Do modified lipids and lipoproteins drive the inflammation in unstable coronary plaques?

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Atherosclerosis is a disease of the arterial intima that affects a large part of the vascular tree. It begins as an asymptomatic accumulation of cells, lipids and extracellular matrix, but later stages of the disease are characterized by an invasion of inflammatory cells, the generation of cytokines, free oxygen radicals and proteolytic enzymes, and the development of unstable plaques. Rupture of an unstable atherosclerotic plaque is today regarded as the major cause of clinical cardiovascular events such as unstable angina pectoris and myocardial infarction.

Our research is focused on understanding the factors that transform the innocent intimal thickening into an inflamed rupture-prone unstable plaque.

Energy depletion in atherosclerotic plaques

In a recent study, we showed that atherosclerotic lesions in vivo are characterized by ATP depletion, low levels of glucose and glycogen, and a high level of lactate, indicating anaerobic glucose metabolism (Fig. 1). The energy depletion may be a major contributor to local cell dysfunction and death (1).

Phospholipase A2 and unsaturated fatty acids: role in inflammation

Modified phospholipids are a major source of bioactive components. Through the action of phospholipase A2 (PLA2), phospholipids are converted into lysophospholipids and arachidonic acid, both potential proinflammatory mediators. We have shown that lipoproteins from subjects with diabetes are more sensitive to PLA2 type V than lipoproteins from control subjects (2). This may partly explain the increased inflammation in atherosclerotic lesions in patients with diabetes. Data suggest that genetic variations of PLA2 may be of functional importance.

Individuals with diabetes have high plasma levels of nonesterified fatty acids, which may be involved in inflammation in the vascular wall. In cell culture studies, we have shown that unsaturated long chain fatty acids increase the inflammatory response in macrophages. Preliminary evidence suggests that this effect may be mediated by ceramide formation.

Statin treatment
We have analyzed atherosclerotic plaques obtained by directed atherectomy in patients undergoing percutaneous coronary intervention to treat stable angina pectoris (Fig. 2) and found that statin treatment reduces the number of T cells in the tissue (3). Furthermore, plaques from subjects on long-term statin treatment have more collagen and fewer macrophages, indicating stable plaques. We also showed a strong correlation between plaque stability and apolipoprotein AI (apoAI) levels in plasma. Levels of ApoAI in plasma are strongly correlated with high-density lipoprotein (HDL) levels, and low apoAI has been shown to be equivalent or better than low HDL cholesterol as a risk marker for atherosclerosis or cardiovascular events.

**Inflammatory markers**

To identify potential markers of plaque instability, we analyzed blood taken from the site of a coronary plaque before and after balloon dilatation in patients receiving treatment for an acute coronary syndrome. We measured an increased local release of the proteolytic enzyme matrix metalloproteinase 9 (4). Further studies are required to determine if this enzyme is an important marker of plaque instability.

In a further study, we measured the plasma levels of inflammatory molecules in samples taken from patients on admission to hospital for an acute coronary syndrome, and determined if we could observe any correlations between these molecules and clinical prognosis (5). The patients were followed for up to eight years. C-reactive protein and interleukin 6 were identified as strong markers for long-term prognosis of morbidity and mortality.

**Conclusion**

Inflammatory activity has been shown to be a marker for plaque instability and also an indicator of long-term prognosis after an acute coronary event. Modified lipids may be driving the inflammatory activity leading to plaque instability and rupture, and we have identified potential molecules that may be of key importance. We also suggest that treatment of lipid disorders with statins may stabilize the plaques and thus reduce the risk of acute coronary events.
Fig. 1. Energy metabolism in atherosclerotic plaques from rabbit aorta. In severe plaques, ATP (A) and glucose (B) are depleted in the core.
Fig. 2. Immunhistochemistry of a coronary plaque obtained by directed coronary atherectomy. The tissue is stained for macrophages (blue) and smooth muscle cells (red).

References


