Chemokine blues

West Nile virus (WNV) causes severe encephalitis and lethality in some but not all people. Although the mechanism responsible for variable clinical manifestations is not known, the chemokine receptor CCR5 has been shown to be critical for survival of WNV in a mouse model. In the *Journal of Experimental Medicine* Murphy and colleagues use a retrospective study to determine if CCR5 is also protective in humans. They find that homozygosity for the CCR5 allele CCR5Δ32 is significantly associated with a fatal outcome. Because homozygosity for CCR5Δ32 also provides substantial protection against infection with human immunodeficiency virus, CCR5-blocking agents are being developed for therapeutic use. But such agents could inadvertently have serious consequences by increasing the likelihood of WNV pathogenesis in patients receiving them. ***DCB***
***J. Exp. Med.* 203, 35–40 (2006)**

FDCs: master craftsmen

Follicular dendritic cells (FDCs) are key in the formation of FDC networks, B cell follicles and germinal centers. Alterations in transcription factor NF-κB signaling pathways disrupt many of these FDC functions, but whether such defects are cell autonomous or arise because of a lack of proper cell-to-cell communication remains unclear. In *Immunity*, Victoratos *et al.* describe several mouse mutants that target specific components of the canonical NF-κB pathway in FDCs. Using a gain-of-function approach, they find that expression of the p55 tumor necrosis factor receptor in FDCs, but not in lymphoid cells, is essential for the generation of proper anatomical organization of peripheral lymphoid tissues and, after immunization, the development of germinal centers and mature B cell responses. In contrast, mice lacking FDC expression of the kinase IKK2 have normal splenic architecture but mount impaired humoral immune responses because of the inability to sustain germinal centers. These findings show that the canonical NF-κB pathway has multiple functions in FDC organization and function. *LAD*
Immunity **24**, 65–77 (2006)

Inflammatory shutdown

The intracellular pathways underlying lipoxin-mediated inflammatory 'shutdown' after bacterial infection or aspirin administration are not well understood. In *Nature Medicine*, Aliberti and colleagues show that the adaptor protein SOCS2 is a 'downstream' component of this anti-inflammatory pathway. *Toxoplasma gondii* induces synthesis of lipoxin A_4 (LXA_4) and, in a mechanism dependent on the lipoxin receptors AhR and LXAR, expression of SOCS2. LXA_4 suppresses the release of interleukin 12 from wild-type but not SOCS2-deficient dendritic cells. Compared with their wild-type counterparts, SOCS2-deficient mice have more proinflammatory cytokines and increased mortality after *T. gondii* infection. Aspirin treatment, which induces lipoxins distinct from LXA_4, inhibits thioglycollate-induced peritoneal neutrophil recruitment in wild-type but not SOCS2-deficient mice. Although it is unclear how SOCS2 influences lipoxin signaling, SOCS2 may represent a potential new target for the treatment of inflammatory disorders. ***CB***
***Nat. Med.* (15 January 2006) doi:10.1038/nm1355**

Written by Christine Borowski, Douglas C. Braaten and Laurie A. Dempsey.

Chromatin-remodeling logic

Changes in chromatin structure can dictate whether a given gene is activated or repressed in response to external stimuli. Although many chromatin-remodeling proteins have been identified, how specific responses are coordinated remains somewhat 'enigmatic'. In *Genes & Development*, Smale and colleagues demonstrate functional antagonism between ATP-dependent nucleosome-remodeling complexes containing the chromatin remodelers SWI-SNF or Mi-2β in lipopolysaccharide (LPS)–stimulated macrophages. LPS induces multiple waves of NF-κB-dependent gene expression. Simultaneous small interfering RNA 'knockdown' of BRG1 and BRM, the catalytic ATPases of SWI-SNF complexes, block expression of many but not all LPS-responsive genes. Conversely, 'knockdown' of Mi-2β leads to higher LPS-inducible gene expression. Accessibility to the remodeling complexes correlates with delayed expression kinetics after LPS induction. Unexpectedly, Mi-2β seems to be recruited to LPS target genes by the SWI-SNF complexes. How Mi-2β alters SWI-SNF function remains unknown, but its activity is critical for proper temporal expression of proinflammatory genes. *LAD*
Genes Dev. (1 February 2006) doi:10.1101/gad.1383206

DC-SIGNaling

Pathogen stimulation of the DC-specific intercellular adhesion molecule–grabbing nonintegrin (DC-SIGN) C-type lectin receptor blocks DC maturation and T helper type 1 cytokine release, thereby preventing pathogen eradication and promoting the establishment of chronic infection. Although viral-, bacterial-, fungal- and parasite-derived DC-SIGN-interacting molecules have been identified, the intracellular mechanisms underlying DC-SIGN-mediated immunosuppression remain mysterious. In *Blood*, Corbi and colleagues demonstrate that ligation of DC-SIGN on DCs induces phosphorylation of the kinase Erk but not the p38 mitogen-activated protein kinase. DC-SIGN stimulation, even in the presence of LPS or tumor necrosis factor, triggers the release of interleukin 10. These results mechanistically explain the immunosuppressive effects of DC-SIGN and are in agreement with previous studies demonstrating that p38 inhibition hampers whereas Erk inhibition enhances DC maturation. ***CB***
***Blood* (24 January 2006) doi:10.1182/blood-2005-03-1252**

Danger signals

Many inflammatory stimuli lead to the activation of a multiprotein cytosolic complex, the 'inflammasome', required for interleukin 1β production and inflammation. In *Nature*, three papers evaluate the function of the procaspase-1 activator NALP3 (also called cryopyrin), a component of the inflammasome, in response to 'danger signals' such as bacterial infection and low intracellular potassium; bacterial RNA; and crystals associated with inflammatory gout and pseudogout. The studies use NALP3-deficient mice and primary cells as well as agonists of other known innate signaling pathways to demonstrate that delivery of 'danger signals' to the cytosol leads to activation of pro–caspase 1 by NALP3. Active caspase 1 then cleaves pro–interleukin 1β, which is synthesized independently of NALP3. These studies greatly expand the understanding of the processes leading to acute inflammation and inflammatory disease. *DCB*
Nature (11 January 2006) doi:10.1038/nature04515; doi:10.1038/nature04516; doi:10.1038/nature04517