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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 buildup 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 chemo-kine 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 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.

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Screening for IL-6ST polymorphisms might thus allow for the early identification of those who are predisposed to coronary artery disease.
EBV covers its tracks

Viruses that lie low inside cells after infection come under attack by the immune system when they reawaken and resume multiplying. Hislop et al. (page 1863) now reveal the mechanism used by the Epstein-Barr virus (EBV) to dodge host immunity during this reactivation phase.

EBV initially infects and replicates within oral epithelial cells but later quietly hides out in B cells. During this latent phase, EBV-infected B cells avoid the immune system by expressing very little viral antigen. To ensure viral spread and survival, however, EBV must reenter the replicative, or lytic, phase and invoke new epithelial tissues.

Previous studies suggested that this herpesvirus also avoids the attention of the immune system during its reawakening. During the lytic phase, EBV-infected B cells dial down the activity of their transporters associated with antigen processing (TAPs)—transmembrane channel proteins that shuttle antigenic peptides into the ER, where they find their HLA partners. Infected B cells thus display few viral antigens at the cell surface.

Known herpesviruses genes encoding TAP-inhibiting proteins were not found in the EBV genome. The authors therefore compared herpesvirus genomes to find a lytic phase TAP inhibitor gene in EBV and its closest relatives. Cloning and expression of candidate genes uncovered BNLF2a, which encodes a protein that blocked both the peptide-binding and ATP-binding sites on TAPs and thereby prevented it from translocating peptides into the ER.

This mechanism differs from those used by all other herpesvirus TAP inhibitors. The team is currently investigating how the relatively small BNLF2a protein blocks access to two distant sites on TAP. JEM

All B cells need is BAFF

B cells usually conspire with T cells to break tolerance against the host and cause lupus. But Groom et al. (page 1959) now show that B cells don’t always need T cells to egg them on. An activating cytokine empowers them to cause trouble all on their own.

This cytokine, called BAFF (B cell–activating factor), helps B cells survive as they transit through developmental checkpoints. BAFF also enhances T cell activation. With too much BAFF, however, even B cells that should have been eliminated—such as self-reactive ones—survive. The autoreactive antibodies first secreted by these cells are relatively harmless. But presumably with help from BAFF-activated T cells, these B cells switch their antibody genes and start producing pathogenic autoantibodies.

Groom et al. now find that the antibody-switching signal doesn’t have to come from T cells. Mice that overexpressed BAFF but lacked T cells still developed lupus. The B cells instead derived the extra push through their Toll-like receptors (TLRs) 7 and 9, whose expression was strongly enhanced by BAFF. The authors speculate that nucleic acids released by dying cells might trigger these TLRs on self-reactive B cells.

The presence of disease-inducing antibodies even when T cells are absent might explain why not all lupus patients respond to treatments that suppress T cell functions. The team is now investigating whether these patients have high levels of BAFF. JEM

New mutations stabilize NOTCH1

A leukemia-associated signaling protein accumulates to dangerous levels when its own mutations shield it from degradation. Now, reports from O’Neil et al. (page 1813) and Thompson et al. (page 1825) identify outside forces that also lead to its buildup. Defects in proteosomal targeting, they find, can also trigger leukemia.

T cell acute lymphoblastic leukemia (T-ALL) is triggered by mutations in the NOTCH1 receptor. Once activated, this transmembrane protein is clipped to release its intracellular domain (NICD), which then activates the transcription of genes that goad stem cells to become T cells.

Many transformed T cells have too much NICD, as their NOTCH1 proteins carry mutations that protect them from proteosomal degradation. This increase sends many NOTCH1 targets, particularly oncogenes, into overdrive.

The new reports show that NICD levels are also high in some leukemic cell lines that lack NOTCH1 mutations. The defect in these cells lay instead in an enzyme called FBW7, which normally ubiquitinates NOTCH1 so it is recognized by the proteasome. The mutated version, which was also found in some T-ALL patients, failed to bind and ubiquitinate NICD.

Thompson et al. also found that the dysfunctional FBW7 did not bind some of its other targets, such as c-Myc and cyclin-E—oncogenes that are turned on by NICD. This failure might account for the resistance of these cell lines to antileukemia drugs that prevent NOTCH1 receptor cleavage. JEM