Raet1e, a New Atherosclerosis Modifier Gene (p 1054)

Rodriguez et al identify a new atherosclerosis modifier gene in mice.

Atherosclerosis is a complex disease involving both environmental factors—for example, diet—and genes. Genetic loci that confer increased or decreased susceptibility to atherosclerosis have been identified in mice and man, but pinpointing the causative sequence changes at these loci is not easy. Out of the 44 or so modifier loci identified in mice, for example, the modifier sequences have been identified at just a handful. Now Rodriguez and colleagues add another locus to that list—Ath11. This locus, which associates with more severe atherosclerosis, maps to a particular stretch of mouse chromosome 10. The team identified five possible candidate genes in the region and analyzed their expression in atherosclerosis-prone mice that were either homozygous or heterozygous for the Ath11 modifier—and that had more or less severe atherosclerosis as a result. One gene, Raet1e, exhibited lower expression levels in the homozygotes. And reinstating high expression of Raet1e, by means of a transgene, reduced the severity of atherosclerosis. The team went on to identify the sequence change in the promoter of Raet1e responsible for the reduced expression. It is not clear why low levels of Raet1e worsen atherosclerosis, but the protein is known to interact with immune cells suggesting that an aberrant immune response may be to blame.

Quaking and VSMC Phenotype (p 1065)

Blocking an RNA-binding factor called Quaking prevents vascular smooth muscle cells from over-proliferating, report van der Veer et al.

Quaking (QKI) is an RNA binding protein that regulates splicing, export and stability of messenger RNAs, and has been shown to be important for vascular development in the embryo. Van der Veer and colleagues investigated whether QKI might also have a role in the adult vasculature. They found that in healthy human vessels, smooth muscle cells (VSMCs) expressed almost undetectable levels of QKI, but that in restenotic vessels—where the VSMCs dedifferentiate and proliferate rapidly—the cells showed a dramatic increase in QKI expression. In concordance, mice that expressed a reduced amount of QKI exhibited less severe restenosis after vessel injury. VSMCs derived from these mice also displayed reduced proliferation, migration and extracellular matrix production—indicators of restenosis. The team went on to show that QKI interacted with the pre-mRNA of myocardin—an important promoter of VSMC maturation—and promoted the excision of one of myocardin’s exons. This splicing event generated a version of myocardin that increased VSMC proliferation. The authors therefore suggest that interfering with QKI activity could be a therapeutic path toward ameliorating pathogenic restenosis after vessel injury.

Cellular Basis of Arteriogenesis (p 1076)

Endothelial cells are principle regulators of arteriogenesis, say Moraes et al.

Recent research into arteriogenesis—the development of arteries and smaller arterioles—indicates that an intracellular signaling protein called synectin is involved. For example, mice and zebrafish that lack synectin exhibit impaired arterial morphogenesis. Their vessels are smaller sized with reduced diameters as well as reduced numbers of branches. Moraes et al were interested in which cell type might be responsible for these synectin-associated arterial defects. They generated mice that specifically lacked synectin in each of the two major artery cell types: vascular smooth muscle cells (VSMCs) and endothelial cells. They found that mice lacking synectin in endothelial cells but not those lacking synectin in their VSMCs exhibited virtually the same developmental arterial defects as the whole-mouse synectin deletion. Furthermore, when the researchers induced ischemia in the hind-limbs of adult mice, those lacking synectin in their endothelial cells had impaired recovery of blood flow while those lacking synectin in their VSMCs did not. The work provides a greater understanding of the molecular and cellular mechanisms behind artery formation, which will aid in the design of future therapies for ischemic vascular diseases, say the authors.