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Low-Density Lipoprotein: Biochemical and Metabolic Characteristics and Its Pathogenic Mechanism

Jie Lin

Abstract

This chapter mainly introduces the physicochemical properties, physiological function, and metabolic pathway of low-density lipoprotein (LDL), with emphasis on the mechanism of atherosclerosis caused by LDL and the existing treatment methods. The content of this paper is detailed and comprehensive, including the latest research results in recent years. Different from the published articles, this paper adopts an innovative “tree” structure, with the disease development process as the main line and the molecular mechanism as the branch, showing the clinical significance of the molecular mechanism. The main purpose of the author of this paper is to take LDL as an example, establish a multidimensional knowledge system, and strive to make the complex molecular mechanism vivid.

Keywords: low-density lipoprotein, metabolism, atherosclerosis, familial hypercholesterolemia, treatment

1. Introduction

In recent years, the research on abnormal metabolism of blood lipids has gradually increased, and the importance of blood lipid management in primary prevention and secondary prevention of cardiovascular diseases has been clarified. This is because dyslipidemia, as a major cardiovascular risk factor, is the common pathway of multiple pathogenic factors, mainly manifested as the qualitative and quantitative changes in low-density lipoprotein (LDL), attacking the endothelium, initiating an inflammatory response, promoting the occurrence and development of atherosclerosis, and ultimately producing cardiovascular events. Thus, the understanding of the quantitative and qualitative changes in LDL is the basis of atherosclerosis treatment and prevention.

2. Physicochemical characteristics and metabolic process of LDL

LDL is a spherical particle, core lipids of LDL particle are composed of cholesterol ester (CE) and triglyceride (TG), an outer monolayer is composed of free cholesterol (FC) and phospholipid (PL) including phosphatidylcholine (PC), and one molecule of apolipoprotein B100 surrounds the LDL particle [1]. Apolipoprotein

B-100 (apoB-100) is composed of the amphoteric α -helical domain and β -sheet domain alternately (NH₂- β α 1- β 1- α 2- β 2- α 3-coOH), in which β -sheet structure accounts for 40%, which is related to the stability of LDL particles, and α -helix accounts for 25%, which is related to the amphiphilicity of LDL particles and the potential of self-repair [2].

LDL is the plasma metabolite of very low-density lipoprotein (VLDL). Plasma lipoprotein lipase or liver lipase catalyzes the hydrolysis of triglyceride (TG) in VLDL particles. At the same time, under the action of cholesterol ester transfer proteins (CETPs), cholesterol ester (CE) of HDL is transferred to VLDL, and phospholipids, apolipoprotein C (ApoC), and cholesterol are transferred to high-density lipoprotein (HDL) on the surface of VLDL. This process continues. In VLDL, TG decreases continuously, CE increases gradually, particles become smaller, and density increases gradually. First intermediate density lipoprotein (IDL) is formed, and then LDL is formed [3]. According to the formation process of LDL, it is easy to see that LDL is not a kind of particle but a class of particles with different sizes, densities, chemical composition, or different charges. In recent years, LDL particles have been divided into two phenotypes: type A (large and light LDL), LDL particle diameter ≥ 25.5 nm, and type B (small and dense LDL, sd-LDL), LDL particle diameter < 25.5 nm. Compared with type A LDL, sd-LDL has a stronger ability to cause atherosclerosis and has been identified for a long time as a new risk factor of cardiovascular disease by the American Cholesterol Education Program and Adult Treatment Program III (NCEPIII) [4].

Natural LDL (nLDL) is in charge of the transport of endogenous cholesterol, and its metabolic process is the transport process of endogenous cholesterol. Among them, two-third were metabolized through the LDL receptor pathway [5]. LDL receptor (LDLR) is widely distributed in the whole body, especially on the cell membrane surface of the liver, adrenocortical, ovarian, testicular, and arterial wall, and specifically binds to ApoB100 on the surface of LDL. Internalization causes the membrane at the junction to sink in for endocytosis. Under the action of the proton pump (H⁺-ATPase), the pH of endocytotic vesicle contents decreased, and LDL is separated from the receptor and fused with the lysosome. ApoB100 is decomposed into amino acids by a lysosomal proteolytic enzyme, and CE is hydrolyzed into free cholesterol and fatty acids by cholesterol esterase for cell utilization.

The remaining one-third is cleared by the mononuclear macrophage pathway. As a major member of innate immunity, macrophages are endowed with an advanced arsenal of sensors, composed of various pattern-recognition receptors (PRR). It is able to identify and bind foreign substances or altered substances to inactivate and degrade them. Therefore, the monocyte-macrophage clearance pathway is mainly aimed at LDL, which has changed its structure for a variety of reasons. It can also be called modified LDL (mLDL). mLDL specifically binds to the scavenger receptors (SRs) on the surface of macrophages and is subsequently removed. The half-life of plasma LDL in normal people is 2–4 days.

The cells prepare their cholesterol needs via two pathways: an exogenous pathway mediated with the LDLR and an endogenous pathway activated with the substrates of mevalonate and HMG-CoA reductase [6]. When the intracellular cholesterol level is too high, sterol regulatory element-binding protein (SREBP), a nuclear transcription factor, is activated, which inhibits the expression of LDL receptor gene from the transcription level, inhibits the synthesis of the receptor protein, and reduces the further uptake of LDL by the cell [7]. It is suggested that the simple increase of the nLDL-C level cannot fully explain the occurrence of atherosclerotic disease. More significantly, contrary to LDLR, SR expression is not inhibited by elevated intracellular cholesterol levels [1]. Then, when the number of modified LDL absorbed by macrophages through SRs far exceeds their scavenging

capacity, significant cholesterol accumulation will occur in macrophages, and then macrophages will be transformed into foam cells, which is a key link in the occurrence of atherosclerosis [8, 9].

3. LDL modification: endowing LDL with special biological activity

3.1 Changes in lipid composition of LDL particles and primary structure of apoB-100

At present, more research is placed on the effects of oxidation and glycosylation on LDL.

LDL oxidation: when circulating LDL is out of extremely high levels, oxidized LDL (ox-LDL) is rarely found in circulation due to the presence of plasma antioxidants and vitamin C. In this case, the oxidation of LDL occurs mainly in the arterial wall. Vascular wall cells (endothelial cells, smooth muscle cells, and macrophages), stimulated by the attack factors, produce and release a large number of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Free radicals rapidly oxidize the polyunsaturated fatty acids (PUFAs) on the surface of LDL into fatty acid fragments [10, 11]. This modification is produced in the surface of the LDL particles, so the physical and chemical properties of LDL change little. We call this LDL the “minimum modified LDL,” which retains the affinity for the LDL receptor. Then the “minimum modified LDL” activates the endothelial anti-apoptosis signaling pathway, induces endothelial cells to express tissue factors and chemokines, promotes the aggregation of inflammatory cells, triggers an inflammatory reaction, generates a large number of free radicals, and leads to the continuous oxidation of LDL. Continuous oxidation further converts fatty acid fragments into aldehydes, and aldehydes interact with the lysine residues of apoB-100 to form new antigenic determinants, inducing the formation of autoantibodies [12, 13]. After complete oxidation, ox-LDL completely loses its affinity to LDLR and binds specifically to the scavenger receptors (SRs) [14].

With an extremely high level of circulating LDL, the antioxidants in the body are insufficient to maintain the antioxidant protection of nLDL. And nLDL oxidizes rapidly even without strong attack factors. Meanwhile, high levels of LDL, in turn, promote the binding of NO with hydrogen peroxide to produce peroxynitrite (ONOO⁻), which is a strong oxidant and constantly attacks endothelial cells, resulting in endothelial dysfunction [15, 16].

LDL glycosylation: LDL glycosylation is a nonenzymatic reaction, and the reaction rate depends on the level of glucose and the duration of exposure [17]. The 67th amino acid region of the N-terminus of apoB-100 is the main site of glycosylation and also the attachment site of LDLR. Glycosylation at this site reduces the affinity of LDL to LDLR, promotes the uptake of LDL by SRs on the surface of macrophages, and induces the formation of foam cells. Glycosylation of LDL enhances the susceptibility to further oxidation of LDL. In addition, the glycosylation process is accompanied by the production of free radicals, which often result in the simultaneous existence of LDL glycosylation and LDL oxidation [18]. This is among the causes of peripheral vascular disease in patients with advanced diabetes.

3.2 Changes in lipid content of LDL particles and secondary structure of apoB-100

The conformation of apoB-100 on the surface of LDL is more dependent on the physical and chemical state of the lipid core, which is linked to the shape and

size of the LDL particles. Related experiments have found that the conformation of ApoB-100 is associated with the coverage of the interfacial area effect existing at the LDL particle-water solution interface. The coverage of the interfacial area effect increases with the decrease of LDL particle size, which can be regarded as an adaptive conformation change. This change is to avoid or minimize the contact between hydrophobic protein residues and aqueous solutions largely. It also ensures the stable existence of cholesterol in a hydrophilic environment and leads to successfully complete the targeted transport. However, this conformation regulation also causes more β -sheet domains to be parallel to the phospholipid monolayer of LDL, making it more vulnerable to adverse factors [19]. This may be one reason why sd-LDL with higher atherosclerosis is more easily oxidized.

The effect of oxidative modification on the secondary structure of LDL is mainly characterized by the destruction of β -sheet domain in the initial stage, resulting in the generation of disordered rings and corners. This change reduces the proportion of β -sheet in ApoB-100 and destroys the stability of LDL, but the alpha-helix ratio increases, triggering the self-repairing potential of apoB-100. At this point, the physical and chemical properties of LDL particles changed very little. When the oxidant continuously penetrates into the core, the physical state and accumulation mode of the lipid inside the hydrophobic core change, leading to the loss of the secondary structure of apoB-100, and the physical and chemical properties of LDL completely change [19].

In summary, compared to nLDL, mLDL has the following characteristics:

- the negative charge on the surface of particles is increased,
- the particle density is increased,
- due to the oxidation of lipids, polyunsaturated fatty acids decreased, and the contents of hemolytic lecithin, cholesterol oxide, and lipid hydroperoxide increased,
- ApoB100 is fragmented,
- reduced affinity with LDLR and specifically binds to scavenger receptors (SRs),
- acquired immunogenicity.

4. Modified LDL (mLDL) is involved in the formation of atherosclerotic lesions

Combined with the current known research results, the concept that the LDL-C level is critical to the occurrence and development of atherosclerotic lesions is too broad. It is better to say that the increase of the mLDL level caused by LDL qualitative change and quantitative change is the “turning point” of the entire event. Now, let us reexamine the role of mLDL in this process by combining the macro with the micro.

The physiological process of life can be divided into two levels: the basic physiological process and the complex regulatory network. Abnormal physiological processes are at the root of all diseases. According to the level of abnormality, we divide the disease into functional disorder and congenital defect.

4.1 Functional disorder: abnormal regulation of the network and damage to the ability to retain stability

The main purpose of the regulation network is to check and balance the basic physiological process and maintain the local and overall steady state. According to the understanding of atherosclerotic lesions, we regard the homeostasis maintenance here as the balance between injury factors and protective factors, and the balance can be broken for the following reasons:

4.1.1 Excessive damage factors

Poor lifestyle such as smoking and alcohol abuse as well as basic diseases such as hyperglycemia, insulin resistance, and hypertension damage vascular endothelial cells, causing oxidative stress on the blood vessel wall and producing a large number of free radicals (ROS and RNS) [11, 20]. There is a close interaction between LDL and vascular endothelial cells, followed by oxidative modification of LDL to form ox-LDL. Ox-LDL is most likely to remain in the intima-media than nLDL. And ox-LDL, which is stuck in the middle layer of the intima, affects the activity of endothelial cells (ECs) by changing the level of microRNAs and other epigenetic factors [21, 22]. It can induce the inflammatory activation of endothelial cells mediated by $\alpha 5\beta 1$ integrity and promote the production of vascular cell adhesion molecule-1 (VCAM-1). These cytokines attract monocytes to adhere to the designated location, promote the transendothelial transport of monocytes, enable them to accumulate in the endometrium, and differentiate into macrophages [23]. This process upregulates the expression of SRs on the surface of macrophages and promotes the uptake of ox-LDL by macrophages. At the same time, ox-LDL acts as an antigen to form an immune complex with auto-antibodies, and then the immune complex is recognized and internalized by the Fc γ receptor on the surface of macrophages [24, 25]. These two mechanisms are associated with the formation of foam cells. LPC, the main phospholipid component of ox-LDL, plays a pro-inflammatory role by regulating the function of a series of immune cells (monocytes, macrophages, T cells, dendritic cells) and vascular cells (endothelial cells, vascular smooth muscle cells). It also acts as a ligand for specific G protein-coupled receptors, activating several atherogenic signal transduction pathways [26].

4.1.2 Abnormal protective factors

At present, the research is mainly about the protective effect of nitric oxide (NO)-based antioxidants and the innate immunity of mononuclear macrophages.

NO, as a signal transduction molecule with free radical properties, can maintain vascular diastolic tension and regulate lipid peroxidation reaction, which subsequently changes the expression of pro-inflammatory genes in endothelial cells. When NO synthesis is blocked, the balance between reactive oxygen species (ROS) released by stressed tissues and antioxidants is broken, and ox-LDL is produced in large quantity. Stress also induces endothelial dysfunction and permeability of endothelial changes. The main consequence of this series of changes is the accumulation of ox-LDL in the subendothelial area [11, 15, 16].

As the principal carrier of circulating cholesterol, LDL contains a certain amount of polyunsaturated fatty acid (PUFAs), which is very sensitive to oxidative modification and is prone to structural changes [10]. In the normal state, innate immunity is activated to clear the ox-LDL produced in the physiological process. When the immune system is extremely responsive, macrophages play an antigen-presenting role and stimulate the proliferation of helper T lymphocytes, and the helper T lymphocytes produce specific

cytokines, realizing cross-dialog between different immune cell groups and initiating adaptive immunity. All the mechanisms work together to launch a sharp attack on ox-LDL, forming a chronic inflammatory process unique to atherosclerotic diseases [27].

The persistent inflammatory response stimulates smooth muscle cells to migrate to the intima-media, proliferate, and secrete large amounts of collagen, and the lesion enters the fibrous plaque stage. In this stage, intima thickening and remodeling first lead to increasing arterial wall stiffness and increased interfacial pressure in the environment where LDL is located, which promotes secondary structural changes of apoB-100 [28]. Secondly, the ability of regional oxygen diffusion was weakened, and the intermediate area of atherosclerotic lesions and intima-media showed ischemia and hypoxia. For the purpose of compensation, glycolysis becomes the primary mode of cell productivity in this region. This metabolic process produces lactic acid, which leads to extracellular space acidification. The state of regional low PH value is beneficial to the activation of macrophages and the upregulation of ox-LDL receptor (mainly LOX-1) expression in macrophages. The upregulated LOX-1 increases the lipid absorption of macrophages and promotes the formation of foam cells [29]. In addition, upregulated LOX-1 increases endothelial permeability and promotes the migration of ox-LDL to subendothelial space by reducing the expression of desmoglein-1 (DSG-1) and desmocollin-2 (DSC-2) [30, 31]. Under the stimulation of ox-LDL, the above process is repeated, the fiber cap becomes thickened, the declining foam cells form a necrotic lipid core, and the lesion enters the atherosclerotic plaque stage. When the compensatory arterial dilatation is unable to compensate for the stenosis caused by plaques protruding into the lumen, blood flow changes. The clinical manifestation is stable coronary syndrome. After that, if the disease continues to evolve, under the action of mechanical stimulation or inflammatory mediators, the fibrous cap becomes thinner, and local macrophages are activated, followed by focal necrosis, plaque rupture, content flow out, and thrombosis. The initiation of this process is the main cause of acute cardiovascular events.

Most of the atherosclerotic lesions caused by functional disorders progress slowly, and the clinical symptoms appear relatively late, which is mainly due to the existence of a series of compensation mechanisms, from the molecular level to the organ level, forming the natural defense line of the body. The breakthrough of the line of defense is characterized by micro decompensation, which corresponds to the progress of the disease at the macro level. The occurrence of cardiovascular events represents the loss of the ability to maintain stability, and treatment such as stenting can quickly relieve symptoms. However, this does not solve problems fundamentally, and it is necessary to effectively control the concentration of LDL particles having atherogenic properties. Combined with clinical experience, controlling the level of circulating LDL-C is the only effective method at present. Fortunately, the basic physiological processes of these patients are complete, and their regulatory network still exists. The focus of treatment is on using drugs to help the body to build a new balance. On the basis of a healthy lifestyle, adequate statin administration is effective in controlling LDL-C levels. For patients with moderate- or high-dose statin intolerance, the use of statins can be reduced by combining with ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which can delay or even prevent the progression of the disease and largely avoid cardiovascular endpoint events [32].

4.2 Congenital defect: familial hypercholesterolemia (FH)

Familial hypercholesterolemia is an autosomal dominant genetic disease characterized by high plasma levels of low-density lipoprotein cholesterol (LDL-C) and premature coronary heart disease, mainly caused by mutations in low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), and proprotein convertase

subtilisin/kexin type 9 genes. The first half of this article has introduced how extremely high levels of LDL-C can initiate LDL modification and attack the endothelium, which will not be described here. The high level of LDL-C in patients with FH since childhood is rooted in the damage to the basic physiological processes, which are genetically determined and inherent defects. Moreover, since the expression products of related genes are widely distributed under normal conditions, gene abnormalities also lead to regulatory network defects with compensation function damage, and the disease progresses rapidly in a short time. The traditional lipid-lowering method based on statins acts on the intracellular cholesterol synthesis process, which depends on the integrity of the basic physiological process, so it cannot effectively control the LDL-C level of FH patients. The key point of FH treatment is to make up for the defects in the basic physiological process and ensure survival. The discovery of PCSK9 inhibitors is a boon to such patients. PCSK9 combines with LDLR to promote LDLR degradation and interrupt the recycling of LDLR. Combined with statins, it can effectively control the LDL-C level of most FH patients. The reason why most but not all FH patients benefit is that this precision also leads to the poor treatment effect of PCSK9 inhibitor on LDLR-deficient FH homozygous [32–36].

5. Conclusions

LDL participates in the whole process of the formation and development of atherosclerotic lesions in the form of mLDL until plaque rupture, thrombosis, and cardiovascular events occur. The understanding of the characteristics of atherosclerosis caused by LDL should be built on the understanding of individual context. At present, a single LDL-C level has been impossible to accurately predict the progression of atherosclerotic lesions. The application value of mLDL, sd-LDL, etc. in the clinical practice needs to be further explored in the future.

Conflict of interest

To the best of our knowledge, the named authors have no conflict of interest, financially or otherwise.

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