Conclusions: OxyLDL leads to impaired NO generation and apoptotic cell death in BAEC. This effect occurs via overexpression of LOX-1 and the subsequent attenuation of protective autophagic response thereby contributing in the pathophysiology of oxyLDL-induced endothelial dysfunction which characterizes early stages of atherosclerotic process.

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The cross talk between oxyLDL and inflammation in atherosclerosis

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Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), one of the scavenger receptors for oxidized low density lipoprotein (ox-LDL), plays a crucial role in signaling pathways involved in the process of oxidative stress and inflammation. As evidence supporting the vital role of LOX-1 keeps accumulating, there is growing interest in LOX-1 as a potential therapeutic target. Here, we review the discovery and genetics of LOX-1, describe existing evidence supporting the role of LOX-1 in atherogenesis and its major complication- myocardial ischemia, and summarize its modulation by some naturally occurring compounds that could be of therapeutic use.

Ox-LDL/LOX-1 relationship appears to be an important player in the development of atherosclerosis and its sequelae, such as MI and cardiac remodeling. The scavenger receptor LOX-1 activates most, if not all, signaling from the beginning to culmination of major life-threatening events related to this malady. From genetic studies, it is quite evident that certain individuals have propensity to develop CAD-related events. Since the current therapies of coronary heart disease, mainly LDL-cholesterol lowering drugs, are ineffective in a large number of patients, there is need for new targets that focus on the underlying signals of the disease process. A host of strategies are being proposed that would either block oxidation of LDL-cholesterol and/or reduce the expression of LOX-1. While the development of these strategies is eagerly awaited, some naturally occurring compounds appear quite promising and deserve clinical trials.

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The role of oxidative stress in vascular pathobiology

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The endothelium regulates vascular homoeostasis through local elaboration of mediators that modulate vascular tone, platelet adhesion, inflammation, fibrinolysis, and vascular growth. Impaired vascular function contributes to the pathogenesis of atherosclerosis and acute coronary syndromes. Impaired endothelial function is associated with atherothrombotic risk factors and atherothrombotic disease, is pathophysiologically linked to acute cardiovascular syndromes. A central feature of impaired endothelial function in the presence of cardiac risk factors and under pathological conditions is impairment in endothelium-derived bioactivity.

Nitric oxide is produced in endothelial cells from the conversion of l-arginine to l-citrulline through the activity of (endothelial) nitric oxide synthase. EDNO regulates vascular tone through a dilator action on vascular smooth muscle cells that depends on soluble guanylyl cyclase activation and consequent increase in guanosine monophosphate. Additional antiatherogenic functions of EDNO relate to inhibition of platelet activity, leucocyte adhesion, and vascular smooth muscle cell proliferation. Mechanisms underlying impaired endothelial function in various disease states such as hypertension, diabetes mellitus, hypercholesterolaemia, and atherosclerosis are likely multifactorial. There is growing evidence that oxidative stress (defined as an imbalance between endogenous oxidants and antioxidants in favour of the former) contributes to mechanisms of vascular dysfunction. These observations fit well with the recognition that increased oxidative stress may be central to the atherogenic process.

Although the mechanism of oxidative modification of LDL remains unknown, the importance of oxidation can be seen by the presence of oxidized LDL in atherosclerotic lesions. Experimentally, the amount of oxidized LDL is reflective of the atherosclerotic burden. Oxidized LDL induces a series of atherogenic processes, including transcription of proatherogenic genes, production of matrix metalloproteinases and tissue factor, antagonism of endothelial cell production of NO, and promotion of vascular smooth muscle cell apoptosis. The augmented production of superoxide anion also rapidly reacts with NO to produce peroxynitrite, a potent oxidant.

However, large trials of antioxidant vitamins, including the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevention Trial, the Heart Outcomes Prevention Evaluation Study (HOPE), and the Heart Protection Study (HPS), have not demonstrated any reduction in clinical events with antioxidant vitamin E therapy. The antioxidants used in these trials, however, have limitations that may have precluded an adequate test of the hypothesis. Conventional antiplatelet therapy has also antioxidant effects by virtue of its ability to limit production of ROS by activated platelets. The importance of oxidative stress in the pathogenesis of atherosclerosis makes clear that the limitations of current therapies should not conclude therapeutic interest in this area but foster investigation into new avenues of treatment.

There is considerable need for additional investigation into the basic mechanisms of atherosclerosis. It is important to clarify the differential role of HDL cholesterol metabolism and other lipid disturbances as well as the biomechanical and rheologic factors in development and progression of disease in the noncoronary circulations. Greater research is needed in understanding regional differences in plaque formation and clinical manifestations of disease. Genetic variability across individuals and populations merits additional exploration using genomics and proteomics. Pathophysiological responses to changes in metabolic demand such as exercise and factors that determine development of collateral vessels and angiogenesis need greater attention. In particular, the interaction between reduced oxygen and substrate delivery and skeletal muscle, neurological, and metabolic function needs additional study. There is a need for improved functional imaging and biomarkers of disease progression and unstable patterns of atherosclerosis to assist in understanding of regional disease pathophysiology.

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Hypertension: Should we ablate all hypertensives? Pro

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