Research News

HAART is hard on the heart

Highly active anti-retroviral therapy (HAART), including protease inhibitors, can improve health and lifespan of HIV-infected patients. However, chronic use of these drugs causes side effects, including abnormal lipid metabolism, insulin resistance and coronary atherosclerosis. Dressman *et al.* now reveal the molecular mechanism for the association between protease inhibitor therapy and atherosclerosis in mice. In the 4 February *JCI* they report that three protease inhibitors—ritonavir, indinavir and amprenavir—directly induce atherosclerosis at doses insufficient to perturb lipid metabolism. Protease inhibitors increased lipid accumulation in macrophages through CD36, a scavenger receptor and fatty acid translocase. CD36 mediates uptake of fatty acids into the heart and uptake of low-density lipoprotein into macrophages. CD36 upregulation in macrophages caused them to become lipid-filled and ultimately produced atherosclerotic lesions. One controversy has been whether atherosclerosis is directly induced by protease inhibitors or occurs as a consequence of impaired lipid metabolism. These results clear up the issue and present CD36 as a potential target for mitigating protease inhibitor-induced atherosclerosis.

p53 invades mitochondria

p53 kills cells by influencing transcription of pro-apoptotic genes that function in the mitochondria. Mihara *et al.* now describe how p53 localizes to the mitochondria to directly influence pro-apoptotic proteins in a transcription-independent fashion. In the 27 January online edition of *Molecular Cell*, the investigators found that in response to DNA damage and stress, some p53 molecules bypass the nucleus and translocate directly to the mitochondrial membrane of tumor cells. p53 binds to and inhibits the anti-apoptotic proteins Bcl2 and Bcl-xL. The formation of these complexes compromises the structural integrity of the outer mitochondrial membrane and causes release of cytotoxic factors located within the organelle. p53 was previously known to initiate apoptosis from the mitochondria, but the new data clarify how. The authors predict that mutations in p53 will eliminate its ability to promote transcription and to complex with pro-apoptotic proteins. The newly identified mechanism could promote rapid apoptosis to augment cell killing by a slower, transcription-dependent method.

Part plant, part parasite

Trypanosomatid parasites, the agents of sleeping sickness and Chagas disease, seem to have picked up a few genes from photosynthesizers, report Hannaert *et al.* in the 4 February issue of *PNAS*. *Trypanosoma brucei* and *T. cruzi* produce enzymes whose closest known relatives can be found in chloroplasts, cyanobacteria and soybeans. Most of these enzymes end up in an organelle peculiar to Trypanosomatids and their kin, an efficient glucose-metabolizing factory called the glycosome. Other enzymes build lipids in a pathway typical of plants and fungi. The authors propose that trypanosomatid ancestors contained a pho-

tosynthetic DNA-containing organelle or endosymbiont, and that the genes encoding plant-like enzymes remain as evolutionary remnants. Indeed, trypanosomatids (one shown here invading a macrophage) are related to *Euglenida*, which contain photosynthetic organelles. The glycosome itself, however, is unlikely to be a remnant as it resembles a more common organelle, the peroxisome; the glucose-metabolizing enzymes have peroxisome-like signal sequences targeting them to the glycosome. The data agree with decades-old observations of plant-like traits and biochemical pathways in trypanosomatids. They also open the door to a new treatment approach—herbicides.

Overachieving angiogenins

The class of proteins called angiogenins stimulates the formation of new blood vessels and may contribute to tumor growth. Hooper *et al.* have discovered another function for angiogenins: killing microbes in the gut and bloodstream. In the March issue of *Nature Immunology*, the investigators report that specialized cells in the mouse intestine, Paneth cells, secrete Ang4, one of four mouse angiogenins. Pathogenic Gram-positive microbes such as *Listeria monocytogenes* were killed by Ang4 in culture. But commensal, Gram-negative bacteria resisted Ang4 destruction and even induced its expression. This inducibility distinguishes Ang4 from other intestinal microbicides secreted by Paneth cells. The authors went on to examine mouse Ang1 and human angiogenin, ANG, both known to circulate during the acute-phase response to infection. Both were able to kill some types of microbes, including *Candida albicans*, in culture. Angiogenins encode RNases, but why some bacteria succumb and others don't remains unknown. Commensal bacteria may have co-opted angiogenin to outcompete nonresident bacteria—a coup that also benefits the host. These multitasking compounds seem to limit infection while also promoting wound healing through angiogenesis.

The persistence of malaria

A new study reveals how the malaria parasite repeatedly invades its victims. Malaria begins with sporozoite infection of the liver, followed by an assault on red blood cells by a different form of the parasite. Previous work suggested that the blood-stage infection represses immune responses. Ocaña-Morgner *et al.* take this concept further. They found that blocking the blood stage of infection in a mouse model results in a robust CD8⁺ T-cell response against liver-specific parasite antigens. In the 20 January *Journal of Experimental Medicine*, they also report that mice infected with irradiated sporozoites, which infect liver but not blood, had a strong immune response. They next implicated dendritic cells in immune impotence. Consistent

with previous studies, the authors found that incubation of dendritic cells with *Plasmodium*-infected erythrocytes inhibits dendritic cell maturation and also T-cell activation *in vitro*. The investigators then infused dendritic cells pre-incubated with *Plasmodium*-tainted sporozoites into mice infected with irradiated sporozoites. These infusions severely dampened the T-cell response and also made mice highly susceptible to re-infection. The authors concluded that the blood stage of infection severely affects dendritic cells, which in turn block immune responses against the liver stage of infection. This process paves the way for recurring bouts of illness.

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