MicroRNA-Mediated Reprogramming (p 1465)

Jayawardena et al report the direct conversion of fibroblasts to cardiomyocytes by transfection with microRNAs (miRNAs).

If cardiologists could transform the scar tissue formed after myocardial infarction into functional muscle, patients might regain better heart function and avoid heart failure. To that end, researchers have shown that mouse fibroblasts can be directly converted into cardiomyocytes by transfection with three particular transcription factors. However, it had not been shown whether such conversion could take place in vivo. Jayawardena et al have now achieved just that, but they did not use the three transcription factors. Their approach was to use miRNAs, on the basis that these small noncoding RNAs can downregulate the expression of multiple genes at once, and that a number of specific miRNAs have been found to control cardiomyocyte development. In summary, the miRNAs might be more effective. The team transfected individual candidate miRNAs, and combinations thereof, into mouse cardiac fibroblasts. They came up with a combination of four miRNAs that could convert fibroblasts to cardiomyocytes in vitro and in the hearts of mice after myocardial infarction. The researchers have yet to show whether such in vivo conversion confers functional improvement; nevertheless, they provide proof of principle that in vivo transformation is a possibility.

RyR2 Phosphorylation in HF Progression (p 1474)

Blocking phosphorylation of RyR2 protects against one sort of heart failure, but not another, say Respress et al.

Heart failure is a major killer in the United States and across the globe, and it is known to be associated with an increase in the activity of a kinase called CaMKII. Inhibiting CaMKII can prevent or delay heart failure in animal models of the disease. CaMKII phosphorylates a number of targets, including the calcium channel RyR2, which regulates release of calcium from the sarcoplasmic reticulum in heart cells. Because inappropriate leaks of sarcoplasmic reticulum calcium are a feature of heart failure, the team investigated whether phosphorylation of RyR2 by CaMKII might be abnormal in the disease. Interestingly, they found that only nonischemic heart failure patients had elevated CaMKII phosphorylation of RyR2. In ischemic heart failure, this phosphorylation was normal. Similarly, preventing this particular phosphorylation in mice protected the animals against induced nonischemic, but not ischemic, heart failure. Although it is not yet clear why this CaMKII phosphorylation of RyR2 is triggered only in nonischemic heart failure, the results suggest that patients with this form of the disease could benefit from RyR2 phosphorylation–inhibiting treatments.

Mitochondrial Fission in PAH (p 1484)

Stopping mitochondria from splitting curbs pathological cell proliferation in pulmonary arterial hypertension (PAH), report Marsboom et al.

PAH is a condition in which the pulmonary arteries become constricted, obstructed, and inflamed, causing increased vascular pressure and, ultimately, right ventricle hypertrophy and heart failure. Although the fundamental cause of the condition is still unknown, part of the problem is that the smooth muscle cells of the arteries begin to proliferate out of control. This hyperproliferation is associated with activation of the transcription factor HIF-1 and with fission of mitochondria. Now, Marsboom et al have figured out how these parts of the puzzle fit together. They show that stimulation of HIF-1 leads to the activation of a protein called dynamin-related protein 1 (DRP-1), a known promoter of mitochondrial fission. And this fission, in turn, drives cell-cycle progression. Importantly, inhibiting DRP-1 with a small molecule called Mdivi-1 prevented both mitochondrial fission and proliferation in human pulmonary artery smooth muscle cells. Mdivi-1 also prevented hyperproliferation in rodent models of PAH and significantly improved symptoms. Inhibiting mitochondrial fission with Mdivi-1 or other factors could be an effective treatment for PAH and potentially other proliferative disorders, say the authors.