New targets for aspirin

On page 1077, Machado et al. reveal a new way in which aspirin reins in inflammation—it triggers the destruction of proinflammatory signaling proteins.

Aspirin’s power was initially attributed to its inhibition of proinflammatory lipids called prostaglandins—a discovery that won the Nobel Prize in 1982. Later, aspirin was also shown to beef up levels of lipids called lipoxins, which help resolve inflammation by blocking NF-κB activation and the recruitment of inflammatory cells.

Lipoxins were recently found to activate SOCS2, a protein that blocks signals from growth hormone receptors by targeting downstream signaling proteins to the proteasome. To determine whether SOCS2 also blocks inflammatory signals, Machado et al. fished for its binding partners among molecules that transmit innate immune receptor signals.

They now find that SOCS2 binds TRAF2 and TRAF6—adaptor proteins that are required for cytokine production by activated dendritic cells (DCs)—and seems to target them to the proteasome. Treating mice with aspirin decreased DC levels of cytokines and TRAF2 and TRAF6—effects that were mitigated by proteasome inhibitors. The same effects were not found in DCs from SOCS2-deficient mice.

Mice treated with a proteasome inhibitor after parasitic infection beat the bug but died from inflammatory damage. The deadly inflammation probably resulted from prolonged signaling via TRAF2 and TRAF6, as inflammation in SOCS2-deficient mice was severe even without the inhibitor. Infected mice that were left untreated resolved the inflammation and survived the infection.

Because proteasome inhibitors also block the degradation of IκB—the molecule that holds NF-κB in check—they are being developed as alternatives to aspirin, which can cause stomach problems and other side effects. But the current findings suggest that this strategy might be counterproductive. JEM

Spreading instead of growing

A protein previously hailed as a tumor suppressor has a sinister agenda, according to Rolny et al. (page 1155). Although this false savior, semaphorin 3B (SEMA3B), tells tumor cells to stop growing, it then sends them on their way to grow elsewhere.

Semaphorins were initially identified as extracellular navigation signals for growing axons. Some of them are now known to enhance tumor progression by increasing the growth of blood vessels that feed the tumor. SEMA3B, however, is thought to be a tumor suppressor because it also inhibits tumor cell proliferation.

Rolny et al. now find that this suppression comes at a potentially fatal price. Most tumor suppressors are either absent or expressed at low levels in cancerous tissues. But the group found high levels of SEMA3B in many cancer cell lines and in metastatic tumors from patients. Although SEMA3B inhibited the proliferation of these tumor cells in vitro, the poor prognosis of these patients suggested that SEMA3B signaling might have detrimental effects in vivo.

To test this hypothesis, the authors engineered human tumor cells in which SEMA3B expression was controlled by a drug-inducible promoter and injected these cells into the skin of immune cell-depleted mice. Drug-treated mice had smaller skin tumors but developed secondary lung tumors, suggesting that SEMA3B induced metastasis.

The authors found that SEMA3B inhibited growth and simultaneously triggered metastasis by activating the signaling kinase p38. p38 then activated a cell cycle inhibitor and induced tumor cells to secrete IL-8, a cytokine known to induce leukocyte chemotaxis. The IL-8–secreting tumors were full of infiltrating macrophages, which are thought to spur metastasis by producing soluble factors such as VEGF. Blocking the release of IL-8 in response to SEMA3B, the group found, blocked the metastasis of these tumors. JEM