DUBA dampens IFN

By removing ubiquitin molecules from target proteins, deubiquitinating enzymes (DUBs) counteract ubiquitin ligases. In *Science*, Dixit and colleagues link DUBA to the suppression of type I interferon production induced by pattern-recognition receptors (PRRs). 'Knockdown' of DUBA, but not of 13 other DUBs, by small interfering RNA enhances interferon production triggered by ligation of Toll-like receptors or the RNA helicases RIG-I and Mda5. By a mechanism dependent on its cysteine protease activity, DUBA suppresses interferon production by cleaving lysine 63–linked ubiquitin chains from TRAF3, a ubiquitin ligase involved in signals emanating from many PRRs. By deubiquitinating TRAF3, DUBA partially blocks the TRAF3-TBK1 interactions required for the transmission of PRR signals. Further work is needed to thoroughly delineate the mechanism by which DUBA binds specifically to ubiquitinated TRAF3 and to determine if these findings are useful in treating diseases characterized by excessive interferon production. ***CB***

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Priming thymocyte sensitivity

Developing thymocytes undergo positive and negative selection to generate the peripheral T cell repertoire. In *Nature*, Gallo *et al.* show that calcineurin-induced activation of the kinase Erk primes double-positive thymocytes to respond to weak T cell receptor signals. Two populations of double-positive thymocytes exist: 'low Erk competence' cells, which precede 'high Erk competence' cells. The latter fail to develop in calcineurin-deficient or cyclosporin A–treated mice. Accordingly, weak agonists fail to positively select 'low Erk' thymocytes. The authors suggest that calcineurin signaling induces a transient state with an increased 'dynamic range' to T cell receptor signals during thymic selection, thereby avoiding overlap of signaling thresholds to discriminate between positive and negative selection. *LAD*

Nature **450**, 731–735 (2007)

The anti-inflammatory response

Stimulation of the interleukin 10 (IL-10) receptor with IL-10 activates the transcription factor STAT3, which inhibits the expression of many proinflammatory genes. In the *Journal of Immunology*, Murray and colleagues characterize two additional factors induced by IL-10 that contribute to its anti-inflammatory effects. Microarray analysis of mRNA from IL-10-deficient macrophages stimulated with IL-10 and the proinflammatory agent lipopolysaccharide shows that the transcriptional repressor ETV3 and transcriptional corepressor SBNO2 are upregulated in a STAT3-dependent way; both mouse and human macrophages have the same response to stimulation with IL-10 and lipopolysaccharide. Transcriptional reporter assays show that ETV3 and SBNO2 repress the proinflammatory functions of the transcription factor NF-κB but not of the transcription factor IRF7. Expression of ETV3 and SBNO2 is not increased much by IL-10-independent STAT3-dependent signals such as those activated by IL-6. Thus, IL-10 selectively regulates proinflammatory gene expression by inducing ETV3 and SBNO2 repressors. ***DCB***

***J. Immunol.* 179, 7215–7219 (2007)**

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

Syndecan-3 capture of HIV-1

Dendritic cells (DCs) capture human immunodeficiency virus 1 (HIV-1) viral particles via the lectin receptor DC-SIGN, but whether DCs express additional HIV-1 receptors is controversial. In the *Proceedings of the National Academy of Sciences*, de Witte *et al.* identify syndecan-3, a heparan sulfate proteoglycan expressed by human DCs that binds glycoprotein-120 to capture and 'protect' HIV-1 viruses for delivery to T cells. Treatment of DCs with heparinase II or III (but not heparinase I) reduces viral binding, as does 'knockdown' of syndecan-3 expression by small interfering RNA. This suggests that DCs use a specific type of heparan sulfate proteoglycan receptor for immune surveillance. Combining heparinase digestion in the presence of mannan to block DC-SIGN completely abrogates HIV-1 binding to DCs. Immunofluorescence imaging of cervical DCs shows that syndecan-3 is located on dendrites, which are extended to the genital mucosal surface where sampling of the microbial flora occurs. These findings suggest HIV-1 exploits both DC-SIGN and syndecan-3 for entry into host cells. *LAD*

Proc. Natl. Acad. Sci. USA **104**, 19464–19469 (2007)

ITAM-Vav-dependent cross-presentation

The presentation of soluble and particulate exogenous antigens by DCs to $CD8^+$ T cells occurs by the process of cross-presentation. In the *Journal of Experimental Medicine*, Swat and colleagues find that the guanine nucleotide–exchange factor Vav mediates the induction of reactive oxygen species (ROS) by the immunoreceptor tyrosine-based activation motif (ITAM)–containing adaptors DAP12 and FcRγ; these ROS are required for the processing of particulate but not soluble antigens for cross-presentation. Vav-deficient DCs and DAP12- or FcRγ-deficient DCs are defective in the cross-presentation of particulate antigen and in ROS production, although initial phagocytic uptake is mostly unimpaired. As in macrophages, Vav in DCs is required for activation of the NOX protein complex that drives ROS production and regulates phagosomal pH. As cross-presentation is diminished in NOX-deficient DCs but is completely ablated in Vav-deficient DCs, Vav may mediate ROS-independent functions. These data link cross-presentation to a Vav-dependent pathway 'downstream' of specific ITAM adaptors. ***DCB***

***J. Exp. Med.* 204, 2889–2897 (2007)**

Tuning CXCL12 responsiveness

B lymphopoiesis in the bone marrow is regulated by binding of the chemokine CXCL12 to its receptor CXCR4, triggering activation of the nonreceptor protein tyrosine kinase FAK. In *Immunity*, Silberstein and coworkers set out to determine why CXCL12 responsiveness wanes as B cells mature. Despite their equivalent expression of CXCR4, immature but not mature B cells show CXCL12 responsiveness, as assessed by FAK phosphorylation and adhesion to VCAM-1. In contrast, CXCL12 stimulates FAK ubiquitination and degradation in mature but not immature B cells. Expression of SOCS3, a protein that ubiquitinates FAK in fibroblasts, increases as B cells mature. SOCS3 overexpression suppresses CXCL12 responsiveness in a pro–B cell line. Conversely, SOCS3-deficient immature B cells show excessive CXCL12 responsiveness as well as impaired localization in and emigration from the bone marrow. Elucidation of the molecular mechanisms regulating SOCS3 expression during B cell development will provide additional insight into the signals that direct B cell maturation. *CB*

Immunity **27**, 811–823 (2007)

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