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IRF2BP2 Inhibits Macrophage Inflammation (p 671)

IRF2BP2 directs macrophages to become anti-inflammatory, suppressing atherosclerosis, report Chen et al.

Macrophages ingest oxidized LDL-cholesterol (oxLDL-C) from tissues and pass it to HDL transporters for removal from the body. But when cholesterol uptake exceeds efflux, macrophages can become lipid-laden foam cells—the fatty cells that accumulate in atherosclerotic lesions. Worse still, oxLDL-C prompts macrophages to assume an inflammatory phenotype (M1), which further decreases their cholesterol efflux. The M1 phenotype of human macrophages is associated with reduced expression of transcription factor regulator IRF2BP2, while the anti-inflammatory M2 phenotype is associated with high levels of this protein. Chen and colleagues now show that macrophages lacking IRF2BP2 exacerbate atherosclerosis in mice prone to the disease. These macrophages exhibited M1 phenotypes, had reduced cholesterol efflux and had unusually low levels of the anti-inflammatory factor KLF2. The team found that IRF2BP2 normally promotes KLF2 expression, and that restoring KLF2 levels attenuates the M1 phenotype. In humans, genetic variants in the vicinity of the IRF2BP2 gene have been linked to coronary artery disease (CAD), and now, the team has identified a CAD-associated variant of the gene itself. This finding together with the mouse experiments further supports the anti-atherogenic role of IRF2BP2.

CardioChimeras Enhance Myocardial Repair (p 695)

Quijada et al create two-in-one hybrid cells for repairing heart injuries.

Myocardial damage caused by infarction can ultimately lead to heart failure. Regenerating the myocardium with the help of therapeutic cells is thus a major focus of current research efforts. Among the cell types tested for their reparative qualities are cardiac progenitor cells (CPCs), which exhibit high proliferation capacity and can partially differentiate into cardiomyocytes, endothelial cells and vascular smooth muscle cells. Mesenchymal stem cells (MSCs), which are thought to enhance the endogenous repair mechanisms in the heart via paracrine effects, such as reducing inflammation and recruiting CPCs, have also been tested. Research in pigs has shown that transplanting both CPCs and MSCs at the same time improves cardiac function more effectively than either cell type alone. Now Quijada and colleagues have taken this idea of combination therapy one step further. The team has fused mouse CPCs and MSCs together to create hybrid cells, which they call cardiochimeras (CCs). They showed that in mice with heart injuries the CCs were more effective at fixing the damage than either CPCs or MSCs alone or combined. Thus, even though in comparison with MSCs and CPCs the CCs require an extra preparatory step, their higher reparative capacity might make the extra effort worthwhile.

Vitamin E and Steroids in Evolocumab Treatment (p 731)

Evolocumab does not affect vitamin E or steroid metabolism in a clinically significant manner, report Blom et al.

Statins are effective at lowering LDL-cholesterol, but they don’t work for all individuals who need them. Therefore alternative cholesterol-lowering drugs are needed to treat individuals with high cholesterol who cannot tolerate statins or in whom statin therapy is less effective. One promising cholesterol lowering drug is evolocumab, a monoclonal antibody that binds to PCSK9, a protein that regulates cholesterol homeostasis. In clinical trials, evolocumab has been shown to reduce plasma LDL-cholesterol levels by up to 75 percent. Such a drastic decrease in cholesterol levels, however, has raised concerns that the drug might interfere with cholesterol-dependent pathways required for normal function. Because LDL cholesterol levels affect both vitamin E and steroid hormone metabolism, Blom and colleagues examined these processes in evolocumab-treated trial participants. They found that while evolocumab treatment reduced the absolute levels of vitamin E, when normalized to cholesterol, these levels were actually increased. Furthermore tissue levels of vitamin E remained constant. Steroid hormones on the other hand were largely unaltered except for modest increases in cortisol, follicle stimulating hormone, and lutenising hormone. Altogether the results suggest that evolocumab does not affect vitamin E or steroid metabolism in a way that would be medically relevant, say the authors.

Written by Ruth Williams
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