RyRS2808 Is Irrelevant to Heart Failure (p 831)

Zhang et al find no role for calcium channel phosphorylation in heart failure, but a controversy continues.

Progressive damage after myocardial infarction can ultimately lead to arrhythmias, heart failure, and sudden death. Although it is known that dysregulation of calcium in cardiomyocytes exacerbates the pathophysiology of heart failure, the underlying cause of this dysregulation is not yet entirely clear. Some studies suggest that hyperphosphorylation of RyR2, a calcium channel found in the sarcoplasmic reticulum of heart cells, leads to aberrant calcium release. Studies also suggest that mice carrying a version of RyR2 that could not be phosphorylated are protected against heart failure. Other reports, however, found no such causative link. Here, Zhang et al provide further evidence that no such link exists. They studied mice carrying the nonphosphorylatable RyR2 and found they were not protected from heart failure after myocardial infarction. The mice had similarly sized infarct regions and decreased pump activity, similar to that of wild-type mice. Molecular changes and electrophysiological properties of cardiac myocytes isolated from these mice also were similar. The authors cannot explain why they found such strikingly different results, but they suggest that the genetic background of the mice used in the different experiments might be responsible.

Role of Type VI Collagen in Post-MI Remodeling (p 851)

Hearts recover better after myocardial infarction when collagen VI is absent, say Luther et al.

Type I and type III collagens are the major fibrillar proteins in the cardiac extracellular matrix. As such, these have received the lion’s share of attention, particularly in studies of postmyocardial infarction wound healing. Collagen VI, which is nonfibrillar, also might be important, however, because it displays increased deposition after infarction. Luther et al studied mice that lacked a functional collagen VI gene and found that recovery from myocardial infarction in these mice was better than that in their wild-type counterparts. The mutant mice had a reduced infarct size, a better-preserved ejection fraction, and reduced left ventricular chamber dilation. Interestingly, these collagen VI-deficient mice are known to have development of severe skeletal myopathy, so it was a surprise that their hearts fared so well. The process of wound healing appeared to begin earlier and resolve faster in the mutant mice, which could underlie their improved outcome. Although working out how collagen VI contributes to normal wound healing is important, the current results suggest that this protein could be a novel therapeutic target for improving recovery after myocardial infarction.

CD28null T Cells in ACS (p 857)

Dumitriu et al discover how an acute coronary syndrome (ACS)-specific T-cell subset is activated and how to stop it.

A principle feature of ACS is unstable angina caused by unstable atherosclerotic plaques. Unlike stable angina, ACS is associated with the expansion of a particular subset of T cells. These ACS-specific cells do not express CD28, a costimulatory molecule traditionally found on T cells, and yet produce proinflammatory cytokines and cytolytic proteins indicative of activated cells. Because T cells require costimulatory molecules to become activated, Dumitriu et al reasoned that the ACS-specific cells must express an alternative costimulator. In fact, the cells expressed two, OX40 and 4-1BB. The OX40/4-1BB–expressing T cells were abundant in the blood of patients with ACS and also in atherosclerotic plaques. Furthermore, plaques contained abundant ligands for OX40 and 4-1BB, and are thus likely to be sites of particularly strong T-cell activation. Importantly, the team showed that antibodies against OX40 and 4-1BB prevented the T cells from producing inflammatory and cytolytic proteins in vitro, which suggests that preventing T-cell activation by blocking these costimulatory molecules might be a clinically useful anti-ACS strategy.
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