Trapping membrane proteins

Specialized membrane microdomains have been postulated as being key in the initiation of signal transduction cascades. In *Cell*, Douglass and Vale describe the dynamics by which specialized CD2-rich membrane domains are formed in activated T cells. Monitoring fluorochrome-labeled molecules by confocal microscopy, they have visualized the motility of individual proteins in the membrane. Both the kinase Lck and the adaptor protein Lat show large reductions in membrane motility after T cell activation. Actin-mediated clustering of CD2 leads to preferential trapping of Lck and Lat, thereby leading to the formation of stable signaling complexes. These subdomains do not rely on lipid rafts for their assembly but instead require protein-protein interactions conferred by Lat. The CD2-Lat-Lck complex then serves as a 'molecular sink' for the assembly of other signaling components. ***LAD***

***Cell* 121, 937–950 (2005)**

Evading Tolls

Pathogens from the ε clade of proteobacteria require flagella motility for infection. Toll-like receptor 5 (TLR5), however, recognizes flagellin, the basic monomer of flagella. In the *Proceedings of the National Academy of Sciences*, Aderem and colleagues show that flagellin from α and ε proteobacteria is not detected by TLR5 because of specific amino acid changes in the TLR5 recognition site. Introduction of these residues into salmonella flagellin, which is normally recognized by TLR5, abolishes TLR5 activation but impairs bacterial motility. The α and ε proteobacteria preserve motility because of compensatory amino acid changes in other regions of the monomer. When engineered into salmonella flagellin, the monomers could evade TLR5 recognition and retain motility. Evasion of TLR5 by flagellated pathogenic bacteria suggests TLR5 is critical for host defense. *JDKW*

Proc. Natl. Acad. Sci. USA (28 June 2005) doi:10.1073/pnas.0502040102

Getting specific with allergy

Protein kinase C-ζ (PKC-ζ) is important in the signaling pathway of B cells that leads to proliferation, survival and antibody production. However, its involvement in T helper cell responses is unclear. In the *Proceedings of the National Academy of Sciences*, Martin *et al.* find that PKC-ζ-deficient T cells are defective in their ability to skew toward the T helper type 2 (T_H2) phenotype, as shown by reduced T_H2 cytokine production and expression of transcription factors, including GATA-3, c-Maf, RelA and NFATc1. This defect is mediated through the interleukin 4 signaling pathway. As a result of defective T_H2 cell development, PKC-ζ-deficient mice have less inflammation in response to antigen sensitization and challenge. Thus, PKC-ζ may be an important target in treating allergic diseases such as asthma. ***PTL***

***Proc. Natl. Acad. Sci.* USA 102, 9866–9871 (2005)**

Unveiling Toll

Although the importance of TLRs as sensors of the innate immune system is clear, their physical characteristics and hence insights into their structure-function relationship are unknown. In *Science*, Choe *et al.* provide the first glimpse of the ectodomain of human TLR3 by solving its crystal structure to 2.1 Å. The structure consists of 23 leucine-rich repeats arranged in the shape of a large horseshoe. Potential *N*-linked glycosylation sites indicate that most of the surface may be masked by carbohydrate, with the exception of one face of the structure. This face is also one of two regions on the structure that is positively charged and hence conducive to binding double-stranded RNA, the known ligand of TLR3. Furthermore, dimerization of TLR3 seems likely at this region, providing new insights into its binding and signaling. *PTL*

Science (16 June 2005) doi:10.1126/science.1115253

Vaccine tattoos

So far, the efficacy of DNA vaccines has been somewhat disappointing, prompting searches for protocols that boost immunogenicity. In *Nature Medicine*, Bins *et al.* report intradermal 'tattoos' of DNA vaccines elicit robust humoral and T cell immunity against both model tumor antigens and influenza virus. Despite low antigen expression that wanes after 4 days, DNA 'tattoos' prime greater numbers of antigen-specific naive T cells. Closely timed 'boosts' at intervals as short as 3 days lead to prolonged antigen expression and confer protective immunity in a period as short as 12 days after the initial immunization. Thus, this strategy may offer a rapid and efficient means for immunizing populations against potential emerging infectious diseases. *LAD*

Nat. Med. (19 June 2005) doi:10.1038/nm1264

Master attractants

Committed mast cell progenitors derived from stem cells in the bone marrow transit via the blood to tissues where they mature. In the *Journal of Experimental Medicine*, Weller *et al.* investigate how release and migration of mast cells to tissues is controlled. Immature mast cells are unresponsive to a range of chemokines as well as stem cell factor. However, leukotriene 4 (LTB_4) released by mature mast cells could potently attract immature, but not mature, mast cells both *in vitro* and *in vivo*. LTB_4 also has a similar effect on human cord blood–derived immature mast cells. Thus, activated mast cells regulate the release of mast cell progenitors from the bone marrow and/or their recruitment to tissues by autocrine production of LTB_4. *JDKW*

J. Exp. Med. **201**, 1961–1971 (2005)

Synchronizing RAG destruction

Antigen receptor variable-, diverse- and joining-region recombination is restricted to the G0-G1 stage of the cell cycle in developing lymphocytes. This is due to targeted destruction of the recombinase protein RAG-2 after entry into the S phase. However, the molecular details of this targeting mechanism have remained obscure. In *Molecular Cell*, Desiderio and colleagues report that the ubiquitin ligase Skp2-SCF, which can target the cell cycle protein p27 for destruction, also 'marks' phosphorylated RAG-2 for proteasome degradation. Using a cell-free system, they show that RAG-2 ubiquitinylation is regulated by the cyclin A–cyclin-dependent kinase (CDK2) complex and its inhibitor p21, confirming previous genetic data indicating their involvement. Thus, by sensing its phosphorylation by cyclin A–CDK2, Skp2-SCF ties RAG-2 destruction to the S phase. *LAD*

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