14q32 miRs in Neovascularization (p 696)

Welten et al suppress microRNAs to boost neovascularization after ischemia.

Neovascularization is a crucial process for restoring blood supply after injury. Hence, finding factors that promote neovascularization is an important goal in promoting tissue recovery after ischemic insults. Welten and colleagues analyzed the sequences of 127 neovascularization genes, searching for putative binding sites for microRNAs that regulate their mRNAs. They found a large number of possible sites, but they also found an unusually high proportion of sites that were predicted to bind miRs clustering at one particular chromosomal location: 14q32. Microarray analysis of ischemic tissue confirmed the upregulation of 14q32 miRs, and they chose four of these miRs for further study. Using specific gene silencing oligonucleotides, they suppressed each of the four miRs in mice and, then subjected the mice to ischemic injury. Suppression of the four miRs improved blood flow recovery to the affected tissue after the ischemia—both increasing the number of large collateral arteries and, in three of the four cases, increasing capillary density.

FOXF1 Stimulates Vascular Development (p 709)

The transcription factor FOXF1 is a crucial regulator of vascular development, report Ren et al.

Heterozygous deletions and point mutations of the gene encoding transcription factor FOXF1 account for approximately 40 percent of cases of alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV), which is a fatal congenital disorder characterized by abnormalities in the pulmonary vasculature. Haploinsufficiency of FOXF1 in mice has been shown to cause ACD/MPV-like abnormalities, confirming the importance of this transcription factor in vascular development. To investigate the role of FOXF1 in vasculogenesis, Ren and colleagues created mice in which FOXF1 was specifically deleted in endothelial cells, where the transcription factor is normally expressed during embryogenesis. As a result, the endothelial cells exhibited decreased proliferation and increased apoptosis, while the mice themselves had severe cardiovascular defects, growth retardation, and died in utero. The team discovered that FOXF1 regulated the transcription of Flk1 and Flt1—receptors for vascular endothelial growth factor (VEGF)—and thus, in the absence of functional FOXF1, endothelial cells were unresponsive to VEGF stimulation. The results indicate that FOXF1 or its downstream targets, such as Flk1 and Flt1, may be promising pharmaceutical targets to treat ACD/MPV patients.

Basigin in Pulmonary Hypertension (p 738)

Cyclophilin A and its receptor basigin promote pulmonary hypertension in mice, report Satoh et al.

Pulmonary hypertension (PAH) is a severe, often life-threatening, disease characterized by vasoconstriction, remodeling of the lung vasculature, vascular smooth muscle cell (VSMC) proliferation and perivascular inflammation. Hypoxia is a characteristic feature of PAH pathogenesis. It induces VSMCs to secrete cyclophilin A (CyPA), which in turn stimulates VSMC proliferation and attracts inflammatory cells. Satoh and colleagues discovered that both CyPA and its extracellular receptor basigin are strongly expressed in the remodeled pulmonary arteries of PAH patients. Furthermore, high levels of CyPA in patient plasma were associated with poor outcome, suggesting that CyPA could be used as a biomarker of disease progression. The team also found that deficiency of either CyPA or basigin in mice ameliorated the development of hypoxia-induced PAH. VSMCs from basigin-deficient mice proliferated less than those derived from wildtype mice, and produced lower levels of inflammatory cytokines, the team showed. Together the results suggest that inhibiting the activity of CyPA and/or basigin could be a therapeutic strategy for future PAH treatments.