Dimers dampen T cell activity

The transcription factor NFAT influences T cell function by acting together with other transcription factors, including AP-1, T-bet GATA-3 and Foxp3. In the *Journal of Experimental Medicine*, Macian and colleagues show that NFAT homodimers are needed for the transcription of some genes associated with T cell anergy. In T cells stimulated with ionomycin, mutant NFAT proteins that bind to AP-1 but not to other NFAT proteins induce activation of some (*Tle4* and *Dgka*) but not other (*Rnf128* and *Casp3*) anergy-associated genes. Tandem κB-like binding sites in the *Rnf128* promoter—to which NFAT homodimers bind—are needed for ionomycin-induced transcription of this gene.
T cells expressing the NFAT mutant that does not form dimers produce more interleukin 2 and have a lower anergy index score than do T cells transduced with a constitutively active form of NFAT. Whether NFAT proteins form dimers with other proteins to facilitate expression of anergy-related genes such as *Tle4* and *Dgka* remains to be determined. ***CB***
***J. Exp. Med.* (23 March 2009) doi:10.1084/jem20082731**

Facilitating cross-presentation

Although macrophages, neutrophils and dendritic cells (DCs) are known to have phagosomal pathways that differ in terms of oxidation, pH and degradation, it is not known whether phagocytic organization differs among DC subsets. In *Immunity*, Amigorena and colleagues compare the phagocytic pathways of splenic $CD8^+$ and $CD8^-$ DCs. The former subset is known to cross-present antigens, and cross-presentation requires a high pH in the phagosome. Consistent with that, $CD8^+$ DCs restrict assembly of the NADPH oxidase complex to the phagosome, which results in the production of reactive oxygen species and local alkalization. $CD8^-$ DCs, however, are unable to assemble this complex on the phagosomal membrane. The ability of $CD8^+$ DCs to assemble the NADPH oxidase complex depends on the GTPas Rac2, and deficiency of Rac2 results in a lower phagosomal pH and cross-presentation efficacy. These data show that DC subpopulations have differences in their endophagocytic pathways that can explain their different abilities to cross-present antigen. *JDKW*
Immunity (26 March 2009) doi:10.1016/j.immuni.2009.01.013

Systemic suppression

Retinoic acid (RA) induces regulatory T cells in the intestine, but whether it is involved in the systemic immune response is unclear. In *Nature Medicine*, Pulendran and colleagues now find that zymosan induces, through TLR2, expression of RA–metabolizing enzyme in splenic DCs. This Erk kinase–dependent pathway produces RA that functions in an autocrine way to upregulate SOCS3, a negative regulator of the kinase p38 and proinflammatory cytokines. Consistent with that, RA, in conjunction with IL-10, acts synergistically to induce regulatory T cells and suppress T helper type 1 (T_H1) and T_H-17 autoimmune responses *in vivo*. In the absence of TLR2, dectin-1, a C-type lectin receptor that also recognizes zymosan, induces a proinflammatory cytokine response in splenic DCs, which promotes T_H1 and T_H-17 responses. Identification of the physiological conditions in which zymosan triggers dectin-1 but not TLR2 in splenic DCs is needed. ***JDKW***
***Nat. Med.* (1 March 2009) doi:10.1038/nm.1925**

Written by Christine Borowski, Laurie A. Dempsey & Jamie D.K. Wilson

Distinguishing danger

How the body distinguishes sterile inflammation from pathogen-induced inflammatory responses has been unclear. In *Science*, Chen *et al.* show that the recognition of endogenous 'danger-associated molecular pattern' (DAMP) proteins by CD24 and the signaling molecule Siglec-10 inhibits activation of the transcription factor NF-κB, thereby braking inflammation due to non–microbe-induced tissue damage. CD24, a glycosylphosphoinositol-anchored protein, in association with Siglec-10, binds DAMP proteins such as high-mobility group box 1 and heat-shock proteins 70 and 90. Mice lacking either CD24 or Siglec-10 succumb to sublethal doses of acetaminophen, which is toxic to liver tissue and induces hepatocyte necrosis. Siglec-10 interacts with the SHP-1 tyrosine phosphatase to block activation and nuclear translocation of the NF-κB family member p65. Despite having more NF-κB activation in response to DAMP proteins, neither CD24- or Siglec-10-deficient dendritic cells show enhanced NF-κB activation in response to pathogen-associated molecular pattern motifs such as lipopolysaccharide. Thus, CD24–Siglec-10 regulation acts to limit tissue damage in response to non-pathogen threats. *LAD*
Science **323**, 1722–1725 (2009)

Regulating stress

Cellular stress triggered by an abundance of unfolded proteins in the endoplasmic reticulum activates the stress sensor IREα1. IREα1 contains an endoribonuclease whose splicing activity produces functional mRNA encoding the transcription factor XBP-1 (called 'XBP-1s'), which, among other functions, is required for immunoglobulin secretion in plasma cells.
In *Molecular Cell*, Glimcher and colleagues identify Bax inhibitor 1 (BI-1) as a negative regulator of this stress-induced activation of IREα1 and XBP-1s. Like IREα1, BI-1 localizes to the endoplasmic reticulum membrane and physiologically associates with IREα1 through its conserved carboxy-terminal cytoplasmic tail and inhibits the endoribonuclease activity of IREα1. After stress induction, cells that lack BI-1 have higher expression of XBP-1s and proteins encoded by its target genes. Lipopolysaccharide stimulation yields much higher titers of IgM in BI-1-deficient B cells than in wild-type B cells. How endoplasmic reticulum stress alters the BI-1–IREα1 interaction remains unknown. ***LAD***
***Mol. Cell* 33, 679–691 (2009)**

Degrading inflammatory mRNA

If left unrestrained, TLR-driven immune responses induce unwanted tissue damage. In *Nature*, Akira and colleagues identify Zc3h12a, a CCCH-type zinc-finger protein that increases in abundance after TLR signaling, as an essential feedback inhibitor of TLR-induced inflammatory responses. *Zc3h12a*$^{-/-}$ mice show impaired survival and rampant inflammation characterized by excessive accumulation of plasma cells and activated T cells in several organs, granuloma formation in lymph nodes, and serum hyperimmunoglobulinemia. Macrophages from *Zc3h12a*$^{-/-}$ mice contain more *Il6* and *Il12p40* mRNA but similar amounts of *Tnf* and *Cxcl1* mRNA after TLR stimulation. Zc3h12a degrades—apparently through an endonuclease activity—*Il6* and *Il12p40* mRNA by a mechanism that depends on the 3′ untranslated regions of these molecules. Additional work is needed to determine if other 'proinflammatory' mRNA transcripts are degraded by Zc3h12a and contribute to the severely detrimental phenotype of *Zc3h12a*$^{-/-}$ mice. *CB*
Nature (25 March 2009) doi: 10.1038/nature07924