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Review

The oxidative modification hypothesis of atherosclerosis: The comparison of atherogenic effects on oxidized LDL and remnant lipoproteins in plasma

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Abstract

A tremendous number of articles on oxidized LDL (Ox-LDL) and scavenger receptor in macrophage have been published since Steinberg proposed Ox-LDL hypothesis as the major cause of atherosclerosis. This hypothesis has provided strong support for the efficacy of LDL lowering drugs, indicating that lowering LDL means lowering Ox-LDL in vivo.

This manuscript proposed a new oxidative modification hypothesis that remnant lipoproteins determined as remnant-like lipoprotein particles (RLP), not LDL are the major oxidized lipoproteins in plasma, resulting from the plasma concentration of these oxidized lipoproteins. Remnant lipoproteins may play a pivotal role for the initiation of atherosclerosis via lectin-like oxidized LDL receptor-1 (LOX-1) in endothelial cells. Isolated remnant lipoproteins were found to be oxidized or susceptible to be oxidized in plasma, not necessary to be further oxidized in vitro as Ox-LDL. High similarity of proatherogenic and proinflammatory properties of isolated Ox-LDL and remnant lipoporteins have been reported and predicted the presence of similar oxidized phospholipids in both lipoproteins as bioactive components. These results suggest the possibility that reducing plasma remnant lipoproteins rather than LDL should be the target for hyperlipidemic therapy especially in patients with metabolic syndrome for the prevention of endothelial dysfunction in the initiation of atherosclerosis.

Keywords: Oxidative modification; Oxidized LDL (Ox-LDL); Remnant lipoproteins; Remnant-like lipoprotein particle-cholesterol (RLP-C); Oxidized phospholipids; Endothelial dysfunction; Scavenger receptor; Lectin-like oxidized LDL receptor-1 (LOX-1); Endothelium-dependent vasorelaxation (EDR); Flow-mediated vasodilation (FMD); Hypercholesterolemia; Metabolic syndrome; Probucol; Cilostazol; Antioxidants

Contents

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1. Introduction

Over the past 150 years, there have been numerous efforts to explain the complex events leading atherosclerosis. In this endeavour, several hypotheses have emerged that currently are under active investigations. However, these hypotheses are not mutually exclusive, but rather emphasize different concepts as the necessary and sufficient events to support the development of atherosclerotic lesions. In this review, the combination concept of "response-to-injury"[1] and "oxidative modifications"[2] for the initiation of atherosclerosis, rather than the progression of atherosclerosis, is discussed with oxidized lipoproteins, notably oxidized low-density lipoproteins (Ox-LDL) together with remnant lipoproteins (RLP) as a new oxidative modification in plasma. The latter have emerged as new independent atherogenic lipoproteins which rival LDL especially in metabolic syndrome. Accordingly, attempts are made to provide an insight into the atherogenecity of remnant lipoproteins including their contribution to endothelial cell dysfunction through the lectin-like oxidized LDL receptor-1 (LOX-1 receptor) [3] which has been discovered as an Ox-LDL receptor. Recently it was recognized that activation of LOX-1 receptor by remnant lipoproteins plays a key role for the endothelial cell dysfunction [4] and may present a major factor in atherogenesis which is independent from plasma LDL concentration.

2. The oxidized LDL hypothesis

In 1989, Steinberg et al. [2] put forward the original oxidative modification hypothesis based on the notion that oxidation represents a biologic modification analogous to chemical modification discovered by Goldstein et al. [5] that gives rise to foam cells. Since then, numerous studies have supported the Ox-LDL hypothesis which says Ox-LDL can promote foam cell formation through the so-called "scavenger receptor" pathways [5,6]. Scavenger receptor, SRA, in macrophage was first characterized in 1988 by Kodama et al. in Krieger's laboratory [7], but it should be noted that macrophages express more than one scavenger receptor. Several new receptors for Ox-LDL in macrophage such as CD36 [8], LOX-1[3] and SR-PSOX [9], etc., have been discovered after Steinberg proposed Ox-LDL hypothesis. Sawamura et al. [3] noticed the absence of scavenger receptors for Ox-LDL in endothelial cells which may cause the endothelial dysfunction to initiate atherosclerosis. They found a new receptor for Ox-LDL in endothelial cells and named LOX-1 receptor. The Steinberg's hypothesis was proposed under the situation that Ox-LDL receptor (SRA) was the only one receptor found in macrophage associated with the formation of atherosclerotic lesions, but no other receptors ware yet found in endothelial cells. The Ox-LDL hypothesis was proposed mainly for the formation of foam cells from macrophages via scavenger receptor as the major cause of atherosclerosis, but not for the dysfunction of endothelial cells which initiate the formation of atherosclerotic lesions.

However, the present concept is that atherosclerosis represents a state of heightened oxidative stress characterized by lipid and protein oxidation in the vascular wall. The current oxidative modification or stress hypothesis of atherosclerosis predicts that LDL oxidation is an early, essential event in atherosclerosis and that Ox-LDL does contribute to both initiation and progression of atherosclerosis. But besides Ox-LDL, the possibility still exists that other lipoproteins which are oxidized in plasma with normal LDL concentration may cause to form the atherosclerotic lesions. A new oxidative modification hypothesis of remnant lipoproteins for the initiation of atherosclerosis in endothelial cells is discussed in this manuscript.

3. Is LDL or VLDL the origin of apo B-100 in atherosclerotic plaques?

The oxidative modification hypothesis focuses on the concept that LDL in its native form is not atherogenic [10]. However, LDL modified chemically is readily internalized by macrophages through the so-called scavenger receptor pathway [5]. Exposure to vascular cells in medium that contains transition metals also results in modification of LDL such that it serves as a ligand for the scavenger receptor pathway [6]. Therefore, it is now clear that only one mechanism whereby cells in vitro render LDL a substrate for the scavenger receptor pathway is via oxidation of LDL which results in modification of apo B-100 as well [11]. These observations form the basis for the oxidative modification hypothesis of atherosclerosis in which LDL traverses the subendothelial space of lesion-prone arterial sites. During this process, LDL lipids are subject to oxidation and modifications of the lysine residues on apo B-100 leads to an increase of the net negative charge on the lipoprotein particles [12]. This modification of apo B-100 renders LDL susceptible to macrophage uptake via a number of scavenger receptor pathways producing cholesterol ester-laden foam cells [13].

The presence of Ox-LDL in atherosclerotic lesions has been studied using antibodies that recognize specific epitopes