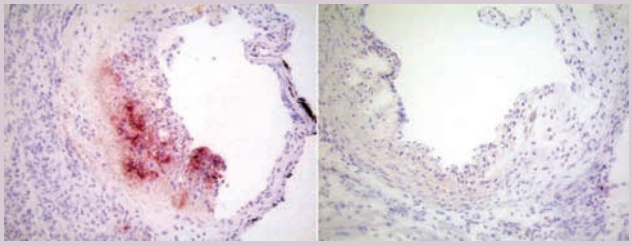
Research Roundup

How cholesterol clogs the arteries

A high-cholesterol diet can be the fast track to a heart attack. But scientists are only now discovering that one of cholesterol's most damaging effects might stem from its ability to make blood cells self-destruct. The findings appear in a pair of recent studies directed by Ira Tabas (Columbia University, New York, NY).

Cholesterol is abundant in atherosclerotic lesions, which become most dangerous when they break apart and plug an arterial passage. Unstable lesions are associated with lots of cellular debris, mostly from dead macrophages. Tabas, along with Bo Feng and colleagues, shows in one article that macrophages die in lesions because cholesterol elicits the unfolded protein response (UPR) in the ER.

Macrophages that were unable to deal with the excess cholesterol they ingested had depleted ER calcium stores and activated the UPR, which can cause cell death. The UPR and cell death were prevented if cholesterol trafficking to the ER was blocked. Tabas speculates that cholesterol might deplete calcium stores by stiffening the ER membrane (which normally contains very little cholesterol), thus impairing integral proteins that pump in calcium and presumably disabling calcium-dependent chaperones.



Tabas/NAS

Lesions have fewer dead macrophages if cholesterol does not get to the ER (right).

The group used low doses of a drug to prevent cholesterol trafficking to the ER in cell cultures, but they also found an in vivo mutation that worked just as well—heterozygous mutations in the late endosomal protein NPC1. In a second article, Feng, Dajun Zhang, Tabas, and colleagues examined lesions in these heterozygous mice. Compared with homozygous NPC1 mice, the npc1 heterozygotes had lesions with less necrosis and fewer apoptotic macrophages.

Long-term studies are still needed to establish whether lesions in NPC1 heterozygous mice are less apt to rupture. But according to Tabas, "our results have already spawned a clinical study to determine if [NPC heterozygous humans] are protected against acute cardiovascular events." If the results are positive, drugs to block cholesterol transport to the ER may follow. ■

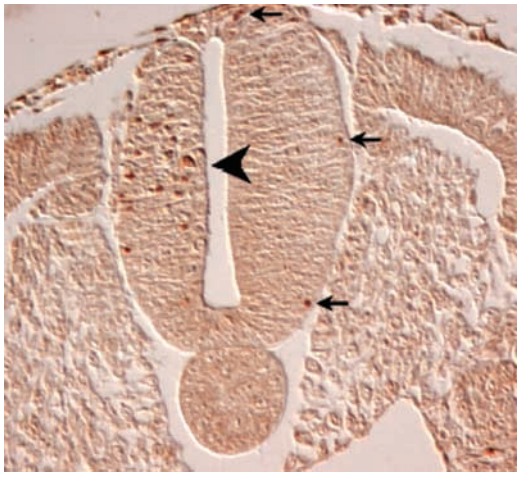
References: Feng, B., et al. 2003. *Proc. Natl. Acad. Sci. USA.*. 10.1073/pnas.1732494100.
Feng, B., et al. 2003. *Nat. Cell Biol.* 10.1038/ncb1035.

Lonely receptors kill cells

Without its partner, a lonely Sonic hedgehog (Shh) receptor chooses death, according to a report from Chantal Thibert, Patrick Mehlen (University of Lyon, Villeurbanne, France), and colleagues. This isolation-induced apoptosis prunes the developing neural tube.

Shh gradients along the ventral–dorsal axis of the neural tube direct neuronal differentiation via two transmembrane proteins: Patched (Ptc) and Smoothened (Smo). Removal of Shh during development is known to cause massive apoptosis in the neural tube, but this outcome was thought to be a byproduct of the failure of cells to differentiate. Mehlen's group now shows, however, that death is actively switched on by unbound Ptc.

Ptc expression in cultured cells induced apoptosis unless Shh was added. Similar results were seen with overexpression of Ptc in the neural tube. "Wherever Patched is expressed, those cells becomes dependent on the presence of the ligand," says Mehlen. This action probably shapes the neural chord by removing cells that fall outside the reach of Shh.



Mehlen/AAAS

Unbound Ptc in the neural tube (left) leads to cell death.

Ptc seems to be activated for apoptosis by caspase cleavage of its COOH-terminal tail, with Shh somehow preventing this cleavage, perhaps via downstream effectors of Smo. A caspase-cleaved version of Ptc initiates apoptosis even in the presence of Shh.

The ligandless action of Ptc is similar to that of UNC5H and DCC, which were dubbed dependence receptors because they induce cell death in vitro unless their ligands are present. The ability to induce apoptosis may make all three putative tumor suppressors "because they control proliferation of cells that are out of their normal context," says Mehlen. ■

Reference: Thibert, C., et al. 2003. *Science.* 301:843–846.