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Repressing combinations

Nuclear receptors such as steroid receptors can alter gene expression in responsive cells. In *Cell*, Ogawa *et al.* show that agonists to the nuclear receptors glucocorticoid receptor, peroxisome proliferator-activated receptor and liver X receptor can block Toll-like receptor 3 (TLR3)– and TLR4-induced gene activation in primary macrophages. Notably, the nuclear receptors inhibit overlapping but distinct sets of genes that are commonly targeted by both TLR3 and TLR4. For example, dexamethasone-activated glucocorticoid receptors compete for binding of transcription factor NF-κB p65 with the transcription factor IRF3 induced by a TLR4-MyD88 pathway, thereby inhibiting activation of a subset of NF-κB–responsive genes. In contrast, dexamethasone treatment of TLR3-stimulated cells fails to inhibit these same genes. The results suggest that signal-dependent and gene-specific repression is induced after nuclear receptor activation. ***LAD***

***Cell* 122, 707–721 (2005)**

BLyS-signaling to DCs

Dendritic cells (DCs) are thought to mediate activation signals. In *Blood*, Franco and colleagues show that DCs also receive signals from cell surface molecules such as B lymphocyte stimulator (BLyS), which activates B cells through transmembrane activator and CAML interactor (TACI). In this exchange with B cells, DCs receive maturation signals from the BLyS molecule. Signaling does not require direct B cell contact, as a chimeric Fc-TACI protein is sufficient for DC maturation. This unique 'reverse signaling' is required for the generation of efficient cytotoxic T cell responses *in vivo*. DC maturation via BLyS is yet another way by which adaptive and innate immune cell interactions regulate effective immune responses. *DCB*

Blood (29 September 2005) doi:10.1181/blood-2004-12-4708

SLP-76 beyond DN3

Thymocyte development in mice lacking the adaptor protein SLP-76 is halted at the double-negative 3 (DN3) stage. Koretzky and colleagues have conditionally deleted SLP-76 after the DN3 checkpoint to evaluate the function of SLP-76 in primary thymocytes. SLP-76 inactivation at the DN3 stage reduces thymic cellularity in the double-positive compartment of young mice and prevents positive and negative selection. The rare CD4 single-positive thymocytes and peripheral T cells that are generated in these mice cannot flux calcium. These data demonstrate that SLP-76 expression is required for productive signal transduction during thymocyte selection. Greater understanding of the function of SLP-76 in the periphery T cell compartment requires further investigation. ***JDKW***

***J. Exp. Med.* (3 October 2005) doi:10.1084/jem.20051128**

Protein gymnastics

The complement component C3 is central to all three complement pathways that play a major role in innate and adaptive immunity. In *Nature*, Gros and colleagues demonstrate the crystal structures of C3 and its largest natural proteolytic fragment, C3c. C3 consists of two well conserved polypeptide chains, α and β, linked by disulfide bonds and hydrophobic interactions. The β-subunit forms a molecular ring–like platform that has limited structural variability between intact C3 and the cleavage product C3c. Conversely, the α-chain undergoes substantial conformational changes after C3 activation. The authors suggest such large structural shifts are necessary for protection of the labile thioester group that is essential for C3 linkage to its targets. *LAD*

Nature **437**, 505–511 (2005)

Trojan horses

Antigen-specific T cells are usually considered direct mediators of target cell destruction. In *Nature Medicine*, Vile and colleagues show how T cells also function as effective transporters of extracellular cargo that mediates effector function. Because T cells are 'sticky' for virus particles (adhesion that can be enhanced after heparanase treatment), preincubation of T cells with retroviruses that express herpes simplex virus thymidine kinase can lead to retrovirus-loaded T cells. After delivery to hosts, these T cells home to target tumor cells, which are then infected and killed by the retrovirus. Productive 'handoff' of the delivered retrovirus is enhanced by local heparanase activity of the tumor cells. Thus, antigen-specific T cells can also serve as effective 'Trojan horses' for retrovirus-delivered genes. *DCB*

Nat. Med. (18 September 2005) doi:10.1038/nm1297

Survival by kinase

Certain pathogens, such as *Bacillus anthracis*, block TLR4-initiated antiapoptotic pathways in macrophages by inhibiting p38 MAP kinase, whereas others impair the more well known prosurvival IKK-β-dependent NF-κB pathway. In *Immunity*, Karin and colleagues investigate how p38 MAP kinase mediates macrophage survival. The transcription factor CREB is regulated by p38 MAP kinase and is required for TLR4–induced macrophage survival. CREB and NF-κB cooperate to induce transcription of the survival factor serpin plasminogen activator inhibitor 2. This protein acts together with another prosurvival factor, Bfl1-A1, to mediate the p38- and NF-κB–dependent antiapoptotic pathway mediated by TLR4. These data show that p38 MAP kinase, like NF-κB, is an important regulator of macrophage survival and innate immunity. *JDKW*

Immunity **23**, 319–329 (2005)

IFN-γ requires DNA helicase

Interferon-γ (IFN-γ)–induced transcription of genes requires the transcription factor STAT1, but the identity of the cofactors required for efficient transcription of these genes remain unclear. In the *Proceedings of the National Academy of Sciences USA*, Zhang *et al.* demonstrate that proteins of the minichromosome maintenance (MCM) family, previously thought to act mainly as essential helicases for DNA replication, associate with STAT1 at the promoter of several IFN-γ target genes. MCM5 binds specifically to STAT1 and associates with RNA polymerase II during transcription elongation. RNA-mediated 'knockdown' of MCM5 results in considerably attenuated STAT1-mediated transcription. These data add a critical involvement in early response transcription to MCM function. ***DCB***

***Proc. Natl. Acad. Sci. USA* (11 October 2005) doi:10.1073/pnas.0507479102**

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