Role of Lipid Peroxidation and Antioxidants in Atherogenesis

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The atherogenicity of LDL associated cholesterol and the involvement of monocyte/macrophages in the development of early atherosclerotic foam cell lesions have been firmly established [1]. The inability of LDL, however, to generate foam cells in vitro, has led to the race in search of an LDL derived progeny that would do so. A wide array of such modified low density lipoproteins [1] and a receptor that specifically interacts with these lipoproteins, acetyl LDL or scavenger receptor [2], have since been identified.

More than a decade ago Henriksen, Mahoney and Steinberg observed that LDL incubated with certain types of cells was modified to a form that was taken up at a faster rate as compared to unincubated LDL by macrophages. A number of different types of cells including monocytes and macrophages [1] since then have been reported to be capable of modifying LDL. The cell mediated modification of LDL has been extensively studied during the past few years [1]. The modification occurred in media that supported lipid peroxidation and as expected large amounts of thiobarbituric acid reactive substances (TBARS) were formed during the incubation of LDL with cells. Antioxidants such as vitamin E, BHT and probucol prevented modification of LDL. The following sequence of events has been suggested to be involved in the modification [1]:

2. Oxidative non-enzymatic cleavage of apoprotein B-100 and oxidative changes in amino acids [4].
3. Breakdown of lipid peroxides into reactive aldehydes, e.g malondialdehyde, 4-OH nonenal, hexanal etc [5].
4. Derivatization of ε-amino groups of lysine residues with the aldehydes forming schiff's bases [6].

The oxidatively modified form of LDL has been suggested to promote atherogenesis in a number of ways:

1. The oxidatively modified LDL is chemotactic to monocytes and may help to draft monocytes into the artery. When monocytes are phenotypically altered into macrophages, oxidized LDL inhibit their chemotactic motility [1].
2. Oxidized LDL is degraded by macrophages by way of its scavenger receptor leading to foam cell formation [1].
3. Oxidized LDL is cytotoxic and may injure the endothelium and promote platelet adhesion and aggregation [7,8].
Several recent findings have suggested that oxidatively modified LDL may represent one of the atherogenic forms of LDL. There is considerable evidence suggesting the atherogenicity of oxidized LDL.

1. Antioxidants probucol and BHT decreased the severity of atherosclerosis in WHHL and cholesterol-fed rabbits respectively [12-14].
2. Probucol also inhibited the degradation of LDL in the macrophage-rich lesions of WHHL rabbit without affecting its degradation in non-lesion areas [12].
3. Immuno-histochemical staining of WHHL rabbit lesions with antibodies raised against LDL, bearing specific epitopes that may be present in oxidized LDL (e.g. MDA-LDL; 4-OH-nonenal LDL) as well as oxidized LDL has revealed the presence of such epitopes in the lesions [15,16].
4. Auto-antibodies to MDA-LDL are present in normal human and rabbit sera [17].
5. The presence of the modified LDL (acetyl LDL) receptor could be demonstrated in the macrophage-rich rabbit lesions by in situ hybridization techniques. Little or no native LDL receptor activity could be detected under similar conditions [18].

How does LDL oxidation occur in vivo? Recent studies as outlined below have suggested that lipoxygenase, particularly, 15-lipoxygenase activity may be involved in the initiation of LDL oxidation.

1. Treatment of LDL with soybean lipoxygenase results in the generation of a modified LDL similar to that produced by cells [19].
2. Lipoxygenase inhibitors inhibit the modification of LDL by endothelial cells and by macrophages [20,21].
3. Increased 15-Lipoxygenase activity and products have been reported in atherosclerotic lesions of WHHL and cholesterol-fed rabbits [22,23].
4. 15-Lipoxygenase mRNA and protein could be demonstrated in macrophage-rich human and WHHL rabbit atherosclerotic lesions [24].
5. Increased levels of 15-lipoxygenase activity in cells correlated with increased rates of LDL modification (Rankin, S.M., Parthasarathy, S and Steinberg, D. unpublished observation).

However, it should be pointed out that cells that do not express 15-lipoxygenase activity are yet capable of oxidizing LDL. It is prudent to conclude that regardless of the source of the initial lipoperoxide, conditions in the extra-cellular environment that favor rapid propagation of lipid peroxidation would be more detrimental to the LDL particle. In the absence of any adverse effects of LDL associated antioxidants at physiological levels, protection of LDL against oxidative damage may afford safe, yet effective deterrent against atherosclerosis.

References:


