Inflammation is a major factor in the progression of atherosclerosis. It is mediated by a progressive influx of monocytes and macrophages into the injured vessel wall, leading to the formation of fatty streaks that develop into arterial lesions. Inflammation within such plaques is further sustained by abundant mitochondrial DNA damage—caused by reactive oxygen species—that further exacerbate pathology. It has been previously reported that mice lacking a key mitochondrial DNA repair enzyme—oxyguanine glycosylase 1 (OGG1)—have larger fatty streaks in their arteries. And now, Tumurkhuu and colleagues report that genetic deletion of OGG1 increases mitochondrial DNA damage and inflammatory cytokines in the plaque, which results in the formation of inflammasomes in macrophages and larger arterial plaques in atherosclerosis-prone mice. They also found that deficiency of a key inflammasome component, NLRP3, counteracted the effects of OGG1 loss and that OGG1 expression tended to drop as atherosclerosis pathology progressed. In mouse and human cells, OGG1 was suppressed by the proatherogenic microRNA miR-33. The levels of OGG1 were reduced in human coronary and carotid arterial plaque samples compared to normal vessels. Together, these results indicate that boosting OGG1, or mitochondrial DNA repair, in plaques could be a putative therapeutic strategy to slow down the progression of atherosclerotic lesions.

Wang et al discover that a lack of LNK promotes atherosclerosis and thrombosis.

Genome-wide association studies (GWAS) have found that a single nucleotide polymorphism (SNP) at the lymphocyte specific adaptor protein (LNK) gene locus is linked with an increase in the risk of coronary heart disease (CHD). The same SNP has also been linked to hypertension, autoimmunity, and increased platelet counts. However, it remains unclear how this genetic variant increases CHD risk. In mice, LNK suppresses thrombopoietin signaling, which in turn suppresses proliferation of hematopoietic stem cells (HSCs). Consistent with these findings, Wang and colleagues now show that, in humans, the LNK risk allele is associated with increased production of HSCs and platelet-producing cells, suggesting that the risk-variant protein has reduced functionality. Using LNK-deficient mice as a model for humans carrying the LNK risk allele, the team showed that reduced LNK function not only boosted leukocyte and platelet production, but it also increased platelet activation. In combination with hyperlipidemia, these effects exacerbated both atherosclerosis and thrombosis. Together, the results indicate that carriers of the LNK risk allele produce more blood cells and activated platelets, which heightens the threat of thrombosis and atherosclerosis. Such individuals presenting with high cholesterol might thus benefit from early and more aggressive treatment.

Gurha et al suggest dysregulation of microRNA miR-184 contributes to arrhythmogenic cardiomyopathy.

Arrhythmogenic cardiomyopathy (AC) is a hereditary condition characterized by the gradual replacement of ventricular cardiomyocytes with fibro-adipocytes causing arrhythmia (particularly of the right ventricle), heart failure, and, possibly, sudden cardiac death. Proteins of the intercalated discs—cell-to-cell adhesion structures in the heart—especially plakophilin2 (PKP2) are commonly mutated in AC, but how these mutations lead to pathology is unclear. To investigate the molecular mechanisms of AC, Gurha and colleagues searched for microRNAs (miRs) that were dysregulated in PKP2-deficient cardiac cells. They found that of the 59 differentially expressed miRs, miR-184 was the most dramatically reduced in this model as well as in two independent mouse models of AC. Suppression of miR-184, which was caused by hypermethylation of the gene locus, led in turn to upregulation of genes involved in, among other things, adipogenesis. This induction of adipogenic genes, together with the observation that the cells tended to accumulate fat droplets, could explain why cardiomyocytes adopt a fibro-adipocytic phenotype in AC. Overexpression of miR-184 in the cells had the opposite effects: reducing fat droplet accumulation and reducing adipogenic gene expression. These results, identifying miR-184 as a novel player in AC, deserve further study.