## BCRs trump TLR tolerance

**Chronic stimulation of Toll-like receptors (TLRs) induces a hyporesponsive state in myeloid cells known as TLR tolerance. In the *Journal of Immunology*, Bishop and colleagues show that repeated stimulation of TLR7 or TLR9 induces a similar tolerance in mouse and human B cells. After TLR stimulation, although expression of interleukin 10 is unaffected, TLR-tolerant B cells proliferate less and produce less immunoglobulin or proinflammatory cytokines (interleukin 6 and tumor necrosis factor) than do naive B cells. Tolerance is associated with impaired activation of the Jnk, Erk and p38 kinase and transcription factor NF-κB pathways; however, unlike tolerized macrophages, TLR-tolerant B cells do not express the signaling pathway inhibitors SOCS3 or IRAK-M. Notably, simultaneous stimulation of the B cell antigen receptor (BCR) prevents or reverses TLR tolerance. Signaling through the phosphatidylinositol-3-OH kinase–Akt kinase pathway is necessary for this BCR mediated effect. Further work is needed to delineate how BCR and TLR pathways intersect and what factors are responsible for establishing the tolerant state.** ***LAD***

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## Away from Notch

Deltex1 has always been associated with noncanonical Notch signaling, although its function in this pathway remains ambiguous. In *Immunity*, Hsiao *et al.* describe a new function for this E3 ubiqutin ligase as an important participant in T cell anergy. Deficiency in the gene encoding Deltex1 leads to more T cell activation, proliferation and cytokine secretion, alters sensitivity to anergy induction and causes more inflammation and autoimmunity. Deltex1 contributes to T cell anergy not only by targeting the kinase MEKK1 for degradation in an E3 ligase–dependent way but also by inducing or augmenting the expression of other E3 ligases, such as Gadd45β and Cbl-b, which in turn target the kinase Jnk and adaptor Vav1 for degradation. Notably, the last effect is independent of the ring finger or Notch-binding domains of Deltex1. The contributions of the other Deltex proteins (DTX2-4) to T cell anergy remain to be determined. *IV*

*Immunity* **31**, 72–83 (2009)

## Cytokines are cell fate 'instructors'

**It is still disputed if cytokines instruct hematopoietic stem cell lineage choices or promote the survival of cells that are already lineage restricted. In *Science*, Rieger *et al.* use a bioimaging approach to allow continuous long-term analysis of hematopoietic stem cells at the single-cell level. They monitor the death or differentiation of progeny of hundreds of granulocyte-macrophage progenitors (GMPs) grown in macrophage or granulocyte colony-stimulating factor only. For colonies showing no cell death, they assume that the cytokine is 'instructive' or that the colony-initiating cell was already lineage restricted. The percentages of no-cell-death colonies that exclusively generate monocytic or granulocytic cells far exceed the percentage of colonies that could have been generated from lineage-restricted precursors contaminating the starting GMP population. These data therefore indicate that cytokines can 'instruct' bipotent GMPs.** ***IV***

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Written by Christine Borowski, Laurie A. Dempsey & Ioana Visan

## Stop and go signals

NK cells kill cellular targets by polarizing and delivering lytic granule contents to the doomed cell. In *PLoS Biology*, Culley *et al.* describe the migration and polarity of NK cells responding to activating or inhibitory receptor ligation. NK cells stop migrating after ligation of activating receptors and rapidly undergo symmetrical spreading over a large surface, followed by a polarizing contraction to form an activating synapse poised to deliver a lethal 'hit'. This response involves the formation of a highly dynamic ring of F-actin at the cell periphery. Ligation of inhibitory receptors, in contrast, blocks formation of the F-actin ring structure and delivers a 'reverse-stop' signal to the NK cell. Inhibitory synapses are smaller, asymmetric and more transient, and thus resemble migratory 'kinapses'. However, once the threshold of activating receptor ligation is reached, as can occur with a high local density of stress- or virus-induced activating ligands, the stop and kill response ensues. *LAD*

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## PLZF$^+$ unconventional T cells

**Unconventional T cell subsets, including natural killer (NK) T cells and γδ T cells, exert 'innate-like' functions and seem to be selected by T cell antigen receptor (TCR) agonists. In the *Proceedings of the National Academy of Science*, von Boehmer and colleagues find that the transcription factor PLZF—previously linked to NK T cell function—is required for some innate-like properties of certain γδ T cells. PLZF is expressed by $V_\gamma1^+V_\delta6.3^+$ and $V_\gamma1^+V_\delta6.4^+$ T cells and is required in a cell-intrinsic way for their ability to simultaneously produce interferon-γ and interleukin 4. TCR crosslinking triggers PLZF expression in thymocytes but not mature T cells that express $V_\gamma1$, $V_\gamma4$ or $V_\gamma7$ TCRs. $V_\gamma1$ and $V_\delta6.4$ TCR transgenes promote the development of PLZF-expressing cells and spontaneous dermatitis in recombination-activating gene 1–deficient mice. The putative agonist responsible for selecting $V_\gamma1^+V_\delta6.3^+$ and $V_\gamma1^+V_\delta6.4^+$ T cells remains unidentified. Nevertheless, these findings suggest that agonist-driven PLZF expression is needed for the complete differentiation of several unconventional T cell subsets.** ***CB***

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## Teasing apart transcriptional controls

Stimulation of TLR4 by lipopolysaccharide (LPS) induces the expression of primary response genes (PRGs) and secondary response genes (SRGs); the latter are expressed later, by a mechanism dependent on protein synthesis. In *Cell*, groups led by Medzhitov and Smale identify molecular processes that regulate LPS-inducible PRG expression. In unstimulated macrophages, the promoters of most LPS-inducible, SWI/SNF-independent PRGs are enriched for CpG islands and permissive histone modifications and inefficiently assemble into stable nucleosomes. Before LPS stimulation, PRG but not SRG promoters are bound by RNA polymerase II and are transcribed into unspliced full-length precursor mRNA. LPS induces recruitment of the NF-κB subunit p65, which facilitates the deposition of additional histone modifications and recruitment of the elongation factor P-TEFb to PRG promoters. Thus, LPS influences PRG expression at a post-transcriptional initiation checkpoint. *CB*

*Cell* **138**, 114–128 & 129–145 (2009)