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Unmasking an inflammatory suppressor

Mice that tend to overreact to infection appear to have a failsafe mechanism that kicks in before inflammation gets out of control, say Conner et al. (page 305). Oddly enough, the dampener was known for its ability to enhance inflammation.

To find genes that unleash uncontrolled inflammation and pathways that inhibit them, the authors turned to mice whose cells overreact to inflammatory stimuli that trigger Toll-like receptors (TLRs). The mice, however, do not suffer ill effects from their overzealous response. One potential explanation, the authors reasoned, is that mutations in TLR response genes might be counterbalanced by mutations in regulatory genes.

The group has now mapped the phenotype of these mice to two loci. The first locus contained the gene for the interleukin receptor–associated kinase (IRAK) 2, which helps turn on inflammatory cytokine genes in TLR-activated cells. The second locus contained a gene encoding IRAK1-binding protein (IRAK1BP) 1, which was previously identified as an enhancer of some proinflammatory signals.

In cells from the easily inflamed mice, however, IRAK1BP1 partially suppressed their proinflammatory phenotype. TLR-activated macrophages from these mice turned on IRAK1BP1, which then suppressed the transcriptional activation of several cytokines. Macrophages from normal mouse strains, however, did not express IRAK1BP1 in response to TLR activation. The prior study suggesting a proinflammatory role for IRAK1BP1 relied on overexpression of the protein in a cell line; the role of endogenous IRAK1BP1 had not been explored.

The team found several differences between the IRAK1BP1 promoter sequence in normal and hyperreactive mice. But whether these differences determine the alternative expression of IRAK1BP1 is not clear. In normal mice, IRAK1BP1 might only kick in when other inflammation-suppressing mechanisms go awry. JEM

Toll signals provoke plaque buildup

Fatty foods plug up arteries in more ways than one, according to Mullick et al., on page 373. They also trigger the expression of an innate immune receptor that makes the arteries more fat friendly.

Recent data suggest that the immune receptor in question, Toll-like receptor (TLR) 2, which recognizes bacterial lipids, might also enhance atherosclerosis—a disease that can lead to restricted blood flow due to the accumulation of fat in blood vessels. Mice that are plaque prone because they cannot properly dispose of fat stay plaque free if TLR2 is knocked out. Its loss from immune cells alone, however, does not protect these mice, suggesting that TLR2 on a nonimmune cell favors plaque growth.

Mullick et al. now find that TLR2 is expressed on the endothelial cells that line the curves of blood vessels. These cells are plaque prone by nature; the uneven blood flow here stimulates them to express more adhesion molecules and chemokines. They thus attract both circulating fat and macrophages that eat the fat and then harden into plaques. A high-fat diet thus increases plaque formation in part by giving macrophages more to chew on.

A high-fat diet also increased endothelial TLR2 levels in the atherosclerosis-prone mice, the authors found. Components of dietary fat may bind to TLR2 and thereby increase expression of the receptor on endothelial cells. These mice accumulated larger fat deposits and more macrophages in vessel curves than did their TLR2-deficient counterparts. The team has yet to determine how TLR2 expands plaques. Perhaps, like uneven blood flow, it increases endothelial cell adhesion molecule or chemokine levels. JEM