Cytosolic ligand uptake

Double-stranded RNA is detected by the intracellular receptors TLR3 and Mda5, but how nucleic acids are captured and gain access to the intracellular compartments that contain these receptors is unclear. In the *Journal of Biological Chemistry*, Matsumoto and colleagues demonstrate that raftlin, a major lipid raft protein, is crucial for the uptake and segregation of the double-stranded RNA analog poly(I:C). Raftlin is normally expressed by a wide variety of cell types, including B cells, T cells, dendritic cells and epithelial cells. In the resting state, raftlin is present diffusely in the cytosol, but after the addition of poly(I:C), it is rapidly recruited to membrane rafts, where it associates with poly(I:C). Raftlin-poly(I:C) is then cycled to the endosomes, where it segregates with TLR3. Notably, knockdown of raftlin results in much lower expression of interferon-β after the addition of poly(I:C), which confirms its role in TLR3 activation. ***ZF***

***J. Biol. Chem.* 286, 10702–10711 (2011)**

Controlling host responses

Successful pathogens can establish chronic infection without killing their host, which suggests that accommodation by the immune system occurs during the infection. In *Science*, Lebreton *et al.* identify a virulence factor, LntA, from *Listeria monocytogenes* that paradoxically induces host type III interferon responses. LntA is expressed by virulent strains of *L. monocytogenes* after infection and accumulates in the nuclei of host cells. LntA forms complexes with the host protein BAHD1, a repressive factor associated with heterochromatin assembly. Cells infected with LntA$^+$ *L. monocytogenes*, but not those infected with LntA$^-$ *L. monocytogenes*, upregulate *IL28A*, *IL28B* and *IL29*, which encode type III interferons, and a suite of interferon-stimulated genes normally repressed by the BAHD1 complex. LntA prevents the recruitment of chromatin-silencing enzymes to target promoters by BAHD1, thereby derepressing the expression of these target genes. Mice infected with *L. monocytogenes* that constitutively express LntA have fewer bacteria in their spleen and liver than do mice infected with wild-type or LntA-deficient bacteria. This finding suggests that *L. monocytogenes* pathogens regulate the secretion of LntA to control host immune responses and establish persistent infection. *LAD*

Science **331**, 1319–1321 (2011)

Interferon effects

Type I interferon is a common therapy for autoimmune and inflammatory disorders, yet its mechanism of action is largely unknown. In *Immunity*, Tschopp and colleagues show that type I interferon inhibits IL-1 production by two distinct mechanisms. First, it signals through the transcription factor STAT1 to inhibit activity of the NLRP1 and NLRP3 inflammasomes, thus repressing caspase-1-dependent IL-1β maturation. In a second inhibitory loop, type I interferon induces IL-10, which in turn signals through STAT3 to diminish production of the precursor form of IL-1β. The ability of type I interferon to repress IL-1 secretion may contribute to the greater risk of infection after exposure to virus and may explain the therapeutic effect of interferon-β treatment in multiple sclerosis and two other inflammatory disorders linked to IL-1 overproduction: familial Mediterranean fever and Behcet syndrome. ***IV***

***Immunity* 34, 213–223 (2011)**

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

PKC-θ goes nuclear

PKC-θ is a protein kinase expressed mainly in T cells and is best known as a cytoplasmic intermediate in the signal-transduction cascades downstream of the T cell antigen receptor. In *Molecular Cell*, Rao and colleagues provide evidence that PKC-θ is present in the nucleus and is a component of the transcription complexes that control the expression of activation-induced genes, such as those encoding interleukin 2 (IL-2), tumor necrosis factor (TNF), interferon-γ and the activation marker CD69, as well as microRNA genes. The authors show that recruitment of PKC-θ to these genes is dependent on continuous T cell activation and requires the catalytically active domain of the kinase. PKC-θ forms an active transcription complex with the chromatin-associated molecules MSK-1, RNA polymerase II, 14-3-3ζ and LSD1 and is required for inducible chromatin accessibility at proximal promoters. Other cytoplasmic signaling kinases shown before to have nuclear functions include IKKα and NIK. *IV*

Mol. Cell **41**, 704–719 (2011)

Turning it on with zinc

Zinc is widely known in the neurosciences to be important for ionic signaling, but has not been well studied by immunologists. In the *Journal of Experimental Medicine*, Goronzy and colleagues focus on the role of ionic zinc in the activation of CD4$^+$ T cells. Using dendritic cells loaded with superantigen, they observe very rapid influx of zinc into responding T cells. The distribution of zinc is not diffuse but instead very characteristically localizes to the subsynaptic space, where it opposes recruitment of the phosphatase SHP-1 and therefore potentiates proximal signals such as Zap70. Zinc originates in the extracellular space, and its influx requires T cell expression of the zinc channel Zip6. Zinc deficiency is thought to be responsible in part for the immunosuppression associated with malnutrition. This study therefore provides a mechanistic basis for this deficiency. ***ZF***

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Sharpin ubiquitin reactions

Many signaling pathways activate the transcription factor NF-κB by assembly of IKK kinase complexes that phosphorylate the inhibitor IκBα, targeting it for degradation. Protein modification by ubiquitination facilitates the formation of these upstream activation complexes. In *Nature*, groups led by Dikic, Iwai and Walczak all identify the protein sharpin as a component of the linear ubiquitin chain assembly complex (LUBAC) necessary for NF-κB activation. LUBAC catalyzes the formation of peptide bonds between the amino-terminal methionine residue of one ubiquitin molecule and the carboxy-terminal glycine residue of another. Sharpin contains both a ubiquitin-like domain and a ubiquitin-binding domain and shares sequence homology with the known LUBAC factor HOIL-1L. Both proteins interact with the 'ring-between-ring' E3 ligase HOIP to mediate linear polyubiquitination of client proteins, including RIP1 and the IKK regulatory protein NEMO. Sharpin and HOIL-1L are both needed to stabilize HOIP, as loss of either diminishes the abundance of LUBAC; however, the phenotypes that result from deficiency in HOIL-1L or sharpin differ. Ablation of sharpin leads to less canonical activation of NF-κB in response to TNF, IL-1β and CD40, as seen in sharpin-deficient mice that have many immune system–related deficiencies and enhanced sensitivity to TNF-induced apoptosis. These findings suggest that many types of ubiquitin linkages are needed to mount appropriate immune responses. *LAD*

Nature (31 March 2011) doi:10.1038/nature09814, doi:10.1038/nature09815 & doi:10.1038/nature09816