Viral infection: the clot thickens

Many invertebrates coopt their coagulation cascade to resist microbial infection; however, it has been unclear whether mammals use an equivalent system. In *Science*, Shayakhmetov and colleagues demonstrate that the human blood-coagulation factor FX is important for the recognition of and immune response to adenovirus. After infection, FX rapidly coats the adenoviral hexon and engages Toll-like receptor 4 (TLR4) on tissue macrophages. FX therefore seems to facilitate binding in a way analogous to the well-known TLR4 coreceptor MD2. Engagement of TLR4 by FX-coated adenovirus triggers a host of inflammatory cytokines via a classic signaling pathway dependent on the adaptor MyD88 and transcription factor NF-κB, whereas mutant virus unable to bind FX does not trigger TLR4 signaling. This mechanism of FX-mediated release of inflammatory cytokines might underlie some of the adverse immunological reactions that have hampered adenoviral gene-therapy approaches. ***ZF***
***Science* 338, 795–798 (2012)**

Plasma-cell survival

Long-term humoral immunity requires memory B cells and long-lived antibody-secreting cells (ASCs). In *Science Signaling*, van Spriel *et al.* show that optimal long-term immunoglobulin G responses require the tetraspanin protein CD37. There is abundant CD37 on the surface of mature B cells, which seems to be necessary for clustering of the integrin $\alpha_4\beta_1$, required for high-affinity binding to its ligand, VCAM-1. The VCAM-1–$\alpha_4\beta_1$ interaction triggers an outside-in signaling cascade that activates the kinase Akt, which in turn phosphorylates and inactivates the proapoptotic molecule Bad. CD37-deficient mice develop germinal centers after immunization but produce less antibody and have fewer immunoglobulin G–producing plasma cells than do wild-type mice. These data suggest CD37-induced clustering of $\alpha_4\beta_1$ contributes to the long-term survival of plasma cells. *LAD*
Sci. Signal. (13 November 2012) doi:10.1126/scisignal.2003113

It takes two

Expression of the transcription factor Foxp3 is essential but might not be sufficient for the development of regulatory T cells (T_{reg} cells). In *Immunity*, Sakaguchi and colleagues show that hypomethylation of certain T_{reg} cell–representative gene regions is required for the development of natural T_{reg} cells (nT_{reg} cells) and that it is established in the thymus independently of *Foxp3* expression. CpG hypomethylation of limited regions (*Foxp3* intron 1, *Tnfrsf1*8 exon 5, *Ctla4* exon 2 and *Ikzf4* intron 1b) is exclusively 'imprinted' in nT_{reg} cells and not in other T cell populations, including inducible T_{reg} cells. Hypomethylation of the nT_{reg} cell type is required for Foxp3$^+$ T cells to acquire nT_{reg} cell–type gene expression and full suppressive activity and to sustain the expression of T_{reg} cell–associated molecules such as Foxp3, CLTA-4 and CD25. The induction of such hypomethylation in developing nT_{reg} cells is dependent on engagement of the TCR by self ligands in the thymus. ***IV***
***Immunity* 37, 785–799 (2012)**

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

Activation by calcium

Several models of inflammasome activation, such as K^+ efflux, generation of reactive oxygen species and lysosomal destabilization, have been proposed. In *Nature*, Chae and colleagues show that recognition of extracellular Ca^{2+} through the calcium-sensing receptor CASR activates the NLRP3 inflammasome. CASR activates phospholipase C, which catalyzes the production of inositol-1,4,5-triphosphate and release of Ca^{2+} from endoplasmic reticulum stores. A greater abundance of cytoplasmic Ca^{2+} promotes assembly of components of the NLRP3 inflammasome. Stimulation via CASR also diminishes the abundance of intracellular cAMP, which binds NLRP3 directly to inhibit inflammasome assembly. Thus, downregulation of cAMP relieves this inhibition. Mutant NLRP3 from patients with cryopyrin-associated periodic syndrome binds cAMP with lower affinity than does wild-type NLRP3. Increasing cAMP attenuates the uncontrolled production of interleukin 1β by peripheral blood mononuclear cells in such patients. These results suggest that extracellular Ca^{2+} can function as a danger signal. *IV*
Nature (11 November 2012) doi:10.1038/nature11588

Building enhancers

Cytokines provide polarizing signals that dictate the outcome of effector T cell responses. In *Cell*, O'Shea and colleagues characterize how STAT transcription factors contribute to chromatin remodeling associated with the polarization of CD4$^+$ T cells into the T_H1 and T_H2 helper T cell subsets. Active enhancer elements are marked by monomethylation of histone 3 at Lys4 (H3K4me1) and the histone acetyltransferase p300, which confers acetylation of H3 at Lys27. Genome-wide profiling shows that deposition of H3K4me1 at enhancer elements does not discriminate T_H1 and T_H2 cells. Instead, STAT proteins occupy lineage-specific enhancer sites together with p300. Such binding of p300 is lost in STAT-deficient T cells and, concomitantly, their expression of lineage-appropriate gene is also lower. Surprisingly, the T_H1-specific transcription factor T-bet does not substantially alter the p300-H3K4me1 landscape; instead, T-bet is necessary for the suppression of alternative gene-expression programs. These findings suggest that STAT proteins are needed to recruit chromatin-remodeling enzymes to activate enhancers and direct lineage-appropriate gene expression. ***LAD***
***Cell* 151, 981–993 (2012)**

Mimicking nickel allergy

An allergy to nickel (Ni^{2+}) is one of the most common forms of contact dermatitis, but how T cells recognize Ni^{2+}-haptenized peptides is unclear. In the *Proceedings of the National Academy of Sciences*, Dai and colleagues use structural insights obtained with ANi2.3, a Ni^{2+}-reactive T cell antigen receptor (TCR), to shed light on the basis of Ni^{2+} allergy. ANi2.3 recognizes an unknown Ni^{2+}-haptenized peptide in the context of HLA-DR52c. Their screen fails to identify the Ni^{2+}-haptenized peptide recognized by ANi2.3, probably because of low abundance of the natural ligand. However, it identifies many 'mimetopes' recognized by ANi2.3 in the absence of Ni^{2+}. Structural and mutational analysis of the mimetope-DR52c complex shows a highly conserved lysine at peptide position 7 that is essential for recognition by ANi2.3. The ε-amino group of this lysine interacts with complementarity-determining region 3 of ANi2.3 in a manner analogous to Ni^{2+}, most probably because of its equivalent positive side chains. *ZF*
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