## Chemokine signal 'wiring'

**Unlike the trimeric G protein $G\alpha_i$ subunit, required for leukocyte movement toward all chemokines, the ectoenzyme CD38 mediates recruitment elicited by only a subset of chemoattractants. In the *Journal of Experimental Medicine*, Lund and colleagues show that CD38 acts together with $G\alpha_q$ in an alternative to the classical $G\alpha_i$-driven chemokine signaling pathway. Although both pathways use $G\alpha_i$, the alternative pathway operates 'downstream' of some but not all chemokine receptors, and its importance varies with cell type and activation state. Essential for calcium influx but dispensable for the release of calcium stores, the alternative pathway is required for trafficking of naive neutrophils and dendritic cells, but not lymphocytes, in inflammatory but not homeostatic conditions *in vivo*. Elucidation of the molecular mechanism linking $G\alpha_q$ to extracellular calcium entry and the basis for the receptor-, lineage- and differentiation state–specific importance of the alternative pathway remains for future study.** ***CB***

***J. Exp. Med.* (15 October 2007) doi:10.1084/jem.20071267**

## Destabilizing mRNA

The protein roquin contributes to peripheral immune tolerance by regulating T cell expression of the costimulator ICOS. In *Nature*, Vinuesa and colleagues show that roquin indirectly alters the stability of ICOS mRNA. ICOS expression is higher in $CD4^+$ T cells from 'sanroque' mice, which express a mutant form of roquin. The 3′ untranslated region of the ICOS transcript contains an element recognized by miR-101, which destabilizes the transcript. Neurophilin 1 mRNA, another miR-101 target, is also overexpressed in sanroque mice. The abundance of miR-101 and ICOS mRNA is inversely correlated in wild-type mice. However, sanroque T cells still have abundant miR-101, ruling out the possibility that roquin regulates miR-101 expression. How roquin and miR-101 interact to mediate mRNA decay remains unknown. *LAD*

*Nature* (8 November 2007) doi:10.1038/nature06253

## Virus perturbation of cholesterol

**West Nile virus (WNV), an enveloped RNA flavivirus, uses host cell processes to its advantage—a general trait of all successful pathogens. In *Cell Host & Microbe*, Parton and colleagues evaluate the effect of WNV infection on cholesterol distribution and metabolism and find that infection leads to altered cholesterol homeostasis that increases virus replication while simultaneously blunting host immune responses. WNV infection promotes the formation of complex membrane 'virus factories' enriched in cholesterol and host proteins modified by geranylgeranlyation, two effects required for robust virus replication. The redistribution of cholesterol to virus factories increases host cholesterol biosynthetic pathways, which in turn increase production geranylgeranylated proteins; redistribution also reduces transcription factor STAT–mediated induction of, and response to, interferon, as STAT function requires cholesterol-rich microdomains. These data demonstrate that WNV induces efficient virus production and 'disarms' host immune responses by modulating cholesterol, two effects that can be reduced by the addition of exogenous cholesterol.** ***DCB***

***Cell Host & Microbe* 2, 229–239 (2007)**

Written by Christine Borowski, Douglas C. Braaten & Laurie A. Dempsey

## Inhibiting pDCs

Plasmacytoid dendritic cells (pDCs) produce abundant type I interferon (interferon-α/β) after stimulation. In *PLoS Biology*, Cao *et al.* identify an inhibitory pathway that suppresses pDC production of cytokines and interferon-α/β in response to Toll-like receptor (TLR) signals. These cells express the receptor BDCA2, which lacks any signaling motif. BDCA2 associates with the signaling-competent receptor FcεR1γ to activate a cascade similar to the B cell receptor signaling pathway. Crosslinking BDCA2 in the presence of FcεR1γ leads to decreased responses to TLR7 and TLR9, suggesting a way to regulate pDC function. This pathway of interference blocks the transcription of all type I interferons examined. How such signals intersect with the TLR signaling pathway remains to be determined. *LAD*

*PLoS Biol.* **5**, 2190–2200 (2007)

## FasL as costimulator

**Although often considered only a mediator of cell death, Fas ligand (FasL), a member of the tumor necrosis factor family of receptors, has been shown to have a costimulatory effect on $CD4^+$ and especially $CD8^+$ T cells. In *Journal of Immunology*, Fink and colleagues delineate these two functions of FasL with mutagenesis and biochemical approaches, showing that a region of FasL encompassing amino acids 45–54, a proline-rich domain, is required for costimulatory activity but not death induction. Deletion of the proline-rich domain has no deleterious effect on cell surface expression of FasL, but costimulation of $CD8^+$ T cell proliferation is abrogated. The signaling pathways affected by the deletion include reduced activity of kinases Akt and Erk1 and Erk2; wild-type FasL itself is phosphorylated by casein kinase I, which is required for 'downstream' activation of transcription factor NFAT and costimulation of T cells. These data show how a single molecule with separable functional motifs can induce separate effects.** ***DCB***

***J. Immunol.* 179, 5639–5643 (2007)**

## Niche builders

Bone marrow fragments are able to transfer bone and the associated hematopoietic microenvironment to heterotopic sites *in vivo*. In *Cell*, Bianco and coworkers identify a bone marrow progenitor cell that can generate the hematopoietic microenvironment as well as bone and all of its constituent cell types. Present only in hematopoietic bone, displaying large amounts of the adhesion molecule CD146 and located in a subendothelial layer lining small blood vessels called sinusoids, these progenitor cells bear strong resemblance to adventitial reticular cells. Clones derived from $CD146^+$ progenitor cells express genes associated with osteogenic precursor cells and hematopoietic stem cell niches and, when transferred subcutaneously into mice, self-renew and successively generate bone, sinusoids and hematopoietic cells. Angiopoietin 1, known to promote hematopoiesis and angiogenesis, is expressed by and, together with CD146 itself, is essential for the hematopoietic microenvironment–and bone-regenerating activity of these $CD146^+$ progenitor cells. *CB*

*Cell* **131**, 324–336 (2007)