IFN-α twists TNF

Type I interferons are pleiotropic cytokines that exert antiviral and immunmodulatory activities. In the *Journal of Experimental Medicine*, Sharif *et al.* find that interferon-α (IFN-α) suppresses Fcγ receptor– and Toll-like receptor–induced proinflammatory responses mediated by tumor necrosis factor (TNF). Macrophages treated with exogenous IFN-α show reduced TNF-mediated gene expression as a result of interferon-induced expression of Twist 1 and 2, basic helix-loop-helix transcription factors that inhibit transcription by binding to E-box sequences in the promoters of certain genes. Twist-mediated inhibition of TNF-induced inflammation is dependent on Axl, a member of the Tyro3 family of receptor tyrosine kinases. Expression of Axl and its ligands, such as Gas6, is directly induced by IFN-α, and TNF-mediated inflammation in Axl-deficient macrophages is not suppressed by IFN-α. These data provide a mechanistic explanation of how IFN-α suppresses TNF-induced inflammation. ***DCB***

***J. Exp. Med.* (10 July 2006) doi:10.1084/jem.20051725**

Attacking defense

The precise molecular mechanisms by which effector proteins of pathogenic bacteria disable plant cellular defenses are not well understood. In *Science*, He and colleagues identify the mechanism by which the *Pseudomonas syringae* effector protein HopM1 subverts *Arabidopsis thaliana* plant defense. HopM1 binds to plant HopM-interactor (AtMIN) proteins, leading to the destruction of AtMIN proteins in a ubiquitin- and proteasome-dependent way. Overexpression of full-length HopM1 leads to the destruction of AtMIN proteins in plant cells, similar to the AtMIN depletion that occurs in plant leaves during bacterial infection. Plants lacking AtMIN proteins are more susceptible to bacterial infection, as AtMIN proteins normally regulate the vesicle trafficking involved in plant immune responses. Although these data elucidate one mechanism by which a plant pathogen attacks and disables plant cellular defenses, it is unclear whether other plant pathogens use a similar strategy. *CB*

Science **313**, 220–223 (2006)

Internal timers

The CARMA1–Bcl-10–MALT1 complex is required for the activation of transcription factor NF-κB pathways after T cell stimulation. In *Molecular Cell*, Wegener *et al.* show that the kinase IKKβ regulates 'upstream' signals in addition to its known 'downstream' function in inactivating the NF-κB inhibitor IκB. After T cell receptor (TCR) and CD28 ligation, IKKβ is recruited to the membrane-proximal CARMA1–Bcl-10–MALT1 complex, where it phosphorylates Bcl-10. Phosphorylation of Bcl-10 induces its dissociation from MALT1, terminating Bcl-10-mediated ubiquitination and subsequent activation of IKKγ. Blocking Bcl-10 phosphorylation leads to enhanced expression of NF-κB target genes. Thus, TCR-dependent activation of IKKβ also leads to a negative feedback control of 'upstream' components of the signaling cascade, thereby limiting the duration of the activating signal. ***LAD***

***Mol. Cell* 23, 13–23 (2006)**

Research notes written by Christine Borowski, Douglas C. Braaten and Laurie A. Dempsey

Emigration blues

The zinc-finger transcription factor Krupple-like factor 2 (KLF2) is thought to be important for T cell survival and quiescence. In *Nature*, Carleson *et al.* demonstrate instead that KLF2 is required for the surface expression of molecules needed for thymocyte emigration to peripheral tissues. Despite grossly normal thymocyte development, chimeric mice reconstituted with KLF2-deficient fetal liver cells have fewer peripheral T cells. Moreover, KLF2-deficient thymocytes have lower surface expression of CCR7, CD62L and β_7 integrin and have less mRNA encoding CD62L, β_7 and sphingosine 1-phosphate type 1 receptor ($S1P_1$), factors required for T cell emigration and distribution in the periphery. Chromatin immunoprecipitation of KLF2 at the $S1P_1$ gene promoter and reporter assays link KLF2 to the regulation of $S1P_1$ gene expression. KLF2 thus seems to regulate factors required for proper T cell trafficking from the thymus to peripheral lymphoid organs. *DCB*

Nature **442**, 299–302 (2006)

pH matters

Cross-presentation by dendritic cells (DCs) is required for the priming of naive $CD8^+$ T cells against exogenous antigens. In *Cell*, Amigorena and colleagues show that DCs actively regulate the pH of phagosomal vesicles and thereby prevent excessive proteolytic destruction of foreign antigens. The generation of antigenic peptides involves a delicate balance of competing proteases that potentially can destroy epitopes. DCs differ from macrophages by limiting that destructive potential through the recruitment of NAPDH oxidase to their endosomal membranes. The generation of superoxide by NAPDH oxidase in these vesicles causes consumption of H^+ ions, thereby raising the internal pH. As a result, the higher pH decreases the activity of vesicular proteases with lower pH optima. In effect, larger peptides are then available for export to the cytoplasm and processing by the proteasome for major histocompatibility complex class I presentation. These findings help to explain why DCs are specialized for cross-presentation. ***LAD***

***Cell* 126, 205–218 (2006)**

Segregating signals

TCR signaling originates in microclusters that form in contact zones between cells and gradually move toward a central supramolecular activation cluster (cSMAC). In *Immunity*, Dustin and colleagues investigate whether TCR signaling also occurs in cSMACs. CD45 tyrosine phosphatase, which can negatively regulate TCR signaling, is excluded from peripheral microclusters but is included in cSMACs. In addition, the lipid LBPA, which is produced at sites of protein degradation, is detected in cSMACs shortly after TCR stimulation. Disruption of TCR–peptide–major histocompatibility complex interactions prevents sustained TCR-induced calcium flux and the formation of new microclusters but does not perturb cSMACs. Similarly, blocking actin polymerization prevents sustained TCR-induced calcium flux and microcluster movement toward the cSMAC, yet leaves cSMACs intact. These results demonstrate that cSMACs are not sufficient to maintain TCR signaling and instead pinpoint cSMACs as sites of TCR signaling shutdown. *CB*

Immunity **25**, 117–127 (2006)