Genome Editing of PCSK9 In Vivo (p 488)

With a single injection Ding et al reduce cholesterol levels in mice. High levels of low-density lipoprotein (LDL) in the blood are one of the primary risk factors for coronary heart disease, and even though statins can decrease LDL levels, their use does not completely mitigate the risk of heart disease. Moreover, some patients are intolerant of statin therapy. Hence, new strategies for reducing LDL levels are highly desirable. In humans, LDL levels are regulated by the liver enzyme PCSK9, and individuals with loss-of-function mutation in the PCSK9 gene are healthy but have lower LDL levels and a lower risk of coronary heart disease. Ding and colleagues therefore wondered whether mutating the Pcsk9 gene artificially in mice would mimic the benefits seen in human PCSK9 mutants.

To mutate Pcsk9, the team performed gene-editing—a process whereby specially designed nucleases are directed to cut a particular DNA sequence of interest. They packaged a Pcsk9–specific nuclease into a liver-homing viral vector, and then injected it into mice. Four days after injection, they found that 50 percent of the liver cells contained the mutated protein. Importantly, the treated mice had lower levels of plasma PCSK9 enzyme and lower cholesterol levels. This proof-of-principle experiment paves the way for developing clinical-grade gene-editing strategies for targeting PCSK9 in humans.

AMPK–ACC Signaling and Fatty Acid Oxidation (p 518)

Theories of fatty acid metabolism in the heart require a rethink, say Zordoky et al.

The kinase AMPK phosphorylates a variety of intracellular targets including the enzyme acetyl-CoA carboxylase (ACC), which is an inhibitor of fatty acid oxidation. AMPK phosphorylation of ACC inhibits the activity of this enzyme and thus AMPK indirectly promotes fatty acid metabolism. In the liver, inactivation of ACC by AMPK is essential for fat metabolism, but Zordoky and colleagues have now discovered that this is not the case in the heart. The team examined fatty acid metabolism in the hearts of genetically engineered mice expressing a version of ACC that was incapable of being phosphorylated by AMPK. They discovered that fatty acid oxidation was unaffected at both low and high workloads and even under ischemic conditions—known to specifically raise AMPK activity. These results indicate that while AMPK may be capable of promoting fatty acid metabolism in the heart it is certainly not required, and that other pathways must be involved. Discovering those pathways may be particularly relevant to the field of ischemia research, because fatty acid metabolism is thought to be the primary energy source in the heart during reperfusion.

Ceramide Changes the Mediator of FID (p 525)

Ceramide promotes hydrogen peroxide production in the vessels of patients with coronary artery disease, report Freed et al.

In response to shear stress, endothelial cells lining the blood vessels release factors that trigger vasodilation. In general, this flow-induced dilation (FID) is mediated by nitric oxide (NO), but in patients with coronary artery disease the endothelium switches from NO to hydrogen peroxide (H2O2) production. Both factors act as vasodilators, but while NO has anti-inflammatory, anti-thrombotic and anti-proliferative effects, H2O2 is pro-inflammatory, pro-thrombotic and pro-atherogenic. It is not clear why or how this switch occurs, but Freed and colleagues suspected that ceramide might be involved. Ceramide is not only a risk factor for atherosclerosis, but it also promotes mitochondrial production of reactive oxygen species, such as H2O2. Hence, they incubated healthy human arterioles with ceramide and showed that FID switched from being NO-dependent to being H2O2-dependent. They also showed that in arterioles from patients with coronary artery disease, inhibiting ceramide synthesis led to the replacement of H2O2 production by NO production. Together these results suggest that ceramide is a pivotal regulator of damaging H2O2 production and that targeting ceramide or its associated pathways may be a novel therapeutic strategy for the treatment of coronary artery disease.