Editorial

Oxidized LDL, a critical factor in atherogenesis

Dayuan Li*, Jawahar L. Mehta

Department of Medicine, University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, United States

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See also article by Zhu et al. [3] (pages 425–432) in this issue.

There is a great deal of experimental, epidemiological, and clinical evidence suggesting that disorders of lipid metabolism play an important role in the pathogenesis of atherosclerosis. To date, there have been many studies investigating the mechanisms by which high levels of LDL-cholesterol affect biology of vessels and cause atherosclerotic lesion formation [1,2]. It has become abundantly clear over the last decade that the oxidatively modified form of LDL (ox-LDL) is more important than native LDL in atherogenesis.

The study in this issue of Cardiovascular Research by Zhu et al. [3] demonstrates that ox-LDL downregulates ATP-binding cassette transporter-1 (ABCA1) in endothelial cells in a dose-dependent manner by inhibiting liver X receptor (LXR) activation. Ox-LDL also attenuates LXR activation by blocking LXR ligand binding and interfering with the generation of 27-hydroxycholesterol, an LXR endogenous ligand. Further, ox-LDL inhibits exogenous cholesterol and oxysterol-induced endothelial ABCA1 induction. Such activity of ox-LDL may contribute to endothelial dysfunction since ABCA1 mediates the active efflux of cholesterol and phospholipids, playing an important role in cholesterol homeostasis and thereby atherogenesis.

2. Oxidized LDL and its receptor LOX-1 in endothelium

The biological effects of ox-LDL are mediated via its receptors. A number of scavenger receptors for ox-LDL, such as SR-A1/II, CD36, SR-B1, and CD68, have been identified on smooth muscle cells and monocytes/macrophages. However, these receptors are not present on endothelial cells in any significant amount. It has been suggested that vascular endothelial cells in culture and in vivo internalize and degrade ox-LDL through a receptor-mediated pathway that does not involve the macrophage scavenger receptors [10]. Sawamura et al. [11] first identified LOX-1 as a critical molecule that is responsible for ox-LDL uptake by endothelial cells. Ox-LDL uptake via LOX-1 causes endothelial activation. Uptake of ox-LDL in endothelial cells (internalization) and subsequent extrusion may be a mechanism by which ox-LDL is transported to the subendothelial region.

Experimental studies have shown that ox-LDL causes injury to endothelial cells via activation of different signal transduction pathways such as those involving PKC and MAPK. Ren et al. [12] suggested that PKCβ may mediate ox-LDL-induced PAI-1 gene expression. Li et al. [8] showed that ox-LDL induces the activation of PKCβ, which plays an
important role in the expression of MMPs and collagenase activity in endothelial cells. In contrast, other PKC isoforms (α, δ and γ) did not change ox-LDL-induced MMP expression. Other studies [4,6] show that the activation of MAPK p42/44 plays a critical role in ox-LDL-induced gene expression of adhesion molecules, monocyte adhesion to endothelial cells, and apoptosis. In addition, the authors [4,6,8] found that these pathological effects of ox-LDL are mediated by its receptor LOX-1 in endothelial cells. Cominacini et al. [5] observed that ox-LDL increases intracellular free radical generation and activates transcription factor NF-κB in bovine endothelial cells. It should be noted that ox-LDL might activate different signal pathways, which interact each other. These interactions may reflect the complicated cross-talk between intracellular signaling pathways induced by ox-LDL and other pro-atherogenic signals.

3. Ox-LDL and atherosclerosis

The importance of ox-LDL in atherosclerosis was first established through the use of the antioxidant probucol in atherosclerosis-prone hyperlipidemic WHHL rabbits [13]. This study showed the significance of the oxidative state in atherogenesis. Now we know that the pro-oxidant state is present in all stages of atherosclerosis from the beginning to the acute thrombotic event. Oxidant state and formation of ox-LDL are potent mitogens for smooth muscle cells [14]. Ox-LDL is taken up by the macrophages, which become foam cells.

To elucidate the role of ox-LDL in plaque instability in coronary artery disease, Ehara et al. [15] measured plasma ox-LDL levels in patients with acute myocardial infarction, unstable angina pectoris, and stable angina pectoris. Plasma ox-LDL levels in patients with acute myocardial infarction were higher than in patients with unstable or stable angina pectoris. Serum levels of total, HDL, and LDL cholesterol did not differ among different patient groups. The pathologic studies in patients who died of acute myocardial infarction revealed that the culprit coronary lesion contained abundant macrophage-derived foam cells with distinct positivity for ox-LDL and its receptors. These results strongly suggest an important role for ox-LDL in the genesis of plaque instability in human coronary atherosclerotic lesions. In addition, the authors [16] found that plasma ox-LDL levels were higher in patients with diabetes mellitus than in those without diabetes mellitus. A recent study [17] found that soluble LOX-1 levels are significantly higher in the serum of patients with acute coronary syndrome than that of the control subjects. Soluble LOX-1 may well become the marker for early diagnosis of acute coronary syndrome.

It still is not clear how ox-LDL particles recognize their receptors and cause activation of intracellular signaling pathways. We do not know how to prevent the binding of ox-LDL to its receptor(s) and thereby prevent the pathological effects of ox-LDL in cardiovascular diseases. Studies in these areas may generate new strategies for treatment of cardiovascular diseases.

References


But we DO know how to prevent ox-LDL from forming in the first place: with apples, and apple polyphenols.