Allosteric IgE recognition

IgE is recognized by two receptors: FcεR1 expressed in mast cells and basophils, and CD23 expressed in B cells, which can be shed as soluble CD23. Allergic reactions are promoted by FcεR1 signaling, whereas IgE abundance is regulated by CD23 binding. In the *Proceedings of the National Academy of Sciences*, Dhaliwal *et al.* report mutually exclusive allosteric modulation of IgE that governs receptor recognition. Structural analysis shows that CD23 contacts the interface formed between the Cε3 and Cε4 domains of each IgE heavy chain, whereas FcεRI contacts the Cε3 dimeric interface formed by heavy-chain pairing. Receptor binding fixes the conformation of the flexible Cε3 domain such that recognition by the other receptor is prohibited. The topology of the CD23-IgE interaction also reveals how receptor crosslinking might occur to trigger intracellular signaling. Mutually exclusive binding thus allows greater control of receptor signaling upon recognition of IgE-allergen complexes. ***LAD***

Proc. Natl. Acad. Sci. USA **(16 July 2012) doi:10.1073/pnas.1207278109**

Family heritage

Toll-like receptor (TLR) signaling has been implicated in the regulation of intestinal microbiota. In the *Journal of Experimental Medicine*, Pamer and colleagues use high-throughput sequencing of 16S rRNA genes from the small and large intestines of mice to assess the contribution of TLR-deficiency versus maternal transmission on the composition of intestinal microbiota. Comparison of TLR-deficient and wild-type littermates that were housed together indicates that deficiency in TLR2, TLR4, TLR5, TLR9 and the adaptor MyD88 does not result in significant changes in the composition, richness or diversity of intestinal microbiota under homeostatic conditions or after recovery from antibiotic treatment. The authors report marked differences between wild-type and TLR-deficient colonies that were bred in isolation of each other for long periods. These results suggest maternal origin is the major factor driving microbiota diversity. *IV*

J. Exp. Med. (23 July 2012) doi:10.1084/jem.20120504

Location dictates function

Spatial compartmentalization of signaling modules is an important aspect of signal transduction in cells. In *Science Signaling*, Sarin and colleagues describe that cytoplasmic localization of the Notch intracellular domain (NIC) and its association with the PI3 kinase and the mTORC2 component Rictor protect T_{reg} cells, but not effector T cells, from apoptosis triggered by cytokine withdrawal. NIC has a predominantly cytoplasmic distribution in natural T_{reg} cells, but not in effector T cells or induced T_{reg} cells, and this correlates with resistance to apoptosis. The cytoplasmic localization of NIC is dependent on TCR engagement and Notch-ligand interactions but is independent of the transcriptional activity of NIC. Expression of the Notch ligand Delta-like 1 on T_{reg} cells is required for this survival effect in culture, whereas the source of Notch ligands in the physiological context of T_{reg} cell function remains unclear. ***IV***

Sci. Signal. **(24 July 2012) doi:10.1126/scisignal.2002859**

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

Building an immune synapse

The molecular requirements for early activation of T cells are still being determined. In *Nature*, James & Vale report a reductionist approach to recapitulate the proximal events of TCR triggering. They selectively reconstitute HEK cells, which otherwise entirely lack T cell signaling molecules, with individual modules of T cell proximal activation. Using this approach they identify a minimal TCR activation unit that requires the kinases Lck and Zap70. Using antigen presenting cells they also interrogate the role of adhesion molecule and peptide major histocompatibility (pMHC) interactions. They observe classic TCR-pMHC immunological synapses with exclusion of T cell molecules like CD45. Stabilization of this structure and activation does not depend on productive signaling but solely on cognate TCR-pMHC interaction. Conversely, intracellular activation can occur even without pMHC or TCR but also with an equivalent but entirely artificial receptor-ligand system as long as CD45 is excluded from the immune synapse. *ZF*

Nature **487**, 64–69 (2012)

Tolerant mammals

Regulatory T cells (T_{reg} cells) can be divided into either thymically derived (tT_{reg} cells) or peripherally derived (pT_{reg} cells) populations, with the former dedicated to controlling responses to self antigens and the latter to non-self antigens. In *Cell*, Rudensky and colleagues examine whether pT_{reg} cells, given their propensity for dampening responses of non-self antigens, maintain maternal-fetal tolerance. The *CNS1* enhancer region is critical for pT_{reg} cell development in that it facilitates expression of the transcription factor Foxp3. Only eutherian mammals have *CNS1*, suggesting that its appearance in evolution coincided with that of placentation. Indeed, in a reporter assay the equivalent enhancer regions of non-placental mammals cannot support *Foxp3* expression. To directly test the role of pT_{reg} cells in maintaining maternal-fetal tolerance, the authors use a mouse T cell receptor (TCR) transgenic system specific for paternal alloantigen and then mated with appropriate males. In the absence of maternal *CNS1* there is increased embryonic resorption and signs of placental inflammation. Maintaining fetal integrity is therefore a major remit of pT_{reg} cells. ***ZF***

Cell **150, 29–38 (2012)**

Local immunity

Gut microbiota are known to influence mucosal immunity, but less is known about the role played by skin microbiota. In *Science*, Naik *et al.* show that skin commensals, such as *Staphylococcus epidermidis*, tune local T cell responses to cutaneous infection. Skin-resident T cells and innate lymphocytes produce interferon-γ and interleukin 17 (IL-17), but this ability is impaired in germ-free mice. Monocolonization of germ-free mice with gut commensals does not restore IL-17 production, but colonization with *S. epidermidis* rescues this ability. Unlike local gut responses that rely on IL-23 signaling, skin responses depend on production of IL-1 to elicit IL-17 by αβ and γδ T cells. IL-1R1–MyD88 signaling, but not TLR or IL-6 signaling, elicits local skin responses, counterbalanced by keratinocyte production of IL-1 receptor antagonist (IL-1RA). Thus local commensals are necessary to influence adaptive immune responses in both gut and skin environments. *LAD*

Science (26 July 2012) doi:10.1126/science.1225152