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Antibacterial TBK1

Cytosolic TBK1, a member of the IκB kinase family, facilitates the production of IFN-α/β after virus infection is 'sensed' by the intracellular RNA helicases RIG-I and Mda5 or after TLR4 is stimulated by lipopolysaccharide. In *PLOS Pathogens*, O'Riordan and colleagues find that TBK1 is also important for the control of Gram-positive and, to a lesser extent, Gram-negative bacteria. Salmonella replicate more rapidly and to larger numbers in TBK1-deficient mouse embryonic fibroblasts than in wild-type cells. Production of IFN-α/β is not required for TBK1-suppression of bacterial growth; instead, the integrity of vacuoles that normally contain intracellular salmonella is impaired in TBK1-deficient cells. As a result, entry of bacteria into the cytosol enables increased bacterial growth. The authors speculate that TBK1 is required for the regulation of autophagy or for the influx and/or efflux of ions or water into and/or out of vacuoles. The precise mechanism of the antibacterial TBK1-dependent function is unclear. ***DCB***

***PLOS Pathog.* (2 March 2007) doi:10.1371/journal.ppat.0030029**

Adaptor cleavage

Various adaptor proteins transmit Toll-like receptor (TLR) signals into the cell interior. In *Proceedings of the National Academy of Science USA*, O'Neill and colleagues show that caspase-1 influences the activity of the TLR adaptor protein Mal. Interactions between Mal and caspase-1 are spontaneous and are inhibited by TLR stimulation. Although Mal is dispensable for TLR-induced activation of caspase-1 and subsequent interleukin 1 processing, caspase-1 is required for TLR- and Mal-induced signal transduction and cytokine production. Caspase-1 cleaves Mal at a caspase-1 consensus cleavage site, and overexpression of a mutant Mal lacking the caspase-1 cleavage site precludes TLR-induced NF-κB activation. Identification of the mechanism by which Mal cleavage promotes TLR signaling remains for future study. *CB*

Proc. Natl. Acad. Sci. USA **104**, 3372–3377 (2007)

'Knocking down' HIV

Human immunodeficiency virus 1 (HIV-1) uses various strategies to overcome innate and adaptive immune defenses. In *Science*, Triboulet *et al.* show that HIV-1 can overcome host cell microRNA (miRNA)–mediated inhibition of viral replication. HIV infection triggers downregulation of miRNAs miR-17-5p and miR-20a. These can indirectly interfere with viral replication by targeting expression of the host histone acetyltransferase PCAF, a cofactor of viral Tat protein. Both miR-17-5p and miR-20a target the 3′ untranslated region of the PCAF message, blocking its translation through a Dicer- and Drosha-dependent mechanism. Inhibition of Dicer, Drosha or the specific miRNAs leads to more viral production *in vitro*, suggesting that infected cells attempt to limit viral replication via miRNAs. How HIV-1 blocks this pathway remains unknown. ***LAD***

***Science* (22 February 2007) doi:10.1126/science.1136319**

Research Highlights written by Christine Borowski, Douglas C. Braaten and Laurie A. Dempsey

Modulating anaphylatoxins

Complement fragments C3a and C5a are anaphylatoxins that amplify innate immune responses. In *Nature*, Yeh and colleagues describe the function of the G protein–coupled receptor C5L2, which binds both C3a and C5a. Genetic studies suggest signaling through C5L2 alone produces weak responses to either anaphylatoxin but can amplify signaling via C3aR and C5aR. Loss of C5L2 leads to less cytokine production and inflammatory cell recruitment *in vivo*, but not to the same extent as loss of either C3aR or C5aR, suggesting that C5L2 is required for optimal responsiveness to the complement fragments. Yet C5L2 has another regulatory function, as mice deficient in C5L2 are hypersensitive to lipopolysaccharide-induced shock. Delineating these multiple signaling and regulatory pathways will be work for the future. *LAD*

Nature (25 February 2007) doi:10.1038/nature05559

'Genealogy' of IKDCs

Interferon-producing killer dendritic cells (IKDCs) and plasmacytoid DCs (pDCs) share some properties, although IKDCs express interferon-γ (IFN-γ), whereas pDCs express IFN-α. In *Blood*, Kincade and colleagues show that lineage specification of IKDCs begins in the Lin$^-$Sca-1$^+$c-Kit^{hi}Thy-1.1$^-$Flk-2$^+$L-sectin$^+$ (LSP) population of Lin$^-$Sca1$^+$c-Kit^{hi} (LSK) bone marrow cells. The LSK fraction also contains RAG-1$^+$Flk-2$^+$CD27$^+$ early lymphoid progenitors that give rise to 'RAG$^+$pDC1' cells, which are distinct from LSP-derived 'RAG$^-$pDC2' cells. A third population of cells, the 'pDC cohort', has been identified before in a bone marrow population called 'fraction A', which also contains pDC1 and pDC2 subsets. The pDC cohort cells are B220$^+$CD11c^{lo}CD19$^-$ Ly6C$^-$ and express natural killer cell lineage markers NK1.1 and DX-5. Data now indicate that IKDCs and pDC cohort cells are the same; they do not require Notch but do require the transcriptional inhibitor Id2, produce less IFN-γ after, but resist depletion by, estrogen treatment that depletes all other lymphoid bone marrow progenitors, and are most efficiently generated from 'T cell lineage–biased' LSPs. These results suggest that IKDC development is unique. ***DCB***

***Blood* (22 February 2007) doi:10.1182/blood-2006-08-042810**

Maintaining motion

Chemokines influence T cell recruitment to and localization in lymphoid organs, but the function of chemokines in regulating the chemokinesis, or movement without chemokine gradients, of naive T cells in lymphoid tissue has not been established. In the *Journal of Immunology* and the *Journal of Experimental Medicine*, the groups of Cyster and Forster show that chemokine signaling is required for the random movement of naive T cells in lymph nodes. T cells pulsed with inhibitors of Gαi-containing heterotrimeric G proteins show reduced velocity in lymph nodes. Injection of the CCR7 ligand CCL19 enhances T cell movement in lymph nodes, and wild-type T cells in mice lacking CCL21 and CCL19 show a partial but significant reduction in movement. CCR7-deficient T cells also show impaired migration in wild-type lymph nodes. Other chemokines and/or Gαi-independent receptors contributing to the chemokinesis of naive T cells in lymph nodes remain to be identified. *CB*

J. Immunol. **103**, 18685–18690 (2007) & *J. Exp. Med.* (26 February 2007) doi:10.1084/jem.20061706