Disruptive T cells

A study on page 239 shows that death–inducing T cells kill smooth muscle cells in atherosclerotic plaques. Sato et al. show that this lethal T cell activity is heightened in patients with heart disease, which could destabilize the plaques in these patients and make them more prone to rupture.

The narrowing of arteries is a natural process caused by the gradual deposition of fat and cholesterol into artery walls. The buildup of arterial plaques (atherosclerosis) is a long-term process that, for some, culminates in acute coronary syndromes (ACSs) such as heart attack and cardiac arrest. These acute attacks are caused by the sudden rupture of atherosclerotic plaques—an event that may happen more readily in some individuals than in others.

Plaques that contain immune cells such as macrophages and T cells are the most vulnerable to rupture, although the mechanism behind this observation is not well understood. Now, Sato and colleagues show that CD4+ T cells that infiltrate atherosclerotic plaques trigger the death of vascular smooth muscle cells (VSMCs), a process proposed to destabilize the plaques.

The plaque-infiltrating T cells expressed high levels of TRAIL, a death receptor normally used by T cells and NK cells to destroy cancerous cells. The expression of this receptor was required for T cells to induce apoptosis in VSMCs (which expressed the TRAIL receptor DR5) both in vitro and in vivo. CD4+ T cells from patients with ACS expressed higher levels of TRAIL when activated and were more adept at triggering VSMC apoptosis in vitro compared with T cells from healthy individuals, possibly explaining why these individuals developed acute disease while others were spared. What causes plaque–residing VSMCs to express DR5 and why T cells infiltrate the plaques in some individuals is not yet known.

These results demonstrate that the TRAIL pathway—previously thought to induce death only in cancer cells—can also trigger apoptosis in nontransformed cells. A recombinant form of TRAIL is currently in clinical trials for the treatment of certain cancers, a therapeutic approach that might need reevaluation in light of its potential negative effects on patients with atherosclerosis. JEM

CCR5 thwarts West Nile virus

A genetic mutation that protects against HIV infection increases the risk of developing clinical West Nile virus (WNV) infection, according to Glass and colleagues on page 35.

The mutation in question is a 32-bp deletion in a gene that encodes the chemokine receptor CCR5, which was identified in 1996 as a cellular coreceptor for HIV. Individuals homozygous for this mutation (CCR5Δ32) are highly resistant to HIV infection, even when repeatedly exposed to the virus. This resistance was the theoretical basis for the development of therapeutic CCR5 inhibitors, several of which are now in clinical trials. CCR5 seemed like an ideal drug target, as people missing the receptor were healthy and no diseases or infections were known to be more frequent or severe in individuals homozygous for CCR5Δ32. Mice appeared to be equally unfazed by the lack of CCR5.

But new evidence suggests that the lack of CCR5 is not completely innocuous. This group recently showed that infection with WNV—a mosquito–borne virus that has spread rapidly across the United States since 1999, often causing fatal encephalitis—was uniformly fatal in mice lacking CCR5. This finding prompted the group to look for the CCR5Δ32 allele in two cohorts of patients in the United States who had symptomatic WNV infections. They now report that 4–5% of the infected individuals were homozygous for the CCR5Δ32 allele, compared with less than 1% of the general population, suggesting that the lack of CCR5 puts people at risk for developing clinical WNV infections. The magnitude of this risk is comparable to the magnitude of protection against HIV that is conferred by this genotype. It remains to be tested whether CCR5-deficient humans, like mice, develop more severe disease because fewer protective immune cells gain access to the brain.

This study identifies not only the first genetic susceptibility factor for WNV infection but also the first association of the CCR5Δ32 allele with susceptibility to an infectious disease. These data might also raise a red flag for the use of CCR5 inhibitors in HIV-infected patients—at least in areas endemic for WNV—as such inhibitors might increase the recipients’ vulnerability to severe WNV infection. JEM