Macrophage sortilin promotes LDL uptake, foam cell formation, and atherosclerosis (p 789)

Sortilin protein drives cholesterol uptake in macrophages and promotes atherosclerosis, report Patel et al.

A characteristic feature of atherosclerosis is the formation of foam cells that arise from cholesterol-loaded macrophages. But exactly how macrophages take up cholesterol from transporter proteins such as low-density lipoprotein (LDL) is unclear, especially since the deletion of known macrophage lipoprotein receptors in mice does not prevent foam cell formation. Patel and colleagues thus turned their attention to a protein called sortilin. This protein mediates hepatic LDL uptake and, through genome-wide association studies, has been linked with coronary artery disease. The function of sortilin in macrophages, however, was unknown. The team found that atherosclerosis-prone mice lacking sortilin—either in all cells or just macrophages—showed a significant reduction in the number of atherosclerotic lesions compared to mice with normal levels of the protein. They also discovered that sortilin-lacking macrophages increased LDL uptake in macrophages that over-expressed sortilin actually increased their LDL uptake. These results suggest that preventing the sortilin-driven uptake of LDL in macrophages might reduce foam cell formation and thus be a novel strategy for treating, and perhaps even preventing, atherosclerosis in the future.

Transcriptional reversion of cardiomyocyte fate during mammalian cardiac regeneration (p 804)

O’Meara et al describe the transcriptional signature of mammalian heart regeneration.

The adult mammalian heart has a limited capacity for regeneration. In contrast, neonatal mice, within the first week of life, can completely repair their hearts after injury. During this regeneration, neonatal heart cells lose their sarcomeric structures, adopt a less-differentiated state, and reenter the cell cycle. If this same regenerative process could be recapitulated in the adult hearts, full recovery from myocardial injury might be possible. Hence to understand the mechanism underlying the regenerative capacity of the neonatal heart, O’Meara and colleagues examined changes in the global gene expression profiles of the neonatal heart after injury and during regeneration. They also studied the expression profiles of normal neonatal and adult cardiomyocytes, mouse embryonic stem cells during differentiation into cardiomyocytes, and adult cardiomyocytes induced to de-differentiate. After cross-referencing these data, the team identified a reference panel of genes involved in the differentiation and regeneration of a normal heart. They found that injury to the neonatal heart essentially reversed the differentiation process such that seven days post-injury the genes encoding sarcomeric proteins were reduced, while the expression of cell cycle genes was elevated. The team highlighted IL-13, STAT3 and STAT6 as regulators of cell cycle re-entry, but their results provide a large number of additional candidates that could be examined in future regeneration studies.

Effects of DNA damage in smooth muscle cells in atherosclerosis (p 816)

DNA damage promotes atherosclerotic plaque instability report Gray et al.

DNA damage occurs in the vascular smooth muscle cells (VSMCs) of atherosclerotic plaques and it becomes more pervasive with disease progression. But whether such damage is a cause or consequence of the condition is unclear. It is known that DNA damage reduces cell proliferation—because cells stop cycling to repair the DNA, and this could arguably slow down plaque growth. If, however, the damage is severe, senescence and apoptosis can occur, which induces proinflammatory cytokine production and immune cell recruitment, thus exacerbating plaque growth. To better define the relationship between plaque growth and DNA damage, Gray and colleagues studied the effects of accelerating or inhibiting DNA repair in human VSMC from normal aorta and atherosclerotic plaques. As expected, they found that VSMCs from plaques had significantly higher levels of DNA damage as well as increased activation of DNA repair pathways. By accelerating this repair in a mouse model of atherosclerosis, they found that while plaque size remained the same, there was an increase in the stability of the fibrous caps of the plaques. Inhibiting repair, on the other hand, promoted plaque instability. Because unstable plaques are associated with a greater risk of myocardial infarction and stroke, preventing DNA damage, or promoting DNA repair could be a novel therapeutic strategy for enhancing plaque stability in patients with atherosclerotic disease.