Aire function

Thymic expression of Aire is required for the establishment of immune tolerance, although how Aire promotes tolerance in lymphocytes is unknown. In *Immunity*, Anderson *et al.* show that Aire interferes with the negative selection of developing thymocytes and alters antigen presentation on thymic medullary epithelial cells (mTECs). By systematically testing various hypotheses posed for Aire function, they show Aire is not required for the production of $CD4^+CD25^+$ T regulatory cells or for positive selection of double-positive thymocytes. Aire is thought to be important for the expression of peripheral self antigens in mTECs, which Anderson *et al.* show include multiple chemokines and components of the antigen processing pathways. Future experiments should elucidate how Aire achieves this. ***LAD***

***Immunity* 23, 227–239 (2005)**

Memory cell sustenance

Type I interferons are important in controlling viral infections. However, whether this has a direct effect on $CD8^+$ T cells during viral clearance is uncertain. In the *Journal of Experimental Medicine*, Kolumam *et al.* find that type I interferons may directly affect the clonal expansion and memory generation of $CD8^+$ T cells in response to a viral infection. When transferred into a wild-type host, antigen-specific $CD8^+$ T cells that are deficient in the type I interferon receptor are substantially impaired in their population expansion after viral infection. As a result, the memory pool of these T cells is less than 1% of that generated by wild-type T cells. The lack of type I interferon signaling seems to result in poor survival of the T cells despite normal proliferation. This finding has implications for the design of vaccines to promote effective memory T cell generation. *PTL*

J. Exp. Med. (29 August 2005) doi:10.1084/jem.20050821

Mitochondrial antiviral protein

Antiviral mechanisms rely mainly on pathways that stimulate the production of interferons through the activation of transcription factor NF-κB. In *Cell*, Seth *et al.* identify a mediator of interferon-β induction involving mitochondrial antiviral signaling protein (MAVS) in association with RNA helicase-containing protein (RIG-1). The caspase recruitment domain (CARD) and the transmembrane region of MAVS target this protein to mitochondria and are essential for the induction of interferon response factors, which are required for antiviral activity. RIG-1 also contains a CARD that may mediate the association with MAVS and the induction of interferon-β via NK-κB and transcription factor IRF3. This newly identified factor uniquely ties an important function in innate immunity to mitochondria. ***DCB***

***Cell* (9 September 2005) doi:10.1015/j.cell.2005.08.012**

Reversing T_{reg} cells

$CD4^+CD25^+$ T regulatory (T_{reg}) cells have the capacity to suppress effector T cell function. This activity is essential for the prevention of autoimmunity, yet it also can hamper antitumor responses. In *Science*, Peng *et al.* report reversal of T_{reg} cell function by activation of Toll-like receptor 8 (TLR8) expressed in these cells. Pretreatment of T_{reg} cells with polyguanine-containing oligonucleotides or single-stranded RNA blocks their ability to suppress activation of naive T cells. Such inhibition is cell autonomous, as it does not require T_{reg} cell interaction with dendritic cells but does require MyD88 and IRAK signaling molecules. Other TLR molecules fail to suppress T_{reg} function. Thus, T_{reg} cell function can be reversed by activation of their TLR8 signaling pathways, although the details of this process remain unknown. *LAD*

Science **309**, 1380–1384 (2005)

Wnt dampens NF-κB

In drosophila, Toll signaling leads to release of Dorsal (NF-κB) from Cactus (an IκB homolog), nuclear translocation and the initiation of an innate immune response. In *Nature*, Gordon and colleagues characterize a previously unknown feedback regulator of NF-κB nuclear translocation in flies. This *wingless-Int1* (*wnt*) family member, *wntD*, is also expressed in embryogenesis and regulates the dorsal-ventral axis. WntD, a secreted factor that signals independently of the Frizzled-Armadillo pathway used by most Wnt proteins, blocks the nuclear translocation of Dorsal independently of Cactus. Thus, these data identify a secreted feedback antagonist of Toll signaling and a Wnt activity in the fly. It remains to be investigated whether mammalian TLR signaling involves a similar feedback mechanism. *DCB*

Nature (17 August 2005) doi:10.1038/nature04073

More than anchors

Inhibitor of NF-κB (IκB) proteins regulate NF-κB gene activation by binding to and sequestering NF-κB in the cytoplasm in nonactivating conditions. In *Nature Cell Biology*, Verma and colleagues show that NF-κB remains anchored in the cytoplasm in the absence of IκB proteins. Using mouse embryonic fibroblasts that lack all IκB molecules, cells were rendered unresponsive to tumor necrosis factor–induced NF-κB activation despite the presence of small amounts of NF-κB in the nuclei in basal conditions. Thus, IκB might be dispensable for the anchoring of cytosolic NF-κB, but this family of proteins is absolutely required for the proper stimulation of NF-κB activation pathways. ***LAD***

***Nat. Cell Biol.* 7, 921–923 (2005)**

CTLA-4 also activates

The CTLA-4 costimulation molecule is thought to mediate negative signals. However, Schneider *et al.* report in the *Proceedings of the National Academy of Sciences USA* that CTLA-4 signaling also can have a positive effect. Similar to signaling through the T cell receptor, ligation of CTLA-4 alone but not other coreceptors is sufficient to enhance clustering of the integrin LFA-1 and its subsequent binding to the adhesion molecule ICAM-1. In addition, *Ctla4*$^{-/-}$ T cells show reduced LFA-1 clustering and impaired enhancement of ICAM-1 binding in response to antibody to CD3. CTLA-4 seems to signal via the adaptor protein Rap-1 to enhance LFA-1 function. This observation may alter the view of CTLA-4 as a negative signaling molecule. *PTL*

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