Serine Proteases in Vascular Calcification (p 758)

Yao et al uncover the molecular details of endothelial-to-mesenchymal cell transition during vascular calcification.

Vascular calcification is a severe complication of vascular diseases such as atherosclerosis and diabetes. It reduces the elasticity of blood vessels due to calcium deposition and increases a patient’s risk of myocardial infarction, heart failure, hypertension, and death. It was originally believed that the deposition of calcium was a passive process, but recent evidence suggests that it is an active pathology resembling bone formation. Indeed, the mouse model for vascular calcification exhibits an overactive bone morphogenetic protein (BMP)—caused by the deletion of a BMP inhibitor. In these mice, BMP promotes calcification by, among other things, stimulating endothelial cells to adopt the features of mesenchymal cells—the cells that give rise to bone. Yao and colleagues have now discovered that this endothelial-to-mesenchymal transition is controlled by the upregulation of five serine proteases, which in turn upregulate a transcription factor called sox2. The team found that blocking the proteases or sox2 reduced calcification in the mice and the mesenchymal transition in cultured endothelial cells. Together the results reveal sox2 and the serine proteases as potential targets for treatments aimed at suppressing or preventing vascular calcification.

GSNOR Regulates Beta-Adrenergic Signaling (p 793)

Adrenergic signaling in the heart leads to S-nitrosylation of calcium handling proteins, report Irie et al.

The rise and fall of calcium levels inside cardiomyocytes controls their contraction and relaxation. This contractility can be modulated by beta-adrenergic receptor (βAR) signaling, which leads to the phosphorylation of calcium-handling proteins in these cells. Chronic activation of βAR and a sustained increase in intracellular calcium can lead to left ventricular hypertrophy and heart failure. Therefore, a thorough understanding of the molecular signals downstream of βAR activation would provide insights into the disease mechanism. Recent evidence suggests that βAR not only phosphorylates calcium handling proteins, but it also increases the production of nitric oxide (NO) by stimulating nitric oxide synthase. Irie and colleagues have now examined this parallel role of βAR activation more closely and discovered that βAR-induced NO production leads to S-nitrosylation of calcium handling proteins—specifically phospholamban and cardiac troponin C. Importantly, they found that suppression of S-nitrosylation prevented left ventricular hypertrophy in mice that were subjected to chronic βAR stimulation. These results suggest that S-nitrosylation of phospholamban, troponin C or other calcium handling proteins might be novel processes to target in future heart failure therapies.

Microbiome Affects Lipids (p 817)

Gut microbes contribute to body mass index and blood lipid levels, report Fu et al.

Accumulating evidence suggests that microbes in the gut are important determinants of a person’s health. In several studies the composition of the gut microbiome has been found to be associated with diabetes, obesity and inflammatory disorders in humans. In mice, the transfer of gut microbes from animals with atherosclerosis to those that are healthy can increase disease susceptibility in the recipients. To examine the association between cardiovascular disease risk and the gut microbiome in greater detail, Fu and colleagues performed the largest human association study to date. They assessed the body mass index (BMI), blood lipids, gut microbes, and genotypes of 893 people and, after controlling for age and gender, they found that 34 bacterial taxa were associated with BMI, triglycerides and high-density lipoproteins (HDL). The team also estimated that differences in microbiome composition could explain approximately four-to-six percent of the variance in people’s BMIs, triglyceride levels and HDL levels, independent of age, gender, or genetic risk factors. Given that a person’s microbiome can be altered, the authors suggest that the development of prebiotics, probiotics, and other microbiome-modifying treatments might be advantageous for the prevention of cardiovascular disease.