A particular variant of the NCAM1 gene poses a risk for left ventricular hypertrophy, report Arnett et al.

Cardiac hypertrophy can, in some cases, lead to cardiac remodeling and, ultimately, heart failure and death. Like many other complex diseases and traits, multiple genetic factors contribute to cardiac hypertrophy. One way to search for genetic variants that might contribute to such complex diseases is to perform genome-wide association studies. And that is just what Arnett et al decided to do. They screened hypertensive African-American families and looked for associations between particular genetic variants, called SNPs (single nucleotide polymorphisms), and electrocardiographic indicators of hypertrophy, including left ventricular (LV) mass, wall thickness, and internal dimension. They found a SNP in the first intron of the gene for NCAM1 that showed strong association with LV hypertrophy. The authors confirmed this association in a screen of white hypertensive families. NCAM1 has previously been shown to be upregulated in the hypertrophic hearts of rats. Thus, although it is not yet clear how this human genetic variant leads to a risk for hypertrophy, the current study implicates NCAM1 in the genesis of this syndrome.

miR-98/let-7 Inhibits Cardiac Hypertrophy (p 305)

Yang et al uncover a new microRNA-based mechanism by which thioredoxin 1 inhibits cardiac hypertrophy.

Thioredoxin (Trx1) is a ubiquitously expressed antioxidant protein with a wide variety of cell-protective functions. Among these is its ability to inhibit pathologic cardiac hypertrophy by a mélange of molecular mechanisms. Yang et al have now discovered yet another mechanism to add to the mix involving microRNA-98 (aka let-7). MicroRNAs, or miRs, are small noncoding RNAs that either translationally suppress or degrade target mRNAs. A number of miRs have been reported to affect cardiac hypertrophy, so Yang et al wondered whether Trx1 might regulate any of them. The answer was no. However, a new candidate miR—miR-98—was affected by Trx1. In mouse hearts overexpressing Trx1, miR-98 was significantly upregulated. Overexpression of miR-98 itself in heart cells inhibited Ang II-induced hypertrophy. One predicted target mRNA of miR-98 is cyclin D2, which has been independently implicated in cardiac hypertrophy. The authors showed that miR-98 suppressed the expression of cyclin D2, which in turn inhibited cardiomyocyte hypertrophy. The discovery of the Trx1/miR-98/cyclin D2 pathway offers researchers new tools in the search for antihypertrophic therapies.

S1P3 and Macrophages in Atherosclerosis (p 314)

Keul et al discover a means to keep macrophages minimal in atherosclerotic plaques.

Macrophages migrate to atherosclerotic lesions as part of the pathologic process that leads to plaque growth. A known promoter of immune cell migration is a bioactive lipid called S1P, found in blood plasma and tissue fluids. Interestingly, S1P serum levels in humans display a positive correlation with severity of coronary artery stenosis (narrowing), suggesting that S1P may be involved in the pathogenesis of atherosclerosis. In apparent contrast to this result, however, an analog of S1P inhibits atherosclerosis in mice. Keul et al realized that the analog experiments did not differentiate between the possible separate effects of S1P’s many cell surface receptors. The team decided to investigate what would happen when one particular S1P receptor, S1P3, is absent. Their in vitro experiments showed that S1P chemoattracted wild-type macrophages but not those lacking S1P3. Furthermore, atherosclerosis-prone mice that lacked S1P3 had less macrophages at their atherosclerotic lesions. Lesion size, however, was not affected. Instead, the lesions contained increased numbers of smooth muscle cells. Although the mechanism behind this remains unclear, an increase in smooth muscle cells suggests an increase in plaque stability. The authors suggest that specific inhibition of S1P3 might be a useful strategy to reduce inflammation in atherosclerotic lesions.
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