

## 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<sup>-/-</sup> 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.

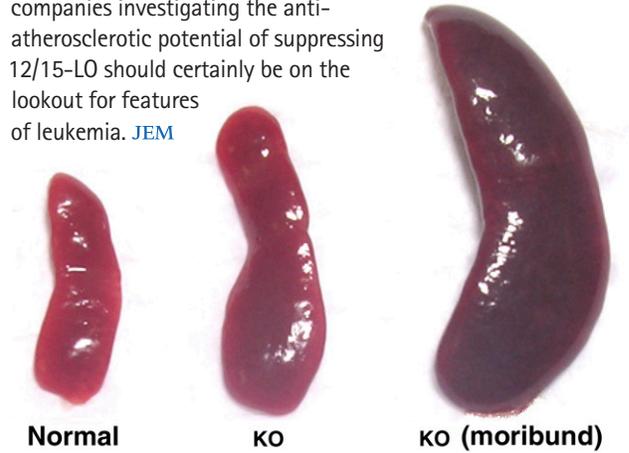
The mice were slightly more likely to die early, but the majority had no obvious external symptoms even up to one year of age. The protracted, chronic phase of the most common form of human MPD, chronic myelogenous leukemia (CML), is also usually asymptomatic. As a result, CML often goes undiagnosed 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

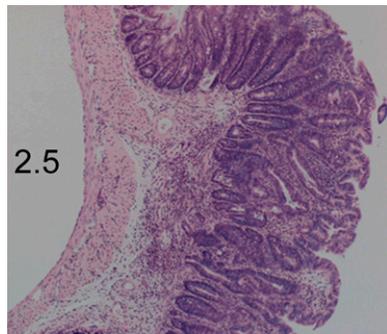
the blast crisis phase only. But the 12/15-LO<sup>-/-</sup> mice are a potentially valuable model system for studying the entire chronic phase as well as disease progression.

12/15-LO<sup>-/-</sup> 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](#)



**Normal KO KO (moribund)**  
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](#)