Wnt signals tolerance

The intracellular signaling networks that program dendritic cells (DCs) to become tolerogenic remain unknown. In *Science*, Pulendran and colleagues report that Wnt–β-catenin signaling in intestinal DCs regulates the balance between inflammatory and regulatory responses in the gut. In contrast to spleen DCs, lamina propria DCs and macrophages have a constitutively active pathway. Conditional deletion of β-catenin in DCs leads to lower expression of vitamin A–metabolizing enzymes and anti-inflammatory cytokines, such as IL-10 and TGF-β, and higher expression of proinflammatory cytokines, such as IL-6 and IL-23. Furthermore, deletion of β-catenin in DCs enhances inflammatory responses to enteric bacteria in a model of inflammatory bowel disease. Thus, β-catenin signaling programs DCs to a tolerogenic state through a mechanism that seems to be independent of commensals, as antibiotic treatment does not interfere with β-catenin programming in DCs. ***IV***

***Science* 329, 849–853 (2010)**

Stem cells stick together

The identity of the cells that form the hematopoietic stem cell (HSC) niche remains unclear. In *Nature*, Frenette and colleagues demonstrate that nestin-positive cells act as true HSC niche cells in the bone marrow. Nestin-positive cells have a very close physical association with the HSC and very high expression of core HSC maintenance genes, which are selectively downregulated by stimulation with granulocyte colony-stimulating factor. In addition, nestin-positive cells act like mesenchymal stem cells, showing multilineage differentiation potential and robust self-renewal in serial transplantation assays. HSCs home near nestin-positive cells after lethal irradiation, whereas *in vivo*, depletion of nestin-positive cells results in fewer hematopoietic progenitors in the bone marrow. This unique stem cell pairing seems to be sensitive to homeostatic hormonal and neural mechanisms that regulate in tandem the maintenance of HSCs and the proliferation and differentiation of mesenchymal stem cells. *IV*

Nature **466**, 829–834 (2010)

Basophils tackle ticks

Ticks, vectors for several important diseases including *Borrelia*, *Rickettsia* and *Babesia*, can induce protective immune responses to the tick itself, but the basis of this has been unclear. In the *Journal of Clinical Investigation*, Karasuyama *et al.* demonstrate that basophils have a critical role in this response to ticks. Basophils are recruited to the site of tick feeding but generally only at the second infestation, which indicates an acquired response. Notably, the researchers generate a mouse model that for the first time can be selectively depleted of basophils through expression of a diphtheria toxin receptor. Using this system they find that the recruitment of basophils to feeding sites is necessary for tick resistance and results in premature dropping off of the parasites. The ability to deplete animals specifically of basophils should now provide researchers an invaluable tool for further characterization of these otherwise elusive cells. ***ZF***

***J. Clin. Invest.* 120, 2867–2875 (2010)**

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

Immunoproteasome and homeostasis

The immunoproteasome is a specialized proteasome that is upregulated after interferon stimulation and can more efficiently generate MHC class I epitopes for presentation to cytotoxic T lymphocytes. In *Cell*, Kruger and colleagues identify a previously unknown and important function of the immunoproteasome in maintaining cell homeostasis. Interferon stimulation also triggers the production of reactive oxygen species, which can result in the accumulation of oxidant-damaged cellular proteins. Left unchecked, these damaged proteins can accumulate as polyubquitylated structures known as 'aggresomes', which leads to lower cell viability. The researchers find that immunoproteasome deficiency leads to more aggresomes under inflammatory conditions and a heightened sensitivity to apoptosis. The immunoproteasome seems to be exceptionally adept at clearing these potentially harmful structures by virtue of their accelerated clearance of polyubquitylated proteins. *ZF*

Cell **142**, 613–624 (2010)

Regulating transcriptional elongation

A subset of proinflammatory genes responsive to the transcription factor NF-κB, such as *TNF* and *IL6*, is poised for rapid expression and thus requires tight regulation to avoid inappropriate inflammation. In the *Journal of Experimental Medicine*, Smallie *et al.* examine the effect of IL-10 on the transcription rate of RNA polymerase II (Pol II) in human macrophages. The presence of IL-10 does not alter the binding of Pol II to the *TNF* promoter in lipopolysaccharide-treated cells, but transcriptional elongation through the gene is diminished. IL-10 treatment blunts phosphorylation of Pol II at Ser2 by the kinase CDK9, which is needed to convert Pol II initiation complexes into elongation complexes. This inhibitory effect is indirect, as IL-10 blocks recruitment of the NF-κB subunit RelA and activation of CDK9 at the target genes. How Pol II elongation is activated at IL-10–insensitive NF-κB target genes remains to be elucidated. ***LAD***

***J. Exp. Med.* (30 August 2010) doi:10.1084/jem.20100414**

Sweet tolerance

The gut lamina propria functions as an antimicrobial barrier but also mediates nutrient uptake and thus requires a means of engendering tolerance to avoid food allergies. In *Nature Medicine*, Zhou *et al.* show that the C-type lectin SIGNR1 can promote oral tolerance. Mice sensitized to bovine serum albumin (BSA) develop anaphylactic responses after challenge with BSA. The coupling of mannose polymers to BSA abrogates this response. Lamina propria $CD11c^+CD11b^+$ DCs expressing SIGNR1 rapidly take up mannosylated antigen and express IL-10, which in turn elicits IL-10–expressing type 1 regulatory T cells. Neither splenic DCs nor $CD11c^-$ subsets express SIGNR1 and fail to express IL-10 in response to stimulation with mannosylated BSA *in vitro*. Blocking SIGNR1 or IL-10 signaling blunts tolerance induction *in vivo*. Thus, SIGNR1 contributes to the establishment of oral tolerance to mannosylated antigens. Whether this pathway can also engender oral tolerance to coingested but unconjugated molecules needs to be explored. *LAD*

Nat. Med. (12 September 2010) doi:10.1038/nm.2201