C4BP runs damage control

The complement inhibitor C4b-binding protein (C4BP) prevents necrotic cells from spilling their pro-inflammatory guts, according to a study on page 1937. Trouw and colleagues now show that C4BP and its binding partner, anticoagulant protein S (PS), cooperate to grab onto necrotic cells and to inhibit the release of cellular DNA.

C4BP short-circuits the complement cascade by binding to the activated complement components C3b and C4b and presenting them to the proteolytic complement inhibitor Factor I for degradation. This inhibitory capacity of C4BP can be coopted by bacterial pathogens, which coat themselves with this protein to avoid complement-mediated destruction by phagocytic cells.

This group recently identified a role for the C4BP–PS complex: it binds to apoptotic cells through the phosphatidylserine-binding domain of PS. This association could prevent the deposition and activation of complement on the surface of the apoptotic cells, allowing the dying cells to be removed without provoking an inflammatory response.

Trouw et al. now show that C4BP–PS complexes bind to necrotic cells in the same manner. This binding limited complement deposition and decreased the capacity of necrotic cells to induce inflammatory cytokine production by macrophages. Once bound to necrotic cells via PS, C4BP could bind and trap cellular DNA as it leaked out of the dying cells. The authors suggest that this function of C4BP may be critical for host protection from autoimmunity, as free DNA can trigger inflammation and elicit the production of anti-DNA antibodies. JEM

An eight-kilobase genetic island encodes an integrated bacteriophage that is associated with disease in hyperinvasive strains of *N. meningitidis*.

Deadly stowaway

A bacteriophage hitchhiker may turn a harmless bacterium into a meningitis-causing menace, according to Bille and colleagues on page 1905. Neisseria meningitidis—a frequent resident of the human upper respiratory tract—may become a killer if it contains this phage integrated into its chromosome.

*N. meningitidis* is usually a commensal bacterium that lives in the upper respiratory tract, most often without incident. However, certain “hyperinvasive” strains of *N. meningitidis* can occasionally invade the bloodstream and cross the blood–brain barrier, triggering outbreaks of life-threatening meningitis. Several bacterial factors are required for bacterial virulence, including the polysaccharides that form the bacterial capsule and the type IV pilus adhesin protein. But these structures are widely distributed among meningococcal strains, including those that do not cause illness, suggesting that other factors are also important in causing disease.

In search of elements that might confer pathogenicity, Bille et al. analyzed 29 hyperinvasive and 20 noninvasive *N. meningitidis* isolates using a gene array. This revealed an eight-kilobase genetic island present in 100% of hyperinvasive isolates and absent from 90% of noninvasive isolates. This island looked and acted like an integrated bacteriophage, existing independently as a double-stranded form in the cytoplasm and being released into the bacterial supernatant as a nuclease-resistant (presumably encapsidated) single-stranded circular form.

The association of the phage-like element with disease was confirmed when the authors analyzed isolates from a previous epidemiologic study and found that those containing the phage were more likely to have caused disease. How the phage renders *N. meningitidis* pathogenic remains a matter of speculation. One possibility, suggest the authors, is that the phage favors bacterial invasion into bloodstream, either by altering bacterial gene expression or manipulating the host immune system. JEM
Indecisive interleukin–4?

A study on page 1899 may explain the seemingly fickle ways of the cytokine interleukin (IL)-4. Yao and colleagues show how this quintessential T helper (Th) 2 cytokine can sometimes promote the opposite Th1 response.

IL-4 is known as the key cytokine for polarizing naive T cells toward a Th2 phenotype, which is important for antibody production and protection against parasitic infections. Under some conditions, however, IL-4 has been shown to instead induce a Th1 response. Indeed, a recent study showed that mice treated with IL-4 during initial infection with *Leishmania major* had increased Th1 responses and were protected. If given later, IL-4 increased Th2 responses and exacerbated disease.

Yao et al. now suggest that the regulation of another cytokine—IL-10—may explain these perplexing observations. They show that dendritic cells (DCs) stimulated in the presence of IL-4 made less IL-10 than those stimulated without IL-4. As a result, the IL-4–treated DCs produced more of the Th1-polarizing cytokine IL-12—known to be inhibited by IL-10—and polarized naive T cells toward a Th1 phenotype more effectively. IL-10 was critical for the increased Th1 response, as IL-4 did not increase IL-12 production or T cell polarization by IL-10–deficient DCs.

IL-4 had the opposite effect on B cells, provoking increased IL-10 production. The authors suggest that the differential effect of IL-4 at different times during infection may reflect a switch from DCs to B cells as the predominant cell type that is presenting antigen. *JEM*

Lymphocytes that can't let go

On page 1987, Semmrich and colleagues show that immune cells expressing a perpetually activated form of the integrin LFA-1 get traction at the front of the cell, but get stuck from behind. Their lagging ends prevent them from crawling through the endothelium and initiating a normal immune response.

Integrins, such as LFA-1, are adhensive molecules that switch between active and inactive conformations and control migration of circulating immune cells to sites of infection and inflammation. LFA-1 is also required for the formation of stable interactions between T cells and antigen presenting cells (APCs). Previous studies had shown that both tumor-specific T cell responses and neutrophil migration are compromised in the absence of this integrin.

The importance of LFA-1 deactivation, however, has been less clear. In vitro studies have shown that locking LFA-1 in its activated conformation impairs both neutrophil chemotaxis and T cell activation. Semmrich et al. now confirm these findings in vivo, and show that lymphocytes from mice expressing a constitutively active LFA-1 moved more slowly than wild-type cells and failed to migrate across endothelial cell monolayers. Video microscopy revealed that these defective movements were due to an inability of the cells to release their trailing edges.

CD4+ T cell proliferation and antibody production were also impaired in these mice. The development of antigen-specific CD8+ cytotoxic T cells, by contrast, was not altered by the mutated LFA-1, but the ability of these cells to lyse target cells was decreased. The authors suggest that defects in T cell activation and function may reflect the need for serial engagement of T cell receptors with peptide–MHC complexes on APCs, a process that may be compromised by the inability to inactivate LFA-1 and thus to terminate cell–cell contacts.

Mice expressing the mutant LFA-1 closely resembled mice lacking the protein completely, suggesting that, for immune cells, letting go is just as important as grabbing on. *JEM*