## Unanchored polyubiquitin chains

**RIG-I is a key cytosolic detector of viral RNA, and until recently very little was known about its regulation. In *Cell*, Chen and colleagues report an unexpected step in RIG-I activation. Using a cell-free system composed of viral RNA–bound RIG-I, cytosol and mitochondria, the authors are able to reconstitute the RIG-I signaling pathway *in vitro*. They note that RIG-I activation requires not only recognition of viral RNA but also subsequent Lys63 (K63) binding of polyubiquitin chains. Binding occurs via the tandem caspase-recruitment domains of RIG-I. Interestingly, free K63 ubiquitin chains composed of at least three ubiquitin moieties function as a potent endogenous ligand for RIG-I. These findings demonstrate a previously unappreciated signaling role for polyubiquitin that may have much wider implications in innate immunity and beyond.** ***ZF***

***Cell*** **(16 April 2010) doi:10.1016/j.cell.2010.03.029**

## Tuning calcium responses

How calcium signaling, which triggers key functional responses during lymphocyte activation, is influenced by reactive oxygen species is unclear. In *Science Signaling*, Niemeyer and colleagues show that hydrogen peroxide ($H_2O_2$) can oxidize and inhibit the stores-operated calcium channel protein ORAI1 but not the related proteins ORAI2 or ORAI3. This difference in redox sensitivity is due to Cys195 in an extracellular loop of ORAI1 (but absent from the other ORAI proteins) that becomes disulfide-linked after $H_2O_2$ exposure. This modification decreases the ORAI-dependent inward $Ca^{2+}$ flux triggered by release of endoplasmic reticulum stores and activation of the $Ca^{2+}$ sensor STIM1. Effector T cells are less sensitive than naive T cells to $H_2O_2$ oxidation, as expression of ORAI3 is higher in effector cells. Knockdown of ORAI3 in effector T cells increases their sensitivity to oxidizing environments, which leads to lower viability and less interleukin 2 (IL-2) production. How *Orai3* expression is upregulated in effector cells remains unknown, but this response is probably critical for effector function at sites of inflammation. *LAD*

*Sci. Signal.* (30 March 2010) doi:10.10.1126/scisignal.2000672

## IκBζ and $T_H17$ development

**The transcription factors RORγt and RORα have an indispensable role in inducing the development of IL-17-producing helper T cells ($T_H17$ cells); however, in the absence of IL-6 and transforming growth factor-β, ectopic expression of RORγt and RORα leads to only modest IL-17 production. In *Nature*, Takayanagi and colleagues show that the nuclear IκB family member IκBζ is required for the generation of $T_H17$ cells in a T cell–intrinsic manner. IκBζ-deficient mice are resistant to the induction of experimental autoimmune encephalomyelitis and have impaired $T_H17$ development. IκBζ expression is upregulated by IL-6 and transforming growth factor-β. The effect is mediated by the transcription factor STAT3 and is RORγt independent. IκBζ binds directly to the ISE1 regulatory region of the *Il17a* promoter, and its recruitment is dependent on RORγt. These findings indicate that the ROR nuclear receptors and IκBζ synergistically promote $T_H17$ development.** ***IV***

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## Bone marrow exit

Expression of sphingosine 1-phosphate receptor type 1 ($S1P_1$) is required for the egress of newly formed T cells from the thymus and of mature T cells and B cells from the secondary organs. In the *Journal of Experimental Medicine*, Allende *et al.* show that $S1P_1$ also mediates the exit of immature B cells from the bone marrow. In mice with conditional deletion of $S1P_1$ in B cells, the number of immature and mature B cells in spleen and blood is lower, which correlates with defective transfer of immature B cells from the bone marrow parenchyma into the blood sinusoids. Interfering with the interaction between the chemokine receptor CXCR4 and its ligand CXCL12, which is required for proper retention of B cells in the bone marrow, does not release $S1P_1$-deficient immature B cells into the blood. The mechanism by which $S1P_1$ mediates egress from lymphoid organs remains unclear. *IV*

*J. Exp. Med* (19 April 2010) doi:10.1084/jem.20092210

## Adapting immunity to SIV

**Infection of humans and Asian nonhuman primates with AIDS-causing virus leads to disease and ultimately to collapse of the adaptive immune system, but it is a different story in natural hosts. African nonhuman primates such as the African Green monkey (AGM) have undergone evolutionary adaptations to cope with infection with simian immunodeficiency virus (SIV). In *Blood*, Schmitz and colleagues deplete monkeys of both $CD8^+$ T cells and B cells during primary SIV infection to investigate the role of the adaptive immune response in this resistance. AGM natural killer cells also undergo depletion by virtue of their CD8 expression. Despite having a brief initial increase in viremia, monkeys with such lymphocyte depletion never progress to disease. Interestingly, $CD4^+$ T cells seem normal. These results contrast with studies of non-natural hosts, which show accelerated mortality after lymphocyte depletion. Collectively, these results demonstrate the robustness of the AGM immune system against SIV, which remains effective even in the absence of cell-mediated and humoral immunity.** ***ZF***

***Blood*** **(15 April 2010) doi:10.1182/blood-2009-10-245225**

## Stress suppresses antimicrobials

Antimicrobial peptides contribute to skin barrier function and help control wound healing. In *Cell Host & Microbe*, Radek *et al.* show that stimulation of the nicotinic acetylcholine receptor (nAchR) suppresses keratinocyte production of antimicrobial peptides, which leads to enhanced susceptibility to skin infection. Topical application of nicotine decreases microbicidal activity. Mice lacking chromogranin A, which is the source of a natural peptide catestatin that antagonizes nAchR function, likewise have lower antimicrobial peptide expression and develop more necrotic skin lesions after cutaneous infection with *Staphylococcus aureus* or group A streptococci. Stress, which also increases acetylcholine release and activates the nAchR signaling pathway, decreases expression of antimicrobial peptides and enhances susceptibility to bacterial infection. In contrast, topical application of the nAchR antagonist α-bungarotoxin restores antimicrobial function to the epidermis of $Chga^{-/-}$ or stressed mice. Acetylcholine stimulation of nAchR specifically suppresses both basal and vitamin D3–induced expression of cathelicidin and β-defensin 2, but how this signaling pathway blocks their gene transcription remains to be elucidated. *LAD*

*Cell Host Microbe* **7**, 277–289 (2010)