

The atherosclerotic plaque was not built in a day: the dynamic nature of plaque progression and instability

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Abstract

Recent studies have determined that atherosclerosis is a dynamic disease, with both progression and regression of plaques possible, as well as marked change in composition that affect plaque stability. Plaque composition, rather than size, determines the clinical course and consequences of atherosclerosis. In particular, recent findings from models of atherosclerosis have emphasized the important contribution of both inflammatory cells and the death of smooth muscle cells. The mechanisms underlying plaque vulnerability and their implications for development of treatment for atherosclerosis are discussed in the light of this knowledge.

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Introduction

Atherosclerotic plaques consist of an accumulation of vascular smooth muscle cells (VSMCs), inflammatory cells (macrophages, T lymphocytes, dendritic cells, and mast cells) underlying a dysfunctional endothelium, together with extracellular lipid, collagen and matrix. These cellular and acellular components are arranged into defined structures within the plaque. Thus many advanced plaques comprise a VSMC-rich fibrous cap overlying a lipid- and macrophage-rich necrotic core. Most atherosclerosis is clinically silent, and the consequences of its presence rarely occur before the development of advanced lesions. This transition from silent to clinically manifest disease is a reflection of profound changes in the components and structure of the plaque, resulting in plaque erosion or plaque rupture, the major triggers to myocardial infarction [1].

Composition of atherosclerotic plaques – the key to clinical outcome

Although plaques can show similar structures, there are defining features that determine whether a plaque is more likely to undergo erosion or rupture. These features of stability are important both to predict the individual risk and as major targets for drug therapy for plaque stabilization. Thus plaques liable to undergo rupture show a thin fibrous cap, a larger necrotic core and lipid component, and a reduced VSMC component compared with plaques that are less likely to rupture [2]. The fibrous cap of advanced plaques is thinned from loss of VSMCs, and these thin-cap fibroatheromata are the most common of the lesions that rupture [3].

Until recently, the plaque has been considered to be a passive structure, caused by gradual accumulation of tissue that obstructs the vessel. In contrast, recent

research has demonstrated the dynamic nature of plaque components. The biological processes that maintain the plaque include cell migration and emigration, cell division and cell death, matrix synthesis and degradation, and accumulation or loss of lipid. The cellular changes occur in many of the different cell types within the lesion, increasing the complexity of plaque dynamics. Each of these processes would be predicted to increase or decrease the relative stability of the plaque, and are thus all targets for therapy. For example, macrophage accumulation, and activation and release of matrix-degrading proteinases would all be predicted to promote plaque rupture, and there is considerable evidence in humans to support this contention. In contrast, loss of VSMCs from the fibrous cap, for example via the process of apoptosis, would be predicted to promote plaque instability, and both human and animal data support this assertion [4,5]. Increased lipid content also promotes instability, and recent studies have shown that reducing lipid content also reduces plaque inflammation, and may in some cases cause plaque regression.

Composition of atherosclerotic plaques – the key to treatment

These observations reinforce the concept that changes in plaque composition, rather than plaque volume per se, can have profound influences on plaque instability and thus the risk to the patient. We would also predict that treatments aimed at several processes that promote plaque instability, or which result in changes in several components of the plaque, would have beneficial effects. For example, statin therapy reduces lipid content of the plaque, reduces the accumulation and activation of macrophages and lymphocytes, increases VSMC content, increases fibrous cap thickness, and improves endothelial reactivity and function [6–9]. These effects are all noted at standard therapeutic doses, and in animal models they occur without any change in serum cholesterol [9]. In contrast, VSMC apoptosis reduces fibrous cap thickness, increases necrotic cores, and increases plaque inflammation – all processes predicted to promote plaque instability [5]. This concept may also suggest why there is more limited benefit for agents that target only one process involved in plaque rupture or its consequences. In such a complex process as atherosclerosis it may be that the more “dirty” the drug, the more processes it affects, and the more benefit may be derived.

Our increasing understanding of plaque dynamics also raises the question of the stage at which a plaque is too far advanced to be altered by therapy. Results from both animal and human studies have demonstrated that atherogenesis is more easily manipulated than are established plaques [10], and the more

advanced the lesion, the less likely that intervention will alter plaque components in a beneficial manner. In advanced plaques, VSMCs become senescent [11], and are thus less able to divide and repair lesions. More advanced plaques, and particularly calcified plaques, are less likely to regress after intensive lipid-decreasing regimens than are more moderate lesions [12,13]. The implications of this are that plaque modification is best achieved by prevention, or at the early stages of disease, and although therapy is hugely beneficial, plaques are less tractable once they present with symptoms.

Not only do we need to treat plaques early, we need systemic therapy to treat the systemic effects of atherosclerosis. Although local treatment with angioplasty/stenting (coronary disease), endarterectomy (carotid disease) and angioplasty/surgery (iliofemoral disease) is effective at relieving symptoms, and in some cases reduces future patient events, it is clear that unstable plaques occur throughout the arterial tree, and what is identified as the culprit lesion may not be so. In particular, recent studies have shown that there are several unstable lesions in coronary arteries both upstream and downstream of what is designated the culprit lesion (reviewed in [14]). Although some workers advocate local coronary stenting at regions most likely to result in myocardial infarcts [15], recent scares over late patency of drug elution stents means that systemic therapy is likely to be both more effective and cost-efficient for the majority of patients.

Summary

Recent studies have demonstrated the complex and dynamic nature of the atherosclerotic plaque. Plaque behavior is governed more by composition than by volume. Early plaques are tractable, although the ability to alter both plaque composition and plaque size decreases with advanced disease. Atherosclerosis is a systemic disease, and early systemic therapy to alter plaque composition is likely to be the most effective method of altering the natural history of atherosclerosis. ■

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Basic article

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