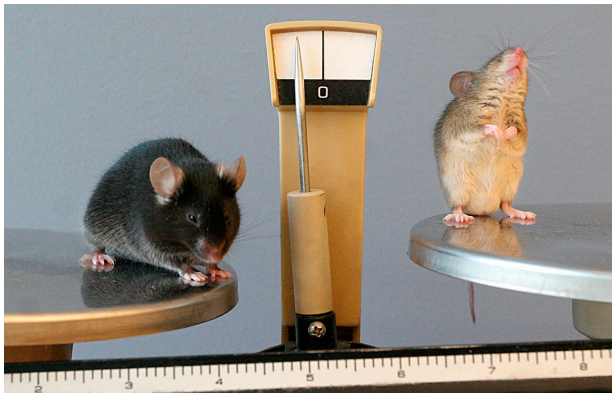
Unmasking an inflammatory suppressor

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.



COURTESY OF P. BRODEUR

Mice that tend to have vigorous inflammatory responses (right) compensate by expressing the antiinflammatory gene *IRAK1BP1*.

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.

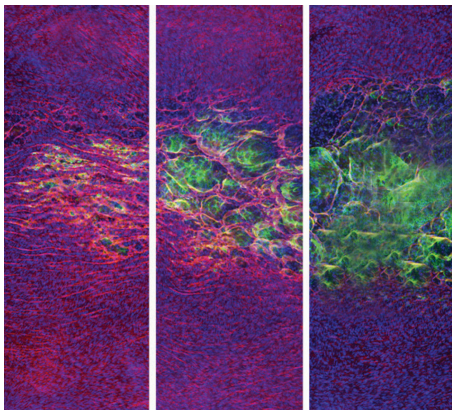
The team found several differences between the *IRAK1BP1* promoter sequence in normal and hyperreactive mice. But whether these differences determine the alternative expression of IRAK1BP1 is not clear. In normal mice, IRAK1BP1 might only kick in when other inflammation-suppressing mechanisms go awry. 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 increases the expression of Toll-like receptor 2 (green) on endothelial cells within four weeks (left to right).

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

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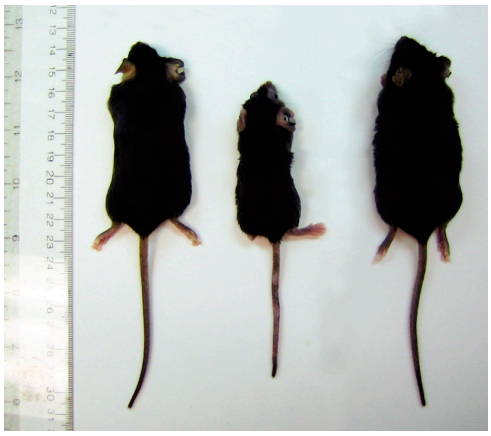


Inflammation-related weight loss caused by symbiotic bacteria in A20-deficient mice (middle) is rescued by loss of MyD88 (right).

Averting danger from within

On page 451, Turer et al. find that loss of a single protein turns symbiotic bacteria into killers.

Helpful bacteria in the gut protect themselves by inducing the gut epithelia and local immune cells to secrete tissue repair factors and low, protective levels of cytokines and heat-shock proteins. This noninflammatory response is triggered by the binding of bacterial components to Toll-like receptors (TLRs). It has been assumed that these bacteria are helpful rather than harmful because the resulting TLR signals are less potent than those triggered by foreign pathogens.

Turer et al. now show, however, that TLR signals triggered by symbiotic microbes are potentially lethal unless they are held in check. The team had previously found that mice lacking an antiinflammatory protein called A20 died from inflammation-related complications even in the absence of infection. They now find that this deadly inflammation is triggered by ligands from the host's own symbiotic bacteria.

Depleting the resident gut bacteria using antibiotics rescued the mice, as did knocking out the TLR adaptor protein MyD88. Protection was less effective, however, if MyD88 was lost only from immune cells, suggesting that A20's inhibitory effect primarily acts in nonimmune cells—possibly in gut epithelial cells. The team is now investigating whether A20 is required for cells to differentiate between pathogenic and protective TLR signals. JEM

Long-lasting Toll suppression

A study by Didierlaurent et al. (page 323) explains why fighting the flu makes us vulnerable to bacterial infections in the following months. A clampdown of innate immune receptors in the lung might leave the door open to opportunistic bacteria.

The team previously showed that mice that had just recovered from the flu had a weak inflammatory response that made them more susceptible to other pathogens over the next six months. The group now finds that post-flu inflammation in these mice is tempered by a dampened innate immune system.

The innate system usually responds to ligands that activate Toll-like receptors (TLRs). But in mice recovering from the flu, these ligands did not activate TLRs on lung macrophages. The cells therefore did not produce the chemokines necessary to attract neutrophils—the main instigators of lung inflammation.

Although the blunted TLR response might protect the lungs against inflammation-induced damage, it made them vulnerable to bacterial infection. After beating influenza, the mice were killed by pneumonia-causing bacteria that are normally held at bay in the airways.

Influenza and other respiratory viruses are not known to encode TLR-suppressing proteins. This suppression may thus represent the lung's attempts to protect itself from damaging levels of inflammation. The authors suspect that the lungs might suppress TLR expression in response to any insult that causes a massive inflammatory response, including pathogens, injury, or environmental allergens. Their theory is bolstered by the fact that another respiratory pathogen, respiratory syncytial virus, also suppressed macrophage TLR signaling. JEM

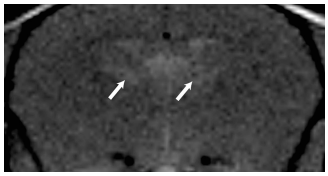
VEGF blockade damages brain vessels

A factor that promotes blood vessel growth keeps two types of brain cells alive, say Maharaj et al. (page 491). Their findings might explain why anticancer drugs that block this factor cause neurological side effects.

The drug target in question—vascular endothelial growth factor (VEGF)—binds to receptors on blood vessel endothelial cells. A localized increase in VEGF, which is produced by underlying epithelial cells and other neighboring cells, promotes vessel growth in developing organs and injured tissues.

Lower levels of VEGF might also be necessary for the survival of endothelial cells, which become apoptotic when cultured in the absence of VEGF. VEGF-blocking drugs that limit tumor growth by inhibiting the tumors' blood supply can cause seizures and brain swelling in some cancer patients. To find out whether these symptoms stem from the destruction of brain blood vessels, Maharaj et al. examined the brains of mice that had been engineered to express high levels of proteins that block VEGF and TGFβ—a cytokine that stimulates VEGF production.

Besides damage to brain endothelia, the mice developed brain lesions due to a breakdown of the barrier that prevents cerebral spinal fluid from seeping into the brain. The specialized type of epithelial cells that make up this barrier expressed VEGF receptors and became apoptotic when VEGF was systemically blocked. Why brain complications only occur in a subset of cancer patients on anti-VEGF therapy is unknown. JEM



Mice that express high levels of VEGF-blocking molecules develop brain lesions (arrows).