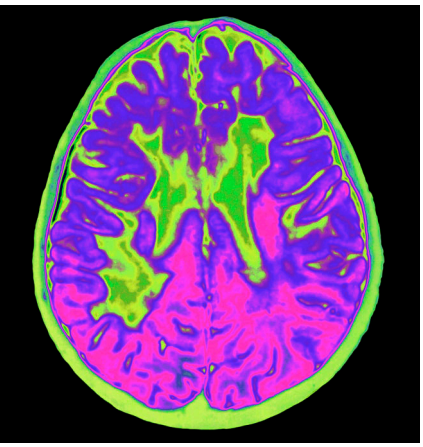


MEHAU KULYK/PHOTO RESEARCHERS, INC.

Image shows the brain of an MS patient. In mice, PPARγ dampens Th17 responses and eases EAE.

PPARγ tackles treacherous T cells

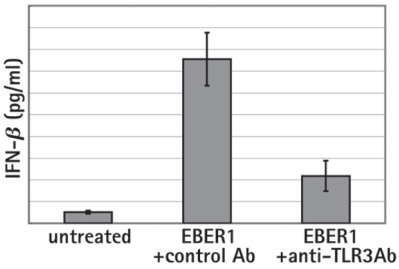
Although Th17 cells help battle bacteria and viruses, they can also turn traitor and promote autoimmune attacks. Klotz et al. report a possible new way to stall development of these self-targeting cells.

Studies have implicated Th17cells in several autoimmune diseases, including multiple sclerosis. The master switch for Th17 differentiation is the transcription factor RORγt, but researchers know little about how cells control RORγt activity. Klotz et al. homed in on one possible regulator, the nuclear receptor PPARγ, whose immune tasks range from quelling inflammation to inhibiting proliferation of T cells.

Mice lacking PPARγ in their T cells developed severe EAE—the rodent equivalent of MS—more rapidly than did mice with normal T cells. Mice with PPARγ-deficient T cells also harbored about three times as many autoreactive Th17 cells in the central nervous system. Stimulating PPARγ with the synthetic molecule PIO ameliorated disease symptoms. In cultured T cells, the same treatment reduced RORγt expression.

These results suggest that PPARγ hampers the differentiation of Th17 cells in mice. The receptor does the same in humans, as naive human T cells stimulated with PPARγ agonists produced less IL-17 in culture. PPARγ exerts its effects, the team discovered, by preventing the SMRT repressor from leaving the RORγt promoter in response to the Th17-promoting cytokines IL-6 and TGF-β.

PPARγ is selective—it had no effect on differentiation of other cell types such as regulatory T cells or Th1 and Th2 T cells. That Th17 cells can be restrained without hobbling other immune cells is good news for potential PPARγ-activating treatments. However, the authors caution that PPARγ only soothed EAE symptoms, rather than eliminating the disease. They are now trying to pin down naturally occurring PPARγ triggers and determine whether any of them malfunction during autoimmune diseases. Although the α and δ isoforms of PPAR also dampen EAE, they seem to have more of an effect on IFN-γ–producing Th1 cells than on Th17 cells, but what governs this specificity is not yet known.



The viral RNA snippet EBER1 activates lymphocytes via TLR3, as indicated by interferon-β release.

EBV takes a toll

Epstein-Barr virus (EBV) can unleash a fatal immune system overreaction. Short RNA molecules released by the virus cue this response, Iwakiri et al. suggest.

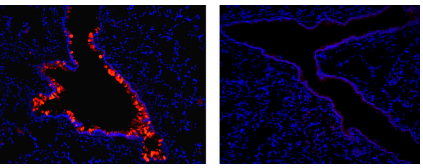
Few people are even aware that they've contracted EBV, as most infections are asymptomatic. But in some cases, the virus can trigger illnesses such as infectious mononucleosis and the potentially lethal EBV-associated hemophagocytic lymphohistiocytosis, in which macrophages destroy large numbers of blood cells. Researchers think that the more severe symptoms of infection result from a tsunami of inflammatory cytokines, but what unleashes this flood wasn't certain.

Iwakiri et al. discovered that the possible culprits are RNA snippets manufactured by the virus. EBV releases two noncoding RNA segments, EBER1 and EBER2, that fold over on themselves to produce double-stranded structures. Using transformed B cells, the researchers showed that EBER1 activates immune cells by prodding Toll-like receptor 3 (TLR3), a sensor of viral double-stranded RNA. Infected cells don't spew out EBER1 when they are dying. Rather, they released the RNA bound to a cellular protein called La, which may help to protect the RNA against degradation.

Blood from patients with mononucleosis and other chronic EBV infections teemed with EBER1, consistent with prior reports. When purified, these viral strands spurred the release of inflammation-promoting cytokines such as interferon-γ and TNF from peripheral blood mononuclear cells.

TLR3 is mainly a dendritic cell (DC) receptor. Indeed, EBER1 induced the maturation of these cells and boosted their ability to present antigens to T cells. The researchers suspect that viral RNA triggers TLR3 on DCs, prompting them to pump out inflammatory cytokines. DCs then enlist T cells that add more cytokines to the mix. In some cases, the result could be a damaging, systematic cytokine surge.

Still a mystery is how releasing RNA benefits EBV. Other viruses use double-stranded RNA to promote infection. Such molecules help the West Nile virus enter the brain, for instance. Iwakiri et al. speculate that RNA might help EBV increase its numbers by promoting division of the cells it infects, including B, T, and natural killer cells.



Mucus-producing goblet cells (red) proliferate in mice with the Q576R polymorphism (left), but not when STAT6 is absent (right).

Suspected asthma mutation leaves mice gasping

Tachdjian et al. establish that an allergy-associated gene variant common in African Americans promotes airway inflammation in mice, pointing the way to possible new approaches for asthma treatment.

Genetic association studies link the Q576R polymorphism in the gene encoding the interleukin (IL)-4 receptor with susceptibility to severe asthma. This receptor responds to the pro-allergy cytokines

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mitchleslie@comcast.net

IL-4 and IL-13, and the polymorphism swaps one amino acid in its alpha chain. Like asthma, this genetic variant is prevalent in African Americans, about half of whom are homozygous for the polymorphism. Because genetic associations don't confirm a cause-and-effect relationship, Tachdjian et al. set out to verify the pro-asthma effect of the Q576R polymorphism by expressing the mutation in mice.

Mice carrying the Q576R polymorphism developed extreme airway inflammation, similar to that shown by asthma patients. Inflammation-promoting eosinophils swept in, mucus-exuding goblet cells multiplied, and the airways stiffened as collagen built up.

IL-4 and IL-13 typically work by firing up the transcription factor STAT6. However, the polymorphism didn't alter STAT6 activity. Rather, it amplified some of the responses spurred by STAT6, suggesting activation of an alternative pathway that synergizes with STAT6. In fact, activation of the MAP kinase pathway was ramped up in mice with the Q576R allele.

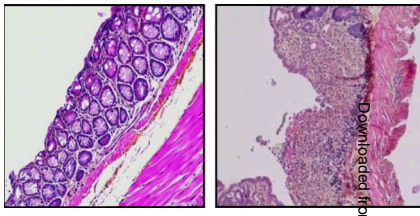
Clingy bacteria and Crohn's disease

Noxious intestinal bacteria can latch onto a sticky glycoprotein called CEACAM6. Now, Carvalho et al. reveal that this cell adhesion molecule enables the bugs to colonize the intestinal lining and cue the symptoms of Crohn's disease in mice.

An abnormal immune response to intestinal microbes is thought to cause the inflammation and tissue damage of Crohn's disease. Whether immune cells turn against harmless bacteria or whether the bacterial balance in the intestine is out of whack is still a matter of dispute. This group had previously discovered that Crohn's disease patients harbor excess amounts of CEACAM6 in the ileum of the small intestine. They also showed that pathogenic *E. coli* binds to CEACAM6 in vitro.

To confirm that the bacteria–CEACAM6 interaction promotes inflammation and disease, the team tested transgenic mice carrying a bacterial artificial chromosome that included the gene for human CEACAM6. Feeding the transgenic animals adherent-invasive *E. coli* (AIEC), which is common in Crohn's disease patients, spurred severe intestinal inflammation and erosion that killed 80% of the animals within a week. Control mice lacking the inserted genes rapidly eliminated the bug and remained healthy.

Extensions on the bacteria, called type 1 pili, enabled bacteria to adhere to CAECAM6 on intestinal surfaces. AIEC lacking these structures were unable to colonize either control mice or animals carrying human CEACAM6. Thus, Crohn's disease patients might benefit from a vaccine or treatment that prevents type 1 pili from getting a grip on CEACAM6. Such an inhibitor might not harm the bacteria directly and thus could have another plus—it wouldn't be likely to provoke drug resistance in the bacteria.



Transgenic mice expressing human CEACAM6 have a healthy colon lining (left) until infection with pathogenic *E. coli* (right).

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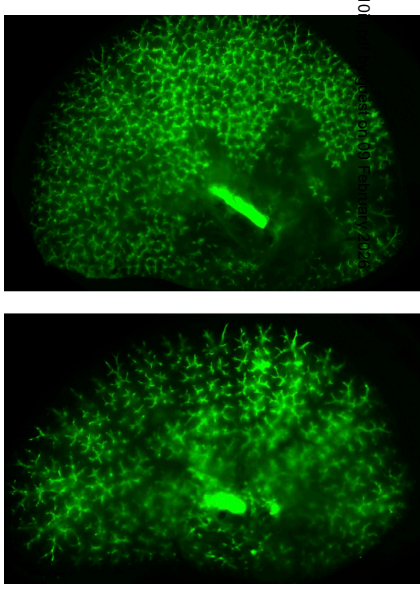
"Killer" pathway not guilty

A receptor and its trigger have been accused of causing a fatal form of lung hypertension, but that could be a bum rap. These molecules actually curb pressure increases in lung arteries and help shield these delicate vessels, Kugathasan et al. conclude.

The children and young adults who develop pulmonary artery hypertension (PAH), excessive pressure in the vessel that pipes blood from the heart to the lungs, usually die within two to five years. The Angiopoeitin-1 (Ang1)/Tie2 pathway seems to be involved in the illness. Tie2 is a surface receptor that spurs angiogenesis before and after birth. And Tie2's ligand, Ang1, guards endothelial cells from inflammation and forestalls apoptosis. However, previous studies have clashed about the effects of this pathway on PAH. After reporting excess Ang1 and high Tie2 activity in samples from patients' lungs, some researchers argued that the pathway exacerbates the illness. But other work has since shown that Ang1 might be just as abundant in healthy lungs and that the pathway might protect vascular cells.

To resolve these contradictions, Kugathasan et al. engineered mice with half the normal amount of Tie2. The animals' right ventricular systolic pressure—an indicator of pulmonary artery pressure—was above normal. And it shot up in response to two triggers of PAH, the neurotransmitter serotonin and the inflammatory cytokine interleukin-6. However, these stimuli didn't spur hypertension in mice that overproduced Ang-1, suggesting that when Ang1 and Tie2 team up, vessels are sheltered.

Tie2 signaling imparts protection in part by blocking death of vessel endothelial cells. Mice with reduced Tie2 activity had increased evidence of apoptosis in their lungs. And blocking apoptosis with a caspase inhibitor prevented the mice from developing disease. The protective effect of this receptor-ligand duo raises questions about the use of Tie2 inhibitors as potential treatments for PAH.



More blood reaches the lung vessels in normal mice (top) than in mice with half the normal amount of Tie2 (bottom).