Give stem cells more CCR1, and give cell replacement therapy a better chance, say Huang et al.

CCR1 is the cell surface receptor for chemokine CCL7, which along with other chemokines, gets ramped up in the heart after myocardial infarction. Chemokines are a known trigger for cell migration, suggesting they might be important in the heart’s healing process. Adult mesenchymal stem cells (MSCs), which are a favorite candidate for cell replacement therapies, have very low levels of CCR1. Huang et al wondered whether this might be the reason that MSCs, when transferred into damaged hearts, neither engraft very well nor survive in big numbers. The team genetically engineered mouse MSCs to express more CCR1. These engineered cells migrated more efficiently and resisted cell death in vitro and, more importantly, engrafted and survived in high numbers in infarcted mouse hearts. The cells also reduced the infarct size, increased capillary density, restored heart function, and prevented adverse heart remodeling. Finding a way to raise CCR1 levels in MSCs may be a new strategy for improving the outcome of heart cell replacement therapies.

If the heart attack does not kill you, the subsequent tissue damage might. Now, Naito et al have found a way to reduce that tissue damage.

The destruction of ischemic heart tissue after a heart attack can lead to adverse remodeling and heart failure. Destruction occurs largely by cellular suicide (apoptosis), and the pro-apoptosis factor p53 is thought to be involved in this process. The levels of p53 rise in the heart after an attack, and deletion of p53 has been shown to improve postattack heart function. Naito and colleagues looked for an endogenous factor that antagonizes p53 function, in the hope that they might ultimately co-opt its mechanism to treat heart attack victims. After screening a heart-specific expression library, they found a protein called CHIP. CHIP reduced p53 levels by tagging it for destruction. Following hypoxia, however, CHIP levels dropped, allowing p53 to accumulate. By overexpressing CHIP in mouse hearts, the team showed that preventing p53 accumulation and apoptosis of heart cells decreased adverse heart remodeling. The drug 17-AAG, which degrades CHIP targets, also reduced p53 levels. The authors caution, however, that 17-AAG has a nonspecific effect, and they recommend instead a more specific CHIP/p53-targeted therapy.

Guo et al describe the molecular dynamics of some key players in heart muscle excitation-contraction coupling.

In muscle cells, excitation-contraction coupling is the process whereby action potential across the cell membrane prompts the release of calcium into the cytoplasm and subsequent activation of calcium-sensitive contractile proteins. Calcium release is controlled by ryanodine receptors—channel proteins in the membrane of the sarcoplasmic reticulum (the calcium store). Dysfunctional ryanodine receptors are thought to cause arrhythmias and heart failure. Guo et al have looked at the dynamics of two proteins, FKBP12.6 and FKBP12, which are known to bind ryanodine receptors, but whose exact function remains elusive. The team found that practically all of the FKBP12.6 in heart muscle cells bind to ryanodine receptors. It binds tightly, much more so than FKBP12, and can directly affect the receptor’s function—reducing the release of calcium. FKBP12 has no such effect. Intriguingly, however, whereas FKBP12 is abundant in the cell, FKBP12.6 is scarce—practically all of it is used up, binding to just 10% to 20% of the receptors. FKBP12.6 is thus unlikely to be critical for guarding against ryanodine receptor disfunction and arrythmia.
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