Regulation of cardiomyocyte polyploidy and multinucleation by Cyclin G1 (p 1498)

Liu et al have discovered a potent promoter of polyploidy in rat hearts. Polyploidy—multiple copies of the genome in one cell—is normal in cardiomyocytes but can also be ramped up in pathological situations, such as cardiac hypertrophy or in regenerative situations, such as after heart injury. The ability to boost or suppress polyploidy might thus have a number of heart health implications.

Cardiomyocytes in the mammalian embryo divide just like regular cells, but shortly after birth, they stop dividing and continue replicating their DNA, creating cells with multiple nuclei. This multinucleation period lasts for about 3 weeks in rats and about 10 years in humans. Liu et al discovered that in the postnatal multinucleation phase in rats, levels of cyclin G1 protein shot up, whereas levels of other cell cycle regulators dropped. Cyclin G1, the team showed, boosted polyploidy in newborn rat cardiomyocytes, whereas the lack of cyclin G1 prevented polyploidy in newborn mice. Without cyclin G1, these mice were also less capable of increasing the number of their nuclei in response to cardiac overload and hypertrophy.

Defective DNA Replication Impairs Mitochondrial Biogenesis in Human Failing Hearts (p 1541)

Failing human hearts have failing mitochondria in their cells. Karamanlidis et al now show that defective mitochondrial DNA (mtDNA) replication is to blame.

The reduced replication, say the authors, was caused by a combination of low levels of replication fork factors and increased oxidative damage to the mtDNA. The problem lay not with replication initiation, but with DNA strand extension, consistent with the need to fix oxidative damage during the process. Preventing the oxidative damage might, therefore, provide a therapeutic avenue. A recent study showed that mitochondrial-targeted antioxidants could protect against both mtDNA depletion and left ventricular remodeling after myocardial infarction in mice. One of the most important aspects of this new report is that it usurps a previous theory for mitochondrial dysfunction in heart failure. Evidence from animal studies had suggested that low levels of the transcription coactivator PGC-1 cause reduced mitochondrial biogenesis. Although mitochondrial biogenesis was certainly reduced in the failing human hearts, mRNA levels of PGC-1 (a regulator of energy metabolism genes) were normal. Protein levels of PGC-1α were, in fact, increased. PGC-1 partner protein, ERRα (a known activator of many mitochondrial biogenesis genes) was significantly reduced, however. The authors, thus, flag ERRα as another possible target for therapy.

Manipulation of Death Pathways in Desmin Related Cardiomyopathy (p 1524)

The good news is that antiapoptosis treatment extends life expectancy in a mouse model of desmin-related myopathy (DRM). The bad news is it only does so minutely, say Maloyan et al.

DRM is a very rare but severe disease in which patients display progressive muscle atrophy and weakness, resulting in eventual death from heart, respiratory failure, or both. Disease progression is associated with the accumulation of aggregates of desmin and other proteins, and also with mitochondrial dysfunction and apoptosis. Although apoptosis can directly cause heart failure, it was not known to what extent apoptosis contributes to heart failure in DRM. Maloyan et al treated a cardiac-specific mouse model of DRM with an apoptosis blocker. Though this extended the life of the mice by a month or two, they still ultimately died of heart failure. Investigations revealed that in the absence of apoptosis, death still found a way, and instead, necrosis pathways were activated. The authors caution against therapies that target only one of the many cell death pathways. Those that target multiple pathways or failing mitochondria, from where many cell death pathways originate, might be a better bet.