Heart attack or cancer?

Suppressing the action of lipoxygenases may reduce "bad cholesterol" deposition and inflammation in the arteries and thereby prevent heart attacks. But doing so might inadvertently cause leukemia, warn Middleton et al. (page 2529).

While studying atherosclerosis (artery hardening) using 12/15-lipoxygenase (12/15-LO) knock-out mice, Ellen Puré's team made an unexpected discovery: the spleens of all the mice were enlarged. Closer inspection of the spleens revealed a distinct increase in the myeloid cell population—a feature indicative of myeloid proliferative disease (MPD). Consistent with this leukemia, lymph nodes displayed an abnormal excess of cells, and the leukocyte count of peripheral blood was markedly increased.

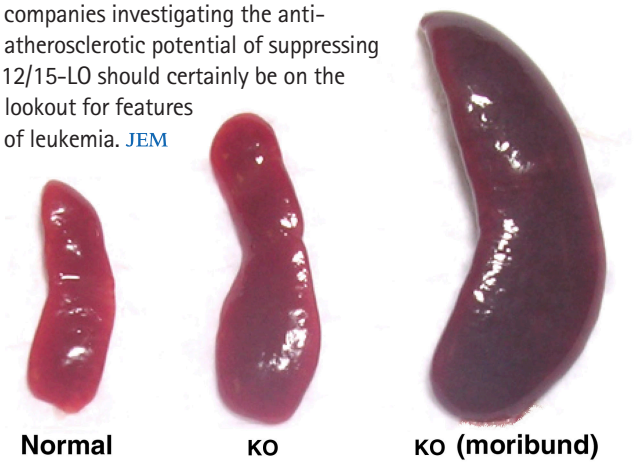
12/15-LO$^{-/-}$ splenocytes showed increased levels of the Bcl-2 oncoprotein and reduced nuclear accumulation of the ICSBP transcription factor, which represses Bcl-2. Exactly how loss of 12/15-LO leads to loss of nuclear localization of ICSBP, however, is yet to be determined.

The mice were slightly more likely to die early, but the majority had no obvious external symptoms even up to one year of age. The protracted, chronic phase of the most common form of human MPD, chronic myelogenous leukemia (CML), is also usually asymptomatic. As a result, CML often goes undiagnosed in the chronic phase and becomes apparent only when the disease progresses to the more life-threatening "blast" phase (when the number of immature white blood cells is extremely high).

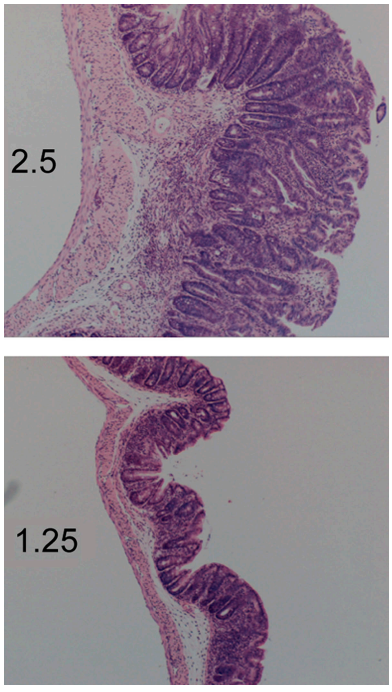
Many existing mouse models of CML show rapid progression of the disease and are thus relevant for studying the blast crisis phase only. But the 12/15-LO$^{-/-}$ mice are a potentially valuable model system for studying the entire chronic phase as well as disease progression.

12/15-LO$^{-/-}$ mice have long been used in the study of atherosclerosis, but other groups possibly overlooked the enlarged spleens, says Puré. Even more astounding is that, although reduced activity of human lipoxygenases had been reported in human leukemia, its direct involvement in the disease had not been studied.

Now that Middleton and colleagues provide stronger evidence for the link between MPD and 12/15-LO, researchers and drug companies investigating the anti-atherosclerotic potential of suppressing 12/15-LO should certainly be on the lookout for features of leukemia. JEM



Myeloproliferation in mice lacking a lipoxygenase (KO) leads to bigger spleens.



Intestinal inflammation is reduced by anti-p19 treatment (bottom).

Gut reaction: the case against IL-23

The prime suspect behind inflammatory bowel disease (IBD) has been wrongly accused. Work by Hue et al. (page 2473) and Kullberg et al. (page 2485) reveals that the cytokine IL-12 was merely a cover for the real IBD culprit, IL-23. IL-23 promotes inflammation by corrupting not only adaptive immunity, as previously thought, but also the innate immune system.

IL-12, an activator of adaptive immunity via the induction of Th1 cells, is composed of two subunits, p35 and p40. In mouse models of intestinal inflammation, antibodies against p40 prevent the chronic inflammation that occurs in IBD in response to intestinal bacteria. Thus, IL-12 was considered responsible for driving IBD.

Case closed? Not quite. In 2000, it was discovered that p40 can also dimerize with p19 to form IL-23. Thus, all studies using antibodies against p40, including studies of other autoimmune diseases (see *J. Exp. Med.* 201:163), required reevaluation. Using mouse models of IBD, Kullberg et al. show that mice incapable of producing p35 but still able to produce the p40 subunit develop intestinal inflammation in response to bacterial challenge, whereas mice that lack IL-23 resist the disease. Furthermore, Hue et al. show that an anti-p19 antibody strongly inhibits bacterially induced intestinal inflammation.

IL-23, which shows increased expression in mice with intestinal inflammation, was previously thought to activate adaptive Th17 cells only. But here, Kullberg et al. show evidence that both Th1 and Th17 cells may be overactivated by IL-23. Hue et al. also show, using mice that lack B and T lymphocytes, that IL-23 can also induce intestinal inflammation via the innate immune system. It remains to be determined both how IL-23 controls these diverse responses and what leads to its own overexpression in IBD. JEM

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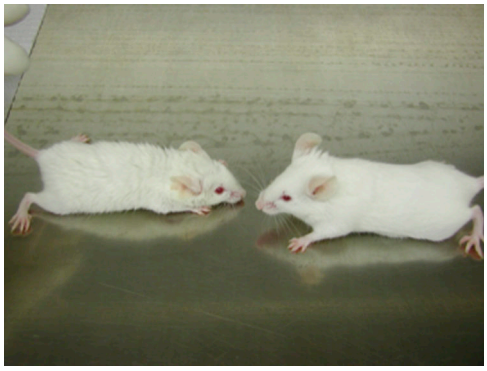
Curtailing infection



Mice with suppressed IL-10 action (right) eradicate persistent viral infection and improve their health.

Certain crafty viruses can cause the host's immune system to suppress itself, and thereby establish persistent chronic infection. But Ejrnaes et al. (page 2461) and Brooks et al. (*Nat. Med.* doi:10.1038/nm1492) have now found that suppressing the suppressor, which they show is the cytokine IL-10, can fight persistent infection.

IL-10 is known to exert a suppressive effect on cells of the immune system, including T cells and antigen-presenting cells, and elevated levels of IL-10 have been observed during persistent infection with hepatitis C virus, human immunodeficiency virus, and Epstein-Barr virus.

Now, both teams have observed that mice lacking IL-10 are resistant to persistent infection with lymphocytic choriomeningitis virus (LCMV). They also show that normal mice infected with LCMV have increased IL-10 production and decreased numbers of virus-killing $CD8^+$ T cells. Ejrnaes et al. show that treating LCMV-infected mice with antibody that blocks the IL-10 receptor restored these antiviral $CD8^+$ T cells and resulted in low or undetectable viral load, less weight loss and healthier coats. Importantly, the same reversal of symptoms and eradication of virus was achieved if treatment was administered later in infection.

Blocking the action of IL-10 might, therefore, be a potential therapy for human cases of persistent viral infection. Prolonged treatment with a potent stimulator of the immune system, however, might lead to undesirable autoimmune conditions, explains Matthias von Herrath, who led the study published here. His team is thus looking into the use of shorter and lower dose IL-10 treatments in combination with vaccines against virus-specific antigens. JEM

Controlling clots with Clk1

Platelets are critical blood cells involved in clotting. An early step in clot construction requires tissue factor (TF), but whether platelets make TF was unknown. New work by Schwertz et al. (page 2433) reveals that these nuclei-free cells doproduce TF by cytoplasmic splicing and further identify the kinase Clk1 as a splicing activator.

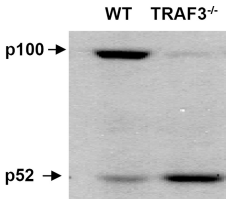
After injury to a blood vessel, platelets are the first cells on the scene to plug the hole. Platelets get activated by attachment to exposed collagen (amongst other things), and promote a TF-dependent coagulation cascade on their cell membranes. This ultimately results in large-scale fibrin production and the assembly of a tough fibrin meshwork over the platelet plug. TF is released from the injured tissue, but whether platelets themselves express TF is a debated question.

Schwertz et al. found that activated human platelets contained TF mRNA. Resting platelets instead contained unspliced TF pre-mRNA. Activation, the team showed, induced splicing and subsequent translation of TF in as little as 5 min.

Cytoplasmic splicing was described for the first time by this group a year ago. The precise mechanism is unknown, but splicing factor SF2/ASF was identified in platelet cytoplasms. In nucleated cells, Clk1 activates SF2/ASF by phosphorylation. Interrupting this modification, the team now shows, prevents processing of TF pre-mRNA.

A number of conditions lead to increased blood clotting. In recent unpublished work, the team found that platelets isolated from septic patients, in whom thrombosis occurs, are more prone to clotting and contain increased levels of spliced TF mRNA. Clk1-controlled splicing might thus be a good target for anticoagulation treatments. JEM

Keeping NF-κB in check



Cells lacking TRAF3 constitutively release active p52 NF-κB.

NF-κB, a central proinflammatory regulator, gets activated by TNF receptor–associated factors (TRAFs). But He et al. (page 2413) now report that one TRAF family member (TRAF3) instead negatively regulates an alternative NF-κB activation pathway.

Classical activation of NF-κB occurs by TRAF-controlled degradation of cytoplasmic inhibitory binding proteins, which leads to nuclear accumulation of the p50 forms of NF-κB. Activation can also occur by a recently discovered route requiring NF-κB–inducing kinase (NIK), which releases a different NF-κB complex, thus one containing p52.

It was known that, unlike other TRAFs, overexpression of TRAF3 does not induce the classical NF-κB pathway. By examining TRAF3-null mice (which die soon after birth), He et al. now show that cells from these mice have constitutively active noncanonical p52 NF-κB. This constitutive activation was associated with aberrant accumulation of NIK protein, but not mRNA, suggesting that TRAF3 blocks noncanonical NF-κB by reducing NIK protein stability.

Crossing the $TRAF3^{-/-}$ mice with mice that lacked p52 prevented their early death, showing that overactivity of p52 was, indeed, the cause of lethality. The final cause of death in $TRAF3^{-/-}$ mice is uncertain but is most likely due to over-inflammation caused by the unfettered activation of NF-κB-signaling. JEM