical to the immunopathology of colitis. Under steady-state conditions, ILC3 cells dynamically enter and exit cryptopatches (lymphoid structures within the gut), but during colitis there is net movement of ILC3 cells into adjacent tissues. These findings suggest how ILC3 cells can disseminate potent proinflammatory effects throughout the colon. *ZF*

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Instructing T_{FH} cells

Follicular helper T cells (T_{FH} cells) and central memory T cells (T_{CM} cells) share various key transcriptional features, which suggests there is some overlap in their developmental programs. In *Nature Communications*, Oestreich and colleagues show that cells with both T_{FH} cell potential and T_{CM} cell potential develop from the T_H1 subset of helper T cells as IL-2 signaling wanes after an immune response winds down. These bipotential cells express receptors for both IL-6 and IL-7 and appear at later time points after infection. Signaling via the IL-6 receptor initiates a T_{FH} cell transcriptional program, whereas IL-7 suppresses that and instead favors T_{CM} cell development. The transcriptional regulator STAT5 downstream of the IL-7 receptor is responsible for repressing genes encoding products critical for T_{FH} cell development, such as *Bcl6*. This work demonstrates a parsimonious mechanism by which both humoral immunological memory (via T_{FH} cells) and cellular immunological memory (via T_{CM} cells) can develop following an immune response. ***ZF***

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Written by Laurie A. Dempsey, Zoltan Fehervari & Ioana Visan

Neutralizing malaria

Mounting efficacious antibody responses during malarial infection has proven challenging. In *Nature*, Lanzavecchia and colleagues report the identification of several broadly neutralizing antibodies obtained from plasma cells isolated from several *Plasmodium falciparum*–infected Kenyans. Analysis of *IGH* sequences encoding immunoglobulin heavy-chain antibodies reveals an unexpected genetic insert from *LAIR1*, which encodes a collagen-binding receptor, between the variable and diversity-joining sequences encoding the antibodies. This large insert can undergo extensive somatic hypermutation in the *IGH* context, and these mutant LAIR1 domains are responsible for the recognition of RIFIN proteins expressed by plasmodium-infected erythocytes. It remains unclear how such insertions are generated, as they contain intron and exon sequences and both alleles of *LAIR1* remain intact on chromasome 19 in both donors, which rules out the possibility of cDNA insertions or chromosomal translocations. Future studies should reveal the prevalence of this *LAIR1* insertion and how it occurs, mechanistically. *LAD*

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Gut macrophage specialization

Gut-resident macrophages represent a highly heterogenous population. In *Cell*, Mucida and colleagues use imaging and transcriptional profiling to demonstrate specialization of two macrophage populations with distinct localization in the intestinal tissue. Lamina propria macrophages tend to express genes encoding pro-inflammatory (M1) factors, while muscularis macrophages, located under the mucosal region, between the circular and longitudinal muscle layers, express genes encoding tissue-protective factors, such as *Il10*, *Mrc1* and *Rentla*, and, overall, resemble M2 macrophages. After intragastric exposure of mice to non-invasive *Salmonella typhimurium*, muscularis macrophages further upregulate M2-associated genes, while lamina propria macrophages increase their expression of *Nos2* and *Il6*. Muscularis macrophages have high expression of genes encoding $β_2$ adrenergic receptors and during infection respond to norepinephrine by upregulating *Arg1*. Thus, communication between sympathetic neurons and muscularis macrophages induces a tissue-protective program. ***IV***

***Cell* (14 January 2016) doi:10.1016/j.cell.2015.12.023**

Deacetylation for viral sensing

RIG-I is a cytosolic sensor of RNA viruses. In *The EMBO Journal*, Lee and colleagues show that deacetylation of the carboxy-terminal region of RIG-I by the cytoplasmic histone deacetylase HDAC6 regulates its RNA-sensing activity. HDAC6-deficient mice are more susceptible to infection with vesicular stomatitis virus, and HDAC6-deficient mouse bone marrow–derived macrophages and embryonic fibroblasts have diminished activation of the type 1 interferon pathway in response to RNA viruses. HDAC6 transiently interacts with RIG-I after viral infection and deacetylates Lys909 of RIG-I. This modification modulates the binding of RIG-I to 5′-triphosphate double-stranded RNA, the activation of type 1 interferon pathways and antiviral responses. These results indicate that acetylation is an additional post-translational modification that can regulate RIG-I function, along with phosphorylation, ubiquitination and sumoylation. *IV*

EMBO J. (8 January 2016) doi:10.15252/embj.201592586