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Review article

Circulating desialylated low density lipoprotein

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In memory of Vladimir Tertov.

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ABSTRACT

Accumulation of lipids is the central event in the development of atherosclerotic lesion. Circulating low-density lipoprotein (LDL) particles are known to be the major source of cholesterol and other lipids stored in atherosclerotic plaque. However, not all LDL particles possess atherogenic properties. In order to induce lipid accumulation in arterial cells, LDL particles have to undergo modifications. Although among such modifications the oxidation remains the most studied one, other atherogenic LDL modifications have been described. According to a series of studies conducted with blood serum and LDL from atherosclerotic patients, desialylation is one of the earliest if not the first atherogenic modification of LDL. Desialylation occurs in the bloodstream and is followed by a cascade of other modifications, including the reduction of LDL particle size and increase of its density, acquisition of negative electrical charge, oxidation and formation of highly atherogenic complexes. In this mini-review we will discuss the concept of multiple atherogenic modification of LDL leading to initiation and progression of atherosclerosis.

Contents

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Introduction

Extra- and intracellular deposition of lipids, predominantly of cholesteryl esters, in the arterial intima is one of the earliest manifestations of atherosclerosis [1–4]. The formation of lipid-laden foam cells is recognized as the triggering factor in the pathogenesis of atherosclerosis [5,6]. By the end of 1970s, it was found that low density lipoprotein (LDL) circulating in human blood is the source of lipid accumulation in vascular cells [7,8]. However, only modified LDL, and not native lipoprotein, causes intracellular lipid accumulation.

Currently, PubMed lists 8692 articles indexed under ''oxidized LDL'' and 4108 under ''oxidized LDL and atherosclerosis.'' The hundreds of reviews on this topic remove the need to emphasize the oxidative modification of LDL in detail. It is generally accepted that oxidized LDL causes foam cell formation and triggers atherogenesis [9–11]. However, other atherogenic modifications of LDL have been detected in the bloodstream of atherosclerosis patients, which have attracted much less attention until now.

Small dense LDL is regarded as atherogenic lipoprotein subfraction circulating in the blood. It has been described in a number of excellent reviews [12,13]. Another form of circulating modified LDL is electronegative LDL (LDL(−)), which was detected using methods, sensitive to the particle's electric charge, such as agarose gel electrophoresis, isotachophoresis or ion exchange chromatography [14,15]. The atherogenic LDL (−) fraction was first isolated by Avogaro and co-authors using ion-exchange chromatography [15]. Further research improved the understanding of the LDL(−) properties [16–18].

The authors dedicate this review to the memory of their colleague, Vladimir Tertov, a recognized leader in the research on modified lipoproteins, who died fifteen years ago. However, the research that he initiated continues. In this review, we provide an overview of the results obtained in course of Dr. Tertov's research, as well as of more recent studies published after his death as a tribute to the memory of our colleague.

Desialylated LDL

The search for atherogenic LDL circulating in human blood resulted in the discovery, isolation and characterization of desialylated LDL followed by the studies of the mechanisms of atherogenic modification. As a first step, LDL was isolated from the blood of healthy subjects and cardiovascular patients with angiographically proven coronary atherosclerosis. The ability of LDL to induce intracellular lipid accumulation (atherogenicity) was tested in a primary culture of human aortic intima smooth muscle α-actin-positive cells (typical smooth muscle cells and pericyte-like cells), which correspond to the cell types accumulating fat in atherosclerotic lesions *in situ* [19]. In most cases, LDL samples obtained from healthy individuals induced no intracellular accumulation of phospholipids and neutral lipids [20,21], whereas most of the samples of LDL isolated from the plasma of patients with coronary atherosclerosis increased the intracellular content of triglycerides, free cholesterol and cholesteryl esters [21,22].

What is the reason for LDL atherogenicity? Comparison of atherogenic and non-atherogenic LDL properties demonstrated a significant difference in the sialic acid content of lipoprotein particles [23,24]. Sialic acid is a terminal monosaccharide of asparagine-bound biantennary carbohydrate chains within LDL glycoconjugate moiety. After removal of sialic acid, galactose becomes the terminal saccharide. This fact was used to isolate the subfraction of desialylated LDL from total LDL preparation using *Ricinus communis* agglutinin (RCA_{120}), which possesses high affinity to the terminal galactose [25]. Incubation of cultured cells with normally sialylated LDL subfraction had no effect on the intracellular phospholipid and neutral lipid content [25,26]. By contrast, desialylated LDL subfraction induced a significant increase in the intracellular lipids.

Atherogenicity of desialylated LDL

Two approaches were used to elucidate the mechanisms of intracellular lipid accumulation caused by desialylated LDL: (1) evaluation of binding, uptake and degradation of LDL; and (2) determination of the rate of hydrolysis and esterification of lipids in LDL particles. The uptake of desialylated LDL was much higher than the uptake of native LDL, especially by cells that were cultured from atherosclerotic lesions [27]. Binding to the scavenger–receptor, asialoglycoprotein–receptor and proteoglycans may account for the enhanced cellular binding and uptake of desialylated LDL. On the other hand, degradation rate of internalized desialylated LDL was lower than that of native LDL [27]. The enhanced uptake and the low rate of intracellular degradation lead to the accumulation of desialylated LDL. Desialylated LDL stimulates intracellular esterification of free cholesterol [27]. This can explain the accumulation of cholesteryl esters in human arterial cells caused by desialylated LDL.

In addition to intracellular lipid accumulation, increased proliferative activity and enhanced synthesis of the extracellular matrix components by subendothelial cells are generally recognized as major manifestations of atherosclerosis at the cellular level [28]. Intracellular lipid accumulation induced by desialylated LDL was found to be accompanied by the enhanced proliferative activity and synthesis of the connective tissue matrix components [28,29]. Therefore, desialylated

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