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New Insights into Plaque Stabilisation by Lipid Lowering

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Abstract

Thrombosis on the substrate of a disrupted plaque causes most acute coronary events. The physical integrity of the plaque thus governs the most important clinical manifestations of atherosclerosis. Of particular importance is the extracellular matrix of the fibrous capsule overlying the thrombogenic core of the atheroma.

Stable atheroma generally have thick fibrous caps, and smaller lipid cores than lesions that have ruptured. Accumulating evidence supports a key role for inflammation as another critical determinant of the stability of human atherosclerotic plaques.

Plaques that rupture usually have more abundant leucocytic infiltrates than those considered stable. Inflammatory mediators such as cytokines can influence several biological processes that regulate the stability of the plaque's fibrous cap, and thus its resistance to rupture.

For example, interferon-γ produced by activated T lymphocytes within atheroma inhibits the production of interstitial forms of collagen by human vascular smooth muscle cells. Inflammatory cytokines such as interleukin-1, tumour necrosis factor (TNF) and CD-40 ligand (a cell surface homologue of TNFα) can also elicit the expression by macrophages and smooth muscle cells of proteolytic enzymes that can weaken the extracellular matrix.

We have hypothesised that lipid lowering reduces stimuli for the inflammatory response within the complex atherosclerotic lesion. Recent studies in rabbits with experimentally produced atherosclerosis have indeed shown that lipid lowering can (i) reduce macrophage numbers, (ii) decrease expression of the collagenolytic enzyme MMP-1, and (iii) reinforce the plaque's fibrous skeleton by increasing the content of interstitial collagen.

By reducing local inflammation, lipid lowering can thus stabilise the plaque's fibrous cap, rendering the atheroma less prone to rupture and to precipitate thrombotic complications.

These observations provide a mechanistic basis for understanding the marked reduction in acute coronary events and cerebrovascular accidents observed in patients treated with agents that reduce plasma lipids.

The traditional concept of atherosclerosis suggests that chronic atheroma develop gradually in the coronary circulation until much of the arterial lumen is occluded and a small incremental obstruction is able to precipitate an acute coronary event. It is now known, however, that this model does not describe the sequence of events underlying most coronary events.

Serial angiographic studies have demonstrated that the degree of stenosis preceding a myocardial infarction (MI) is usually less than 70%.[1] In addition, intravascular ultrasound has shown that some angiographically normal vessels contain large atheromatous lesions.[2]

Studies of plaque regression during lipid-lowering therapy provide further evidence that angiographic regression is not a good measure of the benefit of lipid lowering. Reductions of approximately 25 to 40% in low density lipoprotein-cholesterol have consistently been associated with reductions of approximately 50% in the incidence of coronary events, despite producing only modest regression of stenosis (generally <0.07mm).[3-10]

These studies suggest that reduction in arterial stenosis is not the mechanism by which lipid lowering prevents coronary events. Rather, accumulating evidence suggests that lipid lowering serves to prevent coronary events by stabilising atherosclerotic lesions.

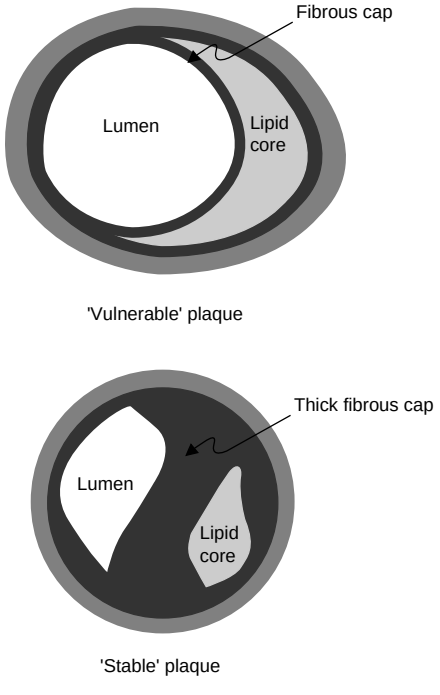

Fig. 1. Schematic representation of 'stable' and 'vulnerable' atherosclerotic lesions (adapted from Libby,[12] with permission).

1. The Structure of Atheromatous Lesions

Atherosclerotic plaques typically consist of a lipid-rich core separated from the vessel lumen by a cap of fibrous tissue. Contained within the plaque are vascular smooth muscle cells that generate collagen, elastin and the other macromolecules that give this extracellular matrix its strength. The lipid-rich core typically contains large numbers of lipid-laden macrophages, known as 'foam cells' because of the foamy appearance of their cytoplasm.

Macrophages resident within the cell wall produce large amounts of procoagulant factors that stimulate thrombus formation when in contact with blood.[11] Thus, disruption of this atherosclerotic plaque frequently precipitates the thrombus formation that leads to acute coronary events.[12-14]

Plaques that rupture generally have more abundant leucocytic infiltrates than those considered stable. These plaques (so-called unstable or 'vulnerable' plaques) have thin, friable caps characterised by a generally low collagen content and pronounced accumulation of macrophages (fig. 1).[13,15-17]

In contrast, angiographically detectable stenotic lesions often have relatively thick fibrous caps (fig. 1). Such plaques may be described as 'stable' because, although a frequent cause of demand angina, they cause fewer myocardial infarctions than the more numerous less stenotic lesions.

Inflammatory processes also play a role in the biology and stability of the atherosclerotic plaque. Activated T lymphocytes in the atherosclerotic plaque produce the cytokine interferon-γ (IFNγ), which acts on vascular smooth muscle cells to

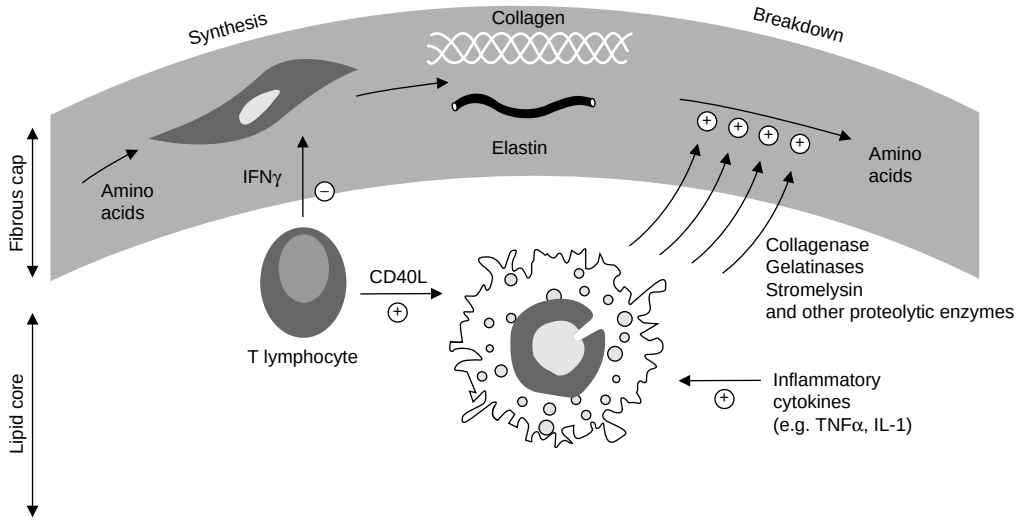

Fig. 2. Schematic diagram showing synthesis and catabolism of collagen and elastin in the extracellular matrix of the fibrous cap (adapted from Libby,[12] with permission). **CD40L** = CD40 ligand; **IFN**γ = interferon-γ; **IL-1** = interleukin-1; **TNF**α = tumour necrosis factor α.

decrease the synthesis of interstitial collagen (fig. 2).[18-20] IFNγ also inhibits smooth muscle cell proliferation,[21,22] providing a further mechanism of reduction of collagen synthesis in the atheromatous lesion.

In addition to impaired collagen synthesis, increased collagen breakdown appears to play a role in critically weakening the fibrous cap. Lesional macrophages produce a variety of proteolytic enzymes that break down collagen.[23,24] Of particular importance are enzymes of the matrix metalloproteinase (MMP) family, such as interstitial collagenase (MMP-1), stromelysin (MMP-3) and gelatinase-B (MMP-9).[23,25,26]

Several studies have established that a variety of inflammatory cytokines contained within the plaque, such as interleukin-1, tumour necrosis factor (TNF) and CD 154, a cell surface homologue of TNFα (also known as CD-40 ligand), can stimulate MMP expression in macrophages and vascular smooth muscle cells (fig. 2).[27-29]

2. The Effect of Lipid Lowering on Plaque Stabilisation

Available evidence suggests that the beneficial effects of lipid lowering are a result of reduced inflammatory stimulation in atheromatous lesions.

Lipid lowering reduces the number of macrophages in experimental atheroma.[30-32] In addition, recent experiments have demonstrated that dietary lipid lowering stabilises plaques by reducing proteolytic activity.[32] In rabbits with aortic atheroma produced by diet-induced hypercholesterolaemia and balloon-injury, baseline lesions were high in macrophage content and expression of MMP-1. These features persisted in rabbits that were maintained on a hyperlipaemic diet. However, in rabbits changed to a low cholesterol diet for 8 or 16 months, significant reductions in lesion MMP-1 expression and macrophage content were observed. This decrease in proteolytic activity was accompanied by a corresponding increase in collagen content in the intima of the vessel, indicating

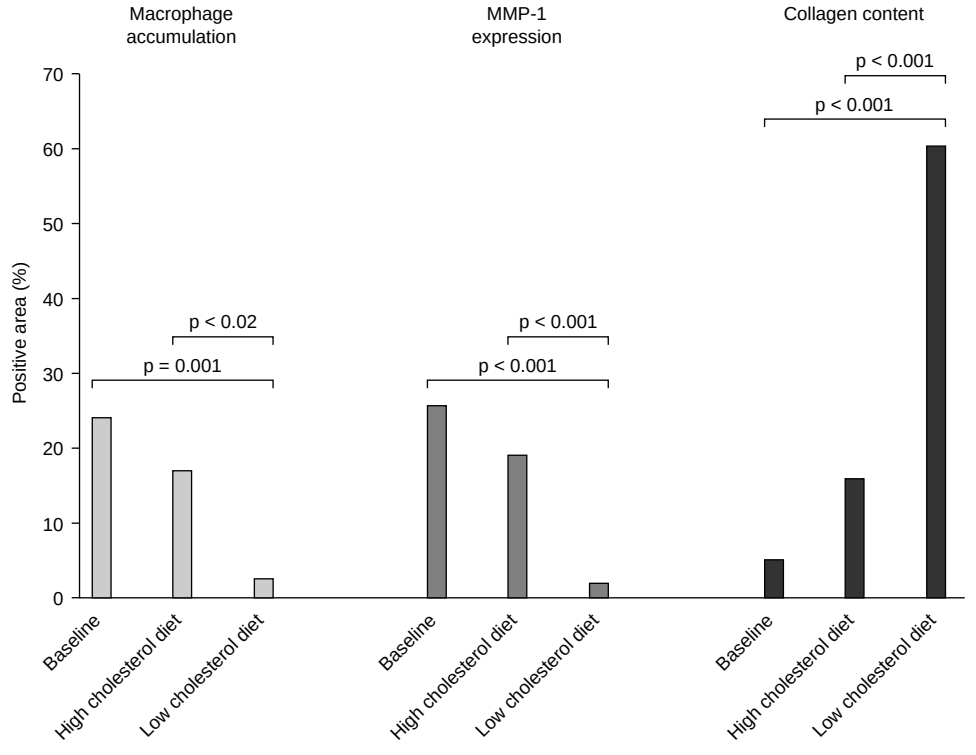

Fig. 3. Macrophage accumulation, interstitial collagenase (MMP-1) expression and interstitial collagen content of aortic atheroma in hypercholesterolaemic rabbits after 16 months of a low or high cholesterol diet. Quantitative analysis expressed as a percentage of immunopositive cross-sectional area within the intima.[32]

that lipid lowering reinforced the fibrous skeleton of the atheroma (fig. 3).

3. Summary

Accumulating evidence suggests that lipid lowering acts to reduce local inflammation and increase the collagen content of the fibrous cap of the plaque, thus stabilising the lesion. Stable atheromatous lesions are less likely to rupture and precipitate thrombotic complications.

These observations provide a mechanistic basis for understanding the marked reduction in acute coronary events and cerebrovascular accidents observed in patients treated with agents that reduce plasma lipids. This improved understanding of the cellular and molecular characteristics of atherosclerotic lesions may one day translate into further reductions in cardiac mortality and morbidity.

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