**LOX Mutations Predispose to TAAD (p 928)**

**Guo et al identify a novel gene associated with thoracic aortic aneurysm.**

A predisposition for weak aortic walls, which can cause the vessel to bulge (aneurysm) or even tear (dissection), can run in families. Indeed, a large fraction of individuals with thoracic aortic aneurysms that lead to acute dissections (TAADs) are believed to have a family history of the condition. Of these familial TAAD (FTAAD) cases, however, only about 25 percent are caused by known genetic mutations. The etiology of the other 75 percent remains unknown. To search for novel FTAAD-associated genes, Guo and colleagues performed whole-exome sequencing of three affected individuals in one FTAAD family with no known mutations. In these individuals, they found a mutation in the LOX gene, which encodes an enzyme required for construction of the aortic wall. This link is strengthened by the observation that mice lacking Lox die young from thoracic aortic rupture. In their examination of another 410 unrelated FTAAD patients, the team found five additional individuals with LOX mutations. Some mutations affected the catalytic activity of the enzyme, while others were predicted to cause haploinsufficiency of the protein. Together these results provide additional support to the notion that LOX contributes to the development of the aorta, and suggest a dysfunctional LOX gene has the potential to drive thoracic aortic disease.

**Hypoxia Preconditioned MSC Therapy for MI (p 970)**

**Hypoxia-conditioned stem cells improve heart function in primates after myocardial infarction, report Hu et al.**

Mesenchymal stem cells (MSCs) have been investigated for their potential to improve recovery after myocardial infarction. Although results of preclinical studies have been generally encouraging, data from clinical trials have shown limited efficacy. One reason for poor performance of MSCs in promoting myocardial repair may relate to insufficient engraftment of the cells into the heart tissue. However, engraftment can be improved by preincubating the MSCs under hypoxic conditions. Indeed rats treated with hypoxia-conditioned MSCs recover better from infarction than animals treated with unconditioned cells. Hu and colleagues now show such hypoxic conditioning improves the performance of MSCs in non-human primates as well. They report that in Cynomolgus monkeys given myocardial infarctions engraftment of hypoxia-conditioned MSCs was approximately 20-fold greater than that of unconditioned cells. Furthermore, over the course of ninety days, the animals that received preconditioned cells exhibited better left ventricle ejection fractions, reduced scar size, no arrhythmias, and more robust revascularization than did animals receiving unconditioned MSCs. Thus, hypoxic-conditioning may be a useful strategy to improve MSC therapies in future clinical trials.

**Cell Therapy in Refractory Angina (p 984)**

**Cellular therapy for refractory angina provides clinical benefits, according to a meta-analysis by Khan et al.**

Angina affects several million people, and even though treatment options are available for most, some patients do not respond to medications and might be ineligible for coronary revascularization procedures. Such patients—between 600,000 and 1.8 million in the US alone—are referred to as refractory, or “no option”, angina patients. It is thought that cell based therapies, which have the potential to promote neovascularization of the myocardium, may offer new hope to these patients. Nevertheless, the effectiveness of such therapies has been difficult to assess, because of the small scale of the phase I and II trials performed to date. To understand better how useful cell therapy might be in such cases, Khan and colleagues performed a meta-analysis of six trials involving 353 refractive angina patients, 192 of whom received treatments with cells—either from bone marrow or peripheral blood. Overall, they found that the cell therapies decreased the incidence of angina episodes, reduced medication use, improved exercise tolerance, improved left ventricle function, and decreased the risk of major adverse cardiac events and arrhythmias. Together the results provide a compelling argument for carrying out much larger randomized controlled phase III clinical trials.