NO regulation

Nitric oxide is a powerful antimicrobial agent, but production of this toxic molecule is tightly regulated. In *The Journal of Immunology*, Lewis *et al.* identify a negative feedback pathway that limits the production of nitric oxide by inducible nitric oxide synthase (iNOS). Toll-like receptor 3 (TLR3) and TLR4 trigger transient upregulation of the ubiquitin ligase adaptor SPSB1. This TLR-mediated TRIF–dependent induction occurs indirectly, as type I interferons or transforming growth factor-β also upregulate SPSB1 expression, albeit with faster kinetics. SPSB1 interacts with iNOS to target it for E3 ubiquitin ligase action and subsequent proteasomal degradation. Transgenic expression of SPSB1 results in lower abundance of iNOS protein and limits the production of nitric oxide, whereas the use of short hairpin RNA targeting SPSB1 leads to pronounced production of nitric oxide. Thus, the delayed induction of SPSB1 by TLRs allows cells to transiently produce nitric oxide via iNOS that is induced by the same stimulus. ***LAD***

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Broadly neutralizing flu

Antigenic drift allows influenza virus to escape seasonal vaccination and necessitates the yearly development of new vaccines. However, two related papers in *Science* by Goudsmit *et al.* and Lanzavecchia *et al.*, as well as one by Harrison *et al.* in the *Proceedings of the National Academy of Science*, suggest the possibility of generating broadly neutralizing but distinct antibodies to influenza virus. Hemagglutinin, the main surface antigen on influenza virus, binds its cellular receptor sialic acid and thereby gains entry to the cell. In the *Science* papers, the authors identify antibodies to the relatively conserved stem region of hemagglutinin. Depending on the antibody, these could effectively neutralize influenza virus *in vitro* and *in vivo* throughout the major influenza subgroup 2 or, to a certain extent, subgroups 1 and 2. In contrast, the antibody identified by Harrison and colleagues demonstrates broad reactivity to influenza H1N1 strains of subgroup 1 by binding to the globular head of hemagglutinin in a way that closely mimics that of the natural receptor sialic acid. *ZF*

Science **333**, 843–850 & 850–856 (2011); *Proc. Natl. Acad. Sci. USA* **108**, 14216–14221 (2011)

The T cell factor

The effectors that induce T lineage specification and commitment downstream of Notch1 signals remain unknown. In *Nature*, Bhandoola and colleagues show that the transcription factor TCF-1 is a critical regulator of T cell specification. TCF-1 is induced in early T cell progenitors by Notch1 signaling and positively regulates its own expression. TCF-1-deficient progenitors inhibit alternative myeloid and B cell fates normally but fail to upregulate T cell–specific genes. Ectopic expression of TCF-1 in progenitor cells is sufficient to induce T cell development on OP9 stromal cells in the absence of Notch ligands or in Notch1-deficient progenitors *in vivo*. TCF-1 directly regulates the expression of many T cell–specific genes, including *Gata3*, *Bcl11b*, *Cd3e* and *Il2ra*, but not of established Notch1 targets such as *Deltex1* and *Ptcra*. Appropriately, TCF-1 is an abbreviation of 'T cell factor 1'. ***IV***

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

Balancing acts by HIF

The induced polarization of T_{reg} cells and interleukin 17 (IL-17)-producing helper T cells (T_H17 cells) requires transforming growth factor-β, and there is plasticity between these two polarized states. In *Cell*, Dang *et al.* provide evidence that the transcription factor HIF-1 (hypoxia-inducible factor 1) contributes to T_H17 polarization and the suppression of T_{reg} differentiation. HIF-1-deficient cells have minimal expression of the transcription factor RORγt and IL-17 under T_H17-polarizing conditions and instead have higher expression of the transcription factor Foxp3. Enforced expression of HIF-1α alone induces a T_H17 phenotype. HIF-1α directly binds the locus encoding RORγt, but its upregulation of the genes encoding IL-17 and the receptor for IL-23 requires binding of DNA by RORγt and the histone acetyltransferase p300. Conversely, the interaction of HIF-1α with Foxp3 targets the latter for proteasome-mediated degradation. Hypoxia further enhances these polarized responses in T cells. These findings suggest oxygen tension and other metabolic cues sensed by HIF-1α can modulate the balance of T_{reg} cells to T_H17 cells. *LAD*

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Early steps of HIV-1 infection

Extracellular ATP signals in an autocrine and paracrine way through purinergic receptors to modulate an array of cellular functions. In the *Journal of Experimental Medicine*, Perfettini and colleagues show that the HIV-1-encoded envelope glycoprotein complex (Env) can stimulate the pannexin-1-mediated release of ATP from target cells, perhaps as a result of mechanical stress on the cell membrane, which in turn favors the initial steps of HIV-1 infection. ATP activates the purinergic receptor P2Y2, which accumulates in the virological synapse and is required for depolarization of the plasma membrane. Phosphorylated Pyk2, a kinase known to participate in actin cytoskeleton reorganization, also accumulates at the virological synapse, although the link between the activation of P2Y2 and Pyk2 and membrane depolarization remains unclear. Inhibition of any of the constituents of this pathway (pannexin-1, ATP, P2Y2, Pyk2) interferes with viral entry. ***IV***

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HLA-B*27 and HLA-B*57 viral resistance

The HLA class I alleles HLA-B*27 and HLA-B*57 are associated with resistance to certain viral infections, but the mechanisms that underlie this have remained obscure. In *Nature Medicine*, Horton and colleagues identify a means by which HLA-B*27 and HLA-B*57 convey resistance to human immunodeficiency virus (HIV). Chronic infection with viruses such as HIV is characterized by T cell expression of the receptor Tim-3, which mediates suppression by regulatory T cells (T_{reg} cells) via the counter-ligand galectin-9 and leads to immune exhaustion. The function of T_{reg} cells in HLA-B*27 and HLA-B*57 people is intrinsically normal, but their HIV-specific cytotoxic T lymphocytes show lower activation-induced upregulation of Tim-3 than do those from people of other haplotypes. Furthermore, HLA-B*27- and HLA-B*57-restricted cytotoxic T lymphocytes activated by HIV epitopes can kill T_{reg} cells in a granzyme B–dependent manner. Therefore, HLA-B*27 and HLA-B*57 may confer resistance to virus-mediated exhaustion in a twofold way directed at the inhibition of T_{reg} cell function. *ZF*

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