Macrophage ABCA1 and SR-BI in Atherogenesis (p e20)

Zhao et al report that two fat-shifting factors work synergistically to keep macrophages healthy and atherosclerosis at bay.

Despite their voracious appetite, macrophages are unable to fully digest the lipids they ingest. Instead, they rely on factors, such as ABCA1, to export excess cholesterol out of the cell. Lipid accumulation inside macrophages can result in their transformation into foam cells that give rise to atherosclerotic plaques. Indeed, loss of ABCA1 from macrophages has been reported to increase atherosclerotic lesion formation. SR-BI is another macrophage cholesterol exporter, but it also promotes cholesterol uptake by the liver. Deletion of SR-BI from macrophages both enhances progression of advanced atherosclerotic lesions and inhibits development of early lesions. Zhao et al wondered what would happen if SR-BI and ABCA1 were deleted together. They discovered that in atherosclerotic-prone mice, macrophage-specific deletion of SR-BI alone caused a large increase in serum cholesterol, whereas deletion of ABCA1 caused a decrease. When both factors were deleted together, serum cholesterol levels were decreased even further. Combined deletion also increased the formation of foam cells and of atherosclerotic lesions. Therefore, a two-pronged approach at increasing these factors’ activities might be an avenue for antiatherosclerotic therapies.

Endothelial NO Modulates APP Expression (p 1498)

Austin et al suggest why cardiovascular risk factors are also risk factors for Alzheimer disease (AD). The common culprit, they say, is a lack of nitric oxide.

Although the precise cause of AD remains unclear, it is well known that high blood pressure, high cholesterol, diabetes, aging, and a sedentary lifestyle are all risk factors. Furthermore, in addition to AD’s classical pathologic features, such as the deposition of amyloid β protein in extracellular plaques and the formation of intracellular tangles of τ protein, vascular endothelial dysfunction is common. Vascular function and homeostasis are regulated, in part, by the signaling molecule nitric oxide. Indeed, nitric oxide-deficient mice suffer from high blood pressure and insulin resistance. Interestingly, the brains of these mice also display features of AD, Austin et al now show. Nitric oxide-deficient brain tissue exhibited increased expression of a protein called APP and an enzyme called BACE, which converts APP into plaque-forming amyloid β. In vitro studies further revealed that when nitric oxide was low, increasing expression of its downstream target, cGMP, could bring levels of BACE and APP back down. Therefore, the authors suggest that boosting the nitric oxide/cGMP pathway might prevent symptoms of AD.

hERG and Reentry (p 1503)

Hou et al reveal how increased expression of a particular potassium channel maintains deadly ventricular fibrillation.

Rapid, irregular, and unsynchronized contraction of the heart leads to fibrillation, which, not surprisingly, can be fatal. Electrical waves called reentrant waves, or rotors, are known to sustain ventricular fibrillation, but the molecular mechanisms that contribute to the development of rotors are not well understood. It is suspected that the rectifier potassium current—that which repolarizes the heart cells at the end of the action potential—might play a role. Hou et al, therefore, investigated whether an increase in expression of hERG—the channel regulating the rapid delayed rectifier potassium current—could affect the frequency, stability, and duration of these rotors. They found that rat ventricular monolayers expressing high levels of hERG had dramatically accelerated rotor frequency. This, say the authors, was due to considerably shorter action potential duration and increased excitability. Gain of function mutations of hERG have been linked to an inherited fatal arrhythmia disorder. Therefore, regulating hERG activity may be a useful therapeutic intervention for controlling fatal arrhythmias.