Common theme in flies

Microbial infections in drosophila activate Toll or peptidoglycan recognition pattern (PGRP) pathways of innate immunity. Relish (REL) and Serpent, orthologs of mammalian NF-κB and GATA transcription factors, respectively, are key in regulating antimicrobial gene expression. In *Molecular Cell*, Levine and colleagues identified conserved linked organization of fly promoter-proximal regions in many genes encoding immune activities. Alteration of the GATA or REL binding site sequence, orientation or spacing interfered with reporter gene expression in response to lipopolysaccharide, which indicated the functional relevance of the linked recognition sites. A synthetic enhancer containing both GATA and REL binding sites in the conserved orientation was sufficient to direct tissue-specific expression in response to microbial infection. Hence, GATA and REL are synergistic in mediating fly immunity. *LAD*
***Mol. Cell* 13, 19–32 (2004)**

PESTering memory cells

PEST domain–enriched tyrosine phosphatase (PEP) negatively regulates T cell receptor (TCR) signaling by dephosphorylating Lck at Tyr394. In *Science*, Chan and colleagues generated PEP-deficient mice to determine the function of this tyrosine phosphatase during thymocyte development and peripheral T cell differentiation. PEP deficiency increased positive selection but had no discernable effect on negative selection. Older PEP-deficient mice had increased effector:memory T cell ratios. Lck phosphorylation at Tyr394 was enhanced and sustained, leading to increased proliferation and cytokine production by these cells. Enhancement of PEP-deficient T cell function was associated with spontaneous development of germinal centers and increased serum immunoglobulin concentrations. Thus, PEP is required for the negative regulation of effector and memory cells and for certain aspects of thymocyte development. *JDKW*
Science **303**, 685–689 (2004)

New contacts

Despite considerable knowledge of the tumor necrosis factor (TNF) signaling pathway that leads to NF-κB activation, the simplistic linear schematic belies an infinitely complicated network. In *Nature Cell Biology*, Bouwmeester *et al.* used a tandem affinity purification strategy to identify new proteins and their interactions in this pathway. From the 80 new interactors in the NF-κB signaling cascade, a physical map was constructed to identify new associations, which provided further mechanistic insight into NF-κB signaling properties. Components of the physical map were functionally validated with RNA interference and then overexpression and were further tested for their function in the pathway. This integration of proteomic and conventional protein analysis has application beyond the TNF–NK-κB pathway. *PTL*
Nat. Cell Biol. **6**, 97–105 (2004)

Bacterial population control

The gut immune system controls the number and distribution of commensal bacteria by secreting antimicrobial peptides and the mucosal-associated immunoglobulin IgA. However, the relative contribution of these two defense mechanisms is unclear. In the *Proceedings of the National Academy of Sciences USA*, Suzuki *et al.* find that activation-induced cytidine deaminase (AID)-deficient mice with IgA deficiency but normal antimicrobial peptides have aberrant expansion of segmented filamentous bacteria. This abnormal bacterial growth is also observed in the intestines of *Rag2*$^{-/-}$ mice, which do not have IgA. Proliferation of gut bacteria can be reduced in *Rag2*$^{-/-}$ and AID-deficient mice by transplanting wild-type bone marrow and providing IgA through parabiosis, respectively. Thus, IgA seems to be essential in maintaining homeostasis of the gut flora. *PTL*
Proc. Natl. Acad. Sci. USA **101**, 1981–1986 (2004)

Stuck on you

Chemokines mediate LFA-1-dependent lymphocyte adhesion by modulating the affinity state and lateral mobility of LFA-1. The small GTPase RhoA and ζ PKC were previously linked to chemokine-dependent LFA-1-mediated adhesion. In *Immunity*, Giagulli *et al.* investigated whether these molecules control both affinity changes and mobility, or if they have different functions during chemokine-induced LFA-1 activation. RhoA controlled the LFA-1 high-affinity state and its lateral mobility via two distinct effector regions (amino acids 23–40 and 92–119). In contrast, ζ PKC controlled only LFA-1 lateral mobility. *In vivo* blockade of the RhoA effector region of amino acids 23–40 abolished the rapid arrest of circulating naive lymphocytes on the high endothelial venules of Peyer's patches. Thus, the high-affinity state of LFA-1 is specifically controlled by RhoA and is essential for lymphocyte homing *in vivo*. *JDKW*
Immunity **20**, 25–35 (2004)

Transcription-independent death

The tumor suppressor p53 can induce apoptosis by upregulating expression of death receptors and other proapoptotic factors. In *Science*, Green and colleagues show cytosolic accumulation of p53 is sufficient to induce Bax-mediated apoptosis. *De novo* transcription and translation of p53-responsive proapoptotic proteins was not required, as cytosolic p53 mutants lacking transcriptional activation domains also triggered cell death. Bax could cooperate with p53 to permeabilize mitochondria and release cytochrome C. Thus, cytosolic p53 can directly activate Bax to mediate mitochondrial damage and effect the death program. *LAD*
***Science* 303, 1010–1014 (2004)**

Ready when needed

Interleukin 10 (IL-10) is constitutively secreted in normal lungs, presumably contributing to an immunosuppressive environment to protect the delicate structure. However, alveolar macrophages (AMs) must overcome this inhibition to respond to microbial pathogens. In the *Journal of Immunology*, Fernandez *et al.* show that stimulation of AMs through the pathogen pattern recognition receptors TLR2, TLR4 or TLR9 blocks signaling of the IL-10 receptor (IL-10R). IL-10R expression is not affected, but phosphorylation and nuclear translocation of the transcription factor STAT3, along with transcription of IL-10-induced genes, are inhibited after stimulation through TLRs. The inhibition of IL-10R signaling prevents IL-10-mediated suppression of TNF. Thus, the recognition of pathogens through TLRs allows AMs to respond effectively to infection. *PTL*
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