Trouble-making NKT cells

The dark side of NKT cells is revealed in a new study showing that they contribute to autoimmune arthritis in mice. On page 41, Kim et al. find that arthritis is worse in joints that are invaded by NKT cells.

NKT cells are innate immune cells that express both NK and T cell markers, and are protective in many other models of autoimmune disease. The authors tested NKT function in K/BxN mice—an established model of rheumatoid arthritis. These mice spontaneously develop a progressive inflammatory disease that is caused by the deposition of autoantibodies in joints. Disease can be transferred to healthy recipient mice by injecting them with K/BxN serum.

Kim et al. now show that mice lacking NKT cells develop only mild joint inflammation when given K/BxN serum. This protection was reversed if the deficient mice were reconstituted with NKT cells.

The nonarthritic mice lacking NKT cells had high levels of TGF-β1 in their joints, which dropped as soon as the NKT cells arrived on the scene. Blocking TGF-β1 in the same NKT cell-deficient mice increased joint swelling, suggesting a protective role for this cytokine. Suppression of TGF-β1 production depended on the ability of the NKT cells to produce both IL-4 and IFN-γ.

Many questions remain unanswered. Future studies might reveal which cells produce the TGF-β1 in the joints, how TGF-β1 prevents arthritis, what attracts NKT cells to the joint, and how NKT cells suppress TGF-β1 production. JEM

Surviving low oxygen

Hypoxia-inducible factor–1α (HIF-1α) prolongs the life of oxygen-deprived neutrophils by inducing NF-κB-driven survival signals, according to a study by Walmsley et al. on page 105. HIF-1α, a transcription factor induced by low oxygen, is required for myeloid cell function but has never been linked to myeloid apoptosis. Walmsley et al. now show that cells lacking this protein are robbed of the ability to resist apoptosis in low-oxygen environments like those encountered in wounds and inflamed tissues.

Neutrophils must function in adverse environments where oxygen and nutrient supplies are low. To do this, they turn on HIF-1α, which drives the synthesis of enzymes that make ATP anaerobically. In mice whose myeloid cells lack HIF-1α, the cells quickly lose their ATP supplies and thus have no energy to migrate or function in response to inflammatory stimuli.

Neutrophils also delay apoptosis during hypoxia, and the authors now show HIF-1α is required for this delay. The accelerated death could be mimicked in HIF-1α-positive cells by blocking NF-κB, suggesting a key role for this transcription factor in prolonging survival. The authors speculate that the ability of HIF-1α to induce neutrophil survival might contribute to a delayed resolution of inflammation, making a bad situation even worse. JEM

MBL is good for the heart

High levels of circulating mannose-binding lectin (MBL) are associated with lower risk of heart attack, according to a report on page 117. The correlation is particularly strong among diabetics and people with elevated cholesterol and may be a useful indicator of future risk.

MBL is a serum protein that binds to sugar residues on a broad range of microorganisms and promotes their clearance. MBL levels have been correlated with incidence of both infectious diseases and heart disease in some studies, but others found no such link.

The current study goes a long way toward settling the heart disease controversy. "This is the first study that examines levels of MBL protein in the context of other known risk factors for myocardial infarction," senior author Helgi Valdimarsson points out. This stratified analysis revealed a particularly strong link between MBL levels and the already increased risk of heart attack in diabetics and people with elevated cholesterol.

Measuring MBL protein levels may also be more reliable than earlier analyses of MBL genotypes. The authors find that levels of MBL protein in the blood remain virtually unchanged in an individual for decades, whereas protein levels among people with the same genotype may vary widely.

Based on unpublished in vitro binding data, the authors suggest that MBL may protect against myocardial infarction in vivo by binding to and helping clear the oxidized forms of cholesterol that build up in arteries. This type of cholesterol is abundant in diabetic patients, which may explain why high levels of MBL are particularly good news for these individuals. JEM

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