Imaging Inflammation in Atherosclerotic Lesions (p 770)

Chèvre et al capture high-resolution images of inflammatory cell dynamics in the mouse carotid artery.

Inflammation plays an important role in atherogenesis from the initiation of lesion formation to the development of unstable plaques. Thus, visualizing the dynamics of inflammatory cells at different stages of plaque growth would provide key mechanistic insights into the pathological process. But in two of the most critical blood vessels—the carotid artery and the aorta—such imaging is technically challenging because the vessels exhibit considerable pulsatile and respiratory movements. Chèvre and colleagues have now developed a method for stabilizing the carotid artery. In this method, they lay an anesthetized mouse on its back, surgically expose the carotid artery and then sandwich the vessel between a metal plate and a microscope coverslip. The mouse and its stabilized artery are then placed under a microscope for imaging. Using this method together with fluorescent labeling of infiltrating cells the team visualized real-time dynamics of neutrophils, T cells, and other inflammatory cells in the atherosclerotic lesions of mice. Among their findings, they observed that a high-fat diet increased the numbers of rolling leukocytes—indicating attachment to the artery wall—and that the recruitment of platelets to the artery wall required interaction with already-recruited myeloid cells. The new system should prove useful for imaging not only atherosclerotic lesions, but a variety of other arterial pathologies, say the authors.

β-Arein1 and Processing of MicroRNAs (p 833)

β-arrestin1 activates microRNA processing in the heart, report Kim et al.

β-arrestins are regulatory proteins that desensitize G protein-coupled β-adrenergic receptors (βARs) by preventing G-protein-mediated signaling. However, β-arrestins can also transduce βAR signals independently of G protein pathways—a recently-discovered function known as biased signaling. Via their G-protein-mediated signaling, βARs are known to activate a number of cardiac microRNAs (miRs)—small non-coding RNAs that regulate gene expression. Kim and colleagues therefore wondered if βARs could also activate miRs via β-arrestin-mediated biased signaling. They found that a biased signaling agonist—the β-blocker drug carvedilol—could indeed activate subsets of miRs in both human cells and mouse hearts. Rather than upregulating miR transcript expression directly, however, carvedilol upregulated the miR maturation process—by promoting the interaction of β-arrestin with the miR processor Drosophila. Carvedilol, which is used to treat congestive heart failure, is a non-specific βAR blocker and a weak activator of the biased signaling pathway. The work by Kim and colleagues lays the foundation for the development of new and more potent drugs that target β-arrestin biased signaling or the downstream miRs for the treatment of cardiovascular disease.

APOL1 Genetic Variants and CV Disease (p 845)

Variants of APOL1 commonly carried by African Americans confer an increased risk for cardiovascular disease, say Ito et al.

APOL1 is a major component of the high-density lipoprotein cholesterol transporter in the blood, but can also act as a trypanolytic factor—part of the body’s innate response against trypanosome infections. For example, many African Americans carry versions of the APOL1 gene that protects them against infection with Trypanosoma brucei, an insect-borne trypanosome that causes sleeping sickness. But this benefit comes at a price. Carriers of the protective APOL1 forms are more likely to suffer from chronic kidney disease (CKD). And as Ito and colleagues now show, they are also more likely to suffer from cardiovascular disease. The team sequenced the APOL1 genes of nearly 2000 African Americans and found that individuals carrying two CKD-risk alleles had a two-fold greater risk of cardiovascular events such as myocardial infarction or stroke. By studying a cohort without CKD, the team also showed that the cardiovascular risk was independent of CKD. Somewhat surprisingly, carriers did not differ from other participants with regard to diabetes status, hypertension, left ventricular function or cholesterol levels. Thus, the pathological basis for the increased cardiovascular risk is as yet unknown. Nevertheless, screening African Americans for the risk alleles might help prevent cardiovascular disease, or guide its treatment.
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Ruth Williams

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