B-1b Cells Attenuate Atherosclerosis (p e28)

*Rosenfeld et al* show that B-1b cells protect against atherosclerosis in mice.

Immune cells are known to play key roles in atherosclerosis, and figuring out which immune cells exacerbate atherogenesis and which are anti-atherogenic could potentially suggest new therapeutic targets to treat the disease. In the case of B2 cells—classic B cells of the adaptive immune system—there is contradictory evidence regarding their role. B-1a cells, on the other hand, have been shown to protect against the disease. B-1b cells closely resemble B-1a cells, but also share some B2 characteristics, hence it is unpredictable how they act in the context of atherosclerosis. Rosenfeld and colleagues have now reported that the B-1b cells produce IgM antibodies, which protect against atherosclerosis, both in vitro and in mice. Furthermore, the cells reduced the size of atherosclerotic plaques when transferred into atherosclerosis-prone mice. The team also showed that the B cell transcription factor, Id3, suppresses this protective effect: deletion of the Id3 gene in mouse B cells boosted levels of protective antibodies, increased the number of B-1b cells, and reduced atherosclerosis. Finally, humans that carry a variant of Id3, which reduces the activity of the protein, had a similar increase in protective antibodies and B-1b-like cells, suggesting that Id3 plays an equivalent role in humans.

Mitochondria and miR-33 in Atherosclerosis (p 266)

More mitochondrial activity results in more cholesterol efflux from macrophages, say *Karunakaran et al.*

To reduce the accumulation of lipids in blood vessel walls, the reverse cholesterol transport (RCT) pathway shuttles cholesterol from resident macrophages to HDL transport proteins in the blood. But, with excessive cholesterol accumulation—such as in atherosclerotic plaques—RCT becomes insufficient. Now, Karunakaran and colleagues have discovered that ramping-up mitochondrial metabolism speeds RCT in mice. They found that the efflux of cholesterol from macrophages increased when mitochondrial metabolism was high, and that blocking mitochondrial function reduced the efflux. The team went on to show that the microRNA miR33 suppressed the expression of many mitochondrial genes. Transfecting macrophages with anti-miR33 increased the transcription of these genes and, in turn, ATP production and cholesterol efflux. Inhibition of miR33 is known to increase HDL levels in mice, which itself would promote cholesterol efflux. However, the team showed that in atherosclerotic animals with little to no HDL, anti-miR33 could still reduce lesion burden. Finally, they showed that plaques from patients with atherosclerosis had both high levels of miR33 and low levels of mitochondrial gene expression, suggesting that increasing mitochondrial activity and/or suppressing miR33 might be a novel anti-atherosclerosis strategy.

Promoter DNA Methylation in Vascular Growth (p 289)

Impaired blood vessel growth in hyperlipidemic and diabetic mice is associated with altered methylation of macrophage genes, report *Babu et al.*

To survive an ischemic insult, tissues must revascularize rapidly. However, in both hyperlipidemia and diabetes the growth of new vessels is severely impaired. This deficiency in vascular growth has been associated with disrupted gene regulation. To study this mechanism in greater detail, Babu and colleagues, examined the methylation state of the promoters of genes across the genome in cells from mice that were hyperlipidemic, diabetic, or that were healthy. Methylation of DNA is an epigenetic modification generally associated with suppression of transcription. Thus promoters with hypermethylation tend to be silent while those with hypomethylation tend to be active. Babu and colleagues found that muscle cells, macrophages and endothelial cells from the hyperlipidemic and diabetic mice revealed numerous genes that were differentially methylated compared with the healthy controls. In particular, the macrophages from both disease model mice displayed a significant shift towards promoter methylation patterns that would indicate a pro-inflammatory, anti-angiogenic M1 phenotype. In contrast, macrophages from healthy mice exhibited a methylation signature of anti-inflammatory M2 macrophages. Thus, therapeutically nudging macrophages towards an M2 fate may be a new approach to treat ischemia in patients with diabetes or hyperlipidemia.