Cardiomyocyte cGMP-FRET Mouse (p 1235)

Götz et al visualize cGMP dynamics in living cardiomyocytes.

In the heart, cyclic guanosine monophosphate (cGMP) regulates contractility as well as hypertrophy. Indeed, elevated cardiac levels of cGMP in mice have been shown to prevent hypertrophic remodeling and improve heart function. To learn more about this cardioprotective molecule, Götz and colleagues have developed a system that allows real-time visualization of cGMP in living cells. They have genetically engineered mice to express a recently developed, highly sensitive cGMP biosensor called cGES-DE5 specifically in the heart. This biosensor emits green fluorescence, but binding to cGMP alters its conformation and switches its fluorescence emission from green to red—a process known as Förster resonance energy transfer (FRET). Using cardiomyocytes isolated from the mice, the team showed that a vasodilator called C-type natriuretic peptide was a strong stimulator of cGMP synthesis while the enzyme phosphodiesterase 3 (PDE3) was a potent degrader of cGMP. In a mouse model of hypertrophy, another phosphodiesterase, PDE5, also contributed to cGMP degradation. Thus, by revealing the real-time dynamics of cGMP this new transgenic system could allow for a more rapid evaluation of interventions and pharmacological agents that affect cGMP levels in the heart.

mTORC2 Signaling and Cardioprotection (p 1268)

Yano et al discover a cardioprotective positive feedback mechanism involving mTORC2 and ribosomal protein S6.

After a myocardial infarction, reperfusion therapy is essential for saving heart tissue and, as a result, the patient’s life. But often reperfusion alone is not enough, and additional cardioprotective treatment strategies are needed to minimize the loss of viable tissue. Researchers have therefore been looking at the protein kinase Akt, which is known to protect heart cells from death. Full activation of Akt requires phosphorylation by a protein called mTORC2, but details of how mTORC2 and Akt are regulated remain unclear. Yano and colleagues show that cardiac preconditioning—a process that increases the resistance of cardiac tissue to ischemic injury—leads to mTORC2-induced phosphorylation of Akt. Furthermore, inhibiting mTORC2 abolished the cardioprotective effects of preconditioning. The team also discovered that the ribosomal protein Rps6 is a downstream target of Akt, and yet also activates mTORC2-induced Akt phosphorylation. Thus Rps6 both sustains and amplifies the cardioprotective signal. Targeting the mTORC2/Akt/Rps6 positive feedback loop may therefore be an effective complement to reperfusion therapy, suggest the authors.

Analysis from the POSEIDON Trial (p 1292)

Injection site matters when it comes to stem cell treatments for heart failure, say Sunicon et al.

Injection of mesenchymal stem cells (MSCs) into the heart can reduce scar size and improve heart function according to the results of a recent clinical trial, but how far from the injection site the beneficial effects spread is unclear. In the trial—called POSEIDON (Percutaneous Stem Cell In- jection Delivery Effects on Neomyogen- esis)—patients with myocardial infarction were injected with stem cells at 10 sites around the infarct border zone. Now, using a high-tech imaging approach, Sunicon and colleagues have studied the patients’ hearts more closely and examined whether injected tissue responded differently from nearby non-injected tissue. They found that there was significant scar reduction at tissue segments that received injections. Non-injected sites also exhibited scar reduction, but to a far lesser degree. In terms of muscle function, however, while injected sites showed significant increases in contractility, non-injected sites displayed no improvements at all. Interestingly, the biggest improvements in contractility were seen at those injected tissue segments that were initially the most damaged by infarction. Based on these results, the authors suggest that tailoring injection strategies to an individual patient’s infarct may yield better clinical outcomes.