A tolerant response to IFN-β

Interferon-β (IFN-β) is used clinically for the treatment of multiple sclerosis (MS), but the basis of its action is unclear. In *Nature Medicine*, Issazadeh-Navikas and colleagues find a role for a previously undescribed regulatory T (T_{reg}) cell population in the control of the mouse MS model experimental autoimmune encephalitis (EAE) and possibly human MS. Normal mice undergoing EAE induction demonstrate the presence of a T_{reg} cell population characterized by expression of the transcription factor FoxA1. The development of these T_{reg} cells depends on IFN-β and they are genetically and phenotypically distinct from other T cell subsets, including conventional thymically and peripherally induced T_{reg} cells. FoxA1$^+$ T_{reg} cells are nonproliferative and suppress effector T cells by killing them in a manner dependent on programmed cell death ligand 1 (PD-L1). FoxA1 is necessary and sufficient for these T_{reg} cells because it positively regulates *Pdl1* expression and its overexpression induces a suppressive phenotype in otherwise normal naive CD4$^+$ T cells. Importantly, MS patients responsive to IFN-β show elevated numbers of FoxA1$^+$ T_{reg} cells. *ZF*

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Synchronous signals

Inhalation of noxious substances and bacteria or viral particles poses a critical challenge for lung tissues, as overexuberant immune reactions can cause immunopathology. In *Nature*, Westphalen *et al.* show that alveolar macrophages instigate a protective response by initiating intercellular Ca^{2+} signaling waves that are propagated by adjoining alveolar epithelial cells. Challenge with lipopolysaccharide induces transient waves of synchronous Ca^{2+} spikes that are transmitted between cells via gap junctions formed by connexin 43 (Cx43). This response triggers activation of the Ca^{2+}-dependent kinase CAMKK and Akt, which prevent excessive cytokine and chemokine release. Mice lacking alveolar macrophage expression of Cx43 are more susceptible to lung injury in response to endotoxin. These findings suggest that intercellular collaboration protects delicate lung tissues. *LAD*

Nature **506**, 503–506 (2014)

Balancing fate with Itk

A reciprocal relationship exists between Akt-mTOR activation and generation of induced regulatory T (T_{reg}) cells. In the *Journal of Experimental Medicine*, Gomez-Rodriguez *et al.* identify the kinase Itk, a downstream mediator of T cell antigen receptor (TCR) signaling, as a critical regulator that influences T_{reg} versus T_H17 cell fate. Itk deficiency leads to preferential generation of T_{reg} cells, even under conditions that favor T_H17 cell differentiation. Loss of Itk reduces TCR- and interleukin-2 (IL-2)-mediated activation of phosphoinositide-3-kinase (PI(3)K)–Akt–mTOR–HIF-1α signaling, which is needed to promote T_H17 cell fate. Itk acts indirectly to repress expression of *Pten*, which encodes a phosphatase that antagonizes PI(3)K-mediated generation of PtdIns(3,4,5)P_3. Itk therefore couples TCR signaling to other activation pathways that regulate PtdIns(3,4,5)P_3 abundance and influences cell fate decisions. *LAD*

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

True adaptor

Toll-like receptors (TLRs) residing in distinct subcellular compartments activate a common signal-transduction pathway. The sorting adaptor TIRAP recruits the signaling adaptor MyD88 to plasma membrane–localized TLRs, but TIRAP-deficient cells respond normally to synthetic ligands of TLR7 and TLR9, suggesting that endosomal TLRs signaling is TIRAP independent. In *Cell*, Kagan and colleagues show that TIRAP is required for signaling from endosomal TLRs in response to natural ligands, such as herpes simplex virus (HSV) DNA. High concentrations of ligands bypass the requirement for TIRAP in all TLRs, explaining the previous observations. The authors show that TIRAP is a component of the MyD88-IRAK2-IRAK4 signaling complex induced by either TLR4 or TLR9, and is required for its assembly. The lipid-binding domain of TIRAP allows promiscuous binding to various lipid targets, such as PI(4,5)P_2 at the plasma membrane and PI(3)P on endosomes, resulting in functional formation of MyD88-IRAK signaling complexes in both locations. *IV*

Cell **156**, 705–716 (2014)

Discrimination power

Cellular responses elicited by cell-surface receptors differ depending on stimulus strength. In *Science*, Rivera and colleagues investigate how the high-affinity IgE receptor (FcεRI) distinguishes high- and low-affinity stimulation to modulate mast cell responses. At antigen concentrations that induce similar receptor phosphorylation, 2NP, a low-affinity antigen, elicits less degranulation and cytokine production, but enhanced chemokine production, as compared to DNP, a high-affinity antigen for the FcεRI-bound DNP-specific IgE. Compared to DNP, 2NP induces more diffuse, less organized FcεRI clusters, resulting in changes in the balance of receptor-associated kinases, namely increased co-localization of the Src family kinase Fgr and increased phosphorylation of the adaptor LAT2 relative to LAT1. Fgr and LAT2 enhance CCL2 chemokine responses at the expense of mast cell degranulation. *In vivo*, 2NP stimulation results in increased recruitment of monocytes and macrophages compared to a DNP response, which recruits more neutrophils, suggesting discrimination of antigen-antibody affinity by the FcεRI receptor results in distinct physiological outcomes. *IV*

***Science* (6 February 2014) doi:10.1126/science.1246976**

Neonatal lung

Infants have elevated susceptibility and impaired immune responses to lower-respiratory-tract infections—in particular those caused by respiratory syncytial virus (RSV). In *PLoS Pathogens*, Graham and colleagues systematically compare the function and behavior of lung migratory dendritic cells (CD103$^+$ and CD11b$^+$) between neonatal mice (3–21 days old) and adult mice to understand the immune response in neonatal lung. RSV directly infects neonatal lung DCs at a higher rate than adult DCs. Neonatal lung DCs are generally also less efficient at uptake, processing and transportation of antigen to draining mediastinal lymph nodes. CD103$^+$ DCs in neonates express smaller amounts of co-stimulatory molecules and as a consequence are impaired at priming CD8$^+$ T cell responses to RSV. Neonatal lung DCs thus have deficient functionality at multiple levels, and normalizing this may inform the development of effective infant vaccines. *ZF*

PLoS Pathog. (13 February 2014) doi:10.1371/journal.ppat.1003934