PKCα C-Terminal Fragment and Cardiomyopathy (p 903)

A suspected degrader of protein kinase C, in fact, liberates the active subunit of the kinase, which wreaks havoc in ischemic hearts, report Kang et al.

Activation of protein kinase C (PKC) is calcium dependent and normally occurs in response to receptor signaling events. Calcium also activates a protease called calpain 1 that cleaves PKC. Thus, it was thought that calcium both induced PKC signaling and then switched it off by calpain-mediated degradation. According to a new study by Kang et al, however, calpain is not the off-switch. Calpain cleaves PKC in two, releasing the catalytically active C-terminal from the regulatory N-terminal. Far from degrading the enzyme, this cleavage unleashed the C-terminal’s unfettered activity, say the authors. They made their discovery by looking in ischemic heart tissue of mice that overexpressed calpain. Ischemia prompts a dramatic rise in intracellular calcium levels and, thus, boosts the activities of PKC and calpain. Overexpression of calpain under ischemic conditions led to increased PKC cleavage, as well as to increased myocardial injury. The increased abundance of the active C-terminal caused hyperphosphorylation of normal PKC targets, as well as phosphorylation of many atypical proteins, which might be responsible for the increased ischemic damage. Drugs designed to inhibit PKC activity might, therefore, work best if aimed at the C-terminal, says the team.

MSCs Stimulate CSCs After MI (p 913)

Transferred stem cells can’t take all the credit for repairing damaged tissues—they recruit host cells to do most of the work, report Hatzistergos et al.

In recent years, there has been much excitement about the potential of transplanted stem cells to mend heart injuries. Bone marrow-derived mesenchymal stem cells (MSCs) have been particularly favored thanks to their capacity for engrafting into, and restoring contractility of, damaged heart tissue. Intriguingly, the ability of MSCs to fix heart injury seems to greatly surpass their ability to differentiate into heart muscle cells. Thus, it has been unclear exactly how these cells repair the infarcted heart. Hatzistergos et al postulated that the MSCs might be recruiting help from within the host. To test this hypothesis, the team produced heart attacks in female pigs and, 3 days later, injected the damaged hearts with MSCs. Sure enough, the MSCs not only engrafted into the hearts and differentiated into muscle cells, but they also stimulated host (endogenous) heart stem cells to proliferate and differentiate. In fact, the MSCs themselves accounted for only about 8% of the new heart cells. The engrafted MSCs made cell-to-cell contacts with the host stem cells, which appears to be important for the repair process, say the authors. Promoting this host-cell interaction, therefore, might be one strategy to optimize stem cell therapies.

S1P Regulates Myogenic Tone in Heart Failure (p 923)

Hoefer et al have unraveled a molecular pathway that maintains vessel constriction in a mouse model of heart failure.

Heart failure is defined as the inability of the heart to supply adequate blood to the body’s organs and tissues. When a heart is failing, arterial blood pressure increases to ensure sufficient blood perfusion of the organs. However, this increase in arterial pressure could weaken the heart further, as the heart has to pump harder to get blood into the pressurized aorta. Putting a stop to this positive feedback loop of pathology is, thus, a major goal of heart failure therapy. One way that arterial pressure is increased is through vessel constriction. Hoefer et al found that sphingosine-1-phosphate (S1P)—a blood-borne signaling lipid—is a major activator of chronic vessel constriction in a mouse model of heart failure. The team has also identified p38 MAPK as a downstream mediator of the S1P signal, the ultimate target being myosin, a protein that drives the vascular smooth muscle cell contraction. Inhibition of the S1P receptor, or p38 MAPK, prevented vessel constriction in the model mice. Thus, both S1P and p38 MAPK may be two possible drug targets for breaking the vicious cycle of disease.
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