Tuning TLR signals

Interferon (IFN)-γ modulates Toll-like receptor (TLR)-induced signaling and gene expression. In *Immunity*, Hu *et al.* find that IFN-γ inhibits cross-talk between TLR and Notch signals. In human macrophages, TLR stimulation induces expression of a subset of Notch target genes including *HES1* and *HEY1*. TLR-triggered expression of *HES1* and *HEY1* occurs independently of new protein synthesis but requires basal activation of Notch signaling and the Notch effector protein RBP-J. IFN-γ suppresses this basal Notch signaling. TLR–Notch signal interplay has complex biological consequences. RBP-J enhances TLR-driven IL-6 production, whereas, in accordance with their established status as feedback inhibitors of Notch signaling, HES1 and HEY1 suppress TLR-triggered proinflammatory cytokine production. Thus, in macrophages, IFN-γ may relieve a Notch signal–mediated 'brake' on TLR signal transduction. ***CB***
***Immunity* 29, 691–703 (2008)**

Sharing signaling endosomes

Hematopoietic stem cells (HSCs) depend on stromal osteoblast cells to provide survival and differentiation signals in bone marrow niches. In *Nature Cell Biology*, Lippincott-Schwartz and colleagues show that HSCs adopt a highly polarized morphology that facilitates 'sharing' of signaling endosomes with the supporting osteoblast. HSC uropods enriched in membrane proteins VLA-4, CD63, CD81 and prominin 1 form at the contact interface. Active transfer of signaling molecules between HSCs and osteoblasts occurs at this interface, through a process distinct from degradative endocytosis or membrane fusion. Although the transfer mechanism remains to be deciphered, transfer of HSC-encoded signaling molecules induces osteoblasts to down-regulate Smad2/3, which in turn upregulates expression of CXCL12, a chemokine known to support HSC homing and adhesion. Hence, intercellular cross-talk between HSCs and osteoblasts engenders positive feedback to maintain the stromal niche. *LAD*
Nat. Cell Biol. **11**, 303–311 (2009)

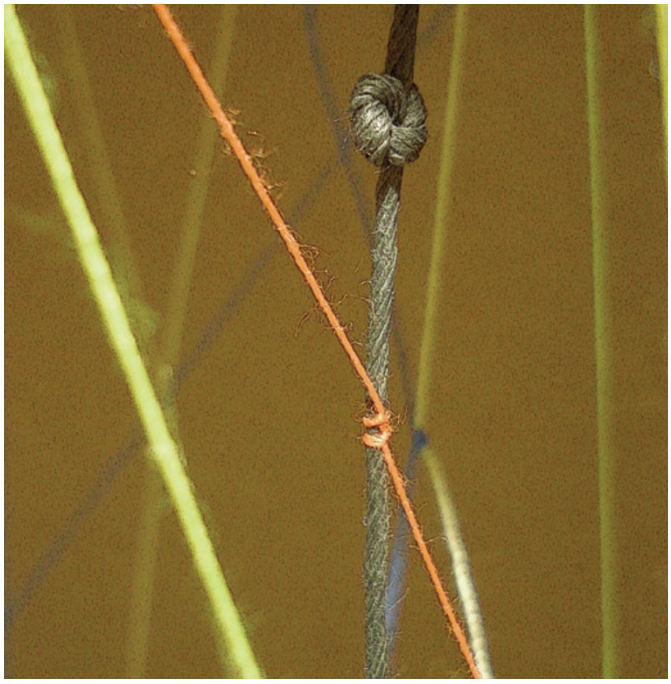
Positive cross-talk by calcium

Cross-talk between Toll-like receptor signaling and other signaling pathways is common. In *Blood*, Cao and colleagues investigate whether the Ca^{2+}–CaMKII pathway cross-talks with TLR signaling, as previous work has shown that lipopolysaccharide (LPS) can elicit Ca^{2+} flux in mouse macrophages. TLR3, 4 and 9 ligands could induce Ca^{2+} mobilization from internal Ca^{2+} stores and induce CaMKII-α phosphorylation. Blockade or knockdown of CaMKII attenuated, whereas overexpression of active CaMKII enhanced, TLR-induced proinflammatory cytokine and type I interferon production. CaMKII could phosphorylate TAK1, a MAPKKK essential for TLR-induced MAPK, NF-κB activation and proinflammatory cytokine production. In addition, CaMKII could phosphorylate the transcription factor IRF3, required for IFN-β production. Consistently, *in vivo* blockade of CaMKII activation lessened the severity of LPS-induced endotoxic shock. These data show that positive cross-talk with the Ca^{2+} signaling pathway is required for TLR responses in macrophages. ***JDKW***
***Blood* 112, 4961–4970 (2008)**

Written by Christine Borowski, Laurie A. Dempsey & Jamie D.K. Wilson

Tempering phagocytosis

Eicosanoid lipid mediators can suppress or enhance immune responses. In the *Journal of Immunology*, Lee *et al.* look at the combinatorial effects of suppressive prostaglandin E_2 (PGE_2) and activating leukotriene B_4 (LTB_4) or LTD_4 on alveolar macrophage phagocytic activities. PGE_2 signaling through $G\alpha_s$ triggers increases in cyclic AMP concentration and suppression of phagocytosis and bactericidal activities, an effect that is counteracted by LTB_4 activation of $G\alpha_i$. FcγR-mediated phagocytosis leads to increased LTB_4 generation and further antagonizes PGE_2 suppression. LTD_4 has no effect on intracellular cAMP concentrations but synergizes with LTB_4 to increase phagocytosis in alveolar macrophages by inhibiting Rap-1 GTPase, a downstream effector of cAMP, through an unknown, cAMP-independent pathway. Future work should further illuminate how macrophages integrate opposing signals encountered in infected or inflamed tissues. *LAD*
J. Immunol. **182**, 530–537 (2009)



IL-15 and NKG2D: dangerous synergy

Only in the presence of high concentrations of interleukin (IL)-15 or IL-2—such as those present in the intestines of patients with celiac disease—can NKG2D trigger cytotoxic T lymphocyte (CTL)-mediated cytolysis independently of T cell antigen receptor (TCR) stimulation. In the *Journal of Experimental Medicine*, Jabri and co-workers designate cytosolic phospholipase A2 ($cPLA_2$) activation a biologically relevant consequence of synergy between IL-15 and NKG2D signals. Inhibition or ablation of $cPLA_2$ suppresses cytotoxicity induced by stimulation with anti-NKG2D and high dose IL-2, or by NKG2D and TCR cross-linking. NKG2D-induced $cPLA_2$ phosphorylation requires Erk and Jnk but not p38 MAP kinases. IL-15 also induces phosphorylation of Erk, Jnk and $cPLA_2$, but the combination of IL-15 and anti-NKG2D triggers more robust $cPLA_2$ activity than either IL-15 or anti-NKG2D alone. A higher proportion of intraepithelial CTL expresses phosphorylated $cPLA_2$ in patients with celiac disease than in healthy individuals. *CB*
J. Exp. Med. doi:10.1084/jem.20071887 (23 February 2009)