Antioxidant therapies may not always be beneficial, say Song et al. Mitochondria, when damaged, produce reactive oxygen species (ROS) such as hydrogen peroxide, which at high concentrations could induce substantial cell injury. Therefore, damaged and dysfunction mitochondria are removed by a process called mitophagy. Mitophagy is mediated by a protein called mitofusin, and mice lacking mitofusin in their hearts exhibit reduced mitophagy and increased ROS production. These mice also develop cardiomyopathy, but whether the ROS themselves are responsible for this deterioration was unknown. To test the role of hydrogen peroxide, the team gave a low dose of catalase to the mitofusin-lacking mice. As expected, they found that cardiomyopathy was attenuated—there was evidence of reduced hypertrophy and improved left ventricle function. Mitochondrial dysfunction also decreased, suggesting that ROS cause additional damage to the mitochondria themselves. Unexpectedly however, a high dose of catalase worsened cardiomyopathy, exacerbating heart enlargement and accelerating functional decline. Importantly, the team observed that mitofusin-lacking cells utilized a secondary disposal pathway for eradicating damaged mitochondria. The authors suggest that ROS are the signals for both mitophagy and this secondary pathway and that overt suppression of ROS inhibits these signals, allowing damaged mitochondria to accumulate and interfere with efficient energy production. Caution should be exercised in the treatment of chronic diseases with antioxidants, the authors warn.

Activating YAP improves heart function after a myocardial infarction, report Lin et al.

The transcriptional co-activator Yes-Associated Protein, or YAP, is essential for controlling cell proliferation and organ growth in the developing mammalian embryo. Indeed, YAP activation in mouse fetal cardiomyocytes drives proliferation of these cells, while heart-specific deletion of YAP causes cardiac hypoplasia. Lin and colleagues therefore wondered whether inducing YAP in adult heart might provide a means of generating new cardiomyocytes to replace those destroyed by ischemia. To test this, the team generated mice in which YAP expression could be induced specifically within the heart. First, they confirmed that YAP activation did indeed induce adult cardiomyocyte proliferation. Then they found that activating YAP one week after experimental myocardial infarctions led to both a reduction in infarct size and better preservation of cardiac function compared with control mice. Similar results were obtained when the team performed gene therapy with a viral vector containing YAP. Taken together these results suggest that boosting YAP activity could be a novel strategy for diminishing the impact of ischemic injury and other forms of myocardial insults.

Loss of Pim kinases promotes premature cardiac aging, report Din et al.

Aging is associated with gradual cardiac deterioration. In the aged hearts, fewer cardiomyocytes are generated, ventricular hypertrophy develops and metabolism switches from mainly fatty acid oxidation to mainly glucose utilization, as seen in heart failure. It was shown recently that overexpression of the protein kinase Pim-1 in aged human cardiac stem cells decreases the expression of senescence markers, and promotes proliferation and survival. Pim-1 is also known to promote mitochondrial integrity and thus protect cells against damaging ROS. Din et al have now examined the effects of Pim deletion on the heart. They generated transgenic mice lacking all three Pim kinases and showed that the mice exhibited premature cardiac hypertrophy—with increased fibrosis and left ventricle enlargement at just 6 months of age. Cardiomyocytes of the mice also showed evidence of senescence, with shorter telomeres, disrupted morphology, reduced ATP production, and a switch to glucose metabolism. Altogether the results corroborate the previous evidence that Pim-1 promotes heart cell rejuvenation and suggest that boosting this kinase might be a useful treatment for attenuating pathogenic changes associated with cardiac aging.