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– Review –

Functional Properties of Low Density Lipoprotein (LDL) and Oxidized-LDL

Tae-Woong Kim

Dept. of Biochemistry, Kangwon National University, Chunchon 200-701, Korea

Abstract

All lipoproteins are made up of three major classes of lipids : triglycerides, cholesterol, and phospholipids. Lipoproteins vary in their relative content of these lipids as well as in size and protein content. Human low-density lipoprotein (LDL) is a main carrier for cholesterol in the blood stream, and it is well established that cholesterol deposits in the arteries stem primarily from LDL and that increased levels of plasma LDL correlate with an increased risk of atherosclerosis. Various lines of research provide strong evidence that LDL may become oxidized *in vivo* and that oxidized-LDL is the species involved in the formation of early atherosclerotic lesions. The most crucial findings in this context are the following : (1) Oxidized-LDL has chemotactic properties and if present in the intimal space of the arteries would recruit blood monocytes which then can develop into tissue macrophages ; (2) macrophages take up oxidized-LDL unregulated to form lipid laden foam cells ; (3) Oxidized-LDL is highly cytotoxic and could be responsible for damage of the endothelial layer and for the destruction of smooth muscle cells.

Key words : low density lipoprotein (LDL), oxidized LDL, atherosclerosis, LDL receptor

INTRODUCTION

Atherosclerotic cardiovascular disease is the leading cause of death in the Western world, and coronary artery disease (CAD) is its major manifestation. Atherosclerosis is the end result of a multifactorial process that includes deposition of lipids, particularly cholesteryl ester, in the subintimal area of arteries. Although numerous factors assocated with increased risk for CAD have been identified in prospective studies of populations around the globe, elevated fasting levels of plasma total and low-dentsity lipoprotein-(LDL) cholesterol, and reduced levels of plasma high-density lipoprotein (HDL) cholesterol have been clearly identified as major risk factors. In some prospetive studies, an increased fasting plasma concentration of triglycerides, the majority of which, in the fasting state, is found in very low density lipoproteins (VLDL), has also been demonstrated to be an independent risk factor for CAD .

The triglyceride-rich chylomicron and the relatively cholesteryl ester-en-enriched chylomicron remnant have been shown to interact with cells of the arterial wall, including the most significant cellular component of early atherosclerotic lesions, the monocyte-derived macrophages. Interactions between both endothelial cells and macrophages and LDL have been observed to modify the LDL so that they are able to interact with monocyte-derived macrophages and produce cholesteryl ester-enriched foam cells.

Low-density lipoprotein (LDL) is the most atherogenic lipoprotein in human plasma. LDL is also the lipoprotein that carries most of the cholestrol transported in the plasma, and apoprotein (apo) B is almost the only structrul apoprotein in LDL. Thus there is a need to understand the mechanisms that regulate the formation and catabolism of LDL-apo B and the association of LDL with the liver-intestine axis, the only route for elimination of cholesterol from the body. This review focus on the functional properties of LDL and oxidized-LDL in human.

PROPERTIES OF LIPOPROTEINS

The five major class of circulating lipoproteins are CM, VLDL, IDL, LDL and HDL (Table 1). The basic structure of the approximately spherical lipoprotein particles consists of a hydrophobic core (mainly TG

and CE) surrounded by a hydrophobic coat comprising a monolayer of amphipathic lipids (FC and PL) interspersed with a mixture. The hydrophilic coating of lipoproteins permits the hydrophobic core lipids to be transported in the aqueous environment of blood to other tissues. The largest of particles are chylomicrons, which are synthesized in the gut and carry dietary triglycerides and cholesterol. They contain TG as their major lipids constituent although their content of cholesterol ester may be very important in regulating the hepatic synthesis of cholesterol [1~3]. The VLDL are synthesized in the liver, carry endogeneously synthesized TG as well as cholesterol. The IDL represents an intermediate in the conversion of VLDL to LDL by LPL[4,5]. The IDL contain relatively less triglyceride and cholesterol ester compared to VLDL, but it is important to recognize that VLDL contain particles that may be functionlly equivalent to IDL. LDL are the major carriers of cholesterol and cholesteryl ester in the plasma. Approximately 60% of the cholesterol is transported as LDL in man and about three-fourths of this is esterified. The HDL are much richer in protein and contain one-half protein and one-half lipid by weight. The lipids of HDL are primarily phospholipid and cholesterol esters. HDL are usually subdivided into at least two subclasses, HDL2 and HDL3 for two reasons. First, rate-zonal ultracentrifugation produces a bimodel distribution of HDL[6,7]. Second, HDL2 appear to have stronger inverse statistical relationship with coronary heart disease than HDL3.

LOW DENSITY LIPOPROTEIN (LDL)

Schematic representation of apo B-100 structure on LDL was presented in Fig. 1[8]. LDL particles range in diameter from ~270 to ~230Å and in molecular weight 2.89 to 1.88×106 over the density range 1.025~1.0597g/ml. The formation of LDL from VLDL is accompanied by further loss of TG and PL and perhaps most critically by the loss of apo E. Only apo B-100 is retained in LDL[9,10]. The lipid loss is thought to result from the action of hepatic lipase upon the remnant particle : loss of apo E may be a passive consequence of altered composition or curvature of the particle surface. The LDL are removed from the circulation by both high-affinity receptor-mediated and receptor-independant pathways, the liver being the major organ responsible for LDL clearance[11,1]. LDL are removed less efficiently by the hepatic receptors through binding to apo B-100, gradually gain access to extravascular compartments of various organs and tissues which contain LDL receptors, so that an appreciable fraction is taken up in extrahepatic tissues as well[3,12]. The distribution of LDL to various tissues de-

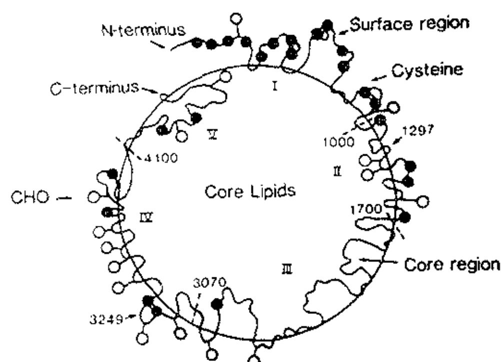

Fig. 1. A schematic representation of apo B-100 structure on low density lipoprotein(LDL).

Table 1. Characteristics of the major classes of lipoproteins in human plasma

Lipoprotein class	Major lipids	Apoproteins	Density ($g \cdot cm^{-3}$)	Particle diameter(A)
Chylomicrons and remnants	Dietary triacylglycerols	A-I, A-II, B-48, C-I, C-II, C-III, E	<0.95	800~5000
VLDL	Endogenous triacyl-glycerols, cholesteryl-esters, cholesterol	B-100, C-I, C-II, C-III, E	0.95~1.006	300~800
IDL	Cholesteryl esters, cholesterol, triacylglycerols	B-100. C-III, E	1.009~1.019	250~350
LDL	Cholesteryl esters, cholesterol, triacylglycerols	B-100	1.019~1.063	180~280
HDL	Cholesteryl esters, cholesterol	A-I, A-II, C-I, C-II, C-III, D, E	1.063~1.210	50~120

pends mainly on the rate of transcapillary transport and the activity of LDL receptors on cell surfaces.

Apo E as well as apo B-100 contain a recognition site for the LDL receptor. The human LDL receptor is a transmembrane protein of 839 amino acids[9]. It's NH_2-terminal portion, which is rich in cystein residues, is composed of a 7-fold repeat is an octapeptide sequence that contains three aspartyl residues and one glutamyl residues. These negatively charged regions presumably constitute the ligand-binding sites of the receptor which interact electrostatically with the positively charged region of the apolipoprotein ligands.

LDL may also be catabolized via a non-specific scavenger pathway involving tissue macrophages. The macrophages contains a receptor which binds and internalized LDL that has been altered as by acetylation, or by acting with malondialdehide[11,12]. This receptor has very poor binding activity toward 'normal' LDL. LDL are heterogeneous in their lipid content, size and density and certain LDL subspecies may increase risk of atherosclerosis possibly due to differences in the conformation of apo B in the particle[11,12].

APOLIPOPROTEIN B-100

Apo B is an important component in the system of plasma lipoproteins[1,2]. It functions as the ligand for the LDL receptor in peripheral cells, In humans, much of the apo B VLDL is transfered to IDL and subsequently to LDL. Apo B exists primarily in two forms : apo B-100 and apo B-48. Apo B-100 is synthesized by the liver and is an obligatory constituent of VLDL, IDL, and LDL.

Apo B-100 is generally an abundant apolipoprotein in plasma being present in normal human plasma in a concentration of about 90mg/dl[8]. Apo B-100 has been the subject of structural studies, but insolubility and aggregability of apo B-100 in aqueous solvents after delipidation complicated its structural analysis. Apo B-100 is the ligand recognized by the LDL receptor, lysine and arginine residues may be important in receptor binding. Human plasma LDL contains approximately 80% lipid and 20% protein by weight. About 4~10% of the mass of apo B-100 consists of carbohydrate chains containing galactose, mannose, N-acetylglucosamin, and sialic acid residues using direct sequencing analysis, N-glycoslation sites of apo B-100 were found 16 sites. Within the LDL particle, disulfide bonds appear to influence the stability of apo B-100, which contains 25 cystein residue[5]. The complete amino acid sequence of apo B-100 has been determined. There are 4536 amino acids in apo B-100.

FOWARD TRANSPORT CHOLESTEROL OF LDL

The secretion rate of apo B in human VLDL is about 1g/day. The mass of cholesterol in cholesteryl ester in VLDL represents about 0.6g of cholesterol, when the contrubution of the acyl moiety in discounted (Table 2). The free cholesterol secreted in VLDL is about 0.7g/day. The cholesteryl ester remains in the particle as VLDL is converted by lipase activity to LDL. About one third of total LDL cholesteryl ester is reported to be delivered to the extrahepatic tissues, mainly by the LDL receptor and nonspecific pathways. As a result, forward cholesterol transport from VLDL and LDL is about 0.7g of cholesterol per day(mostly in the esterified form, reflecting the composition of the LDL cleared). To maintain cholesterol homeostasis, this mass, plus whatever is synthesized in the peripheral tissues, must be balanced by the reserve cholesterol transport promoted by HDL (relatively small amounts of cholesterol are lost by the synthesis of steroid hormones).

Such calculations are only approximate, but serve to illustrate the general dimensions of the forward and reverse pathways in cholesterol transport. Other cholesterol transported by the same pathway is the free cholesterol lost from the surface of VLDL and LDL to HDL during their recirculation, estimated to be about 0.3g/day. These calculations suggest that

Table 2. Estimate of forward cholesterol transport (estimates are on the basis of a body wt. of 70kg)

a.	Cholesteryl ester in VLDL	0.6g/day
b.	Free cholesterol in VLDL	0.9g/day
c.	Free cholesterol lost to HDL	0.3g/day
d.	Total cholesterol carried on (a + b − c)	1.0g/day
e.	Lost from LDL to peripheral tissues	0.3g/day
f.	Peripheral synthesis	0.4g/day
g.	Reverse transport at equilibrium (e + f)	0.7g/day

the total cholesterol returned from the plasma to the liver per day may be of the order of 1.0g/day[3,13].

Accumulation of free and esterified cholesterol in tissue of the arterial wall is a characteristic feature of atherosclerosis. Pathological accumulation of cholesterol in the intima can result from an excessive influx from LDL or impaired via HDL (Fig. 2).

OXIDIZED LDL

A) Biological properties of oxidized LDL

LDL particles are incoporated into tissue by LDL-receptor that recognizes LDL's apoprotein component[3]. *In 1979, Goldstine discovered that macrophage,* ordinary indifferent to LDL, have scavenger receptors by which they can recognize and ingest modified LDL [11,1,12]. Initial studies involved LDL particles acetylaetd *in vitro* ; subsequent research showed that scavenger receptors also bind oxidized LDL-a modification more likely to occur *in vivo*[14,15]. These findings set the stage for today's evolving models of atherosclerosis, in which not just the abundance and type of lipoprotein particles, but also the oxidative modification of LDL, may promote atheroma formation in animals and humans[3].

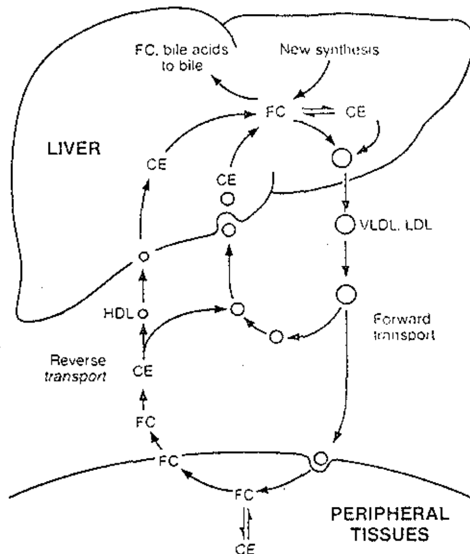

Fig. 2. Metabolism pathway of LDL and HDL cholesterol. (FC : Free cholesterol, CE : Cholesterol ester)

B) Macrophage scavenger receptor

It is generally agreed that atrerosclerotic plaque formation begins with the attachment of monocytes *to the lumenal surface of the endothelium and their* subsequent migration into the subendothelial space. There the monocytes differentiate into macrophages, and if plasma LDL levels are high, they accumulate massive amounts of lipoprotein cholesterol and become foam cells. Several lines of evidence suggest that the LDL receptor pathway is not required for and may not normally be involved in cholesterol accumulation during foam cell development. For example, in humans and animals with genetic defect is LDL levels are abnormally high and plaque formation is accelerated. Currently, and attractive model for lipoprotein-chlesterol accumulation in macrophage foam cells is the macrophage foam cells is the macrophage scavenger receptor model[15,16]. Scavenger receptor pathway is shown in Fig. 3.

The physiological and pathophysiological functions of the scavenger receptor have not been established with certainty. It seems likely that macrophage scavenger receptors are involved in form cell formation during atherogenesis[14,17].

C) Mechanism of oxidized LDL

In the course of lipid metabolism, some circulating LDL particles migrate across the endothelial border and enter the arterial subendothelial space[11,17]. This itself is normal, but if there is a presence of excess LDL or if other conditions pertain, a significant proportion of those LDL particles can undergo oxidative modification. The subendothelium is a more favora-

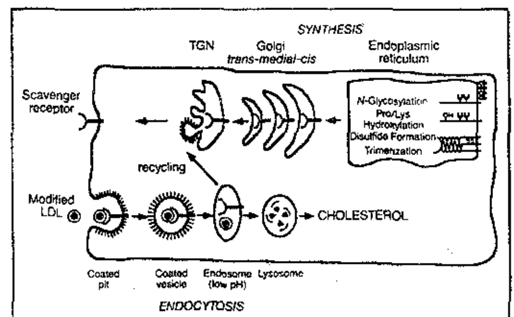

Fig. 3. Pathways of scavenger receptor and modifided LDL in liver.

ble environment for such changes than circulating plasma, because natural antioxidants are abundant in plasma. Circulating LDL, modified or not, is swept up and reprocessed by the liver[18~20].

In vitro studies show that lipoproteins can be oxidized when incubated with endothelial or smooth muscle cells[16]. Several mechanisms have been postulated for the oxidation of subendothelial LDL *in vivo*[21,22]. LDL lipids may become oxidized when the LDL particles come in contact with cells, or cells may release oxygen free radicals that interact with LDL (Fig. 4). Various exogenous compound, such as nitrogenous product of tobacco smoke or airpollution, ozon (the most oxidative substance known), and such compounds as carbon tetrachloride, paraquat, bleomycin and some modificators, may also facilitate oxidative modification of LDL[23,24].

In culture, macrophages take up native LDL only slowly, and even if incubated over long periods with high LDL concentrations, they do not accumulate cholesterol esters and transform to lipid-laden cells. This receptor is not under the control of intracellular cholesterol. The majority of these cells are macrophages and are derived from circulating monocytes-macrophages. It is currently belived that post secretory modifications of LDL may render the lipoprotein more atherogenic[13,25]. Recent studies have suggested that oxidatively modified LDL may represent one such modified form of LDL. The oxidative modification of LDL can be compartmentalized into the following steps (Fig. 4) ; (a) the cellular generation of the oxidant (b) oxidation of the lipoprotein lipids ; and (c) the generation of the epitopes on the modified LDL that leads to its recognition by the macrophage scavenger receptor. This process encompasses the generation of the effectors of monocyte/macrophage chemotaxis. Based on the cell culture studies, the oxidatively modified LDL has been suggested to promote atherogenesis in the following ways (Fig. 5) ; (a) facilitating intimal recruitment of monocyte ; (b) ret-

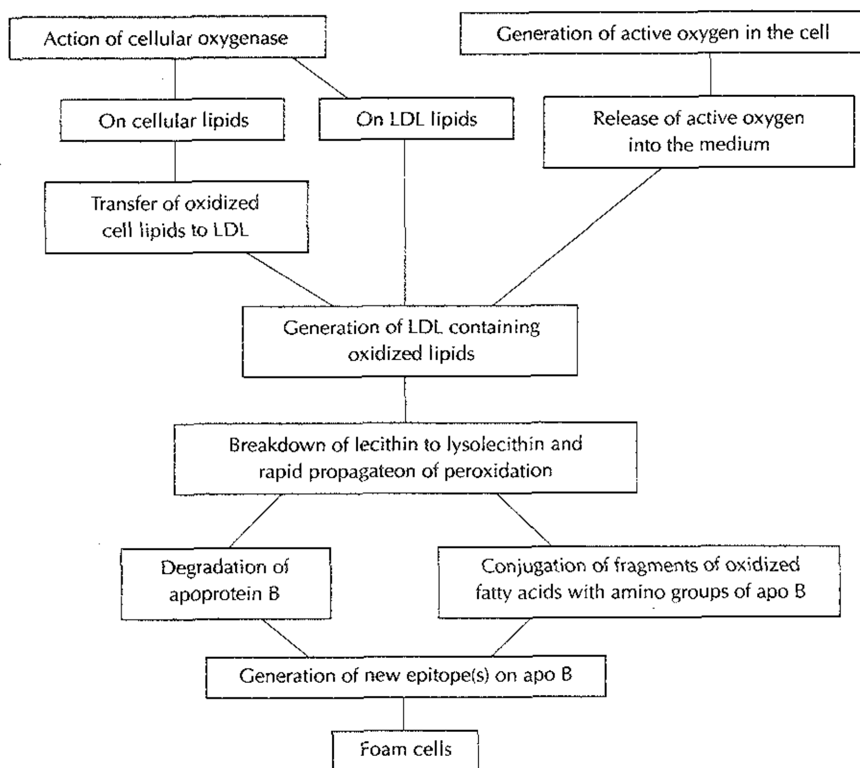

Fig. 4. Mechanism thought to lead to the oxidatively modification of LDL by cell ; cited from Steinberg *et al.*[7].

aining macrophages in the arterial wall ; (c) contributing to foam cell formation by way of the scavenger receptor ; and (d) causing injury to the endothelium[14,15].

Unsaturated fats, although less closely associated with coronary heart disease than saturated fats, are actually more vulnerable to oxidation. Among the polyunsaturated fats, arachidonic acid is of particular interest. A key byproduct of arachidonic acid's oxidation is malondialdehyde (MDA). MDA can directly

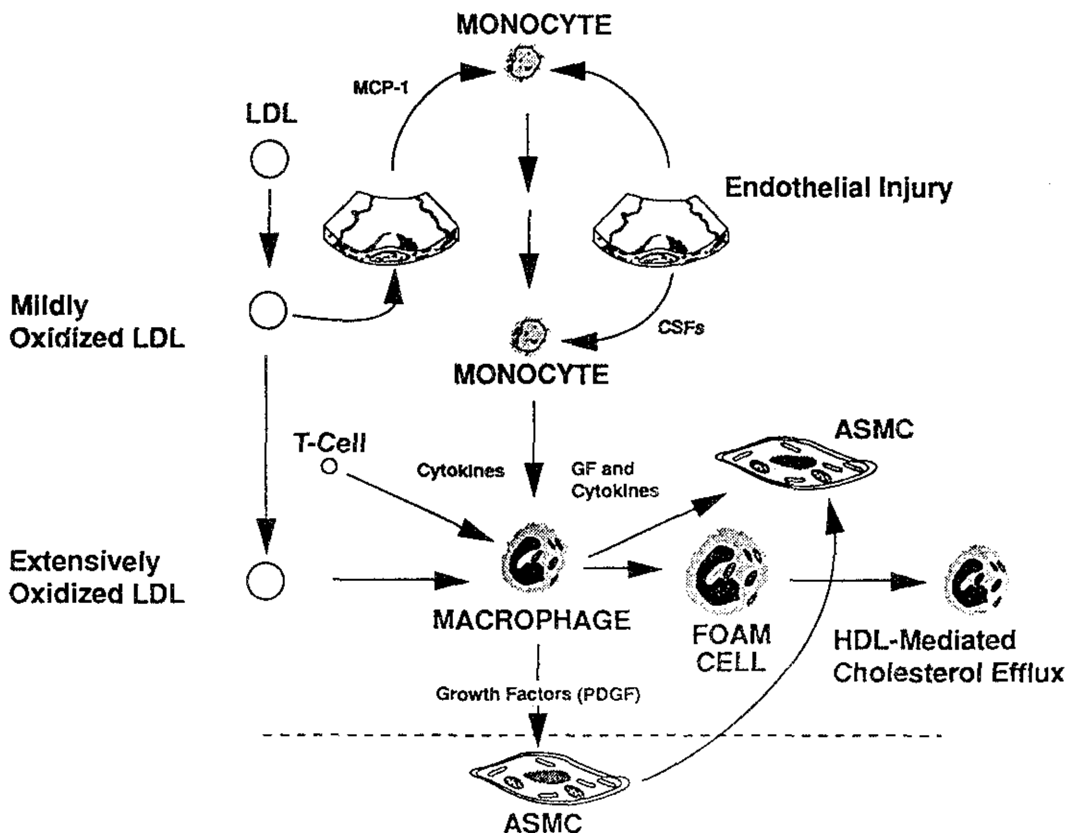

Fig. 5. Simplified view of atherogenesis by mildly and extensively oxidized LDL to form foam cell on endothelial cell.

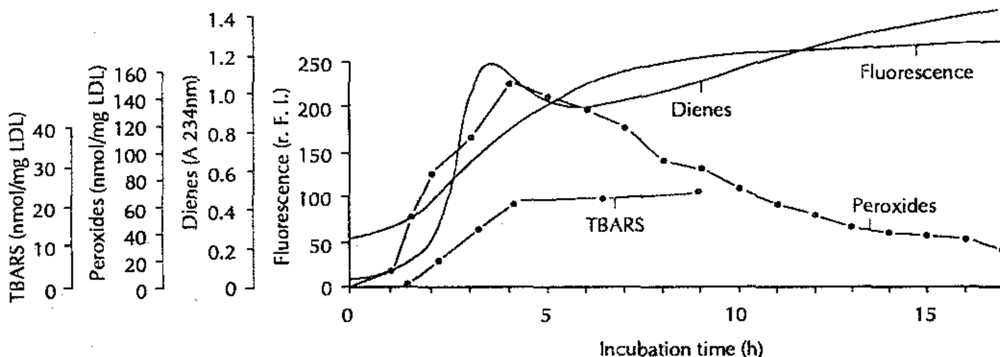

Fig. 6. Time course of LDL-oxidation ; cited from Gebicki *et al.*[22].

alter the conformation of apo B-100. It is reported that once 16% of the lys residues of the apo B-100 protein have been modified by MDA, the new conformation becomes recognizable to the macrophage scavenger receptor. An LDL particle carring MDA-modified apo B-100 has a diminished affinity for the normal LDL receptor and an increased likehood of being taken up by a macrophage[1,11].

D) Methods to determine oxidation of LDL

In the course of oxidation the physicochemical, functional and biological properties of LDL become progressively altered. The onset and progression of LDL oxidation in vitro can be followed by measuring the increase of TBARS, lipid hydroperoxides, conjugated diense, aldehydes and fluorescent proteins or lipids (Fig. 6). Other possibilities include measurement of the disappearance of the endogenous antioxidant and polyunsaturated fatty acids, fragmentation of the apolipoprotein B to smaller peptides, and increase of the relative electrophoretic mobility of LDL. The biological assays used most frequently for the evaluation of the extent of oxidative modification of LDL are available and can be used for immunocytochemical analysis[14,22].

The most commonly used assay in LDL oxidation studies, both in the presence and absence of cells, is the determination of thiobarbituric acid reactive substance. It is known that in LDL the major sources of malonaldehyde (MDA) are arachidonic and docosahexaenoic acids. Since the concentration of these fatty acids in LDL can vary considerably from donor to donor, it follows also that significant variations the the TBARS values of oxidized LDL can be expected. Nevertheless, all reports agree that TBARS values must reach a certain threshold level so that LDL is recognized and taken up by the scavenger receptor[13,26].

Very useful parameters for monmitoring the rate of LDL oxidation are the conjugated diense. If the LDL lipids are oxidized, the polyunsaturated fatty acids will be converted to fatty acid hydroperoxides with conjugated double bonds, showing a UV absorption maximum at 234nm. Since oxidized LDL remains fully soluble in buffer, the increase of the 234 nm diene absorption can be measured direcly in the LDL solution, i.e. without extraction of the LDL lipids. As with the TBARS time-course, the increase of the diene absorption remains constant or only slightly increase. Thereafter, the 234nm absorption rapidly increase (propagation period) more or less in parallel with the TBARS values to a maximum value[27,28].

E) Pathological aspects of oxidized LDL

The alteration of apo B-100 on the surface of LDL particles renders the particles recognizable to scavenger receptors and thus vulnerable to uptake by subendothelial macrophage. Unfortunately, macrophage do not down regulate their scavenger receptors after consuming their fill of cholesterol ; instead, they turn into giant, obese, cholesterol ester rich foam cells, key ingradients of atheromas[6,26].

Foam cell growth through scavenger receptor uptake of oxidized LDL is one cornerstone of current models of atherogenesis, but there are other ways modified LDL can contribute as well. Oxidized LDL particles have increased levels of lysolecithin, which both attracts circulating monocytes into the subendothelial space (where they become macrophages) and inhibits subendothelial macrophages from migrating else where. Macrophages themselves can secrete potentially atherogenic substances ; by inhibiting macrophage migration, oxidized LDL gives those substances a better chance of being secreted where they can do the most harm[22].

In addition, oxidized LDL is directly cytotoxic. It might promote endothelial damage, exposing the basement membrane and facilitating platelet aggregation and other processes central to thrombo-atherosclerosis. Furthermore, there is evidence to suggest that the damage is self-perpetuating, with the release of oxidative substances continually enhancing lesion growth, perhaps in a localized area of the artery[29,30].

ROLE OF ANTIOXIDANTS IN PREVENTING OF LDL

If modification of LDL mediated by cells or occurring in cell-free medium is in fact a lipid peroxidation process, water- and lipid-soluble antioxidants should have a prominent effect in preventing or retarding

the modification. Inclusion of high concentrations of vitamin E (100μM) in the culture medium largely prevented cell-mediated oxidation of LDL over 24 h. A concentration of 100uM vitamin E is very high and corresponds to about 200nmol of vitamin E/mg of LDL, which is about 100-fold higher than the endogenous vitamin E contents of LDL. It is evident that the first protective barrier is vitamin E, i.e., α-and γ-tocopherol[31~34]. If v itamin E is consumed, the carotenoids(lycopene, β-carotene, and phytofluene) become effective, and only when this second defense line is destroyed does the lipid peroxidation process enter into a propagating chain reaction as indicated by the rapid increase of the 234nm absorption. This sequence of destruction of endogenous antioxidants was observed in all other oxidation experiments performed so far. The sequence remained also the same when water-soluble antioxidants were included in the PBS. For example, urate and also ascorbate prolong the lag period in a concentration-dependent manner, and even more importantly, these water-soluble antioxidants can retard the destruction of the endogenous antioxidants in LDL in a concentration-dependent manner. Here the endogenous antioxidants remained virtually unchanged for 90min ; during this time the ascorbated decreased to zero. Thereafter, vitamin E and carotenoids decreased in the same sequence as in the absence of ascorbate, and lipid peroxidation entered into a propagating chain reaction when the LDL was depleted from its endogenous lipophilic antioxidants[22,34].

Vitamin E is a chain-breaking antioxidant which prevents the propagation of lipid peroxidation by scavenging lipid peroxyl radicals according to LOO · + vit E-LOOH+vit E. Vitamin E is most likely located in the LDL in the outer phospholipid layer with the chromanol ring facing the acqueous phase. It is reasonable that the protective effect of ascorbic acid roles on its capacity of reactivating vitamin E according to vit E+ascorbic acid-vit E ascorbyl radical. The emporal relationship of the disappearance of the endogenous antioxidants also suggests that vitamin E has a protective effect on the carotenoids. The mechanism for vitamin E reactivation of carotenoid radicals or oxidized carotenoids is however unclear copper-stimulated LDL oxidation[35~37].

Additionally, other factors, such as, for example, the content and distribution of ployunsaturated fatty acis and the amount of performed lipid peroxides, probably contribute to the susceptibility of LDL toward prooxidants. Wide variation cannot fully be explained by the antioxidants and polyundsaturated fatty acid content ; therefore, LDL must possess additional donor-specific factors which increase or decrease the resistance to oxidation[7,38~40].

CONCLUSION

Low-density lipoprotein (LDL) is the most atherogenic lipoprotein in human plasma. LDL is also the lipoprotein that carries most of the cholestrol transported in the plasma, and apoprotein (apo) B is almost the only structrul apoprotein in LDL. Thus there is a need to understand the mechanisms that regulate the formation and catabolism of LDL-apo B and the association of LDL with the liver-intestine axis, the only route for elimination of cholesterol from the body.

From total cholestrol to lipoprotein fractions to considerations of lipoprotein modification, models of atherogenesis have grown increasingly detailed and complex. As new data emerge, the picture is likely to become more complex still. However, key aspects of today's model hold up, antioxidation may prove to be a way to inhibit some of the earliest events in the progression of atherosclerosis.

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저밀도 지질단백질 및 산화 LDL(Oxidized-LDL)의 특성

김 태 웅
강원대학교 생화학과

요 약

최근 지방 섭취의 증가에 따른 혈관계 질병이 증가 추세에 있다. 이러한 동맥경화 및 고지질의 질병을 지질단백질 (lipoprotein)과 관련하여, LDL 및 산화 LDL의 특성을 중심으로 고찰하였다. 인체의 혈장에 함유된 LDL 함량의 증가는, 동맥경화와 직결되는 것을 의미하며, 이러한 LDL은 매우 hydrophobic한 특성을 가진 550Kd의 단일 polypeptide인 Apo B-100라는 단백질이, 지질성분인 triglyceide, phospholipid 및 cholesterol와 결합되어 있다. 최근 이러한 LDL은 산화 (oxidation)되는 경우, 정상적인 LDL-receptor pathway를 따르지 않고, macrophage와 결합하므로서, foam cell을 형성하여 동맥경화가 촉진되는 것으로 알려지고 있다.