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Molecular 'stress relief valves' in the heart

Some folks with narrowed coronary arteries get along just fine, while others develop congestive heart failure and die. New research in mice suggests that a molecular component in the heart could explain the stark differences in human physiological responses to constricted heart vessels.

Andre Terzic of the Mayo Clinic (Rochester, MN) and his collaborators simulated the stress of narrowing arteries by mechanically constricting the aortas of normal and genetically altered mice, forcing their hearts to cope with the stress of reduced blood flow (*J. Physiol. Lond.*, published online 12 October 2006; doi: 10.1113/jphysiol.2006.119511). The genetically manipulated mice were missing a gene for an essential subunit of the ATP-sensitive potassium channels (K_{ATP}) found in the heart. These channels are located in cardiac muscle cell membranes and control the import and export of potassium, an ion that helps regulate the balance of cellular electrical charge.

Half of the K_{ATP}-deficient mice in Terzic's study died by 48 hours after the aortic constraints were imposed, while the survivors suffered from cardiac malformation. The stress, however, did not affect the normal mice—strong evidence that K_{ATP} channels protect against congestive heart failure. An understanding of how the K_{ATP} channels help the heart to cope with stress will hopefully aid clinicians searching for preemptive heart failure treatments.

Light at the end of the retina

A new transplantation technique for retinal cells in blind mice markedly improves their sight, a milestone that could turn into eye-opening treatments for human retinal disease.

Many people go blind because of damaged photoreceptors—the rods and cones in the eye that translate light into neural signals. In mammals, previous transplant work has not been able to reconnect transplanted photoreceptors with the nervous system. Now, a group led by Robin R. Ali at the University College London (UK) has shown that past failures may be because transplanted cells of the wrong developmental stage were used. In a series of experiments, Ali's team transplanted retinal cells from embryonic and newborn mice of various ages into mice blinded by a genetic lack of rhodopsin (a rod protein). To their surprise, only the cells from 3–5-day-old donor mice were capable of bestowing the power of sight on the erstwhile blind mice, allowing them to respond to low levels of light (*Nature*, 9 November 2006).

The 3–5-day-old mouse retinal cells, however, correspond to cells of a second trimester human embryo—clearly not suitable for clinical use. Other research, however, has shown that cells of the same developmental status can be derived from human embryonic stem cells, a possibility that may lead to sight for some of the blind.

Putting the brakes on dysentery

Shigella, a bacterial genus that causes severe dysentery and kills more than a million people every year, relies upon a newly discovered protease for its pathogenic effects. This protein-degrading enzyme could be a new drug target.

Shigella bacteria are known to burrow through their host cell's cytoplasm, the complex matrix of proteins that forms the internal cellular environment. As part of the burrowing process, *Shigella* hijack one component of the cytoplasm, a protein called actin, and use it to form a long tail that propels them through the cell. With so many other cellular proteins, however, *Shigella* could not get far without another mechanism to clear a path through the jumbled 'cellular jungle'.

In the 10 November 2006 issue of *Science,* Chihiro Sasakawa and his colleagues at the University of Tokyo in Japan report that they have identified *Shigella*'s 'molecular machete,' a protease dubbed VirA that cuts through microtubules, a major cytoplasm component, clearing an intracellular path for these bugs. What's striking is that the researchers also show that mutant *Shigella* lacking functional VirA are no longer pathogenic in mice. Researchers hope to target VirA with a new antibiotic to replace the increasingly ineffective compounds currently used to fight *Shigella* infections.