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Oxidized Low-Density Lipoproteins and Atherosclerosis

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Basic research has provided strong evidence that LDL oxidation plays an important role in atherogenesis. Several mechanisms have been identified which can lead to LDL oxidation *in vivo*. Clinical and epidemiological studies have provided circumstancial evidence that oxidized LDL may be involved in the progression of atherosclerotic vascular disease. Better understanding of mechanisms that lead to LDL oxidation or protect LDL against oxidative damages should help the development of new strategies for the prevention of cardiovascular diseases. *J Clin Basic Cardiol 2000; 3: 87–8.*

Key words: antioxidative mechanisms, atherogenesis, free radicals, oxidative mechanisms

Atherosclerosis and cardiovascular diseases remain a major health problem in industrialized countries [1]. High plasma total cholesterol and low-density lipoprotein (LDL) cholesterol values show significant positive correlation to the development of atherosclerosis and cardiovascular diseases [2]. Recent evidence suggests that oxidized LDL (Ox-LDL) plays an important role in the pathogenesis of atherosclerosis [2–4]. The purpose of this article is to review recent findings regarding the role of Ox-LDL in atherogenesis.

LDL oxidation

Lipid peroxidation can damage LDL particles in several ways. Many reactive radical species can initiate lipid peroxidation. These reactions involve lipoxygenases, superoxide anion, hydroxyl radical, peroxinitrite, haem proteins, ceruloplasmin and myeloperoxidase [4]. *In vitro* studies have demonstrated that at least 15-lipoxygenase, superoxide anion, peroxinitrite and myeloperoxidase can oxidize LDL [4]. Peroxinitrite may be formed in the arterial wall in the reaction of superoxide anion with nitric oxide [5]. It is also possible that oxidized membrane lipids are transferred to LDL.

In addition to lipid peroxidation, LDL oxidation also involves modification of apolipoprotein B (apoB). ApoB in Ox-LDL is fragmented and contains covalently bound malondialdehyde and 4-hydroxynonenal conjugates [2, 3]. These reactions change LDL properties so that it is metabolized through macrophage scavenger receptors [6] and other receptors recognizing modified LDL [7]. Ox-LDL is also more susceptible to aggregation. Additional modifications of LDL can be caused by phospholipases, proteoglycans and platelet secretion products [8].

LDL antioxidant levels do not fully explain individual differences in the susceptibility of LDL to oxidative stress [9]. It is likely that other factors, such as fatty acid composition and LDL particle size may also affect LDL oxidation. It has been shown that small, dense LDL particles are more susceptible to oxidation than larger LDL subfractions [9]. On the other hand, LDL particles enriched with monounsaturated fatty acids are less prone to oxidation than particles enriched with polyunsaturated fatty acids [9].

Atherogenic properties of oxidized LDL

Ox-LDL has several atherogenic properties (Table 1). It causes lipid accumulation in macrophages and foam cell formation. Ox-LDL is also cytotoxic to many cell types and chemotactic for monocyte macrophages [2]. In addition, Ox-LDL can inactivate endothelial cell-derived relaxing factor and cause apoptosis.

It is becoming clear that the biological properties of minimally oxidized LDL (MM-LDL) are different from those of fully Ox-LDL [10]. Table 1 summarizes some of the properties of MM-LDL and Ox-LDL. MM-LDL seems to have several specific effects on gene expression. It can stimulate monocyte chemotactic factor-1 and macrophage colony stimulating factor-1 expression and activate prothrombotic properties in the vascular wall [10]. However, MM-LDL does not cause lipid accumulation in arterial cells since it is not metabolized through scavenger receptors. Ox-LDL appears to be immunogenic causing autoantibody formation in humans and in experimental animals [11–13]. According to preliminary results, presence of autoantibodies may predict the progression of atherosclerosis in human populations [13]. Ox-LDL autoantibodies also show a significant association to endothelial dysfunction *in vivo* [14].

Evidence for the presence of oxidized LDL *in vivo*

Substantial evidence now indicates that Ox-LDL is present in atherosclerotic lesions: (1) LDL isolated from human atherosclerotic lesions, but not from normal arteries, re-

Table 1. Biological properties of minimally oxidized LDL and fully oxidized LDL

	Minimally oxidized LDL	Oxidized LDL
Cellular lipid accumulation	No	Yes
Reactive aldehyde conjugates in ApoB	No	Yes
Metabolism through scavenger receptor	No	Yes
Metabolism through LDL receptor	Yes	No
Stimulates proinflammatory cytokines	Yes	No
Inhibits endothelial-derived relaxing factor	No	Yes
Immunogenic	No	Yes
Cytotoxic	No	Yes
Chemotactic for plasma monocytes	No	Yes
Apoptosis	No	Yes

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sembles Ox-LDL [3]; (2) epitopes characteristic of Ox-LDL can be demonstrated in atherosclerotic lesions by immunocytochemistry [11]; (3) atherosclerotic lesions contain immunoglobulins which recognize Ox-LDL [12]; (4) serum contains autoantibodies against oxidized LDL [11, 13]; and (5) antioxidant treatment reduces the rate of development of atherosclerotic lesions in experimental animals. Antioxidants shown to be effective in animal models include probucol [15], α-tocopherol [16], butylated hydroxytoluene [17], and diphenylphenylenediamine [18]. However, it remains to be determined whether small quantities of Ox-LDL are present in plasma [19].

Although antioxidants are effective in preventing atherosclerosis and coronary heart disease in animal models and in prospective epidemiological studies [20–23], recent randomized placebo-controlled intervention trials [24–27] and drug studies [28] have shown no beneficial effects. Based on currently available information [25–27] it can be concluded that β-carotene is not useful for the prevention of coronary heart disease. On the other hand, the role of vitamin E is still unclear since a protective effect was seen in a recent secondary prevention trial [29]. Thus, further randomized placebo-controlled intervention trials using vitamin E and flavonoids [30] are warranted to test the hypothesis that increased antioxidant protection could be useful in the prevention of cardiovascular diseases.

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