International Journal of Biomedicine 12(3) (2022) 339-343
http://dx.doi.org/10.21103/Article12(3)_RA2

REVIEW ARTICLE

INTERNATIONAL JOURNAL OF BIOMEDICINE

Oxidized Low-Density Lipoprotein and its Atherogenic Potential

Harish Rangareddy*, Shashidhar Kurpad Nagaraj, Soumya Narayanaswamy

Department of Biochemistry, Sri Devaraj Urs Medical College,
Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar, India

Abstract

The emergence of oxidized low-density lipoprotein (OxLDL) is crucial for the progression of cardiovascular diseases (CVD) linked to atherosclerosis. OxLDL stimulates endothelial activation and smooth muscle proliferation and has an atherosclerotic-promoting effect. The measurement of OxLDL correlates with the presence of CVD and may be a prognostic marker for future health outcomes. Circulating OxLDLs can be used as biomarkers since their levels rise in patients with advanced atherosclerosis. Immunological methods have proven to be very useful methodologies. Anti-OxLDL monoclonal antibodies have been developed that bind strongly to OxLDL and are used in ELISA for OxLDL measurements. Routine inclusion of OxLDL estimation in an at-risk population can help the clinicians understand the disease initiation and progression and improve early intervention and management.(**International Journal of Biomedicine. 2022;12(3):339-343.**)

Keywords: oxidized LDL • oxidative stress • atherosclerosis • ELISA

For citation:Rangareddy H, Nagaraj SK, Narayanaswamy S. Oxidized Low-Density Lipoprotein and its Atherogenic Potential. International Journal of Biomedicine. 2022;12(3):339-343. doi:10.21103/Article12(3)_RA2

Abbreviations

ABCA-1, ATP-binding cassette transporter A1; **APH**, 2,2'-Azobis(2-amidinopropane) dihydrochloride; A**poB**, apolipoprotein B-100; **CVD**, cardiovascular diseases; **ELISA,** enzyme-linked immunosorbent assay; **HDL-C**, high-density lipoprotein cholesterol; **LDL**, low-density lipoprotein; **LDL-C**, low-density lipoprotein cholesterol; **LXR**, liver X receptor; **MAB**, monoclonal antibody; **MDA**, malondialdehyde; **MPO**, myeloperoxidase; **OxLDL**, oxidized LDL; **OxPC**, oxidized phosphatidylcholines; **PUFAs**, polyunsaturated fatty acids; **SRs**, scavenger receptors; **SMCs**, smooth muscle cells; **sdLDL**, small dense LDL.

Introduction

Oxidized low-density lipoprotein (OxLDL) is formed by the modification of LDL, a major group of lipoproteins that enable the transport of multiple, different lipid molecules. OxLDL is labeled as "bad cholesterol" for its key role in the pathogenesis of atherosclerosis leading to cardiovascular diseases (CVD).[1] The formation of atheromatous plaques, a major cause of morbidity and mortality, in the tunica intima of coronary arteries supplying the myocardium manifests as CVD.

Globally, CVD is the major cause of death. Statistics show that in 2019, 17.9 million people died from cardiovascular diseases, which is 32% of the total number of deaths in the world. Atherosclerosis is a long-term inflammatory condition of the arterial wall that is mainly caused by environmental and genetic risk factors, which result in a variety of complications – myocardial infarction, stroke, and other CVDs.[2]

OxLDL is a potent atherogenic lipoprotein that is known to alter endothelial functions. OxLDL is a form of LDL or "bad" cholesterol, which is formed during oxidative stress.[3] LDL particles are the main carriers of cholesterol in the circulation. The LDL particle is made of a hydrophobic core of polyunsaturated fatty acids (PUFAs) and esterified cholesterol surrounded by phospholipids, unesterified cholesterol, and one molecule of apolipoprotein B-100 (ApoB-100). LDL PUFAs (mainly linoleic acids [4] with minor amounts of arachidonic acid and

***Corresponding author:** Dr. Harish Rangareddy. Department of Biochemistry, Sri Devaraj Urs Medical College. Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar, India. E-mail: harishreddy1349@gmail.com*

docosahexaenoic acid) are protected against oxidation by abtooxidants, primarily α-tocopherol. There are different sizes of LDL.[5]

Brown and Goldstein were the first to postulate that LDL has to undergo some structural changes to achieve atherogenic properties.[6] Oxidative stress is an important trigger of lipid oxidation.[7] LDL oxidation leads to the alteration of ApoB recognition sites and the unregulated uptake of LDL by macrophages via scavenger receptors (SRs). The uptake of OxLDL by SRs leads to the accumulation of cholesterol within the foam cells. The emergence of such cells is a specific feature of early atherosclerotic lesions. Oxidation of LDL particles in the vascular endothelium has been reported to be an initial event in atherosclerotic plaque formation. OxLDL stimulates endothelial activation and smooth muscle proliferation evincing pro-atherosclerotic effects. Moreover, the studies demonstrate that all of the changes associated with endothelial cell modification of LDL can be attributed to oxidation.[8]

Inflammation and lipid metabolism alterations play a critical role in atherogenesis. However, the details of the relationships and causality among these fundamental processes still remain a puzzle. According to the classical hypothesis, atherosclerotic plaques are formed over a long duration with an accumulation of OxLDL, thus increasing the risk of myocardial infarction and stroke. A large number of studies indicate that OxLDL is a useful marker of CVD. [9-11]

Chemical nature of OxLDL

There are several oxidizable components in LDL, but PUFAs are the major targets of free radicals. Saturated fats are less involved in peroxidation due to their chemical nature and are resistant to oxidative damage. The majority of PUFAs in LDL are present as cholesteryl esters, and therefore, quantitatively, most of the oxidized fatty acids in the fully oxidized LDL are esterified to cholesterol. LDL-PUFAs are oxidized by enzymatic and nonenzymatic pathways in the arterial tissue, specifically by the endothelial cells and macrophages.

It should be noted that LDL particles are rich in antioxidants such as α-tocopherol, β-carotene, and ubiquinol-10, which protect LDL from free radical attack and oxidation.[12,13] However, at the end of the lag phase of LDL oxidation, the antioxidant property of LDL is diminished, and PUFAs in LDL particles are rapidly oxidized to hydroperoxide, further breaking down to generate more reactive aldehyde products and metabolites, such as MDA and 4-hydroxynonenal.

OxLDL exists in multiple forms, characterized by different degrees of oxidation, including minimally modified LDL, which is still recognized by the LDL receptor, and fully or extensively OxLDL, which is recognized by SRs. Whereas native LDL has no effect on the immune system, OxLDL is immunogenic, and immune complexes formed by oxidized LDL and corresponding antibodies are pro-atherogenic and proinflammatory.[14,15]

It has been well documented that small dense LDL (sdLDL) has a greater atherogenic potential than that of other LDL subfractions. sdLDL particles have a decreased affinity for the LDL receptor resulting in a prolonged retention time in the circulation. Additionally, they more easily enter the arterial wall. sdLDL particles contain less antioxidative agents and are therefore more susceptible to oxidation than larger forms of lipoproteins.[16] Circulating sdLDL readily undergoes multiple atherogenic modifications in blood plasma, such as desialylation, glycation, and oxidation, that further increase its atherogenicity.[17]

OxLDL contains unoxidized and oxidized fatty acid derivatives both in the ester and free forms, their decomposition products, cholesterol and its oxidized products, proteins with oxidized amino acids and cross-links, and polypeptides with varying extents of covalent modification with lipid oxidation products, and many others.[11]

Formation of OxLDL in vivo and in vitro

There are a number of mechanisms for the oxidation of LDL: lipoxygenase reaction, copper and ceruloplasmin-mediated oxidation, iron-mediated oxidation, peroxidase-mediated oxidation, peroxynitrite-mediated oxidation, thiol-dependent oxidation, xanthine oxidase, NADPH oxidase, and other superoxide generators.

The most common hypothesis for LDL oxidation is that it occurs in microdomains isolated from the antioxidant environment of the arterial tunica intima. LDL particles react with free radicals and their by-products. Reacted LDL aggressively interacts with the surrounding tissues, causing tissue damage. In vivo, LDL oxidation occurs mainly within the subendothelial space of the arterial wall, in any of the cells within the artery, including the endothelial cells, macrophages, SMCs, and T- lymphocytes. Wen et al. found that LDL oxidation can occur intracellularly, most probably within lysosomes. Transition metals such as iron and copper can do this in a cell-free system.[18] Ojo and Leake [19] have postulated that LDL is oxidized by iron at lysosomal pH by the hydroperoxyl radical (HO2•), which is more reactive and hydrophobic than the superoxide radical (O2•−).

In vivo, LDL oxidation occurs mainly within the subendothelial space of the arterial wall. Studies have suggested that superoxide, myeloperoxidase (MPO), 15-lipoxygenase, peroxynitrite (ONOO−), and thiols may contribute to LDL oxidation (Figure 1). 15-lipoxygenase, produced by endothelial cells and monocytes/macrophages, converts PUFAs into lipid hydroperoxides and thereby oxidizes LDL. Activated macrophages secrete MPO, which generates reactive species, thereby oxidizing LDL. Finally, OxLDL interacts with SRs presented on endothelial cells, macrophages, and SMCs. [20]

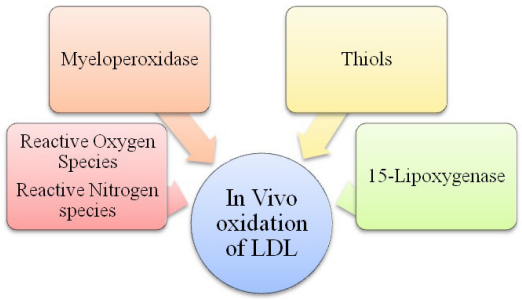

Fig. 1. *In vivo mechanisms for oxidation of LDL.*

In in vitro experiments, fully (80%-100%) oxidized LDLs are usually prepared by exposure to transition metal ions, such as Cu2+[21,22] or Fe2+.[23] Incubation with cells producing ROS, or exposure to MPO secreted by activated macrophages, leads to minimally oxidized LDLs, which appear to be better related to the degree of oxidation in vivo. [24-26]

Mertens and Holvoet detail the 3 stages of in vitro oxidation of LDL by metal ions: an initial lag phase (consumption of endogenous antioxidants), a propagation phase (rapid oxidation of PUFAs to lipid hydroperoxides), and a decomposition phase (formation of reactive aldehydes). Reactive aldehydes such as hydroxynonenal, hexanal and MDA react with lysine residues in ApoB, resulting in OxLDL.

Atherogenic effects of OxLDLs

The most important atherogenic effect of LDL oxidation is that this modification of LDL shifts the recognition and internalization of the lipoprotein from the LDL receptor (LDLR) to SRs.[27-30] The binding of OxLDL to SRs can trigger a number of intracellular events that depend on the type of cell and SR involved.(27) Interaction of OxLDL with SRs (SR-A, SR-B1, CD36, LOX-1) induces rapid and unregulated uptake of OxLDL by special cells. Thus, macrophages uptake OxLDL via SR-A and CD36; endothelial cells uptake OxLDL via CD36 and LOX-1. These receptors internalize OxLDL in a specific manner until foam cells are formed.[31] Uptake of OxLDL by macrophages leads to marked accumulation of cholesterol, converting the macrophages to foam cells [18,32] and initiating the development of atherosclerotic lesions (Figure 2).

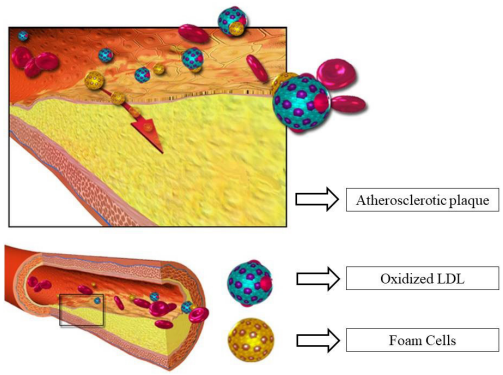

Fig. 2. *Uptake of OxLDL by macrophages, formation of foam cells and atherosclerotic plaque.*

Source: Picture retrieved from https://commons.wikimedia.org/wiki/File:Blausen_0227_Cholesterol.png

Free to use and License attributable to BruceBlaus, CC BY 3.0 <https://creativecommons.org/licenses/by/3.0>, via Wikimedia Commons.

OxLDL also activates a number of cellular responses in macrophages, dendritic cells, endothelial cells, T cells, SMCs, and platelets, which in the aggregate promote inflammation, lesion formation, atherogenesis, unstable atherosclerotic plaques, and thrombosis.[33-39] OxLDL stimulates the expression of endothelial adhesion molecules, has chemotactic effects, and inhibits the migration of macrophages outside the subendothelial space, thus increasing the number of leukocytes and proinflammatory elements involved in atherogenesis.[24] As a highly atherogenic moiety, OxLDL was reported to upregulate endothelial ABCA1, a cell membrane protein that mediates the transport of cholesterol, phospholipids, and other metabolites from cells to lipid-depleted HDL apolipoproteins, through the activation of the peroxisome proliferator-activated receptor gamma (PPARγ)–liver X receptor (LXR) pathway in lipid-loaded macrophages.[40] OxLDL appears to transcriptionally downregulate ABCA1 via the inhibition of LXR. Thus, OxLDL-regulated ABCA1 may contribute to endothelial dysfunction, accumulation of lipid within the vascular wall, and the subsequent development of atherosclerosis.[41,42] Wang et al.[43] showed that OxLDL up-regulates arginase I, which contributes to endothelial dysfunction by reducing L-arginine availability to eNOS for NO production and thus vasodilation. Thus, OxLDL instigates atherosclerotic events throughout the disease progression, starting from endothelium dysfunction, white blood cell activation, foam cell formation, SMC migration, and proliferation to platelet adhesion and aggregation[18] (Figure 3)

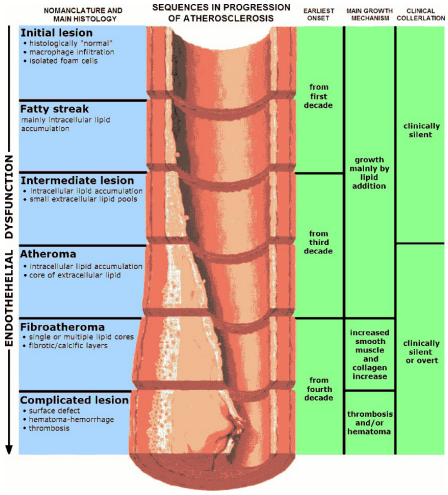

Fig. 3. *Endothelial dysfunction and progression of atherosclerosis*

Source: Picture retrieved from https://commons.wikimedia.org/wiki/File:Endo_dysfunction_Athero.PNG

Free to use and License attributable to Transferred from en.wikipedia to Commons, CC BY-SA 3.0 <http://creativecommons.org/licenses/by-sa/3.0/>, via Wikimedia Commons.

Measurement of OxLDL

OxLDL levels could be a useful marker for predicting future cardiovascular events; however, substantial differences exist among the different methods of OxLDL measurement.[44] In the past 10 years, it has been possible to generate MABs to OxLDL to measure OxLDL in the plasma directly.[21]

Challenges in estimating OxLDL in humans have been overcome with ELISA. ELISA methods are used to determine OxLDL levels in plasma by either "sandwich assays or competitive assays." ELISA methods have demonstrated that OxLDL levels increase under certain pathological conditions, including acute

myocardial infarction and carotid artery atherosclerosis.[45] Human Oxidized LDL ELISA Kit is an enzyme immunoassay developed to detect and quantify human oxidized LDL in plasma, serum, or other biological fluid samples. The kit contains a copper oxidized LDL standard against which unknown samples may be compared. Each oxidized LDL assay is configured to selectively measure either carboxymethyl-lysine-modified LDL, 4-Hydroxynonenal-modified LDL(HNE–LDL), or MDA-LDL.[44]

Accumulation of OxLDL in atherosclerotic lesions has also been demonstrated by immunohistochemical and biochemical studies using the DLH3 antibody. This antibody recognizes oxidized phosphatidylcholines (OxPC) generated during oxidative modification of LDL, and OxPC-apoB adducts formed in OxLDL are the presumed antigens. The presence of OxLDL in the LDL fraction of human plasma was demonstrated by introducing a sandwich ELISA procedure using DLH3 together with an anti-apoB antibody.[46]

Several immunoassays with antibodies against OxLDLs, MDA-modified LDLs, lysine-substituted LDLs, and OxPCs have been developed and widely used to measure OxLDLs in biological samples. Among many antibodies against atherosclerotic lesions, a clone that strongly reacts with copper-induced OxLDL was raised. The antibody, DLH3, recognizes OxPCs, where 1-palmitoyl-2-(9-oxo)nonanoyl-PC (9CHO-PC, also called PONPC) is one of the potent antigenic molecules.[46]

Tan et al.[47] established a simple, specific and rapid gold nanoparticle-based lateral flow immunoassay (LFIA) on quantifying OxLDL/β2GPI complexes from test samples. β2GPI recognizes the structural part of 7-ketocholesteryl-9-carboxynonanoate(oxLig-1), a specific ligand in OxLDL, to form indissociable OxLDL/β2GPI complexes.[48] Presently, serological levels of OxLDL/B2GPI complexes are measurable by ELISA. Tan et al.[47] fabricated another MAB, 3H3, which shares antigen-specificity similar to WB-CAL-1, yet with improved affinity and specificity towards β2GPI complexed with OxLDL.[49] The developed OxLDL/β2GPI LFIA offers a simple test procedure to quantitatively assess OxLDL/β2GPI in serum or a sample containing the same.

A valid measure of in vivo OxLDL formation is represented by the susceptibility to oxidation of isolated plasma LDLs, as assessed by the lag time for forming conjugated dienes[50] induced by Cu2+ that can be spectrophotometrically detected at 234 nm. Another method is to evaluate the acid hydrolysis products of lipoperoxides such as MDA, which reacts with thiobarbituric acid (TBA) to form MDA–TBA adducts. The TBA-reactive substances can be measured spectrophotometrically, fluorometrically, or by high-pressure liquid chromatography.[24]

In conclusion, oxidative stress is an important trigger of lipid oxidation. OxLDL was found to modulate different signal transduction cascades leading to gene expression, apoptosis, adhesion, inflammation, differentiation, and migration, all of which contribute to the development of atherosclerosis. Circulating OxLDLs can be used as biomarkers since their levels rise in patients with advanced atherosclerosis. Routine inclusion of OxLDL estimation in an at-risk population can help the clinicians understand the disease initiation and progression and improve early intervention and management.

Competing Interests

The authors declare that they have no competing interests.

References

1. Hua J, Malinski T. Variable Effects Of LDL Subclasses Of Cholesterol On Endothelial Nitric Oxide/Peroxynitrite Balance - The Risks And Clinical Implications For Cardiovascular Disease. Int J Nanomedicine. 2019 Nov 18;14:8973-8987. doi: 10.2147/IJN.S223524.
2. Hartley A, Haskard D, Khamis R. Oxidized LDL and anti-oxidized LDL antibodies in atherosclerosis - Novel insights and future directions in diagnosis and therapy. Trends Cardiovasc Med. 2019 Jan;29(1):22-26. doi: 10.1016/j.tcm.2018.05.010.
3. Lara-Guzmán OJ, Gil-Izquierdo Á, Medina S, Osorio E, Álvarez-Quintero R, Zuluaga N, et al. Oxidized LDL triggers changes in oxidative stress and inflammatory biomarkers in human macrophages. Redox Biol. 2018 May;15:1-11. doi: 10.1016/j.redox.2017.11.017.
4. Jürgens G, Hoff HF, Chisolm III GM, Esterbauer H. Modification of human serum low density lipoprotein by oxidation—characterization and pathophysiological implications. Chemistry and physics of lipids. 1987 Nov 1;45(2-4):315-336. doi: 10.1016/0009-3084(87)90070-3
5. Feingold KR. Introduction to Lipids and Lipoproteins. 2021 Jan 19. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 26247089.
6. Brown MS, Goldstein JL. Lipoprotein metabolism in the macrophage: implications for cholesterol deposition in atherosclerosis. Annu Rev Biochem. 1983;52:223-61. doi: 10.1146/annurev.bi.52.070183.001255.
7. Yang X, Li Y, Li Y, Ren X, Zhang X, Hu D, Gao Y, Xing Y, Shang H. Oxidative Stress-Mediated Atherosclerosis: Mechanisms and Therapies. Front Physiol. 2017 Aug 23;8:600. doi: 10.3389/fphys.2017.00600.
8. Steinbrecher UP, Witztum JL, Parthasarathy S, Steinberg D. Decrease in reactive amino groups during oxidation or endothelial cell modification of LDL. Correlation with changes in receptor-mediated catabolism. Arteriosclerosis. 1987 Mar-Apr;7(2):135-43. doi: 10.1161/01.atv.7.2.135.
9. Li H, Cao Z, Wang L, Liu C, Lin H, Tang Y, Yao P. Macrophage Subsets and Death Are Responsible for Atherosclerotic Plaque Formation. Frontiers in Immunology. 2022 Jan 1;13: 843712. doi: 10.3389/fimmu.2022.843712
10. Kattoor AJ, Kanuri SH, Mehta JL. Role of Ox-LDL and LOX-1 in Atherogenesis. Curr Med Chem. 2019;26(9):1693-1700. doi: 10.2174/0929867325666180508100950.
11. Madonna R, Balistreri CR, De Rosa S, Muscoli S, Selvaggio S, Selvaggio G, et al. Impact of Sex Differences and Diabetes on Coronary Atherosclerosis and Ischemic Heart Disease. J Clin Med. 2019 Jan 16;8(1):98. doi: 10.3390/jcm8010098.
12. Mantle D, Dybring A. Bioavailability of coenzyme Q10: An overview of the absorption process and subsequent metabolism. Antioxidants. 2020 May; 9(5):386. doi: 10.3390/antiox9050386
13. Marshall WJ. Lipids and lipoproteins. Clin Chem. London: Mosby; 1995.
14. Lopes-Virella MF, Virella G. Pathogenic role of modified LDL antibodies and immune complexes in atherosclerosis. J Atheroscler Thromb. 2013;20(10):743-54. doi: 10.5551/jat.19281.
15. Witztum JL, Steinberg D. Role of oxidized low density lipoprotein in atherogenesis. The Journal of clinical investigation. 1991 Dec 1;88(6):1785-1792. doi: 10.1172/JCI115499
16. Tribble DL, Rizzo M, Chait A, Lewis DM, Blanche PJ, Krauss RM. Enhanced oxidative susceptibility and reduced antioxidant content of metabolic precursors of small, dense low-density lipoproteins. Am J Med. 2001 Feb 1;110(2):103-10. doi: 10.1016/s0002-9343(00)00700-2.

17. Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small Dense Low-Density Lipoprotein as Biomarker for Atherosclerotic Diseases. Oxid Med Cell Longev. 2017;2017:1273042. doi: 10.1155/2017/1273042.
18. Khatana C, Saini NK, Chakrabarti S, Saini V, Sharma A, Saini RV, Saini AK. Mechanistic Insights into the Oxidized Low-Density Lipoprotein-Induced Atherosclerosis. Oxid Med Cell Longev. 2020 Sep 15;2020:5245308. doi: 10.1155/2020/5245308.
19. Ojo OO, Leake DS. Vitamins E and C do not effectively inhibit low density lipoprotein oxidation by ferritin at lysosomal pH. Free Radical Research. 2021 Aug 16; 55: 525-534. doi: https://doi.org/10.1080/10715762.2021.1964494
20. Mertens A, Holvoet P. Oxidized LDL and HDL: antagonists in atherothrombosis. FASEB J. 2001 Oct;15(12):2073-84. doi: 10.1096/fj.01-0273rev.
21. Ferns GA, Lamb DJ, Taylor A. The possible role of copper ions in atherogenesis: the Blue Janus. Atherosclerosis. 1997 Sep;133(2):139-52. doi: 10.1016/s0021-9150(97)00130-5.
22. Mazur A, Gueux E, Bureau I, Feillet-Coudray C, Rock E, Rayssiguier Y. Copper deficiency and lipoprotein oxidation. Atherosclerosis. 1998 Apr;137(2):443-5. doi: 10.1016/s0021-9150(97)00301-8.
23. Sullivan JL. Iron in arterial plaque: modifiable risk factor for atherosclerosis. Biochim Biophys Acta. 2009 Jul;1790(7):718-23. doi: 10.1016/j.bbagen.2008.06.005.
24. Zingg JM, Vlad A, Ricciarelli R. Oxidized LDLs as Signaling Molecules. Antioxidants (Basel). 2021 Jul 26;10(8):1184. doi: 10.3390/antiox10081184.
25. Essler M, Retzer M, Bauer M, Heemskerk JW, Aepfelbacher M, Siess W. Mildly oxidized low density lipoprotein induces contraction of human endothelial cells through activation of Rho/Rho kinase and inhibition of myosin light chain phosphatase. J Biol Chem. 1999 Oct 22;274(43):30361-4. doi: 10.1074/jbc.274.43.30361.
26. Retzer M, Siess W, Essler M. Mildly oxidised low density lipoprotein induces platelet shape change via Rho-kinase-dependent phosphorylation of myosin light chain and moesin. FEBS Lett. 2000 Jan 21;466(1):70-4. doi: 10.1016/s0014-5793(99)01762-7.
27. Linton MF, Yancey PG, Davies SS, Jerome WG, Linton EF, Song WL, et al. The Role of Lipids and Lipoproteins in Atherosclerosis. 2019 Jan 3. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 26844337.
28. Jürgens G, Hoff HF, Chisolm GM 3rd, Esterbauer H. Modification of human serum low density lipoprotein by oxidation--characterization and pathophysiological implications. Chem Phys Lipids. 1987 Nov-Dec;45(2-4):315-36. doi: 10.1016/0009-3084(87)90070-3.
29. Greaves DR, Gough PJ, Gordon S. Recent progress in defining the role of scavenger receptors in lipid transport, atherosclerosis and host defence. Curr Opin Lipidol. 1998 Oct;9(5):425-32. doi: 10.1097/00041433-199810000-00006.
30. van Berkel TJ, Fluiter K, van Velzen AG, Vogelezang CJ, Ziere GJ. LDL receptor-independent and -dependent uptake of lipoproteins. Atherosclerosis. 1995 Dec;118 Suppl:S43-50.
31. Di Pietro N, Formoso G, Pandolfi A. Physiology and pathophysiology of oxLDL uptake by vascular wall cells in atherosclerosis. Vascul Pharmacol. 2016 Sep;84:1-7. doi: 10.1016/j.vph.2016.05.013.
32. Levitan I, Volkov S, Subbaiah PV. Oxidized LDL: diversity, patterns of recognition, and pathophysiology. Antioxid Redox Signal. 2010 Jul 1;13(1):39-75. doi: 10.1089/ars.2009.2733.
33. Greig FH, Kennedy S, Spickett CM. Physiological effects of oxidized phospholipids and their cellular signaling mechanisms in inflammation. Free Radic Biol Med. 2012 Jan 15;52(2):266-80. doi: 10.1016/j.freeradbiomed.2011.10.481.
34. Maiolino G, Rossitto G, Caielli P, Bisogni V, Rossi GP, Calò LA. The role of oxidized low-density lipoproteins in atherosclerosis: the myths and the facts. Mediators Inflamm. 2013;2013:714653. doi: 10.1155/2013/714653.
35. Miller YI, Chang MK, Binder CJ, Shaw PX, Witztum JL. Oxidized low density lipoprotein and innate immune receptors. Curr Opin Lipidol. 2003 Oct;14(5):437-45. doi: 10.1097/00041433-200310000-00004.
36. Selley ML, Bartlett MR, Czeti AL, Ardlie NG. The role of (E)-4-hydroxy-2-nonenal in platelet activation by low density lipoprotein and iron. Atherosclerosis. 1998 Sep;140(1):105-12.
37. Chen R, Chen X, Salomon RG, McIntyre TM. Platelet activation by low concentrations of intact oxidized LDL particles involves the PAF receptor. Arterioscler Thromb Vasc Biol. 2009 Mar;29(3):363-71. doi: 10.1161/ATVBAHA.108.178731.
38. Magwenzi S, Woodward C, Wraith KS, Aburima A, Raslan Z, Jones H, et al. Oxidized LDL activates blood platelets through CD36/NOX2-mediated inhibition of the cGMP/protein kinase G signaling cascade. Blood. 2015 Apr 23;125(17):2693-703. doi: 10.1182/blood-2014-05-574491.
39. Wraith KS, Magwenzi S, Aburima A, Wen Y, Leake D, Naseem KM. Oxidized low-density lipoproteins induce rapid platelet activation and shape change through tyrosine kinase and Rho kinase-signaling pathways. Blood. 2013 Jul 25;122(4):580-9. doi: 10.1182/blood-2013-04-491688.
40. Chawla A, Boisvert WA, Lee CH, Laffitte BA, Barak Y, Joseph SB, et al. A PPAR gamma-LXR-ABCA1 pathway in macrophages is involved in cholesterol efflux and atherogenesis. Mol Cell. 2001;7(1):161-71. doi: 10.1016/s1097-2765(01)00164-2.
41. Zhu Y, Liao H, Xie X, Yuan Y, Lee TS, Wang N, et al. Oxidized LDL downregulates ATP-binding cassette transporter-1 in human vascular endothelial cells via inhibiting liver X receptor (LXR). Cardiovasc Res. 2005 Dec 1;68(3):425-32. doi: 10.1016/j.cardiores.2005.07.003.
42. Rasheed A, Cummins CL. Beyond the Foam Cell: The Role of LXRs in Preventing Atherogenesis. Int J Mol Sci. 2018 Aug 7;19(8):2307. doi: 10.3390/ijms19082307.
43. Wang W, Hein TW, Zhang C, Zawieja DC, Liao JC, Kuo L. Oxidized low-density lipoprotein inhibits nitric oxide-mediated coronary arteriolar dilation by up-regulating endothelial arginase I. Microcirculation. 2011 Jan;18(1):36-45. doi: 10.1111/j.1549-8719.2010.00066.x.
44. Itabe H, Ueda M. Measurement of plasma oxidized low-density lipoprotein and its clinical implications. J Atheroscler Thromb. 2007 Feb;14(1):1-11. doi: 10.5551/jat.14.1.
45. Tsimikas S. Oxidized low-density lipoprotein biomarkers in atherosclerosis. Current atherosclerosis reports. 2006;8(1):55-61. doi:10.1007/s11883-006-0065-1
46. Itabe H. Oxidized low-density lipoproteins: what is understood and what remains to be clarified. Biol Pharm Bull. 2003 Jan;26(1):1-9. doi: 10.1248/bpb.26.1.
47. Tan XW, Takenaka F, Takekawa H, Mastuura E. Rapid and specific detection of oxidized LDL/β2GPI complexes via facile lateral flow immunoassay. Heliyon. 2020 Jun 8;6(6):e04114. doi: 10.1016/j.heliyon.2020.e04114.
48. Kobayashi K, Matsuura E, Liu Q, Furukawa J, Kaihara K, Inagaki J, Atsumi T, Sakairi N, Yasuda T, Voelker DR, Koike T. A specific ligand for beta(2)-glycoprotein I mediates autoantibody-dependent uptake of oxidized low density lipoprotein by macrophages. J Lipid Res. 2001 May;42(5):697-709.
49. Sasaki T, Kobayashi K, Kita S, Kojima K, Hirano H, Shen L, et al. In vivo distribution of single chain variable fragment (scFv) against atherothrombotic oxidized LDL/β,-glycoprotein I complexes into atherosclerotic plaques of WHHL rabbits: Implication for clinical PET imaging. Autoimmun Rev. 2017 Feb;16(2):159-167. doi: 10.1016/j.autrev.2016.12.007.
50. Le NA. Lipoprotein-associated oxidative stress: a new twist to the postprandial hypothesis. Int J Mol Sci. 2014 Dec 26;16(1):401-19. doi: 10.3390/ijms16010401.