PHLPP-1 Negatively Regulates Akt in the Heart (p 476)

Inhibiting PHLPP-1 might keep injured heart cells alive after a heart attack, say Miyamoto et al.

The death of heart cells after ischemia and reperfusion leads to scarring and reduced contractile function. Minimizing the extent of such cell death is, thus, a prime objective for cardiologists. A protein kinase and antiapoptosis factor called Akt is well known for its cardioprotective ability. Thus, figuring out how to boost Akt activity in injured heart tissue might help cardiologists in preserving viable myocardium and preventing scarring. Switching off Akt inhibitors might be one approach. A number of protein phosphatases are known to inhibit Akt but they are not specific to Akt, raising concern that unrelated proteins and pathways might also be affected. Recently, a protein phosphatase called PHLPP-1, which selectively dephosphorylates Akt, has been identified. Whether PHLPP-1 exists or works in heart cells, however, is unknown. Miyamoto et al have now reported that PHLPP-1 was, indeed, expressed in mouse heart cells and that genetically deleting PHLPP-1 increased Akt activation in both heart cells and the ex vivo mouse heart. Since Akt is an antiapoptotic factor, boosting its activity in the long term might pose a cancer risk. The next step for researchers, therefore, is to figure out how PHLPP-1 might be inhibited both transiently and locally at the site of ischemic injury.

Arrhythmogenic Purkinje Cells (p 512)

Long-suspected to be behind ventricular arrhythmias, Purkinje cells have finally been nailed as the culprits, thanks to Kang et al.

The first suggestion that Purkinje cells of the cardiac conduction system might be involved in cardiac arrhythmias came 40 years ago. Although many studies have provided data that support this hypothesis, formal proof has been lacking. To address the issue, Kang et al observed the behavior of Purkinje cells and ventricular myocytes—another possible culprit—to see which of the two was more electrically erratic. Spontaneous calcium sparks—unprovoked releases of calcium from intracellular stores—were significantly more common in Purkinje cells, the team showed. Purkinje cells from a mouse model of catecholaminergic polymorphic ventricular tachycardia (CPVT)—a life-threatening arrhythmia—were particularly erratic, with up to 62% of cells showing spontaneous sparks. This figure rose to 90% of cells upon catecholaminergic stimulation. Such stimulation is a trigger for tachycardia in CPVT sufferers. The authors suggest that antiarrhythmia drugs, focused to target Purkinje cells, may be beneficial for CPVT and other arrhythmia disorders.

Elastin and Aortic Valve Disease (p 549)

Elastin-lacking mice are excellent models for latent aortic valve disease, claim Hinton et al.

Aortic valve disease, including aortic stenosis (insufficient valve opening) and aortic regurgitation (backward blood flow), is a common cardiac condition, with approximately 100,000 valve replacements being performed in the United States each year. Little is known about the pathology, although abnormalities in extracellular matrix (ECM) proteins are often associated with the disease. Hinton et al focused on one of the major ECM proteins—elastin. Mice with only one functional elastin allele, and thus expressing only half of the normal level of the protein, developed progressive aortic valve disease, showed the team. Valve structural abnormalities, such as thinning of the cusps, got progressively worse, as did aortic stiffening. The team also looked at genes, pathways, and cells affected by the absence of elastin. Among other things, they found aberrant activation and proliferation of valve interstitial cells and maladaptive ECM remodeling. Malformations were particularly apparent in the annulus—the ring of connective tissue that anchors the valve to the artery wall—pointing to this structure for future clinical focus.