Terminating LPS 'tolerance'

After encountering microbial products such as the Toll-like receptor 4 (TLR4) ligand lipopolysaccharide (LPS), macrophages undergo temporary 'reprogramming' that results in less release of proinflammatory mediators after subsequent microbial stimulation. In *Cell Host & Microbe*, Lu *et al.* show that the lipase acyloxyacyl hydrolase (AOAH), which removes secondary acyl chains required for the LPS stimulatory ability, ends this period of LPS 'tolerance'. For up to 3 weeks after injection with LPS or *Escherichia coli*, AOAH-deficient mice injected with the same stimulus produce less tumor necrosis factor (TNF) but more interleukin 10 (IL-10) than wild-type mice do. LPS-primed AOAH-deficient mice also survive less well after subsequent infection with *E. coli*. Macrophages from AOAH-deficient LPS-primed mice retain more acylated LPS than wild-type macrophages do, and TNF release varies in inverse proportion to the degree of acylated LPS retention. Introducing exogenous AOAH might help treat clinical disorders associated with LPS tolerance. ***CB***

***Cell Host & Microbe* 4, 293–302 (2008)**

Blimp-1 targets

The transcriptional repressor Blimp-1 regulates T cell fate after activation of the T cell antigen receptor (TCR), and mice lacking Blimp-1 in T cells develop fatal colitis. In the *Journal of Experimental Medicine* and the *Journal of Immunology*, Calame and colleagues identify direct targets of Blimp-1 repression in T cells, including *Il2*, *Fos*, *Ifng*, *Tbx21* and *Bcl6*. As IL-2 upregulates Blimp-1 expression, targeting *Il2* and *Fos* sets up an autoregulatory loop that limits T cell population expansion and survival. Blimp-1 expression also contributes to the maintenance of T helper type 2 responses by repressing expression of *Ifng* and *Tbx21*. The cytokine IL-4 also upregulates Blimp-1 expression. Mice deficient in T cell Blimp-1 generate less immunoglobulin G1 (IgG1) and more IgM and IgG2a after immunization, which suggests that their ability to mount type 2 humoral responses *in vivo* is altered. As in activated B cells, reciprocal regulation occurs between Blimp-1 and Bcl-6. Thus, Blimp-1 activity adds more complexity to the regulatory interactions that govern T cell differentiation and function. *LAD*

J. Exp. Med. **205**, 1959–1965 (2008) & *J. Immunol.* **181**, 2338–2347 (2008)

Retroviral resistance factors

Mice have heritable survival traits that manifest after infection with Friend virus. In *Science*, Greene and colleagues identify *Apobec3*, which encodes a deoxycytidine deaminase, as the gene underlying the resistance trait *Rfv3*. Genetic inactivation of *Apobec3* (*mA3*) does not yield an obvious phenotype in uninfected mice but after retroviral infection leads to an inability to generate high-titer neutralizing antibodies and lower survival. BALB/c mice are naturally susceptible as a result of alternative splicing patterns that delete exon 2 from expressed *Apobec3*. Cells transfected with *Apobec3* lacking exon 2 have lower antiviral activity. How APOBEC-3 contributes to B cell responses should be the focus of future research. ***LAD***

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GILT makes infection worse

Infection of macrophages with *Listeria monocytogenes* occurs after phagocytosis and depends on 'escape' of the bacteria from the phagosome through activity of the listeria-expressed hemolysin listeriolysin O (LLO). In *Nature*, Cresswell and colleagues find that the thiol reductase GILT, normally present in phagolysosomes and important for generating some major histocompatibility class II–restricted $CD4^+$ T cells, is needed to activate LLO and facilitate escape of the bacteria into the cytosol. Replication of *L. monocytogenes* in GILT-deficient macrophages or mice is impaired, whereas replication of *L. monocytogenes* expressing a mutant LLO not requiring reductase activity for activation is not. LLO and GILT immunoprecipitate together in macrophages transduced with a mutant GILT protein that enables enzyme-substrate dimers to be isolated, and a recombinant, enzymatically active GILT precursor protein activates LLO *in vitro*. In addition to activating LLO, GILT similarly activates hemolysin from *Streptococcus pyogenes*. Thus, GILT is a critical host factor required for infection by some hemolytic pathogenic bacteria. *DCB*

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Toll changes in HIV pathogenesis

One hallmark of pathogenic infection with human immunodeficiency virus (HIV) is generalized immune activation, a condition also found after infection of rhesus macaque (RM) but not sooty mangabey (SM) primates with simian immunodeficiency virus (SIV). In *Nature Medicine*, Feinberg and colleagues determine that one factor contributing to generalized immune activation in HIV and SIV infection is the response of plasmacytoid dendritic cells to infection. During infection, interferon-α (IFN-α) production is lower in SMs than in humans or RMs, and RMs have more lymph node plasmacytoid dendritic cells. The abundant IFN-α in RMs and humans requires TLR7 and TLR9 signaling. Sequencing of the genes encoding TLR7 and TLR9 in RMs and SMs, and comparison with the human genes, identifies changes in the transmembrane domain of TLR7 in SMs. These differences probably account for the lower immune activation in SMs and help explain the pathogenic immune activation in humans and RMs. ***DCB***

***Nat. Med.* (14 September 2008) doi:10.1038/nm.1871**

Freezing filamentous actin

Oxidative stress inflicted by reactive oxygen species (ROS) results in T cell hyporesponsiveness. In *Immunity*, Samstag and colleagues show that ROS suppress T cell activity by oxidizing cofilin, a protein essential for TCR-induced actin remodeling, formation of the immunological synapse and T cell activation. T cells treated with ROS have more filamentous actin (F-actin) but show impaired chemokine-induced actin polarization, adhesion and migration and defective TCR- and CD28-induced formation of the immunological synapse and CD69 expression. Cofilin dephosphorylation, induced by TCR signals and essential for cofilin-mediated F-actin depolymerization, is enhanced by ROS treatment. However, by inducing the formation of an intramolecular disulfide bridge in cofilin, ROS alter the shape of cofilin. Oxidized cofilin depolymerizes F-actin less efficiently. Whether cofilin oxidation facilitates T cell hyporesponsiveness in normal conditions (as in the gut) and/or pathological conditions (as in tumor microenvironments) remains to be determined. *CB*

Immunity **29**, 404–413 (2008)