How inflammation signals heart trouble

Liver-secreted inflammatory proteins and thickened arteries are two harbingers of heart disease. Luchtefeld et al. (page 1935) now find a cause-and-effect link between these risk factors. Their study shows that the pathway to inflammation amplifies plaque build-up in the arteries.

Plaques are a consequence of high dietary cholesterol, which gloms onto arterial walls. Macrophages ingest the fat, die, and further harden the area into plaque. This condition, known as atherosclerosis, is associated with high levels of inflammatory cytokines such as interleukin (IL)-6. Liver cells activated by these cytokines release “acute phase” proteins (APPs), which are markers of heart disease.

When released during an immune response, however, APPs have an immediate benefit. They trigger the complement cascade and recruit macrophages to the inflamed areas. These events help clean up infection and injury—situations that require a strong, swift response. But APPs can cause a lot of damage if they are perpetually present, as seen in patients suffering from arthritis or lupus. These chronically inflamed individuals also suffer from atherosclerosis and are at high risk for heart failure.

Luchtefeld and colleagues now reveal the mechanism that links chronic inflammation to heart disease: APPs seem to amplify plaques by attracting macrophages. The team inactivated the IL-6 receptor, gp130, in mice that are genetically predisposed to atherosclerosis. The mice thus had fewer APPs. Even on a high cholesterol diet, these animals had smaller plaques that contained fewer macrophages. Normally, cells in the plaque lure more macrophages by secreting the chemokine CCL2. But without APPs, this chemokine was not produced.

The continuous triggering of gp130 might also worsen cardiac health in humans. The authors tracked genetic variations in the human gp130 homologue IL-6ST in families with a history of heart disease. They found that individuals who had developed coronary plaques carried the same IL-6ST allele.

CpGs relieve arthritis

Arthritis sufferers might get some therapeutic relief from bacterial nucleic acids that usually goad on inflammation, if results from Wu et al. (page 1911) are any indication. Some of these short CpG repeats (CpGs) are now shown to prevent arthritis progression in a mouse model.

CpGs are well-known proinflammatory molecules that activate dendritic cells (DCs) via toll-like receptor (TLR)-9. The DCs then stimulate T cells and B cells. CpGs are therefore used in the clinic to enhance protection against infections and tumor development. But immune enhancement can be harmful if the response is directed against the host’s own antigens. CpGs and other TLR ligands, for example, further disease progression in many mouse arthritis models.

In some mouse models of allergy and asthma, however, CpGs exert a protective role. In these mice, CpG-activated DCs somehow jumpstart the proliferation of protective T cell subsets and stop B cells from secreting allergy-causing antibodies. Wu et al. wondered whether CpGs had a similar therapeutic effect on arthritis.

The team tested several known CpGs in mice that had developed arthritis in response to injected serum antibodies. Two structurally similar CpGs halted disease progression. Unlike disease-promoting CpGs, these helpful CpGs stimulated DCs to activate natural killer (NK) cells instead of T and B cells. The NK cells then produced interferon (IFN)–γ. This normally proinflammatory cytokine blocked neutrophil trafficking into the diseased joints, thereby lessening inflammation.

The authors attribute this disease-dampening effect to the fact that the T/B cell-mediated initiation phase had passed by the time the CpGs were delivered. The NK-mediated therapeutic effects may translate to human arthritis treatments, as T and B cells have usually already done their dirty work by the time patients arrive in the clinic.