miR-195 and Aortic Aneurysms (p 857)

MicroRNA-195 is a biomarker, but not a target, for aortic aneurysmal disease, report Zampetaki et al.

Abdominal aortic aneurism (AAA) is the ballooning of the aorta, creating a risk of life-threatening rupture. The condition is associated with a loss of elastin and increased turnover of collagen in the vessel wall. Previous work has shown that miR-29 inhibits the expression of both elastin and collagen and, that inhibition of miR-29 consistently reduces aortic aneurysm in mice. Zampetaki and colleagues now show that miR-195 also targets elastin. They found that overexpression of miR-29 or miR-195 caused a comparable decrease in elastin levels in vitro, while inhibiting miR-195 in mice prompted an increase in elastin expression. Unlike miR-29 inhibition, however, the inhibition of miR-195 did not protect mice from aortic aneurysm. This appears to be related to the upregulation of matrix metalloproteinase enzymes that degrade the collagen and elastin containing extracellular matrix, upon miR-195 inhibition. The team also found that miR-195 levels in human plasma were inversely correlated with AAA diameter and with the occurrence of AAA. Therefore, even though miR-195 may not be a target for inhibition in AAA therapies, it could serve as a useful biomarker of the condition, say the authors.

Hypoxia and IL-1β Production in Macrophages (p 875)

Hypoxia boosts inflammation in atherosclerotic plaques, say Folco et al.

Atherosclerosis is primarily an inflammatory condition associated with the influx of a large number of macrophages and the production of inflammatory cytokines—such as IL-1β—within plaques. Now Folco and colleagues report that not only does inflammation drive atherosclerosis, the conditions within the plaques make inflammation even worse, perpetuating the problem. Most cells within plaques experience a moderate to severe lack of oxygen, and the team found that this hypoxia drives IL-1β production. They exposed human macrophages to 2% oxygen for 24 hours and discovered that, when activated, the cells could produce and secrete approximately three times more IL-1β protein than macrophages exposed to normal oxygen levels. IL-1β mRNA levels in the cells remained similar indicating post-transcriptional control. Indeed, they found that hypoxia stabilized IL-1β by limiting degradation of the protein in autophagosomes—a waste disposal system within cells. The team went on to show that the most hypoxic regions of dissected human plaques accumulated IL-1β. The results indicate that neutralizing IL-1β, which is currently being tested in patients with coronary artery disease, could help reduce chronic inflammation in atherosclerosis.

De Novo CNVs in Congenital Heart Disease (p 884)

Glessner and colleagues detect increased copy number variations and novel candidate loci involved in congenital heart disease.

Congenital heart disease (CHD) is one of the most common birth defects, but in a majority of cases the etiology remains unknown. Several genome-wide studies to find loci associated with CHD have been conducted; however, they generally employed low-resolution methods such as comparative genomic hybridization and low-density single nucleotide polymorphism (SNP) analysis. Such studies have identified broad regions of the genome that may be involved in the disorders, but not specific genes. Glessner and colleagues have therefore performed high-density SNP analysis and/or whole-exome sequencing on a total of 538 CHD trios (affected offspring and their parents). They confirmed previous findings that locus copy number variations (CNVs) tend to be increased in these individuals and identified a total of 65 novel CNV sites. Importantly the higher resolution approaches led to the identification of candidate genes associated with CHD. For example, the recurrent CNV at chromosome location 15q11.2 incorporates three genes: CY-FIP1, NIPA1, and NIPA2. These and the other new loci might act both as new diagnostic markers of CHD as well as possible targets for therapy.