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ATHEROSCLEROSIS
Pathoprofile

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Introduction

Atherosclerosis, characterized by plaque development and subsequent narrowing of arteries, is the precursor to coronary artery disease, heart attacks, and strokes. Known as major adverse cardiovascular events, these conditions are the leading causes of death in the United States, Europe and much of Asia, making atherosclerosis responsible for approximately 31% of all global deaths.[1] Atherosclerosis can be conceptualized as an inflammatory response resulting in the formation of arterial wall lesions through the accumulation of cholesterol-rich lipids and fibrous material.[2]

Pathophysiology

Atherosclerotic lesions can occur due to damage to the endothelium caused by alterations in blood flow at arterial branches, bifurcations, and curvatures. Cardiovascular risk factors which promote the development of atherosclerosis include dyslipoproteinemia, diabetes mellitus, hypertension, smoking, and hypercholesterolemia. Arterial endothelial damage facilitates monocyte entry through cell adhesion and trans-endothelial migration, while also allowing low-density lipoproteins (LDL) to cross the barrier.[3] Upon their entry, monocytes differentiate into macrophages which further bind to oxidized LDL (oxLDL) through scavenger receptors.[4]

Normal artery maintenance turns into atherosclerosis when the aforementioned cardiovascular risk factors promote local, unresolved inflammation. In atherosclerosis, the LDL uptake process is deregulated, resulting in increased cholesterol storage and insufficient export. This increase in oxLDL uptake and subsequent deregulation of enzymes leads to the accumulation of cholesterol esters and encourages foam cell formation.[5] Clustering of these foam cells form a fatty streak, the initial atherosclerotic lesion.[3] These foam cells release proinflammatory cytokines which recruit additional immune cells —including mast cells, dendritic cells, and T-cells— to the lesion. Proinflammatory cytokines TNF-α and IL-17 increase the expression of selectin and increase vascular permeability, resulting in further leukocyte migration and lesion development.[6]

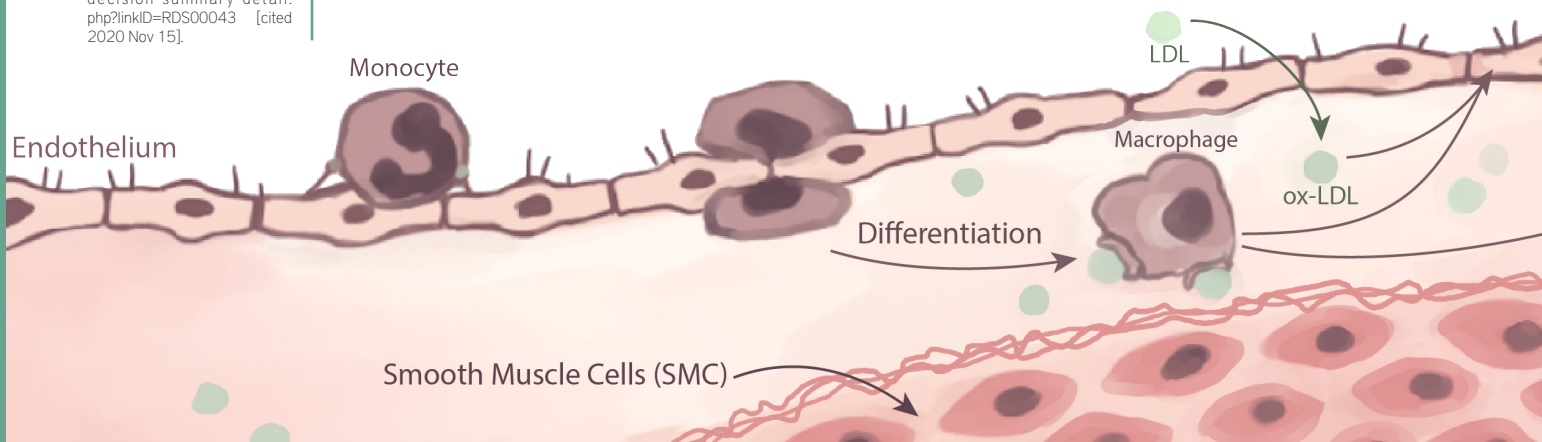
Additional growth factors released by the immune cells recruit vascular smooth muscle cells to the intima and proliferate to produce an extracellular matrix. As the lesion progresses, apoptosis of foam cells and smooth muscle cells can lead to the formation of a necrotic core. The development of a fibrous plaque from smooth muscle cells protects the advanced fibroatheroma from rupturing. Increased activation and expression of matrix metalloproteinases by macrophages can reduce the thickness of the fibrous cap, resulting in increased plaque vulnerability.[7]

While atherosclerosis may obstruct blood flow, it is unlikely to be fatal without the presence of thrombosis or plaque hemorrhage. The rupturing of the atherosclerotic plaque exposes the thrombogenic interior, resulting in clotting. Rupturing and thrombosis, rather than the hardening of the artery, is the main cause of myocardial infarction and ischemic stroke.[7]

Treatments

Traditional therapeutic efforts have focused on addressing relevant cardiovascular risk factors. Statins can reduce LDL cholesterol, antihypertensives can treat hypertension, and antithrombotics can reduce the formation of blood clots.[8]

Several therapeutics, including PLA2 inhibitors and antileukotrienes, are now being developed following the identification of various key anti-inflammatory targets.[8]



It is important to note that statins, despite being successful in lowering levels of atherogenic lipoproteins, are often inadequate for some patients. Maximal doses of the most potent statins are sometimes insufficient in achieving desired levels of LDL cholesterol; additional interventions may also be needed to further lower the risk for cardiovascular disease (CVD). Additionally, some patients are unable to tolerate statin therapy due to adverse effects including myalgia and rhabdomyolysis. Recent meta-analyses have also indicated that statin therapy is associated with an increased incidence of diabetes mellitus. To tackle these problems, various other treatments are being researched for clinical use.[9]

Among these is a therapeutic target identified as proprotein convertase subtilisin/kexin type 9 (PCSK9), a hepatic protease involved in LDL receptor (LDLR) degradation. Gain-of-function mutations in PCSK9 have been shown to lead to high LDL cholesterol levels due to increased LDLR degradation, whereas loss-of-function variants lead to low LDL cholesterol levels, and subsequently lower the risk of CVD. Furthermore, statin therapy has been shown to increase PCSK9 levels through negative feedback, which decreases its efficacy in lowering LDL cholesterol. Accordingly, inhibition of PCSK9 with monoclonal antibodies in conjunction with statin therapy has been shown to produce a 50-60% decrease in LDL cholesterol levels, as compared to statin monotherapy. PCSK9 inhibitors have also been well tolerated with a low incidence of adverse effects in short-term trials.[9] These have also recently received approval for use in Canada.[10]

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