Luong et al discover how the enzyme Cezanne reduces ischemia-reperfusion injury.

Ischemia-reperfusion, which occurs in a number of clinical settings—such as during coronary angioplasty or organ transplant—can induce inflammation causing damage to the reperfused tissue. This inflammation is in part controlled by the activation of the transcription factor NF-κB, which in turn activates inflammatory genes. The protein Cezanne is a deubiquitinating enzyme and a known negative regulator NF-κB. Luong et al now report that a substrate of Cezanne is a protein called TRAF6, the polyubiquitination of which activates NF-κB and the inflammatory signaling.

The team found that the silencing of Cezanne in cultured cells led to greater TRAF6 ubiquitination, while the deletion of Cezanne in mice increased injury and inflammation following ischemia-reperfusion. Interestingly, the team also found that the mRNA and protein levels of Cezanne were increased following hypoxia and reoxygenation in both cultured cells and animals, suggesting that Cezanne is automatically activated to dampen the effects of NF-κB and prevent over-inflammation. Artificially boosting Cezanne activity could further reduce inflammation and thus serve as an effective clinical strategy to prevent reperfusion injury, suggest the authors.

Ramirez et al identify a microRNA that reduces cholesterol export from macrophages as well as the body.

The transporter protein ABCA1 is essential for removing cholesterol from macrophages and it helps in preventing these cells from developing into foam cells that form atherosclerotic lesions. In the liver, ABCA1 controls the biogenesis of HDL, which promotes cholesterol removal from the blood for excretion in bile. A number of microRNAs (miRs) have been shown to regulate ABCA1, and now Ramirez and colleagues have identified miR-144 as a new ABCA1 regulator through an unbiased screen for miRs upregulated in macrophages that had been stimulated to undergo cholesterol efflux. They found that ABCA1 mRNA has seven potential binding sites for miR-144, and that over-expressing miR-144 in macrophages and in mice suppressed ABCA1 expression, confirming that miR-144 and ABCA1 mRNA do indeed interact. Importantly, the inhibition of miR-144 by an antisense oligonucleotide not only increased ABCA1 levels and the efflux of cholesterol in macrophages, but also increased HDL levels in mice, thereby potentially boosting cholesterol export in two ways. Thus, miR-144 inhibition could be a novel therapeutic strategy for lowering cholesterol.

de Aguiar Vallim et al independently identify microRNA-144 as a regulator of ABCA1.

At the same time when Ramirez and colleagues were screening macrophages for microRNAs (miRs) related to cholesterol efflux, de Aguiar Vallim and his team were searching for miRs that might be involved in lipid and lipoprotein metabolism in the liver. And both teams independently identified miR-144. Initially, de Aguiar Vallim’s team identified two miRs—miR-144 and miR-451. Both were highly conserved and also co-transcribed in response to hepatocyte stimulation with FXR—a transcription factor that regulates lipoprotein metabolism, among other things. But in a search for putative targets of miRs, only miR-144 yielded strong, highly conserved candidates. And at the top of the list was ABCA1. The team over-expressed miR-144 in human and mouse hepatocytes and found that, ABCA1 protein levels were suppressed in both these cells. Similarly, the over-expression of miR-144 in mice decreased ABCA1 in the liver and HDL in the blood. Silencing of miR-144 with antisense oligonucleotides, on the other hand, increased ABCA1 and HDL levels, just as Ramirez and colleagues observed. Although FXR induced miR-144, the transcription factor has also been reported to reduce atherosclerosis in mice, suggesting FXR’s particular role in cholesterol efflux is complex and requires additional study.