Commensals control inflammation

Together with other commensal bacteria, staphylococcal species colonize the skin epidermis but do not elicit inflammation. In *Nature Medicine*, Gallo and co-workers identify a molecular mechanism by which these bacteria promote immune homeostasis. A product of *Staphylococcus epidermidis* <10 kilodaltons in size inhibits poly(I:C) and wound-induced production of interleukin 6 (IL-6) and tumor necrosis factor (TNF) from keratinocytes *in vitro* and *in vivo*. Staphylococcal lipotechoic acid, a Toll-like receptor 2 (TLR2) agonist, is necessary and sufficient for this suppression of TLR3-driven inflammation. *S. epidermidis* lipotechoic acid inhibits TLR3 signaling by inducing expression of TNF receptor–associated factor 1 (TRAF1), which inhibits activation of the transcription factor NF-κB. Consistent with the idea that commensal bacteria prevent excessive inflammation by upregulating TRAF1 expression, the skin, lungs and small intestines of germ-free mice have lower expression of TRAF1 than do those tissues in conventional wild-type mice. ***CB***

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The life pathway

Mature B cells depend on survival signals delivered to the cell by their antigen receptor (BCR), but the downstream pathway that transmits the signal is not clearly defined. In *Cell*, Rajewsky and colleagues show that mature B cells that have lost their BCR through conditional ablation *in vivo* are fully restored by activation of the phosphatidylinositol-3-OH kinase (PI(3)K) signaling pathway rather than by the canonical NF-κB pathway, as previously thought. B cells restored by an active form of P110α, the catalytic subunit of PI(3)K, or by deletion of PTEN, the key negative regulator of the PI(3)K pathway, are resting, long-lived cells that accumulate in normal numbers in their peripheral habitats and are subject to normal homeostatic control via the survival factor BAFF. A central element of the BCR-controlled, PI(3)K-mediated survival signal is modulation of expression of the transcription factor Foxo1, but additional targets are probably involved. *IV*

Cell **139**, 573–586 (2009)

Help needed throughout

CD4$^+$ T cells are essential for the priming of CD8$^+$ T cells as well as the promotion of memory CD8$^+$ T cell development. In *Nature*, Nakanishi *et al.* now show that CD4$^+$ T cell help has an additional role. Fully differentiated cytotoxic T lymphocytes (CTLs) are not self-sufficient for recruitment to the vaginal tissue during infection with herpes simplex virus type 2. CD4$^+$ T cell help is needed to 'license' the local environment for entry of effector CTLs. Secretion of interferon-γ from CD4$^+$ T cells induces expression of the chemokines CXCL9 and CXCL10 *in situ*, probably from infected epithelial cells, and enables the CXCR3$^+$ CTLs to migrate from the peripheral blood into the infected areas. Thus, certain mucosal tissues, such as the lung and intestine, are permissive to the migration of effector CTLs, whereas other sites, such as the vagina, are restricted and rely on CD4 help and inflammatory chemokines to recruit effector cells when they are required. ***IV***

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Written by Christine Borowski, Laurie A. Dempsey & Ioana Visan

Turning off TRAF3

Although the ubiquitin ligase TRAF3 promotes expression of type I interferon after activation of adaptor TRIF–dependent TLRs and the RNA helicase RIG-I, it must be tightly regulated to avoid autopathogenesis. In *PLoS Pathogens*, Hiscott and colleagues identify the RING-finger ubiquitin ligase Triad3A as a negative regulator that targets TRAF3 to terminate expression of type I interferon after RIG-I activation. Triad3A protein expression is upregulated by type I interferon or at later times after infection with Sendai or vesicular stomatitis virus, which suggests it functions as a classic feedback inhibitor. Knockdown of Triad3A leads to TRAF3 stabilization and prolonged interferon-stimulated gene expression. Triad3A seems to compete with the adaptor protein MAVS for TRAF3 binding and mediates Lys48-linked polyubiquitination of TRAF3, which leads to its proteasomal destruction. As Triad3A-mediated TRAF3 targeting does not upregulate proinflammatory gene expression, other TRAF3-regulated signaling molecules are probably regulated by Triad3A. *LAD*

PLoS Pathogens (6 November 2009) doi:10.1371/journal.ppat.1000650

Tailoring suppression

Regulatory T cells (T_{reg} cells) restrain autoaggressive lymphocyte responses by a variety of mechanisms. In *Science*, Chaudhry *et al.* show that T_{reg} cells blunt the responses of IL-17-producing T helper cells (T_H17 cells) in a manner that requires the IL-6-activated transcription factor STAT3. The transcription factor Foxp3 binds to active phosphorylated STAT3 dimers in T_{reg} cells. Conditional deletion of STAT3 specifically in T_{reg} cells leads to severe colitis and anemia due to chronic inflammation. The STAT3-deficient T_{reg} cells can still inhibit T helper type 1 (T_H1)- and T_H2-associated cytokine expression, but expression of the T_H17 cytokines IL-17 and IL-22 by CD4$^+$Foxp3$^-$ T cells is enhanced. Blocking IL-17 in *Foxp3*^{Cre}*Stat3*$^{f/f}$ mice results in a lower frequency of T_H17 cells and inhibits colitis development. STAT3-deficient T_{reg} cells express less IL-10, IL-35 and chemokine receptor CCR6 than wild-type T_{reg} cells do, which suggests that cooperation of STAT3 with Foxp3 is necessary for their expression. These results suggest the STAT3 function in T_{reg} cells is specifically tailored to regulate excessive T_H17 responses. ***LAD***

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Stimulus-specific polyubiquitin chains

Existing evidence suggests that the generation of Lys63-linked polyubiquitin chains by the E2 ubiquitin-conjugating enzyme Ubc13 is necessary for activation of the kinase IKK in some but not all immune cell types. In *Molecular Cell*, Chen and colleagues find that IL-1β and TNF trigger IKK activation via distinct E2 enzymes and polyubiquitin chain linkages. Inducible deletion of endogenous ubiquitin and expression of Lys63-mutant ubiquitin impairs IL-1β- but not TNF-driven activation of IKK. IL-1β-induced IKK activation requires Ubc13-mediated polyubiquitination of the adaptor IRAK1, whereas TNF-triggered IKK activation requires polyubiquitination of the adaptor RIP1 by the Ubc5 E2 enzyme and cIAP ubiquitin ligases. These findings indicate that different cytokines use different ubiquitination enzymes to induce IKK activation. Further experiments are needed to understand precisely which polyubiquitin chain linkages facilitate TNF-driven IKK activation. *CB*

Mol. Cell **36**, 302–314 (2009)