STATE-OF-THE-ART REVIEW

Regression of Atherosclerosis: Insights from Animal and Clinical Studies

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ABSTRACT

Background: Based on studies that date back to the 1920s, regression and stabilization of atherosclerosis in humans has gone from just a dream to one that is achievable. Review of the literature indicates that the successful attempts at regression generally applied robust measures to improve plasma lipoprotein profiles. Examples include extensive lowering of plasma concentrations of atherogenic apolipoprotein B and enhancement of reverse cholesterol transport from atheromata to the liver.

Findings: Possible mechanisms responsible for lesion shrinkage include decreased retention of atherogenic apolipoprotein B within the arterial wall, efflux of cholesterol and other toxic lipids from plaques, emigration of lesional foam cells out of the arterial wall, and influx of healthy phagocytes that remove necrotic debris as well as other components of the plaque. This review will highlight the role key players such as LXR, HDL and CCR7 have in mediating regression.

Conclusion: Although much progress has been made, there are many unanswered questions. There is, therefore, a clear need for preclinical and clinical testing of new agents expected to facilitate atherosclerosis regression with the hope that additional mechanistic insights will allow further progress.

Key Words: atherosclerosis, CCR7, HDL, macrophages, regression

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INTRODUCTION

Atherosclerosis, a chronic inflammatory disease that occurs within the artery wall, is one of the underlying causes of vascular complications such as myocardial infarction, stroke, and peripheral vascular disease. Atherogenesis is a process that occurs over many years with the initiation phase being the subendothelial accumulation of apolipoprotein B-containing lipoproteins (apoB). These particles undergo modifications, including oxidation and hydrolysis, leading to the activation of endothelial cells. These cells secrete chemoattractants called chemokines that interact with specific receptors expressed on monocytes essentially "recruiting" the cells into the lesion. The monocytes then roll along the endothelial cells via interactions of specific selectins (ie, P-selectin glycoprotein ligand-1) with attachment being mediated by monocyte integrins such as very late antigen-4 and lymphocyte function-associated antigen 1 to the respective endothelial ligands vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1. Once attached, a process called diapedesis occurs by which monocytes enter the subendothelial space. Having accessed the subendothelial space, recruited monocytes differentiate into macrophages, a process driven by interactions with the extracellular matrix and cytokines, including macrophage colony-stimulating factor and members of the tumor necrosis factor family. The uptake of oxidized low-density lipoprotein (LDL) by the macrophages occurs via scavenger receptors, notably the type A scavenger receptor and CD36, a member of the type B family. The cholesteryl esters of the apoB particles that are ingested are hydrolyzed into free cholesterol, which occurs in late endosomes. The free cholesterol is then delivered to the endoplasmic reticulum where it is re-esterified by acyl-coenzyme A:cholesterol ester transferase. It is this process that leads to the macrophages having the "foamy" appearance. It is well-known that macrophages contribute to formation of the necrotic core and fibrous cap thinning that characterizes the vulnerable plaque. How do these macrophages ultimately contribute to the vulnerable plaque? Macrophage-derived matrix metalloproteinases (MMPs) are a family of proteins that can degrade various types of extracellular matrix and hence promote rupture. Moreover, once activated, certain MMPs can activate others. Studies have shown a temporal and spatial correlation between the presence of macrophages in rupture-prone shoulder regions of plaques, thinning of the fibrous cap in these regions,

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and local accumulation of activated MMPs. Another potential mechanism of how macrophages may promote plaque thinning and increase vulnerability is via causing smooth muscle cell (SMC) apoptosis. Vulnerable plaques show evidence of SMC death and decreased numbers of SMCs. Even after plaque rupture, the macrophage continues to play a role as it secretes prothrombotic tissue factor thereby accelerating thrombus formation.[1-8]

The idea that human atheromata can regress at all has met considerable resistance over the decades.[1-3] Resistance to the idea of lesion regression has been due to the fact that advanced atheromata in humans and in animal models contain components that give an impression of permanence, such as necrosis, calcification, and fibrosis. Furthermore, numerous theories have been proposed to explain atherogenesis that included processes thought to be difficult, if not impossible, to reverse including injury,[6] oxidation,[7] and cellular transformations resembling carcinogenesis.[8] In this review, data are presented that demonstrate that indeed changes in the plaque environment can stabilize and regress even advanced lesions.

PLAQUE REGRESSION: EVIDENCE FROM ANIMAL STUDIES

Regression of Atherosclerosis: Is It Possible?

In the 1920s, Anichkov and colleagues reported that switching cholesterol-fed rabbits to low-fat chow over 2 to 3 years resulted in arterial lesions becoming more fibrous with a reduced lipid content,[9] which from a modern perspective suggests plaque stabilization.[10,11] To our knowledge, however, the first prospective, interventional study demonstrating substantial shrinkage of atherosclerotic lesions was performed in cholesterol-fed rabbits and was reported in 1957.[12] The dietary regimen raised total plasma cholesterol to ~26 mmol/L (~1000 mg/dL) and induced widespread lesions involving ~90% of the aorta. To mobilize tissue stores of cholesterol, animals received IV bolus injections of phosphatidylcholine (PC). After <10 days of treatment, the remaining plaques were scattered and far less severe than initially, and 75% of arterial cholesterol stores had been removed.

Over the next 20 years, similar arterial benefits from injections of dispersed phospholipids were reported by a number of groups using a variety of atherosclerotic animal models, including primates.[4] Given the heavy reliance of atherosclerosis research on animal models, it is surprising that these impressive, reproducible results were largely ignored, even in numerous historical reviews of regression.[1,3,5,9,13,14]

The concept of regression gained support with a short-term study in squirrel monkeys,[15] and more extensive work reported that advanced arterial lesions in cholesterol-fed Rhesus monkeys underwent shrinkage and remodeling during long-term follow-up when their diet was switched to low-fat or linoleate-rich diets.[13,16] The cholesterol-feeding induction period lasted 17 months, producing widespread coronary lesions, with fibrosis, cellular breakdown, intracellular and extracellular lipid accumulation, and 60% luminal narrowing. The subsequent regression period lasted 40 months, bringing total plasma cholesterol values down to ~3.6 mmol/L (~140 mg/dL) and resulting in the loss of ~66% of coronary artery cholesterol, substantial reduction in necrosis, some improvement in extracellular lipid levels and fibrosis, and substantial lesion shrinkage, so that only 20% luminal narrowing remained.[13,16] Further work confirmed and extended these findings.[9,14] Three decades ago, in an overview of this work, it was concluded that "In the primate the answer is clear: all grades of induced lesions studied to date improve … the primate lesion shows amazing metabolic responsiveness: some extracellular as well as intracellular lipid is depleted, there is resolution of necrotic lesions, crystalline lipid tends to diminish slowly, and fibroplasia is eventually contained."[13]

Regression of advanced lesions in cholesterol-fed swine after reversion to a chow diet demonstrated an important sequence of events.[17] Histological examination of atheromata from these animals immediately after the high-cholesterol induction phase showed hallmarks of complex plaques, including necrosis and calcification. The regression regimen reduced total plasma cholesterol to ~1.8 mmol/L (~70 mg/dL), implying an even lower LDL cholesterol (LDL-C) level. Interestingly, the early phase of regression showed loss of foam cells from the lesions, and an increase in non—foam-cell macrophages around areas of necrosis. Long-term, the necrotic areas virtually disappeared, indicating removal of the material by a flux of functioning, healthy phagocytes.[17]

To revive the long-neglected finding of rapid atherosclerosis regression after injections of dispersed phospholipids, researchers have sought to determine the underlying mechanism of action.[4,18] Aqueous dispersions of PC spontaneously form vesicular structures called liposomes. Initially, cholesterol-free PC liposomes remain intact in the circulation[19] and can mobilize cholesterol from tissues in vivo[19-22] by acting as high-capacity sinks into which endogenous high-density lipoprotein cholesterol (HDL-C) shuttles lipid.[4,23,24] Bolus injections of PC liposomes rapidly restore normal macrovascular and microvascular endothelial function in hyperlipidemic animals,[22] remove lipid from advanced plaques in rabbits in vivo,[25] and rapidly mobilize tissue cholesterol in vivo in humans.[26] Importantly, the optimum liposomal size (~120 nm) has been achieved in animal model studies, which allows these particles to gradually deliver cholesterol to the liver without suppressing hepatic LDL receptor expression or raising plasma concentrations of LDL-C.[21,27]

In 1976, success in atherosclerosis regression also was achieved in rabbits following reversion to normal chow diet in combination with hypolipidemic and other agents.[9] Decades later, a series of studies achieved