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Desialylated Atherogenic Low-Density Lipoprotein in Atherosclerosis

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Abstract

Pathogenesis of atherosclerosis and the search for novel therapies and diagnostic markers remain major problems of modern medicine. Currently available therapeutic approaches are often not sufficiently effective, probably due to the complexity of the disease mechanisms. This review focuses on the evaluation of low-density lipoprotein (LDL) as risk factors of atherosclerosis. We summarize the current paradigm of LDL involvement in atherogenesis. We question the currently widely accepted hypothesis of the central role of oxidized LDL in atherogenesis and present an alternative concept of multiple modification of LDL that confers its pro-atherogenic properties. 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.

Pro-inflammatory cytokines may influence lipid accumulation in macrophages under incubation with desialylated LDL. We found that pro-inflammatory cytokines, such as IL-6 and IL-15, can increase cholesterol concentration in cells, activated by these cytokines. Moreover, we showed that IL-15 and IL-22 can enhance lipid accumulation in activated macrophages under incubation with desialylated LDL compared to non-activated control cells under the same conditions. Cytokines may increase cholesterol concentration in macrophages by stimulating de novo cholesterol synthesis. In early studies, it was shown that the cytokines IL-1□, IL-6, and TNF-□ can trigger endoplasmic reticulum stress (ER) through the change in the production of reactive oxygen species or the calcium content in the ER. ER stress through activation of the PERK and ATF6 signalling pathways can contribute to the activation of the SREBP1 and 2 sterol synthesis genes. This may explain the observed effect of increased cholesterol in macrophages upon stimulation by IL-6 and IL-15.

IL-6, as it is known, can cause lipid accumulation during stimulation of macrophages by oxidized LDL (oxLDL) through increased expression of the SR-AI receptor. On the other hand, this cytokine can contribute to cholesterol efflux by increasing the expression of the ABCA1 receptor. IL-1□ can promote foam cell formation through the up-regulation of LOX-1 receptor and down-regulation of ABCA1 receptor. IL-32 may reduce the expression of ABCA1 through PPARγ-LXRα-ABCA1 pathway. IL-34 can enhance the expression of CD36 via the p38 MAPK pathway. INF-□ can promote the formation of foam through the up-regulation of CD36 via JAK/Stat pathway. TNF-□ can induce the expression of SR-A and LOX-1. It is also known that IL-17 can promote the formation of foam cells under the incubation of macrophages with oxLDL through the up-regulation of the LOX-1 receptor.

IL-15 and IL-22 are likely to increase the expression of one or more scavenger receptors (CD36, SR-AI, LOX1) and/or decrease the expression of ABCA1. The exact mechanisms of action of these cytokines remain to be determined in further studies.

№	Comparison groups	Intracellular Cholesterol, % of Control (SD)	P (t-test)	P (M-W)		
			Vs Control	Vs LDL	Vs Control	Vs LDL
1	Control	100.0 (9.3)	N/A	N/A	N/A	N/A
2	+ LDL, 100 µg/mL	149.0 (22.7)	<0.01	N/A	<0.01	N/A
3	+ LDL + IL-6, 50 ng/mL	143.8 (15.5)	<0.01	0.46	<0.01	0.70
4	+ IL-6, 50 ng/mL	129.5 (14.5)	<0.01	<0.01	<0.01	0.02
5	+ LDL + IL-15, 50 ng/mL	171.8 (15.7)	<0.01	<0.01	<0.01	<0.01
6	+ IL-15, 50 ng/mL	125.0 (18.3)	<0.01	<0.01	<0.01	0.01
7	+ LDL + IL-22, 50 ng/mL	172.4 (12.1)	<0.01	<0.01	<0.01	<0.01
8	IL-22, 50 ng/mL	110.3 (12.1)	0.05	<0.01	0.02	<0.01

Table 1 the effect of interleukins on the accumulation of cholesterol Cells without prior stimulation. Substances and LDL were added simultaneously to the cells and incubated for 24 hours in RPMI-1640 medium without fetal bovine serum (FBS).

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Keywords

atherogenic modification; atherosclerosis; desialylation; low-density lipoprotein; cytokines

Professional Biography

Alexander N. Orekhov has completed his PhD at the age of 29 years from Moscow State University and second doctoral degree (DSc) from Institute of Experimental Medicine (St. Petersburg). He is the head of laboratory of Institute of General Pathology and Pathophysiology. He has published more than 400 papers in reputed journals and has been serving as an editor-in-chief, guest editor and editorial board member of several biomedical journals.

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