Gene Therapy for CPVT (p 663)

Denegri et al cure arrhythmia in model mice by viral gene transfer.
Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited heart arrhythmia that predisposes people to cardiac arrest and sudden death. It is caused by mutations in 1 of 2 calcium regulatory proteins: RYR2 or CASQ2. The latter protein is found in the sarcoplasmic reticulum of cardiac myocytes and binds calcium ions, which restricts calcium release to the cytoplasm and prevents premature muscle contraction. Mice that either lack or have mutations in CASQ2 are good models of human CPVT. Therefore, Denegri et al investigated whether they could treat such mice with gene therapy. They injected newborn CPVT model mice with a heart-homing viral vector carrying the CASQ2 gene and after 20 weeks found that correct expression and cell localization of CASQ2 were restored. Cellular electrophysiology was also comparable to that of wild-type cells. Importantly, the treated mice displayed normal heart rate and a significant reduction in ventricular tachycardia after epinephrine stimulation. Although stem cells have been identified in the adult mammalian heart, it is unclear whether they are native to the heart or are continuously supplied from distant organs. It is also unclear whether heart muscle cells arise from such cardiac stem cells or from a proliferating pool of immature myocytes. Ferreira-Martins et al have now shown that at least in the prenatal and newborn heart, stem cells are the building blocks that give rise to both muscle and vascular cell types. The team found that cells that expressed the stem cell marker c-kit were abundant in the heart from early embryogenesis to birth. These cells could divide, self-renew, and differentiate into myocytes, endothelial cells, and smooth muscle and thus fulfilled the criteria of tissue-specific stem cells. The team also found that calcium levels inside these c-kit–positive cells oscillated, that these oscillations were controlled by a cell surface receptor called IP3, and that IP3 activation drove cell division. The fact that these c-kit–positive cells are also present in the adult heart suggests that harnessing their potential might be a useful approach for restorative therapies.

Cardiac Stem Cells and the Developing Heart (p 701)

The developing heart is built from cardiac-specific stem cells, say Ferreira-Martins et al.

NO Inhalation and Brain Damage (p 727)

Nitric oxide might be the ideal treatment for preventing brain damage in stroke, say Terpolilli et al.

When a person has a stroke, there is a short window of opportunity—a few hours—in which eliminating a vessel blockage and restoring blood flow to ischemic tissue can prevent brain damage. To achieve this, the thrombolytic drug tissue plasminogen activator (tPA) is given. In cases in which stroke is caused by cerebral bleeding (hemorrhagic stroke), however, tPA treatment can be fatal. Because brain imaging is required to differentiate hemorrhagic from ischemic stroke, the crucial window of opportunity is often missed. Terpolilli et al now report that in animal models of stroke, inhalation of nitric oxide (NO) dilated blood vessels in ischemic brain tissue but had no effect on healthy tissue. Such targeted vasodilation in humans would remove the risk of exacerbating hemorrhagic stroke, indicating that NO could be given immediately. The authors propose that NO achieved tissue specificity because it was released from transporter proteins only when blood oxygen was low. NO-treated model mice and sheep showed improved blood flow in ischemic brain tissue and, encouragingly, better poststroke recovery. NO inhalation might thus be a lifesaving tool for stroke patients.
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