**EHD-Targeting Proteins in Heart (p 84)**

*Gudmundsson et al* have identified four new members of the membrane maintenance team of heart cells.

The excitability of heart cells depends on the tight regulation of their plasma membrane-associated proteins, such as ion channels, transporters, and receptors. Although much is known about the function of these frontline players, much less is understood about how they get to and from the membrane. Gudmundsson et al looked for members of the behind-the-scenes protein trafficking troops. They knew ankyrin B was such a protein and that it was present in heart cells, so they looked for ankyrin B interaction partners. They found EHD3—a protein known to be involved in trafficking in other cell types. One of ankyrin B’s cargoes is the conduction-controlling Na+/Ca2+ exchanger. The team found that EHD3 enhanced membrane delivery of the exchanger and accordingly increased the heart cells’ conduction. EHD3 has a number of close relatives—EHD1, 2, and 4—and these also bound ankyrin B in heart cells. All four proteins were upregulated in the absence of ankyrin B, and the authors suggest this may reflect some form of compensatory mechanism aimed at maintaining the delivery of membrane proteins.

**Therapeutic Targeting of Mitochondrial Superoxide (p 106)**

*Dikalova et al* unveil a potential new treatment for high blood pressure—a mitochondrial-targeted antioxidant.

Reactive oxygen species (ROS) are known perpetrators of pathology in hypertension and many other human diseases, yet clinical trials with antioxidants have proven largely ineffective. An important natural cellular antioxidant is superoxide dismutase, and mammals have three versions of this enzyme—one extracellular, one cytoplasmic, and one mitochondrial. Mice that lack just one copy of their mitochondrial superoxide dismutase (SOD2) are prone to hypertension. Furthermore, the hypertension-inducing hormone, angiotensin II, increases mitochondrial ROS. Dikalova et al, therefore, reckoned that targeting an antioxidant drug directly to the mitochondrial ROS production site might halt hypertension. mitoTEMPO is one such drug. The team showed that mitoTEMPO reduced mitochondrial production, and cellular levels, of ROS in cultured aortic endothelial cells. The drug also reduced blood pressure and improved vascular relaxation in mice that had been given angiotensin II or a high-salt diet. Importantly, mitoTEMPO did not lower blood pressure in normal mice—an undesirable effect of many existing hypertension treatments.

**(P)RR/ATP6AP2 Is Essential for V-ATPase Assembly (p 30)**

The blood pressure regulator, (pro)renin receptor, has a secret double life that *Kinouchi et al* have now uncovered.

When blood pressure drops, the kidneys secrete the hormone renin. This sets up a chain of events that leads to blood vessel constriction and water and sodium reabsorption into the blood, both of which increase blood pressure. The (pro)renin receptor is a crucial activator of this pathway, and its function has been well studied. It was reported recently, however, that a truncated version of the receptor associates with V-ATPase—a membrane-associated proton pump that controls acidification of intracellular vacuoles, such as lysosomes and endosomes. The relationship between (pro)renin receptor and V-ATPase in vivo was unknown, so Kinouchi et al set out to investigate just that. They showed that mice that specifically lacked (pro)renin receptor in their hearts suffered heart failure after only a few weeks of life. The cells of the mutant hearts had large vesicles containing partially or completely undigested cell components, suggesting acidification of these vesicles was impaired. Indeed, further studies in cell culture suggested that (pro)renin receptor was needed for assembling the V-ATPase subunits into a functional pump.
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