Title:
Linking Common Risk Factors to the Biological Mechanisms Behind Atherosclerosis

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Abstract:

Background:

Summary
Atherosclerosis is the narrowing and hardening of arteries due to the formation of plaque in the arterial walls that results in blockage of blood flow. A variety of diseases can occur due to atherosclerosis, depending on the specific artery affected, such as peripheral artery disease or coronary artery disease, which is the leading cause of death in the United States for both men and women. Many risk factors for the development of atherosclerosis are known, for example, smoking, exercise, diet, obesity, cholesterol, and aging, amongst other factors, have been found to correlate with atherosclerosis, and further, many of these factors are interrelated. The goal of this study is to understand the interrelations between the risk factors of atherosclerosis and their links to the underlying biological mechanisms that directly enhance the progression of this condition.

Process of Atherosclerosis
Initiation of the pathogenesis of atherosclerotic lesions occurs typically in regions of the vascular endothelial lining of the inner blood vessel wall that are more prone to lesion formation. Atherosclerosis resistant regions have the transcription factors Kruppel-like factors (KLF) 2 and 4 activated by MEK5/ERK5/MEF2 signaling, which in turn expresses endothelial nitric oxide synthase (eNOS). Greater eNOS means increased nitric oxide (NO) production, which aids in maintenance of the barrier. [1]

These prone regions suffer from low endothelial shear stress, more common in arterial branch points and areas with inner curvature. Before atherosclerosis develops, these sites show changes in endothelial turnover and the local genetic expression. This results in adaptive intimal thickening, which sets the stage for plaque development. The intimal thickening along with plaque development can affect local flow patterns to further cause stress in the region. [2]
Genes related to inflammation, CXCR4 and ICAM-1, have been found to be differentially regulated as a result of this shear stress. In particular, the gene ICAM-1 is known to be involved in atherosclerosis and showed a significant downregulation, while the gene CXCR4 showed a strong upregulation as a result of shear stress. CXCR4 is a chemokine receptor involved in the

migration inhibitory factor (MIF) function that induces lesion progression by inducing transmigration of macrophages and dendritic cells and causing plaque inflammation. [3]

After initiation, the presence and uptake of low-density lipoproteins (LDLs) causes atherosclerosis by accumulating within the arterial intima and subsequently acting as stimulators of immune response. Specifically, lipoproteins containing apolipoprotein B (apoB) have been found to be critical in initiating an inflammatory response. Multiple factors play can play a role in this uptake phase. Stress or injury of an arterial wall results in the infiltration of monocytes into the endothelial space, which results in the internalization of apoB containing lipoproteins by macrophages. Alternatively, CD36 and scavenger receptor class A (SR-A) have been found to be responsible for uptake of LDL by macrophages. [4]

The presence of LDL within the macrophages within the arterial walls promotes the formation of "foam cells". This creates an enhanced local oxidative stress on the LDLs, and the oxidatively modified LDL (oxLDL) initiates bioactivities that drive lesion formation. [1]

Further, this accumulation of LDLs induces the expression of adhesion molecules, growth factors, and chemoattractants including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and monocyte chemoattractant protein-1 (MCP-1). These cause the migration and differentiation of macrophages and dendritic cells, which in turn can have pro inflammatory effects and promote the next steps of atherosclerosis. [1]

It has also been found that because plaque development is dependent on LDLs, people with elevated levels of LDL and/or certain lipoproteins are more prone to atherosclerosis. Conversely, elevated high-density lipoprotein (HDL) and endogenous apolipoprotein E (apoE) reduce the risk of atherosclerosis as HDL functions to remove excess cholesterol from the intima, and also inhibits lipoprotein oxidation. [5]

Certain genetic disorders affecting lipoproteins and cholesterol in the blood predispose afflicted persons to be more susceptible to atherosclerosis. One such disorder affecting cholesterol is familial hypercholesterolemia (FH), which is a monogenic autosomal codominant trait in which affected persons have elevated plasma cholesterol bound to LDL. Other disorders linked to higher risk of atherosclerosis are familial hypobetalipoproteinemia (FHBL) and familial ligand-defective apoB-100 (FDB), both of which are the result of mutations in the APOB gene. FHBL is characterized by low blood plasma levels of cholesterol, LDL, and apoB, while FDB is characterized by hypercholesterolemia. [6]

Finally, the last phase of plaque formation is marked by an accumulation of a large number of these inflammatory cells, which are primarily lymphocytes and macrophages, comprising a lipid

rich necrotic core. Macrophage inflammation causes chemokine and cytokine secretion, LDL oxidation, monocyte recruitment, and foam cell formation. [1]

Genes/Gene Products List:
Kruppel-like factors (KLF) 2 and 4 activated by MEK5/ERK5/MEF2
eNOS
CXCR4 and ICAM-1
MIF
LDL
apoB
CD36
SR-A
oxLDL
VCAM-1
M-CSF
GM-CSF
MCP-1
apoE

Methods:

Results:

Discussion:

Conclusions:

References:

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