LDL and HDL Oxidative Modification and Atherosclerosis

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Abstract

Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are two kinds of common lipoproteins in plasma. The level of LDL cholesterol in plasma is positively correlated with atherosclerosis (AS), which is related to the complex macromolecular components, especially the easy oxygenation of protein and lipid components. However, the plasma HDL cholesterol level is negatively correlated with AS, but the results of recent studies show that the oxidative modified HDL in pathological state will not reduce and may aggravate the occurrence and development of AS. Therefore, the oxidative modification of lipoproteins is closely related to vascular homeostasis, which has become a hot research area for a long time.

Keywords

Lipoproteins · LDL oxidative modification · HDL oxidative modification · Atherosclerosis · Cardiovascular diseases

10.1 LDL Oxidative Modification

LDL is a compound particle of lipid and protein in human blood circulation. The mature LDL particles are composed of hydrophobic core and hydrophilic outer layer [1]. The lipid hydrophobic core of LDL consists of triglycerides and cholesterol esters, mainly cholesterol esters. The surface lipid phospholipid and free cholesterol are amphiphilic. The main protein component of LDL is apoB-100, which contains only one apoB-100 in each lipoprotein particle [2]. ApoB-100 has a binding region with LDL receptor, which binds to apoB-100 through the ligand-binding domain of LDL receptor on cell membrane, recognizes and absorbs lipids. LDL granules can contain a little apolipoprotein E (ApoE) and paraoxonase (PON). The paraoxonase in lipoproteins is an antioxidant, which can resist LDL lipid peroxidation. LDL granule is also the main carrier of lipophilic antioxidant vitamin E, carrying k-tocopherol and a small amount of q-tocopherol [3]. However, LDL granules in plasma have weak antioxidation and anti-inflammatory ability and are prone to oxidative modification. This oxidative modification causes lipid deposition in the vascular intima and triggers the pathological process of AS.

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10.1.1 LDL Oxidative Modification Types

LDL oxidative modification types may include nonenzyme-mediated modification, such as free radical, proteoglycan, glycosylation, repair of immune complex; enzyme-mediated modification, such as lipase, oxidase, MPO, etc. In addition, according to the different modified components, it can also be divided into lipid component modification and protein component modification. The physical structure, chemical properties and biological activity of LDL particles will be changed after nonenzyme modification and enzyme modification [4]. The results showed that endothelial cells, macrophages, and smooth muscle cell (SMC) could also modify LDL. LDL is a complex particle with different oxidation sensitivity. LDL oxidation is a gradual process, leading to the formation of a continuous oxidation LDL from mild to extensive, containing various potentially toxic components of oxidized lipids and oxidized proteins in different proportions, i.e., the composition, metabolism and biological characteristics of oxidized LDL are heterogeneous. Lipid aldehyde and sterol and lipid peroxide were oxidized and existed in different proportion. All kinds of bioactive lipids of oxidized LDL interact with cell molecular targets through various mechanisms and play physiological or pathological roles. So far, many mechanisms remain unclear [5].

10.1.2 LDL Oxidative Modification Degree

LDL oxidative modification can occur during fetal growth, and lipoprotein oxidative modification can be observed in human fetal artery samples [6]. LDL oxidation is a gradual process from minimum to mild to severe extensive oxidation. The smallest oxidized LDL and mild oxidized LDL mainly changed in lipid, while the extensive oxidized LDL showed lipid oxidation and aldehyde carbohydrate modification [7]. Obviously, LDL oxidation process can be divided into two stages. The first is the initial stage of LDL oxidation, at which the consumption of lipophilic antioxidants occurs in LDL particles, and then the oxidation of polyunsaturated fatty acids of phospholipids. In this stage of oxidation, LDL particles with low levels of lipid oxide products and relatively complete apoB-100 are considered as the minimal modified LDL particles (MM-LDL) [8], which can also be recognized by LDL receptors. In the stage of severe modification, the lipid and protein components of LDL will be further modified by oxidation, and a large number of lipid components will be modified to generate aldehyde lipid peroxides. ApoB-100 will also be modified by oxidation. In this stage, the oxidized LDL will lose the ability to recognize LDL receptor, but it can combine with scavenger receptor (SR) of macrophages infiltrating into the subcutaneous, and then it will be swallowed by cells, which will lead to macrophages moving to foam cell transformation.

10.1.3 LDL Oxidative Modified Site

It is still believed that the oxidative modification of LDL may occur in the arterial wall, specifically in the subendothelial layer, rather than in the circulating blood. Endothelial cells retain LDL in the subendothelial layer through endocytosis, vesicular transport and particle exocytosis. The fluorescent labeled LDL was transported to the subendothelial layer in a scavenger receptor-b1 dependent manner. Small dense LDL (sdLDL) is more likely to bind to proteoglycan, trapped in extracellular matrix, where it is susceptible to oxidative modification. LDL oxidation is unlikely to occur in plasma because of the high concentration of antioxidants and proteins chelating metal ions. Although in vitro experiments show that transition metal ions can oxidize LDL, it is unlikely that there are a large number of free metal ions in vivo, because they are mostly combined with proteins to form ceruloplasmin or transferrin [9].

10.1.4 LDL Lipid Oxidative Modification

10.1.4.1 Nonenzymatic (Free Radical) Mechanism of Lipid Peroxidation

The surface lipids of LDL, including phospholipids and their derivatives and free cholesterol, can undergo enzymatic or nonenzymatic reactions, and the surface lipids are oxidized to form modified lipids. Lipid peroxidation may be caused by oxidants in the vascular system. The new chemical commonality of as plaque in vivo is the formation of oxidized LDL [10] through the mechanism involving free radicals or lipoxygenase. LDL lipid peroxidation is a free radical-mediated process involving the peroxidation modification of polyunsaturated fatty acids (PUFAs) in phospholipids [11]. The phospholipid components of LDL cause lipid peroxidation under the action of hydroxyl radicals, which generate active hydroxyl radicals in the cell system and react with adjacent lipids as soon as they are produced. Polyunsaturated fatty acids in lipids can react with free radicals. The lipid radicals can react with the neighboring lipid molecules to form lipid peroxides and lipid hydroperoxides, which lead to more and more lipid peroxidation. Lipid hydroperoxides can split under the action of transition metals and break into various oxygen-containing products, such as alkanes, olefins, aldehydes, ketones, and other products. The oxidation reaction is terminated by the depletion of substrate or the formation of stable lipid peroxide derivatives (alkanes, alcohols, ketones, aldehydes, carboxylic acids) [5].

10.1.4.2 Enzyme-Mediated Lipid Peroxidation of Lipoproteins

LDL can be directly modified by various enzymes, such as phospholipase, sphingomyelinase, and lipoxygenase. The cells of arterial wall contain lipoprotein lipase, cholesterol esterase, phospholipase A1, phospholipase A2, phospholipase C and phospholipase D, lipoxygenase, and cholesterol ester oxidase. Enzyme modification of LDL lipids may occur in the arterial wall [4].

10.1.5 LDL Lipid Peroxidation Products

10.1.5.1 Lysophosphatidylcholine (LPC) and Lysophosphatidic Acid (LPA)

The first component of oxidized LDL is LPC, which also exists in normal LDL, but the concentration is low. A large amount of LPC is continuously produced in plasma through the action of sn-2 position of LCAT hydrolysis phospholipid. LPC is the chemokine of monocyte, which can stimulate the production of superoxide and inflammatory cytokines, and stimulate the proliferation of lymphocytes. LPA is produced from LPC by lysophosphatidy esterase D, which is a known mitogen and plays a role through a specific G protein coupled receptor.

10.1.5.2 Sn-2 Short-Chain Phosphatide

The position of sn-2 of LPC in LDL may be changed, and the derivatives obtained by this change include 1-palmitoyl-2-(5-oxomethyl)-sn-glycerol-3-phosphocholine (povpc), 1-palmitoyl-2-glutaryl-sn-glycerol-3-phosphocholine (pgpc), 1-palmitoyl-2-(9oxononyl)-sn-glycerol-3-phosphocholine (ponpc), and palmitoyl-2-arachidonol-Sn phosphatidylcholine (PAPC) [12, 13].

10.1.5.3 Other Lipid Peroxidation Products

Sn-2 epoxide is generally considered as one of the most reliable markers of oxidative stress in vivo [12]; sphingosine-1-phosphate (s-1-p), the metabolite of ceramide, can induce the proliferation of vascular smooth muscle cells, platelet activation, and endothelial cell stimulation [13]; FFA and its metabolites 15-hete, 9-hode, and 13-hode can be further oxidized to form a large number of complex isoprostaglandin (ox-ce) products [12]; arachidonic acid and linoleic acid, as well as esterified fatty acids, are oxidized to

hydroperoxides derivatives, 15-hete, 9-hode, and 13-hode. These modified FFA have been proved to be ligands of PPARa and PPARG [14]; in lipid peroxidation products, 27 hydroxycholesterol, 7-ketcholesterol and 5 α, 6 α-epoxide, 5b, 6b-epoxide, and cholesterol-3b, 5A, 6b-triol are the most abundant oxidized sterols in plasma and as lesions [15]; CE hydroperoxides and hydroxides are the main lipid oxidation products found in human as lesions [14]; 4-hydroxynonene aldehyde and malondialdehyde (HNE and MDA), HNE, and MDA are carbonyl compounds and also the most abundant ones in LDL lipid peroxidation abundant α, β-unsaturated hydroxyene [4].

In short, LDL produces a large number of different types of lipid peroxidation bioactive molecules, which promote the occurrence of local inflammation of endothelium, stimulate the migration and infiltration of chemotactic inflammatory cells and smooth muscle cells through different mechanisms and molecular pathways, and constantly promote the slow occurrence and development of AS.

10.1.6 LDL Protein Oxidative Modification

10.1.6.1 Protein Modification Caused by Lipid Peroxidation Products

LDL lipid peroxidation products can react with apoB-100 amino acid residues. There are 357 lysine residues in apoB-100, of which a considerable part (225 lysine residues) are exposed on the surface of LDL, and the remaining 132 are embedded in the lipid part of LDL [16]. Polyunsaturated fatty acids in LDL oxidize aldehydes, such as HNE and MDA, which can react with lysine and other amino acid residues.

10.1.6.2 Modification of ApoB-100 by Enzyme Mechanism

Exposure of LDL to reagents or enzyme-catalyzed hypochlorite (HOCl) results in the oxidation of amino acid residues of apoB-100, which transforms LDL into the high uptake form of macrophages [16]. Myeloperoxidase is an enzyme related to inflammation and oxidative stress. It can catalyze H2O2 and chloride to form a powerful cytotoxin, HOCl, and then react with the tyrosine residue of apoB-100. Chlorinated biomolecules such as 3-chlorotyrosine are considered to be specific markers of MPO catalyzed oxidation [17]. The modification of LDL by the active nitrogen produced by MPO of monocyte transformed lipoproteins into NO2-LDL with high uptake and promoted the lipid loading of macrophages and the formation of foam cells through CD36 pathway [18].

10.1.7 LDL Acetylation and Oxidation

Deacetylation may be the first step in the chain of as changes caused by LDL particles in the blood of as patients. LDL is deacetylated firstly, followed by the loss of free cholesterol and cholesterol ester, phospholipid and triglyceride, the increase of particle density, and the decrease of particle size; secondly, the increase of particle negative charge leads to the formation of electronegative LDL part and the appearance of misfolded apolipoprotein B in large quantities; in the later stage, the increase of LDL particle oxidant and the decrease of antioxidant, and the heavily modified LDL particle can produce autoantibody [19].

10.1.8 LDL Glycation and Oxidation

LDL glycosylation is a nonenzymatic reaction between the carbonyl group of reducing sugar and the amino group of L-lysine residue of apoB-100. It can also occur in the phospholipid component of LDL, leading to functional changes in LDL and increased susceptibility to oxidative modification [20]. The body can also have nonenzymatic glycosylation reaction at the normal blood glucose level, and the carbonyl metabolites can be eliminated by the body's enzymes, which will not cause harm to the human body [21]. But in diabetes and hyperglycemia, the concentration of sdLDL increased. It has been reported that sdLDL apoB isolated from individuals without

diabetes mellitus is more widely glycosylated than general LDL granules, and more than 90% of glycosylated apolipoprotein B in plasma is present in sdLDL granules. SdLDL may be more susceptible to glycosylation [22]. The glycosylation and oxidation of LDL are not mutually exclusive modification of LDL, because the glycosylation itself will produce free radicals. Even in vitro, glycosylation is accompanied by some degree of oxidation when molecular oxygen and oxygen free radical generation processes do not exist [23].

10.1.9 Cellular Mechanism of LDL Oxidation on AS

10.1.9.1 Effect of Oxidized LDL on Endothelial Cells

Endothelial cells play an important role in maintaining vascular homeostasis. They can synthesize and secrete a large number of enzymes and cytokines to maintain the balance between vasodilation and contraction, inhibition and stimulation of smooth muscle cell proliferation and migration, thrombosis, and fibrinolysis [24]. Cardiovascular risk factors such as hyperlipidemia, diabetes, hypertension, obesity, smoking, and chronic mental stress can lead to endothelial dysfunction and oxidative stress reaction of endothelial cells, and initially aggravate the pathological process of AS [25]. Endothelial dysfunction can be manifested as endothelial activation, which eventually leads to the transformation of arterial endothelial cells from a resting phenotype to an inflammatory phenotype involving host defense response [26]. Under the action of endothelial cells, or because of its own characteristics, sdLDL in the circulatory system stays in the subendothelial space or the extracellular matrix of the arterial wall. Under the action of free radicals and enzymes, LDL components are modified. A large number of LDL-oxidized lipid components stimulate scavenger receptor (SR), toll-like receptor, and other receptors of activated endothelial cells, which lead to NF-kB activation, and activate a variety of target genes related to vascular wall pathophysiology, including cytokines, chemokines, and leukocyte adhesion molecules, as well as genes regulating cell proliferation and cell survival [27]. Various lipid components of oxidized LDL participate in the activation of NF-kB. 13-hpode, oxidized phospholipid of MM-LDL, and LPC can activate NF-kB and induce the expression of VCAM-1, ICAM-1, and MCP-1. However, some bioactive components of oxidized LDL can inhibit NF-kB activation, indicating that oxidized LDL has biphasic effect on NF-kB [26].

10.1.9.2 Effect of Oxidized LDL on Macrophages

In the early pathological changes of AS, oxidized LDL promotes the activation of endothelial cells and the activation of inflammatory pathway, which results in the increase of the expression of inflammatory factors; under the chemotaxis of MCP-1 and oxidized lipid components, blood monocytes enter into the endothelium, derive into macrophages, and develop into foam cells through SR recognition and phagocytosis of oxidized LDL. Oxidative LDL stimulates macrophages to express a large number of SR, CD36, LOX-1, SR-A, SR-B1, CD68, etc. and to recognize and ingest specific oxidative LDL components. Under normal conditions, the phagocytized lipids form an endocytosome, and cholesterol esters (CE) and TG related to lysosomal fusion lipoproteins are hydrolyzed by cholesterol esterase with high activity in the acidic pH of lysosomal lumen [28]. In order to prevent the potential cytotoxicity caused by excessive accumulation of free cholesterol (FC), FC can be re-esterified by ACAT to form CE on the endoplasmic reticulum, which is stored in the cytoplasm as lipid droplets. Cholesterol esterification is considered as a protective defense mechanism, which can avoid excessive accumulation of cytotoxic FC. Under the background of serious lipoproteins oxidation, lipid uptake, and cholesterol esterification increase, while cholesterol outflow is insufficient. The final result is excessive accumulation of CE in macrophages, forming foam cells. The formation of foam cells depends on the balance of three main related biological processes, including fat uptake, cholesterol

esterification, and cholesterol efflux. A large amount of oxidized LDL also promotes macrophages to absorb modified lipids without restriction, and it destroys the pathway of cholesterol outflow, promotes cholesterol storage, and then the cholesterol esterification mechanism is also destroyed [29].

In addition, macrophages absorb a lot of oxidized LDL through SR, which destroys the normal lipid outflow pathway, and more and more oxidized lipid and protein components are trapped in the cytoplasm. These components interfere with the function of ER modified folding proteins, resulting in the accumulation of misfolded proteins in ER and ER stress. In the case of ERS, the ability of protein folding must be restored rapidly to meet the needs of protein folding. In the presence of high levels of misfolded proteins in the endoplasmic reticulum, an intracellular signaling pathway called UPR induces a series of transcription and translation events to restore the homeostasis of the endoplasmic reticulum. Macrophage-derived foam cells engulf a large number of oxidized lipids, and the FC esterification in the cytoplasm is blocked. A large number of FC is trapped in the cytoplasm, which reflects its cytotoxicity and starts the process of apoptosis. In the early pathological changes of AS, the apoptotic foam cells can be phagocytized by local macrophages, and then be cleared. This effect is called exocytosis, which can maintain the stability of early pathological plaques and reduce the extracellular disintegration of foam cells, thus causing lipid accumulation under the intima [30]. However, in the middle and late stage of AS, excessive ERS will aggravate the lipid phagocytosis and even apoptosis of macrophages, resulting in more subintimal lipid accumulation, forming a typical atheroma [31].

10.1.9.3 Effect of Ox LDL on Vascular Smooth Muscle Cells

In early pathological changes of AS, with the infiltration of LDL and the function of entering into the vascular wall, a variety of lipid active components are activated to diffuse and act on smooth muscle cells, NADPH oxidase is activated to produce a large number of oxygen free radicals; the polarity of smooth muscle cells changes, from contractile to synmorphic [32]; and matrix metalloproteinases activated, secreted, and degraded the matrix components around cells, making them smooth. Under the action of ox LDL, smooth muscle cells located in the middle membrane of blood vessels pass through the inner elastic layer, migrate into the inner membrane, proliferate [33], synthesize, and secrete a large number of extracellular matrix components, and form fiber caps. In the early pathological process of AS, the formation of fibrous cap is helpful to reduce plaque rupture and prevent the occurrence of vascular embolism. However, when the disease entered the progressive stage, under the stimulation of ox LDL, smooth muscle cells expressed LOX-1 and other scavenger receptors, and phagocytized lipids through scavenger receptors. In the late stage of AS, the foam cells derived from smooth muscle cells secrete a large number of matrix metalloproteinases to degrade the collagen fibers of the fibrous cap, resulting in the thinning of the fibrous cap. Under the effect of the blood flow shear force in the vascular cavity, it is easy to locate in the upstream and downstream of the plaque on the lumen surface, namely, the shoulder rupture, leading to lipid outflow of plaque, and then to thrombosis, acute clinical event of vascular stenosis [34].

10.2 HDL Oxidative Modification

10.2.1 Introduction of HDL

High-density lipoprotein (HDL) is a kind of small, dense, and rich in a variety of lipid and protein macromolecular components in the blood. The average size is 8–10 nm, and the density is 1.063–1.21 g/ml [35]. HDL mainly contains polar lipids and apolipoproteins, in addition to many other proteins, including enzymes and acute phase proteins, and may contain a small amount of nonpolar lipids. HDL can be isomers with different macromolecule components, which have different structure, chemical and biological characteristics. HDL has strong antioxidant

modification ability in physiological state, but it also has various modifications in pathological state [36], such as oxidation [37]. The lipids of HDL are mainly the surface phospholipids and the internal cholesterol esters and triglycerides. Phospholipids are mainly phosphatidylcholine, accounting for 32–35 mol% of total lipids in HDL. Another important phospholipid of HDL is lysophosphatidylcholine, which accounts for 1.4–8.1 mol% of total lipids. Sphingomyelin on HDL is a kind of structural lipid, which can enhance the rigidity of surface lipid. It is also the main sphingolipid in blood circulation, accounting for 5.6–6.6 mol% of the total lipid. It is mainly derived from triglyceride rich lipoproteins, only to a small extent from new HDL. The cholesterol ester (CE) on HDL is the result of lecithin cholesterol acyltransferase (LCAT) catalyzed transesterification of phospholipids with cholesterol. These high hydrophobic lipids form the lipid core of HDL, accounting for 36 mol% of the total lipids of HDL. A small amount of free sterol is located in the lipid monolayer on the surface of HDL particles, which regulates its fluidity.

HDL carries a large number of different proteins, which can be divided into apolipoproteins, enzymes, lipid transfer proteins, acute phase response proteins, complement components, protease inhibitors, and other protein components. Apolipoproteins and lipases are widely considered as the key functional components of HDL, while the secondary protein components mainly play the role of complement regulation, infection prevention and acute phase response. ApoAI is the main structural and functional component of HDL, accounting for 70% of HDL protein. Almost all HDL particles are believed to contain apoAI. The main functions of apoAI include the interaction with cell receptor, activation of LCAT, and multiple anti-atherosclerosis (as) activities of HDL. ApoA II is the second largest HDL apolipoprotein, accounting for 15–20% of the total HDL protein. About half of the HDL particles may contain ApoA II [35].

10.2.2 Clinical Evidence and Pathological Effect of Oxidative Modification of HDL

10.2.2.1 Evidence of Oxidative Modification of HDL In Vivo

There is oxidized HDL (ox HDL) in the human body [38]. With the specific antibody of Cu2 + oxidized HDL, the presence of ox HDL was detected in the intima and endothelial cells of human abdominal aortic atheroma plaque by immunohistochemistry. The enzyme-linked immunosorbent assay (ELISA) based on monoclonal antibody can detect ox HDL in hemorrhagic plasma sensitively and has reliable specificity. In addition, ox HDL also exists in plasma of patients with endogenous hypertriglycerides. At present, the oxidation mechanism of HDL is not clear. In vitro, HDL can be oxidized by different media, such as metal ions Cu2 +, Fe2 +, Mn2 +, etc., among which Cu2 + oxidation is the most commonly used method in vitro. Hypochlorite (HOCl) can also cause oxidative modification of HDL, but HOCl and Cu2 + mediated oxidative modification of HDL are different in properties and kinetics. In 2004, it was found for the first time that tyrosine can be nitrated and chlorinated by myeloperoxidase (MPO) in plasma and plaque of patients with coronary heart disease, reducing the cholesterol reverse transport capacity of HDL granules. HDL in the intima of aortic atherosclerotic plaque contains 3-chlorotyrosine, which is the product of HOCl oxidation, and its content is much higher than that of HDL in blood [39]; it is also found that MPO is a component of HDL in plaque, and MPO can produce HOCl, so it is speculated that MPO can mediate HDL oxidation through HOCl. MPO is the only source of 3-chlorotyrosine [40], which proves that MPO can oxidize HDL in vivo. Paraoxonase-1 (PON-1) in HDL granules is negatively related to the oxidative susceptibility of HDL, which can inhibit the oxidative modification of HDL mediated by Cu2 +. PON-1 can inhibit the oxidative modification of HDL in a dose-dependent manner, and the ability of

oxidative modified HDL to obtain and stabilize PON-1 from hepatocytes decreases. The decrease of PON-1 content makes HDL easier to be oxidized. In patients with coronary heart disease, tyrosine at 166 and 192 sites can be nitrated and chlorinated by MPO, and the modified content is inversely proportional to the reverse transport capacity of cholesterol [41]. In vitro studies have shown that MPO can modify several amino acid residues of human ApoA1 by producing nitrite and hypochlorite, such as methionine residues at 86, 112, and 148, tryptophan residues at 8, 50, 72, and 108, and tyrosine residues at 192, 236, etc., which can be modified by nitration or chlorination. The mutation of tryptophan in ApoA1 to phenylalanine can not only protect, it can keep HDL normal function and avoid oxidative modification of HDL. The oxidation of specific areas of ApoA1 was measured by tandem mass spectrometry with selective reaction monitoring mode. It was found that 192 tyrosine residues of ApoA1 were the main chlorination sites, and 18 tyrosine residues were the main nitration sites in human as plaque. 192 tyrosine residues of ApoA1 in healthy human blood circulation were both the main chlorination sites and the main nitration sites [42]. Trp72 is a site of ApoA1 oxidation, and its main mechanism is mpo-h2o2-cl-system. Trp72 can resist the oxidative modification and functional degradation of HDL induced by mpo-h2o2-cl-system. Tyrosine 166 is a nitration site of ApoA1, which accounts for 8% of human atherosclerotic plaque, and its function is damaged compared with normal HDL [43].

10.2.2.2 Functional Abnormality After Oxidative Modification of HDL

In vitro study shows that HDL oxidized by plasma and MPO hypochlorite system in patients with coronary heart disease has significantly reduced reverse transport capacity of cholesterol and its ability to activate LCAT. Other important functional molecules in HDL, such as ApoA1, PON-1, CETP, and so on, are oxidized and modified to change the structure, which also causes the reverse transport of cholesterol to be blocked. For example, ApoA1 as a ligand mediates the binding of HDL with ATP-binding cassette transporter (ABCA1) on foam cell membrane, and ABCA1 becomes one of the main pathways for cholesterol transfer to HDL in foam cell. The combination of ApoA1 and ABCA1 is the initial link of cholesterol reverse transport in AS plaque, but the change of structure of ApoA1 cannot combine with ABCA1, which results in the obstruction of cholesterol outflow in foam cells. It was also found that the antioxidation and anti-inflammatory ability of HDL decreased significantly in the plasma of patients with psoriasis, which may have an impact on the pathogenesis of psoriasis [44].

10.2.3 Cellular Mechanism of HDL Oxidative Modification Impairing Anti-AS Function

10.2.3.1 Effect of HDL Oxidative Modification on Endothelial Cells

Vascular endothelial cells (EC) cover the smooth intima on the surface of blood vessels and maintain the state of blood flow. Meanwhile, endothelium is the largest endocrine organ of the body. It can secrete a variety of bioactive substances, including vasodilator factor and vasoconstrictor factor, which are in balance under physiological state. For vascular endothelial cells, the steady state of holding cycle plays a very important role. HDL oxidized by MPO in vitro significantly reduced the migration ability of endothelial cells. In the model of electrical injury of carotid artery, HDL modified in vitro decreased the endothelial repair ability [45]. Vascular endothelial cell injury and dysfunction are the early links of AS, which are manifested in the decrease of endothelial nitric oxide synthase (eNOS) activity and no production. HDL has the functions of activating eNOS, promoting no production and anti-endothelial apoptosis. As a gas signal molecule, NO plays an important role in maintaining normal vasodilation, inhibiting platelet aggregation and proliferation of arterial smooth muscle cells, and inhibiting monocyte and endothelial adhesion. In addition, NO is also an oxygen free radical

scavenger in vivo, which can inhibit the oxidation of lipoproteins. ENOS is the key enzyme of NO synthesis. Its activity and function directly regulate the production and biological function of NO. The oxidative modification of HDL can improve the endothelial function and reduce the ability of anti-endothelial apoptosis [46]. At the same time, ox HDL can promote the release of endothelin-1 (ET-1), which can promote the proliferation of smooth muscle cells (SMC), constrict blood vessels and raise blood pressure, thus aggravating the injury of EC and promoting the development of AS.

10.2.3.2 Effect of HDL Oxidative Modification on Macrophages

As a main feature of advanced atherosclerotic plaques, macrophage apoptosis promotes enlargement of the necrotic cores and plaque rupture, and then leads to cardiovascular complications [47]. Ox HDL, like ox LDL, also plays a crucial role in macrophage-derived foam cell formation and apoptosis. It has been reported that ox HDL exerts a cytotoxic effect on macrophages and accelerates atherosclerosis progression [48, 49]. It has been found that ox HDL prepared in vitro and HDL isolated from patients with metabolic syndrome (MS) activated ER stress-CHOP-mediated apoptotic pathway in macrophages, which could be blocked by oxidative stress inhibitors, toll-like receptor 4 (TLR4)-specific small interfering RNA (siRNA), and TLR4 antibody [50]. HDL exposure to hyperglycemic conditions could contribute to the acceleration of atherosclerosis in DM patients. Glycated HDL may induce macrophage apoptosis through activating ER stress-CHOP pathway, and ER stress mediates glycated HDL-induced autophagy, which in turn protects macrophages against apoptosis by alleviating CHOP pathway [51].

10.2.3.3 Effect of HDL Oxidation on Other Cells

Smooth muscle cell (SMC) is the main cell component in as plaque, and its proliferation plays an important role in the formation of as. As early as the twentieth century, it has been reported that ox HDL can promote the proliferation of SMC. In addition, platelets are also affected by HDL oxidative modification. Under physiological condition, HDL can inhibit platelet aggregation and prevent as. The effect of ox HDL on platelets in pathological state is concerned, although there are inconsistent reports. For example, HOCl oxidized HDL can cause inflammation and coagulation by binding to CD36 on platelets [52]. CD36 belongs to class B scavenger receptor family and is the receptor of ox LDL on macrophages. When CD36 helps to absorb ox HDL, it will increase foam cell formation [53]. At the same time, ox HDL will reduce the expression of CD36 mRNA and protein in human peripheral macrophages in vitro. CD36 can selectively ingest lipids in Cu2 + oxidized HDL, but not in ordinary HDL or LDL [54], which may lead to AS. MPO or Cu2 + oxidized HDL can bind SR-BI receptor on platelets, inhibit platelet aggregation, and produce antithrombotic effect [55]. Adipocyte differentiation is also affected by oxidative modification of HDL. Ox HDL changes the number and size of adipocytes through several unknown mechanisms.

10.2.4 Effect of HDL Oxidative Modification and Intervention on Its Anti-AS Function

10.2.4.1 Oxidative Modification of HDL Protein Components and Its Effect on Anti-AS Function

There are more than 80 protein components in HDL, and the modification of some protein components will also affect the anti-AS function. The oxidative modification of HDL occurs on the methionine and aromatic amino acid residues of apoAI, which leads to the separation of apoAI from HDL and the decrease of lipid content in HDL. After oxidative modification, the structure and function of apoAI changed [56], resulting in the inability of apoAI to combine with ABCAl, the loss of the ability to activate LCAT, the failure of cholesterol esterification, and the obstruction of cholesterol transfer to LDL, thus affecting the whole reverse cholesterol transport process. The

oxidative modification of apoAI by HOCl resulted in the cleavage of apoAI and apoAI, which reduced the anti-AS function of HDL. HDL glycosylation may be a nonenzymatic glycosylation of protein, which mainly occurs on the lysine of apoAI, thus affecting the cholesterol outflow, antioxidant, anti-inflammatory, endothelial protection, and other functions of HDL. PON1 in HDL can resist oxidation, but it can also be oxidized. PON1 itself is oxidized and ox HDL can inactivate PON1 [57]. PON1 activity is negatively correlated with age, and its mechanism may be related to the decrease of free sulfhydryl group on the 284th cysteine related to the active site of lipid peroxidation [58]. The activity of PON1 in glycosylated HDL decreased, and the degree of decline was positively correlated with glucose concentration and incubation time [59]. Therefore, this modification of PON1 can affect its activity, thus leading to the decline of antioxidant function of HDL.

10.2.4.2 Oxidative Modification of HDL Reduces the Protection of LDL and Promotes AS

Normal HDL has antioxidant capacity, which can inhibit the oxidative modification of LDL by macrophages, endothelial cells, and smooth muscle cells, but the oxidized HDL loses the ability to inhibit the oxidative modification of LDL. When macrophages sense that LDL changes into ox LDL, they enter the endothelium and phagocytize ox LDL. These macrophages come from plasma monocytes. Stimulated by chemical factors such as plasma monocyte chemoattractant protein-1 (MCP-1), monocytes infiltrate into the vascular wall, recognize, and phagocytize ox LDL specifically by scavenger receptor, then become macrophages, and further form foam cells. The accumulation of a large number of foam cells in the arterial wall promotes the formation of lipid striation and early pathological changes of as. Foam cells are the early signs of the formation of as lipid striation. It is believed that the inhibition of LDL oxidation by ox HDL loss is related to the decrease of PON1 activity in HDL. PON1 is synthesized by hepatocytes, and the ability of obtaining and stabilizing PON1 from hepatocytes after HDL oxidative modification decreases, resulting in the decrease of HDL antioxidant capacity. There is a negative correlation between PON1 activity and HDL oxidation in obese patients [60], which may be related to the increased risk of cardiovascular disease in obese patients. In addition, when Cu2 + oxidizes HDL in vitro, the activity of PON1 in HDL decreases significantly, and the inactivation mode is inconsistent with that of PON1 mediated by Cu2 +, which indicates that ox HDL promotes PON1 inactivation [61].

10.2.4.3 HDL Modification Intervention and Its Effect on Anti-AS Function

HDL function is the result of multiple protein synergies, and any abnormal component will affect its function. Therefore, the intervention of HDL components and its modification may be an important measure for as prevention and treatment. It was found that antioxidants can inhibit the oxidative modification of HDL in vitro and in vivo, and enhance its anti-AS effect. Improving the level of apoAI can resist the toxic effect of inflammation. ApoAI mimic peptide d4f can significantly reduce the level of oxLDL in serum of mice fed with high-fat diet, reduce the total area of aortic root lesions, the percentage of lipid positive areas, macrophage aggregation and apoptosis rate [62]. Omega-3 polyunsaturated fatty acids modify the lipoproteins containing the apoAI proteome. These protein changes can improve the function of HDL. After eating foods with high omega-3 polyunsaturated fatty acids content, PON1 and apoAI in HDL increase, thus enhancing its antioxidation and anti-inflammatory ability [63]. The combination of statins and niacin can improve the protein function of HDL in patients with coronary heart disease, increase the expression of cholesterol reverse transporter, and promote the anti-AS effect [64]. Animal experiments and population experiments show that the new small molecule antioxidant hydrogen molecule has a clear role in promoting HDL antioxidation and anti-inflammatory and inhibiting as [65]. In addition, the anti-AS function of HDL can also be improved by proper regular aerobic exercise [66].

In conclusion, the complexity of HDL structure and function can maintain its vascular homeostasis under physiological conditions. However, in some pathological conditions, the main component modification changed its anti-AS function and vascular homeostasis. Further study on the molecular mechanism of component modification is beneficial to the precise location of intervention target and the restoration of biological characteristics of HDL against AS.

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