IN THIS ISSUE

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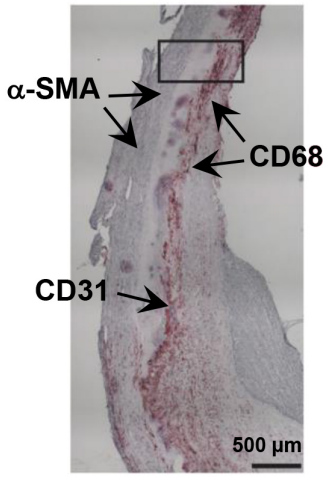
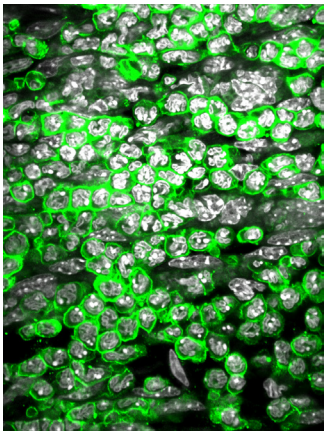


Alternative Macrophages in Vascular Calcification (p 19)

Osteoclast-like macrophages drive atherosclerotic plaque calcification, report *Chinetti-Gbaguidi* et al.

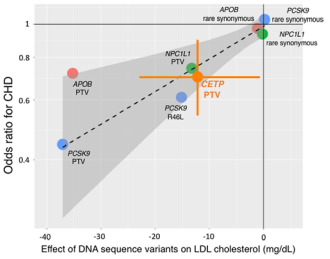
The accumulation of calcium deposits in major arteries is associated with aging and with atherosclerotic plaque formation. Once thought to be a passive process, vascular calcification is now known to occur via the same mechanism as bone formation, suggesting that the balance of osteoblastic (bone-forming) and osteoclastic (bone resorptive) activity becomes somehow skewed. Osteoclasts derive from the same lineage as monocytes and macrophages. And since such cells are abundant in plaques, Chinetti-Gbaguidi and colleagues decided to examine human plaque macrophages for their osteoclastic activity. The researchers specifically focused on cells surrounding calcium deposits and found that, while these macrophages expressed the osteoclastic marker CA2, their expression of a key osteoclastic enzyme involved in bone resorption was abnormally low, as was their bone resorptive activity in vitro. These osteoclast-like macrophages were of the alternative, or M2, phenotype, which tends to be associated with anti-inflammatory mechanisms and plaque stability. The discovery of these cells with deficient osteoclast behavior, however, suggests that M2 macrophages are not always atheroprotective. The findings also indicate that therapeutic modulation of the osteoclast-like cells may reduce plaque calcification and slow atherosclerosis progression.



Flow and Neutrophils Mediate Superficial Erosion (p 31)

Franck et al investigate superficial plaque erosion in a mouse model.

The rupturing of atherosclerotic plaques is a major cause of heart attacks, but in recent years, because of the increased use of statins, and other lifestyle and medical interventions, the incidence of plaque rupture is reducing, while the occurrence of superficial plaque erosion with consequent thrombus formation is on the rise. Despite plaque erosion becoming an increasing concern, little is known about its underlying mechanisms. To investigate, Franck and colleagues recapitulated eroded plaques in the carotid arteries of live mice. The team fed atherosclerosis-prone mice a diet of chow rather than high-fat so as to limit lipid and foam cell content of plaques. Then they induced small endothelial injuries that mimicked erosion-prone plaques of human arteries. In these mice, the team showed that there was plaque erosion when blood flow perturbations caused endothelial cell activation, neutrophil accumulation, and consequent endothelial cell death. Neutrophil accumulation was found to be critical to the process, because deletion of the TLR2 receptor on endothelial cells both prevented neutrophil adherence and thrombus formation. The development of this mouse model of superficial plaque erosion will be a valuable tool in the study of this increasingly important pathological process.



CETP Protein Truncating Variants and Risk for CHD (p 81)

People with truncated cholesteryl ester transfer protein are at lower risk of heart disease, report *Nomura* et al.

Cholesteryl ester transfer protein (CETP) transfers lipids between high-density lipoproteins (HDL) and low- or very-low–density lipoproteins (LDL or VLDL). In genetic studies, it has been shown that individuals with naturally low CETP expression are at lower risk of coronary heart disease (CHD). This finding has prompted research into pharmacological inhibition of CETP to increase HDL and reduce atherosclerosis. However, trials of small molecule CETP inhibitors have failed to show reduced CHD risk. In addition to people with low levels of CETP, some individuals have truncated versions of the protein, and Nomura and colleagues considered that such truncations might be more akin to pharmacological protein inhibition. The team examined over 80 000 individuals who had or did not have truncated CETP and found that, just like people with low CETP expression, those with truncated CETP were at significantly lower risk of developing CHD. Such individuals also had higher plasma HDL and lower LDL and triglycerides. It is not clear why pharmacological inhibition does not recapitulate genetic deficiency of CETP, but the authors suggest, among other things, possible off-target effects of the small molecules, or limited statistical power of the trials, both of which deserve further investigation.

Written by Ruth Williams
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