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Introduction to Lipids and Lipoproteins

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ABSTRACT

Cholesterol and triglycerides are insoluble in water and therefore these lipids must be transported in association with proteins. Lipoproteins are complex particles with a central core containing cholesterol esters and triglycerides surrounded by free cholesterol, phospholipids, and apolipoproteins, which facilitate lipoprotein formation and function. Plasma lipoproteins can be divided into seven classes based on size, lipid composition, and apolipoproteins (chylomicrons, chylomicron remnants, VLDL, IDL, LDL, HDL, and Lp (a)). Chylomicron remnants, VLDL, IDL, LDL, and Lp (a) are all pro-atherogenic while HDL is anti-atherogenic. Apolipoproteins have four major functions including 1) serving a structural role, 2) acting as ligands for lipoprotein receptors, 3) guiding the formation of lipoproteins, and 4) serving as activators or inhibitors of enzymes involved in the metabolism of lipoproteins. The exogenous lipoprotein pathway starts with the incorporation of dietary lipids into chylomicrons in the intestine. In the circulation, the triglycerides carried in chylomicrons are metabolized in muscle and adipose tissue by lipoprotein lipase releasing free fatty acids, which are subsequently metabolized by muscle and adipose tissue, and chylomicron remnants are formed. Chylomicron remnants are then taken up by the liver. The endogenous lipoprotein pathway begins in the liver with the formation of VLDL. The triglycerides carried in VLDL are metabolized in muscle and adipose tissue by lipoprotein lipase releasing free fatty acids and IDL are formed. The IDL are further metabolized to LDL, which are taken up by the LDL receptor in numerous tissues including the liver, the predominant site of uptake. Reverse cholesterol transport begins with the formation of nascent HDL by the liver and intestine. These small HDL particles can then acquire cholesterol and phospholipids that are effluxed from cells, a process mediated by ABCA1 resulting in the formation of mature HDL. Mature HDL can acquire additional cholesterol from cells via ABCG1, SR-B1, or passive diffusion. The HDL then transports the cholesterol to the liver either directly by interacting with hepatic SR-B1 or indirectly by transferring the cholesterol to VLDL or LDL, a process facilitated by CETP. Cholesterol efflux from macrophages to HDL plays an important role in protecting from the development of atherosclerosis. For complete coverage of all related areas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

INTRODUCTION

Because lipids, such as cholesterol and triglycerides, are insoluble in water these lipids must be transported in association with proteins (lipoproteins) in the circulation. Large quantities of fatty acids from meals must be transported as triglycerides to avoid toxicity. These lipoproteins play a key role in the absorption and transport of dietary lipids by the small intestine, in the transport of lipids from the liver to peripheral tissues, and the transport of lipids from peripheral tissues to the liver and intestine (reverse cholesterol transport). A secondary function is to transport toxic foreign hydrophobic and amphipathic compounds, such as bacterial endotoxin, from areas of invasion and infection (1).

STRUCTURE OF LIPOPROTEINS (2)

Lipoproteins are complex particles that have a central hydrophobic core of non-polar lipids, primarily cholesterol esters and triglycerides. This hydrophobic core is surrounded by a

hydrophilic membrane consisting of phospholipids, free cholesterol, and apolipoproteins (Figure 1). Plasma lipoproteins are divided into seven classes based on size, lipid composition, and apolipoproteins (Table 1 and Figure 2).

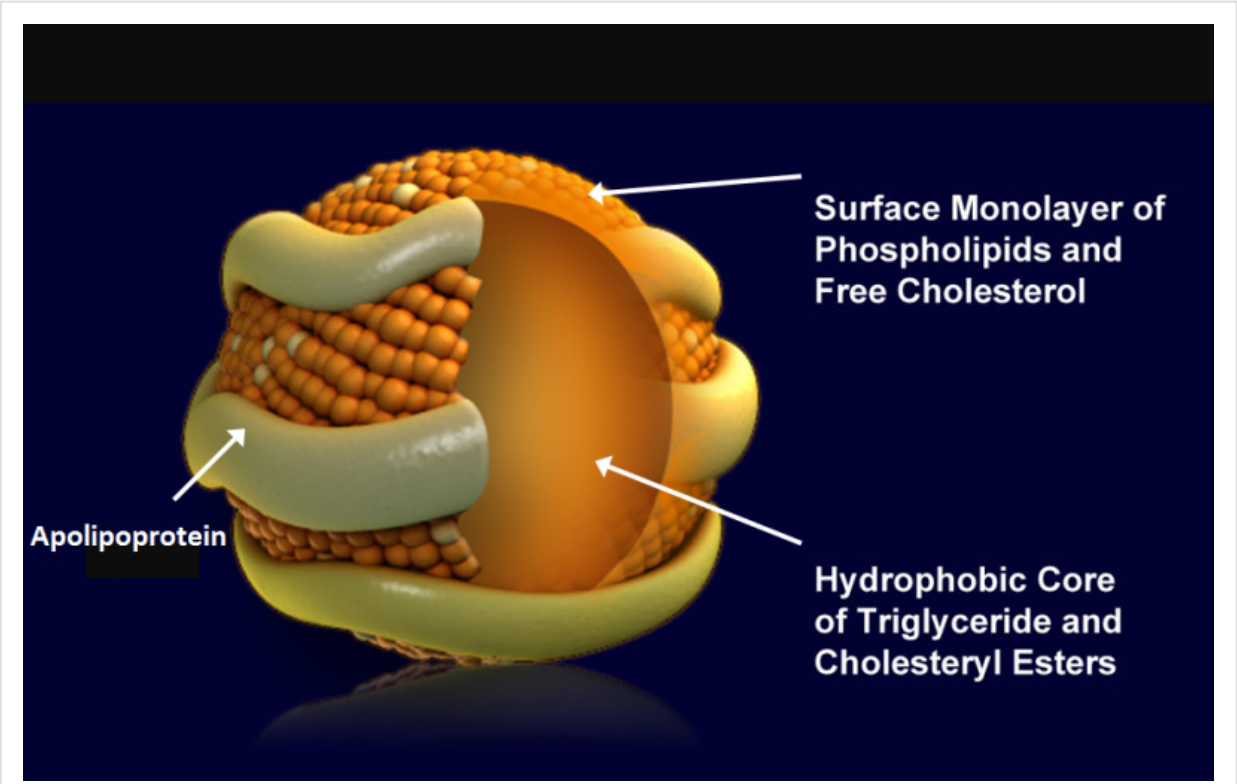


Figure 1.
Lipoprotein Structure (figure modified from Biochemistry 39: 9763, 2000)

Table 1.
Lipoprotein Classes

Lipoprotein	Density (g/ml)	Size (nm)	Major Lipids	Major Apoproteins
Chylomicrons	<0.930	75-1200	Triglycerides	Apo B-48, Apo C, Apo E, Apo A-I, A-II, A-IV
Chylomicron Remnants	0.930-1.006	30-80	Triglycerides Cholesterol	Apo B-48, Apo E
VLDL	0.930-1.006	30-80	Triglycerides	Apo B-100, Apo E, Apo C
IDL	1.006-1.019	25-35	Triglycerides Cholesterol	Apo B-100, Apo E, Apo C
LDL	1.019-1.063	18- 25	Cholesterol	Apo B-100
HDL	1.063-1.210	5- 12	Cholesterol Phospholipids	Apo A-I, Apo A-II, Apo C, Apo E
Lp (a)	1.055-1.085	~30	Cholesterol	Apo B-100, Apo (a)

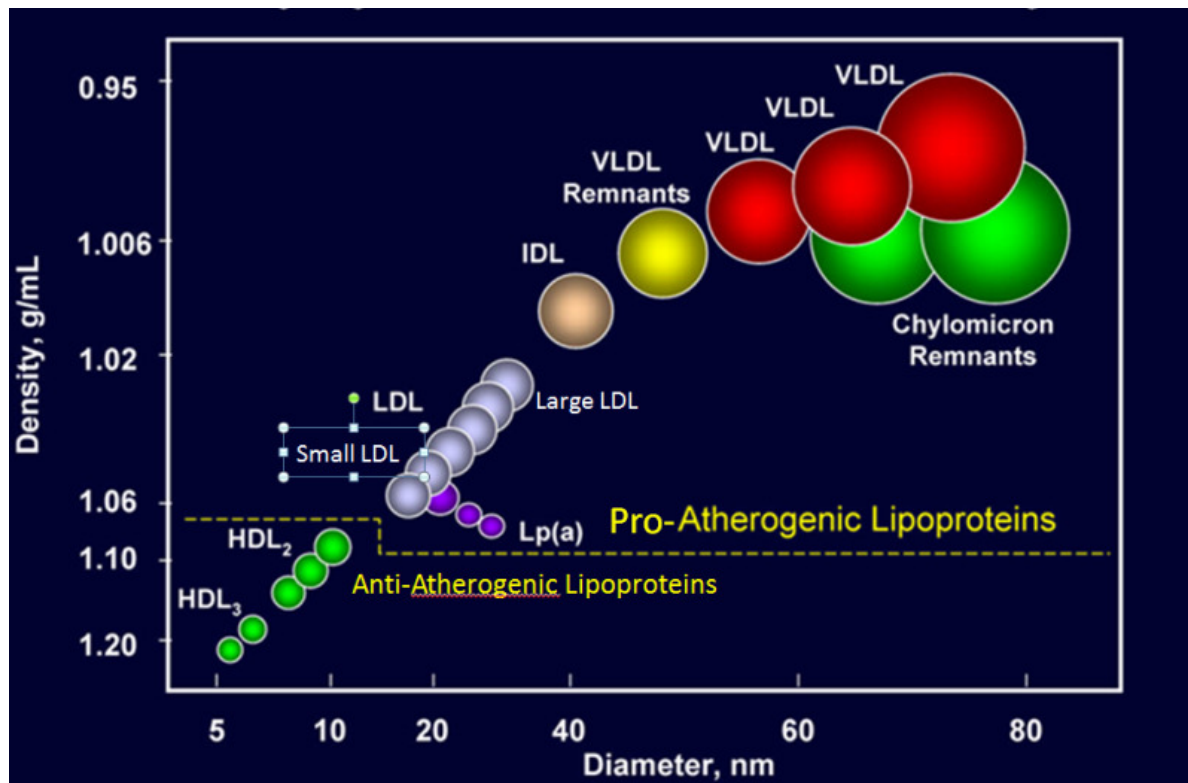


Figure 2:

Classes of Lipoproteins (figure modified from Advances Protein Chemistry 45:303, 1994)

Chylomicrons

These are large triglyceride rich particles made by the intestine, which are involved in the transport of dietary triglycerides and cholesterol to peripheral tissues and liver. These particles contain apolipoproteins A-I, A-II, A-IV, A-V, B-48, C-II, C-III, and E. Apo B-48 is the core structural protein and each chylomicron particle contains one Apo B-48 molecule. The size of chylomicrons varies depending on the amount of fat ingested. A high fat meal leads to the formation of large chylomicron particles due to the increased amount of triglyceride being transported whereas in the fasting state the chylomicron particles are small carrying decreased quantities of triglyceride.

Chylomicron Remnants

The removal of triglyceride from chylomicrons by peripheral tissues results in smaller particles called chylomicron remnants. Compared to chylomicrons these particles are enriched in cholesterol and are pro-atherogenic.

Very Low-Density Lipoproteins (VLDL)

These particles are produced by the liver and are triglyceride rich. They contain apolipoprotein B-100, C-I, C-II, C-III, and E. Apo B-100 is the core structural protein and each VLDL particle contains one Apo B-100 molecule. Similar to chylomicrons the size of the VLDL particles can vary depending on the quantity of triglyceride carried in the particle. When triglyceride production in the liver is increased, the secreted VLDL particles are large. However, VLDL particles are smaller than chylomicrons.

Intermediate-Density Lipoproteins (IDL; VLDL Remnants)

The removal of triglycerides from VLDL by muscle and adipose tissue results in the formation of IDL particles which are enriched in cholesterol. These particles contain apolipoprotein B-100 and E. These IDL particles are pro-atherogenic.

Low-Density Lipoproteins (LDL)

These particles are derived from VLDL and IDL particles and they are even further enriched in cholesterol. LDL carries the majority of the cholesterol that is in the circulation. The predominant apolipoprotein is B-100 and each LDL particle contains one Apo B-100 molecule. LDL consists of a spectrum of particles varying in size and density. An abundance of small dense LDL particles are seen in association with hypertriglyceridemia, low HDL levels, obesity, type 2 diabetes (i.e. patients with the metabolic syndrome) and infectious and inflammatory states. These small dense LDL particles are considered to be more pro-atherogenic than large LDL particles for a number of reasons. Small dense LDL 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 and bind more avidly to intra-arterial proteoglycans, which traps them in the arterial wall. Finally, small dense LDL particles are more susceptible to oxidation, which could result in an enhanced uptake by macrophages.

High-Density Lipoproteins (HDL)

These particles play an important role in reverse cholesterol transport from peripheral tissues to the liver, which is one potential mechanism by which HDL may be anti-atherogenic. In addition, HDL particles have anti-oxidant, anti-inflammatory, anti-thrombotic, and anti-apoptotic properties, which may also contribute to their ability to inhibit atherosclerosis. HDL particles are enriched in cholesterol and phospholipids. Apolipoproteins A-I, A-II, A-IV, C-I, C-II, C-III, and E are associated with these particles. Apo A-I is the core structural protein and each HDL particle may contain multiple Apo A-I molecules. HDL particles are very heterogeneous and can be classified based on density, size, charge, or apolipoprotein composition (Table 2).

Table 2.

Classification of HDL

Method of classification	Types of HDL
Density gradient ultracentrifugation	HDL ₂ , HDL ₃ , Very high-density HDL
Nuclear magnetic resonance	large, medium, and small
Gradient gel electrophoresis	HDL 2a, 2b, 3a, 3b, 3c
2-dimensional gel electrophoresis	pre-beta 1 and 2, alpha 1, 2, 3, 4
Apolipoprotein composition	A-I particles, A-I: A-II particles, A-I: E particles

Lipoprotein (a) (Lp (a))

Lp (a) is an LDL particle that has apolipoprotein (a) attached to Apo B-100 via a disulfide bond. This particle is pro-atherogenic. The physiologic function of this lipoprotein is unknown.

APOLIPOPROTEINS (3,4)

Apolipoproteins have four major functions including 1) serving a structural role, 2) acting as ligands for lipoprotein receptors, 3) guiding the formation of lipoproteins, and 4) serving as activators or inhibitors of enzymes involved in the metabolism of lipoproteins (Table 3). Apolipoproteins thus play a crucial role in lipoprotein metabolism.

Apolipoprotein A-I

Apo A-I is synthesized in the liver and intestine and is the major structural protein of HDL accounting for approximately 70% of HDL protein. It also plays a role in the interaction of HDL with ATP-binding cassette protein A1 (ABCA1), ABCG1, and class B, type I scavenger receptor (SR-B1). Apo A-I is an activator of lecithin: cholesterol acyltransferase (LCAT), an enzyme that

converts free cholesterol into cholesteryl ester. High levels of Apo A-I is associated with a decreased risk of atherosclerosis.

Apolipoprotein A-II

Apo A-II is synthesized in the liver and is the second most abundant protein on HDL accounting for approximately 20% of HDL protein. The role of Apo A-II in lipid metabolism is unclear. Apo A-II is a strong predictor of risk for CVD.

Apolipoprotein A-IV (5)

Apo A-IV is synthesized in the intestine during fat absorption. Apo A-IV is associated with chylomicrons and high-density lipoproteins, but is also found in the lipoprotein-free fraction. Its precise role in lipoprotein metabolism remains to be determined but studies have suggested a role for Apo A-IV in regulating food intake.

Apolipoprotein A-V (6)

Apo A-V is synthesized in the liver and associates with triglyceride rich lipoproteins. It is an activator of LPL mediated lipolysis and thereby plays an important role in the metabolism of triglyceride rich lipoproteins.

Apolipoprotein B-48

Apo B-48 is synthesized in the intestine and is the major structural protein of chylomicrons and chylomicron remnants. There is a single molecule of apo B-48 per chylomicron particle. There is a single apolipoprotein B gene that is expressed in both the liver and intestine. The intestine expresses a protein that is approximately ½ the size of the liver due to mRNA editing. The apobec-1 editing complex is expressed in the intestine and edits a specific cytidine to an uracil in the apo B mRNA in the intestine creating a stop codon that results in the cessation of protein translation and a shorter Apo B (Apo B-48). Notably Apo B-48 is not recognized by the LDL receptor.

Apolipoprotein B-100

Apo B-100 is synthesized in the liver and is the major structural component of VLDL, IDL, and LDL. There is a single molecule of Apo B-100 per VLDL, IDL, and LDL particle. Apo B-100 is a ligand for the LDL receptor and therefore plays an important role in the clearance of lipoprotein particles. High levels of Apo B-100 is associated with an increased risk of atherosclerosis.

Apolipoprotein C (7,8)

The C apolipoproteins are synthesized primarily in the liver and freely exchange between lipoprotein particles and therefore are found in association with chylomicrons, VLDL, and HDL.

Apo C-II is a co-factor for lipoprotein lipase (LPL) and thus stimulates triglyceride hydrolysis (7). Loss of function mutations in Apo C-II result in marked hypertriglyceridemia due to a failure to metabolize triglyceride rich lipoproteins.

Apo C-III is an inhibitor of LPL (9). Additionally, Apo C-III inhibits the interaction of triglyceride rich lipoproteins with their receptors. Recent studies have shown that loss of function mutations in Apo C-III lead to decreases in serum triglyceride levels and a reduced risk of cardiovascular disease. Interestingly, inhibition of Apo C-III expression results in a decrease in serum triglyceride levels even in patients deficient in lipoprotein lipase indicating that the ability of Apo C-III to modulate serum triglyceride levels is not dependent solely on regulating lipoprotein lipase activity.

Apolipoprotein E (10)

Apolipoprotein E is synthesized in many tissues but the liver and intestine are the primary source of circulating Apo E. Apo E exchanges between lipoprotein particles and is associated with chylomicrons, chylomicron remnants, VLDL, IDL, and a subgroup of HDL particles. There are three common genetic variants of Apo E (Apo E2, E3, and E4). ApoE2 differs from the most common isoform, Apo E3, by a single amino acid substitution where cysteine substitutes for arginine at residue 158. Apo E4 differs from Apo E3 at residue 112, where arginine substitutes for cysteine. Apo E3 and E4 are ligands for the LDL receptor while Apo E2 is poorly recognized by the LDL receptor. Patients who are homozygous for Apo E2 can develop familial dysbetalipoproteinemia. Apo E4 is associated with an increased risk of Alzheimer's disease and an increased risk of atherosclerosis.

Apolipoprotein (a) (11)

Apo (a) is synthesized in the liver. This protein is a homolog of plasminogen and its molecular weight varies from 300,000 to 800,000. It is attached to Apo B-100 via a disulfide bond. High levels of Apo (a) are associated with an increased risk of atherosclerosis. Apo (a) is an inhibitor of fibrinolysis and can also enhance the uptake of lipoproteins by macrophages, both of which could increase the risk of atherosclerosis. The physiologic function of Apo (a) is unknown. Interestingly this apolipoprotein is found in primates but not in other species.

Table 3.

Apolipoproteins

Apolipoprotein	MW	Primary Source	Lipoprotein Association	Function
Apo A-I	28,000	Liver, Intestine	HDL, chylomicrons	Structural protein for HDL, Activates LCAT
Apo A-II	17,000	Liver	HDL, chylomicrons	Structural protein for HDL, Activates hepatic lipase
Apo A-IV	45,000	Intestine	HDL, chylomicrons	Unknown
Apo A-V	39,000	Liver	VLDL, chylomicrons, HDL	Promotes LPL mediated TG lipolysis
Apo B-48	241,000	Intestine	Chylomicrons	Structural protein for chylomicrons
Apo B-100	512,000	Liver	VLDL, IDL, LDL, Lp (a)	Structural protein, Ligand for LDL receptor
Apo C-I	6,600	Liver	Chylomicrons, VLDL, HDL	Activates LCAT
Apo C-II	8,800	Liver	Chylomicrons, VLDL, HDL	Co-factor for LPL
Apo C-III	8,800	Liver	Chylomicrons, VLDL, HDL	Inhibits LPL and uptake of lipoproteins
Apo E	34,000	Liver	Chylomicron remnants, IDL, HDL	Ligand for LDL receptor
Apo (a)	250,000-800,00	Liver	Lp (a)	Inhibits plasminogen activation

LIPOPROTEIN RECEPTORS AND LIPID TRANSPORTERS

There are several receptors and transporters that play a crucial role in lipoprotein metabolism.

LDL Receptor (12)

The LDL receptor is present in the liver and most other tissues. It recognizes Apo B-100 and Apo E and hence mediates the uptake of LDL, chylomicron remnants, and IDL, which occurs via endocytosis (Figure 3). After internalization, the lipoprotein particle is degraded in lysosomes and the cholesterol is released. The delivery of cholesterol to the cell decreases the activity of HMGCoA reductase, a key enzyme in the biosynthesis of cholesterol, and the expression of LDL receptors. LDL receptors in the liver play a major role in determining plasma LDL levels (a low number of receptors is associated with high plasma LDL levels while a high number of hepatic LDL receptors is associated with low plasma LDL levels). The number of LDL receptors is regulated by the cholesterol content of the cell (13). When cellular cholesterol levels are decreased the transcription factor SREBP is transported from the endoplasmic reticulum to the golgi where proteases cleave and activate SREBP, which then migrates to the nucleus and stimulates the expression of LDL receptors (Figure 4). Conversely, when cellular cholesterol levels are high SREBP remains in the endoplasmic reticulum in an inactive form and the expression of LDL receptors is low. As discussed later PCSK9 regulates the rate of degradation of LDL receptors.

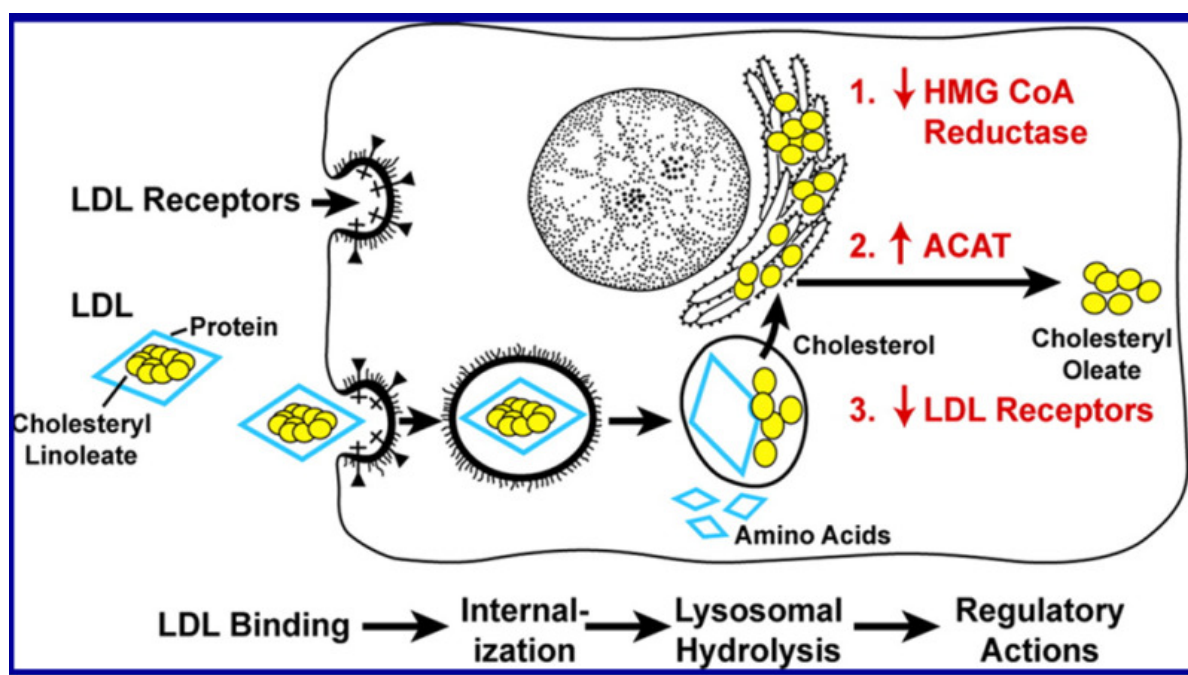


Figure 3.

LDL Receptor Pathway (figure modified from Annual Review of Biochemistry 46: 897, 1977)

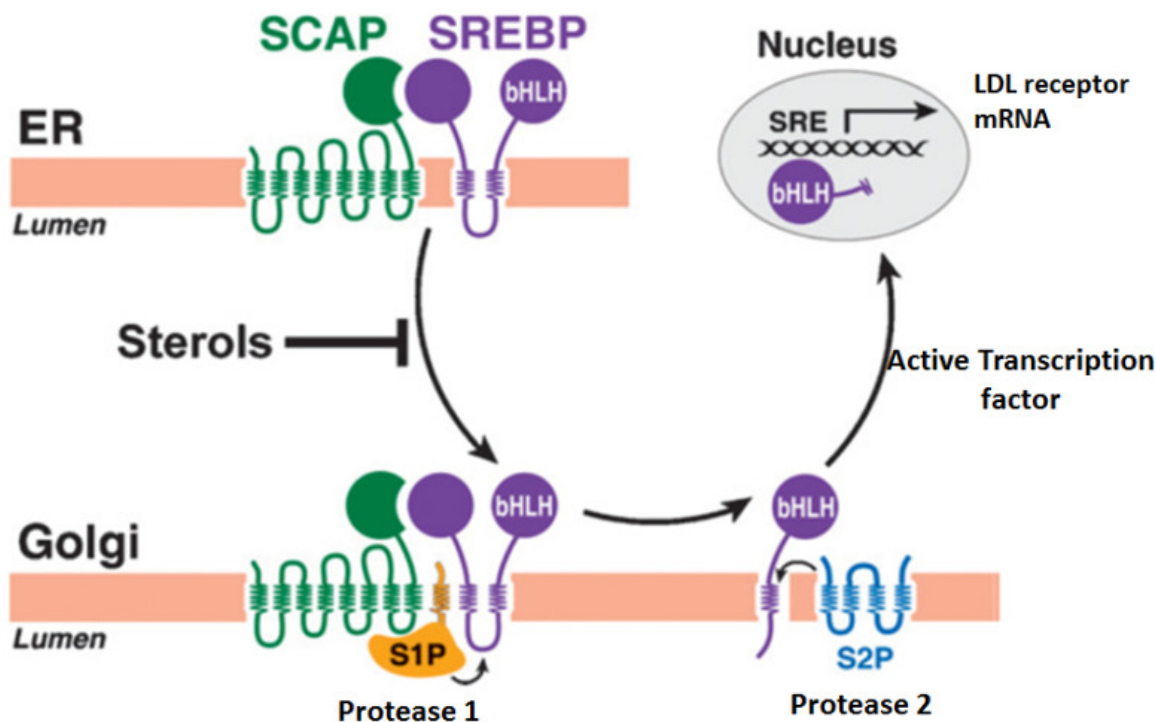


Figure 4.

SREBP Pathway (figure modified from Journal of Lipid Research 50: Supp S15, 2009)

LDL Receptor Related Protein (LRP) (14)

LRP is a member of the LDL receptor family. It is expressed in multiple tissues including the liver. LRP recognizes Apo E and mediates the uptake of chylomicron remnants and IDL.

Class B Scavenger Receptor B1 (SR-B1) (15)

SR-B1 is expressed in the liver, adrenal glands, ovaries, testes, macrophages, and other cells. In the liver and steroid producing cells, it mediates the selective uptake of cholesterol esters from HDL particles. In macrophages and other cells, it facilitates the efflux of cholesterol from the cell to HDL particles.

ATP-Binding Cassette Transporter A1 (ABCA1) (16)

ABCA1 is expressed in many cells including hepatocytes, enterocytes, and macrophages. It mediates the transport of cholesterol and phospholipids from the cell to lipid poor HDL particles (pre-beta-HDL).

ATP-Binding Cassette Transporter G1 (ABCG1) (17)

ABCG1 is expressed in many different cell types and mediates the efflux of cholesterol from the cell to HDL particles.

ATP-Binding Cassette Transporter G5 and G8 (ABCG5/ABCG8) (18)

ABCG5 and ABCG8 are expressed in the liver and intestine and form a heterodimer. In the intestine, these transporters mediate the movement of plant sterols and cholesterol from inside the enterocyte into the intestinal lumen thereby decreasing their absorption and limiting the uptake of dietary plant sterols. In the liver, these transporters play a role in the movement of cholesterol and plant sterols into the bile facilitating the excretion of plant sterols.

Niemann-Pick C1-Like 1 (NPC1L1) (18)

NPC1L1 is expressed in the intestine and mediates the uptake of cholesterol and plant sterols from the intestinal lumen into the enterocyte.

ENZYMES AND TRANSFER PROTEINS INVOLVED IN LIPOPROTEIN METABOLISM

There are several enzymes and transfer proteins that play a key role in lipoprotein metabolism.

Lipoprotein Lipase (LPL) (19)

LPL is synthesized in muscle, heart, and adipose tissue, then secreted and attached to the endothelium of the adjacent blood capillaries. This enzyme hydrolyzes the triglycerides carried in chylomicrons and VLDL to fatty acids, which can be taken up by cells. The catabolism of triglycerides results in the conversion of chylomicrons into chylomicron remnants and VLDL into IDL. This enzyme requires Apo C-II as a cofactor. Apo A-V also plays a key role in the activation of this enzyme. In contrast Apo C-III and Apo A-II inhibit the activity of LPL. Insulin stimulates LPL expression and LPL activity is reduced in patients with poorly controlled diabetes, which can impair the metabolism of triglyceride rich lipoproteins leading to hypertriglyceridemia.

Hepatic Lipase (20)

Hepatic lipase is localized to the sinusoidal surface of liver cells. It mediates the hydrolysis of triglycerides and phospholipids in IDL and LDL leading to smaller particles (IDL is converted to LDL; LDL is converted from large LDL to small LDL). It also mediates the hydrolysis of triglycerides and phospholipids in HDL resulting in smaller HDL particles.

Endothelial Lipase (21)

This lipase plays a major role in hydrolyzing the phospholipids in HDL.

Lecithin: Cholesterol Acyltransferase (LCAT) (22)

LCAT is made in the liver. In the plasma, it catalyzes the synthesis of cholesterol esters in HDL by facilitating the transfer of a fatty acid from position 2 of lecithin to cholesterol. This allows for the transfer of the cholesterol from the surface of the HDL particle (free cholesterol) to the core of the HDL particle (cholesterol ester), which facilitates the continued uptake of free cholesterol by HDL particles by reducing the concentration of cholesterol on the surface of HDL.

Cholesteryl Ester Transfer Protein (CETP) (23)

This protein is synthesized in the liver and in the plasma mediates the transfer of cholesterol esters from HDL to VLDL, chylomicrons, and LDL and the transfer of triglycerides from VLDL and chylomicrons to HDL. Inhibition of CETP activity leads to an increase in HDL cholesterol and a decrease in LDL cholesterol.

EXOGENOUS LIPOPROTEIN PATHWAY (CHYLOMICRONS)

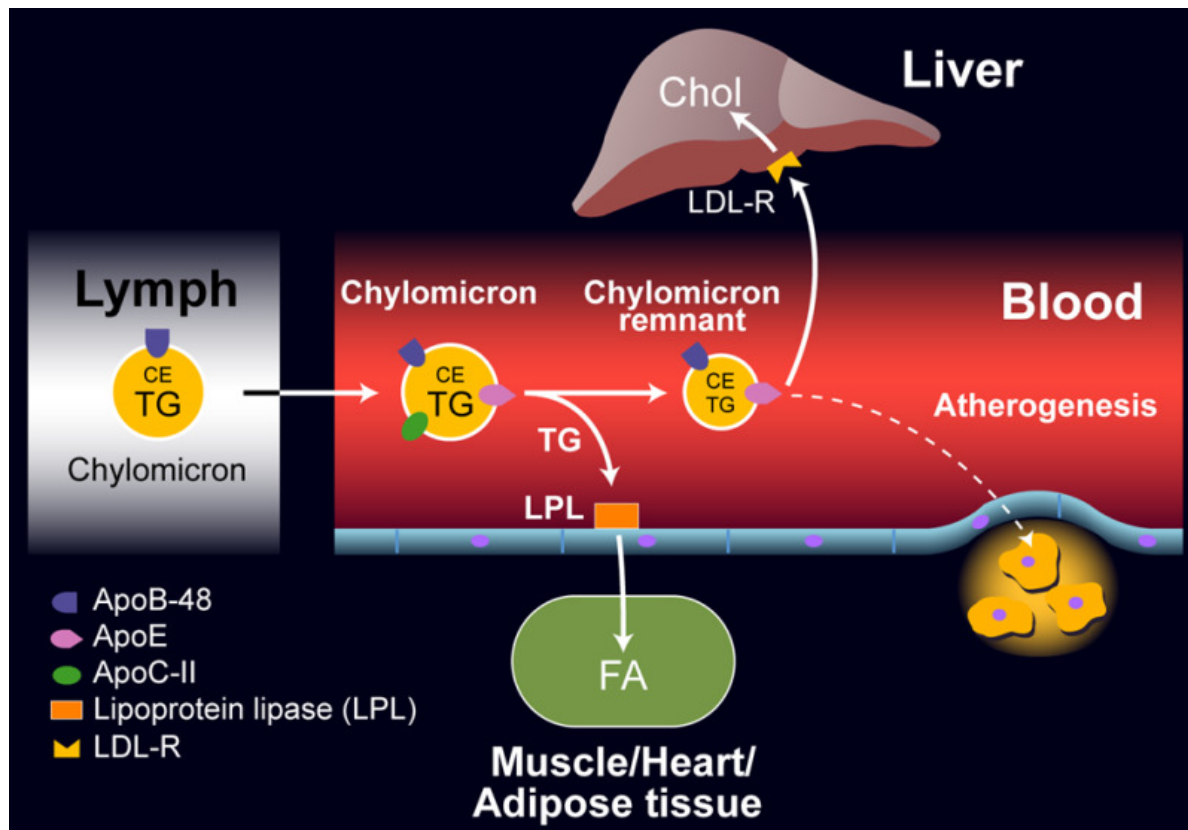


Figure 5.

Exogenous Lipoprotein Pathway

Fat Absorption (24-27)

The exogenous lipoprotein pathway starts in the intestine. Dietary triglycerides (approximately 100 grams per day) are hydrolyzed to free fatty acids and monoacylglycerol by intestinal lipases and emulsified with bile acids, cholesterol, plant sterols, and fat-soluble vitamins to form micelles. While the fatty acids in the intestine are overwhelmingly accounted for by dietary intake the cholesterol in the intestinal lumen is primarily derived from bile (approximately 800-1200mg of cholesterol from bile vs. 300-500mg from diet). Plant sterols account for approximately 25% of dietary sterol intake (approximately 100-150mg/day). The cholesterol, plant sterols, fatty acids, monoacylglycerol, and fat-soluble vitamins contained in the micelles are then transported into the intestinal cells. The uptake of cholesterol and plant sterols from the intestinal lumen into intestinal cells is facilitated by a sterol transporter, Niemann-Pick C1-like 1 protein (NPC1L1) (Figure 6). Ezetimibe, a drug which inhibits intestinal cholesterol and plant sterol uptake, binds to NPC1L1 and inhibits its activity. Once in the intestinal cell the cholesterol and plant sterols may be transported back into the intestinal lumen, a process mediated by ABCG5 and ABCG8, or converted to sterol esters by acyl-CoA cholesterol acyl transferase (ACAT), which attaches a fatty acid to the sterol. Compared to cholesterol, plant sterols are poor substrates for ACAT and therefore the formation of plant sterol esters does not occur as efficiently as the formation of cholesterol esters. In humans, <5% of dietary plant sterols are absorbed and the vast majority are transported out of the intestine cell, a process mediated by ABCG5 and ABCG8, which are very efficient at effluxing plant sterols from the intestinal cell into the intestinal lumen. Patients with sitosterolemia have mutations in either ABCG5 or ABCG8 and net absorption of dietary plant sterols is increased (20-30% absorbed vs. < 5% in normal subjects). Thus, ABCG5 and ABCG8 along with ACAT serve as gate keepers and block the uptake of plant sterols and likely also play an important role in determining the efficiency of cholesterol absorption (humans typically absorb only approximately 50% of dietary cholesterol with a range of 25-75%).

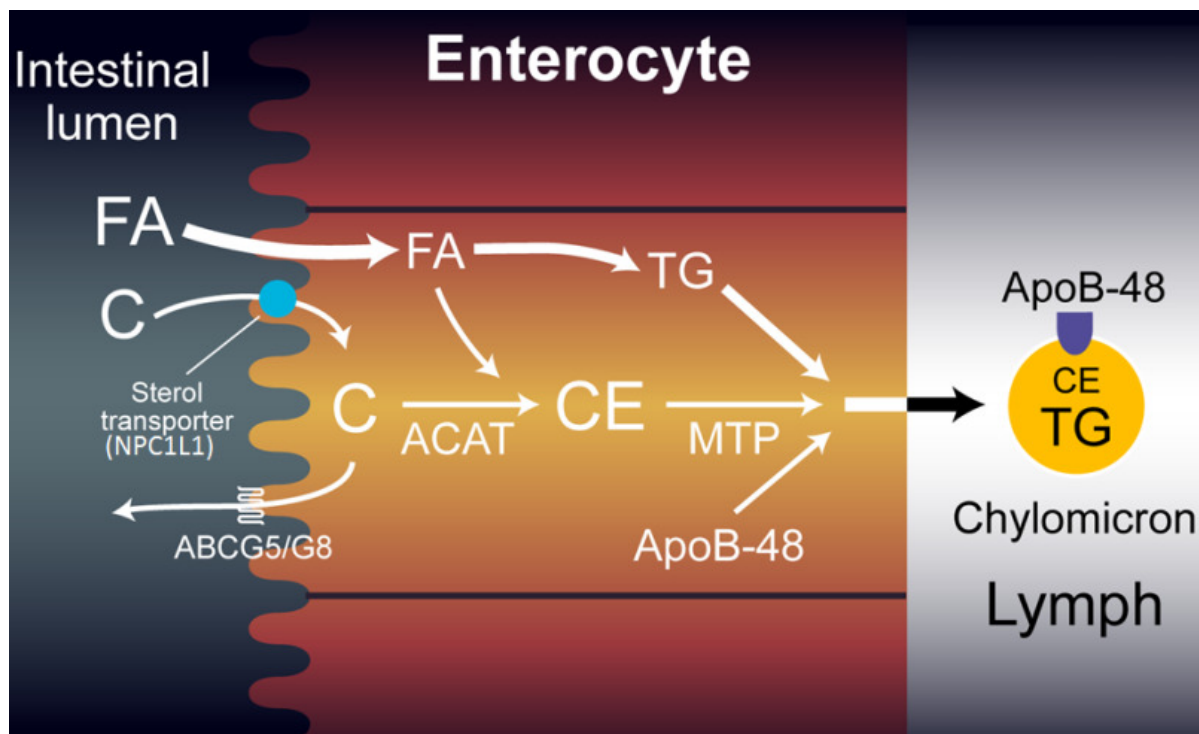


Figure 6.

Intestinal Cell and Sterol Metabolism

The pathway of absorption of free fatty acids is not well understood but it is likely that both passive diffusion and specific transporters play a role. The fatty acid transporter CD36 is strongly expressed in the proximal third of the intestine and is localized to the villi. While this transporter likely plays a role in fatty acid uptake by intestinal cells, this transporter is not essential as humans and mice deficient in this protein do not have fat malabsorption. However, in mice deficient in CD36 there is a shift in the absorption of lipid to the distal intestine, suggesting pathways that can compensate for the absence of CD36. Fatty acid transport protein 4 (FATP4) is also highly expressed in the intestine. However, mice deficient in FATP4 do not have abnormalities in fat absorption. The pathways by which monoacylglycerols are absorbed by intestinal cells remain to be defined.

Formation of Chylomicrons (24,27)

The absorbed fatty acids and monoacylglycerols are utilized to synthesize triglycerides. The key enzymes required for triglyceride synthesis are monoacylglycerol acyltransferase (MGAT) and diacylglycerol transferase (DGAT). MGAT catalyzes the addition of a fatty acid to monoacylglycerol while DGAT catalyzes the addition of a fatty acid to diacylglycerol resulting in triglyceride formation. As noted above, the majority of the cholesterol absorbed by the intestine is esterified to cholesterol esters by ACAT. The triglycerides and cholesterol esters are packaged into chylomicrons in the endoplasmic reticulum. The size and composition of the chylomicrons formed in the intestine are dependent on the amount of fat ingested and absorbed by the intestine and the type of fat absorbed. Increased fat absorption results in larger chylomicrons. The formation of chylomicrons in the endoplasmic reticulum requires the synthesis of Apo B-48 by the intestinal cell (Figure 6). Microsomal triglyceride transfer protein (MTP) is required for the movement of lipid from the endoplasmic reticulum to the Apo B-48. The absence of MTP results in the inability to form chylomicrons (Abetalipoproteinemia). Lomitapide inhibits MTP function and is used to treat patients with homozygous Familial Hypercholesterolemia.

Chylomicron Metabolism (7,9,19,28-31)

Chylomicrons are secreted into the lymph and delivered via the thoracic duct to the circulation. It should be noted that this results in the newly formed chylomicrons being delivered to the systemic circulation and not delivered directly to the liver via the portal circulation. This facilitates the delivery of the nutrients contained in the chylomicrons to muscle and adipose tissue. In muscle and adipose tissue lipoprotein lipase (LPL) is expressed at high levels. LPL is synthesized in muscle and adipocytes and transported to the luminal surface of capillaries. Lipase maturation factor 1 plays a key role in the stabilization and movement of LPL from muscle cells and adipocytes to the capillary endothelial cell surface. Glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPIHBP1) binds LPL and transports it to the capillary lumen and anchors LPL to the capillary endothelium. Activation of LPL by Apo C-II, carried on the chylomicrons, leads to the hydrolysis of the triglycerides that are carried in the chylomicrons resulting in the formation of free fatty acids, which can be taken up by the adjacent muscle cells and adipocytes for either energy production or storage. Fatty acid transport proteins (FATPs) and CD36 facilitate the uptake of fatty acids into adipocytes and muscle cells. Some of the free fatty acids released from chylomicrons bind to albumin and can be transported to other tissues. Apo A-V also plays an important role in activating LPL activity. Loss of function mutations in LPL, Apo C-II, GPIHBP1, lipase maturation factor 1, and Apo A-V can result in marked hypertriglyceridemia (chylomicronemia). In addition, there are proteins that inhibit LPL activity. Apo C-III inhibits LPL activity and loss of function mutations in this gene are associated with increases in LPL activity and decreases in plasma triglyceride levels. Similarly, angiopoietin like protein 3 and 4, which target LPL for inactivation, regulate LPL activity. Loss of function mutations in these proteins also are associated with decreases in plasma triglyceride levels. Finally, the expression of LPL by muscle cells and adipocytes is regulated by hormones (particularly insulin), nutritional status, and inflammation.

The metabolism of the triglycerides carried in the chylomicrons results in a marked decrease in the size of these particles leading to the formation of chylomicron remnants, which are enriched in cholesterol esters and acquire Apo E. As these particles decrease in size phospholipids and apolipoproteins (Apo A and C) on the surface of the chylomicrons are transferred to other lipoproteins, mainly HDL. The transfer of Apo C-II from chylomicrons to HDL decreases the ability of LPL to further breakdown triglycerides. These chylomicron remnants are cleared from the circulation by the liver. The Apo E on the chylomicron remnants binds to the LDL receptor and other hepatic receptors such as LRP and syndecan-4 and the entire particle is taken up by the hepatocytes. Apo E is crucial for this process and mutations in Apo E (for example the Apo E2 isoform) can result in decreased chylomicron clearance and elevations in plasma cholesterol and triglyceride levels (Familial dysbetalipoproteinemia).

The exogenous lipoprotein pathway results in the efficient transfer of dietary fatty acids to muscle and adipose tissue for energy utilization and storage. The cholesterol is delivered to the liver where it can be utilized for the formation of VLDL, bile acids, or secreted back to the intestine via secretion into the bile. In normal individuals, this pathway can handle large amounts of fat (100 grams or more per day) without resulting in marked increases in plasma triglyceride levels. In fact, in a normal individual, a meal containing 75 grams of fat results in only a very modest increase in postprandial triglyceride levels.

ENDOGENOUS LIPOPROTEIN PATHWAY (VLDL AND LDL)

from the IDL particles to other lipoproteins leading to the formation of LDL. These LDL particles predominantly contain cholesterol esters and Apo B-100. Thus, LDL is a product of VLDL metabolism.

LDL Metabolism (12,34-37)

The levels of plasma LDL are determined by the rate of LDL production and the rate of LDL clearance, both of which are regulated by the number of LDL receptors in the liver. The production rate of LDL from VLDL is partially determined by hepatic LDL receptor activity with a high LDL receptor activity resulting in a decrease in LDL production due to an increase in IDL uptake. Conversely, low LDL receptor activity results in an increase in LDL production formation due to a decrease in IDL uptake. With regards to LDL clearance, approximately 70% of circulating LDL is cleared via hepatocyte LDL receptor mediated endocytosis with the remainder taken up by extrahepatic tissues. An increase in the number of hepatic LDL receptors therefore increases LDL clearance leading to a decrease in plasma LDL levels. Conversely, a decrease in hepatic LDL receptors slows LDL clearance leading to an increase in plasma LDL levels. Thus, the level of hepatic LDL receptors plays a key role in regulating plasma LDL levels.

The levels of LDL receptors in the liver are mainly regulated by the cholesterol content of the hepatocyte. As cholesterol levels in the cell decrease, inactive sterol regulatory element binding proteins (SREBPs), which are transcription factors that mediate the expression of LDL receptors and other key genes involved in cholesterol and fatty acid metabolism, are transported from the endoplasmic reticulum to the golgi where proteases cleave the SREBPs into active transcription factors (Figure 4). These active SREBPs move to the nucleus where they stimulate the transcription of the LDL receptor and other genes, including HMG-CoA reductase, the rate limiting enzyme in cholesterol synthesis. If cholesterol levels in the cell are high, then the SREBPs remain in the endoplasmic reticulum in an inactive form and do not stimulate LDL receptor synthesis. In addition, cholesterol in the cell is oxidized and oxidized sterols activate LXR, a nuclear hormone receptor that is a transcription factor, which stimulates the transcription of E3 ubiquitin ligase that mediates the ubiquitination and degradation of the low-density lipoprotein receptor (Inducible degrader of the low-density lipoprotein receptor (IDOL)). Thus, the cell can sense the availability of cholesterol and regulate LDL receptor activity. If the cholesterol content of the cell is decreased LDL receptor activity is increased to allow for the increased uptake of cholesterol. Conversely, if the cholesterol content of the cell is increased LDL receptor activity is decreased and the uptake of LDL by the cell is diminished. Finally, the LDL receptor is targeted for degradation by PCSK9, a secreted protein that binds to the LDL receptor and enhances LDL receptor degradation in the lysosomes. Loss of function mutations in PCSK9 result in increased LDL receptor activity and decreased LDL levels while gain of function mutations in PCSK9 lead to decreased LDL receptor activity and elevations in LDL levels.

Thus, the endogenous lipoprotein pathway facilitates the movement of triglycerides synthesized in the liver to muscle and adipose tissue. Additionally, it also provides a pathway for the transport of cholesterol from the liver to peripheral tissues.

HDL METABOLISM AND REVERSE CHOLESTEROL TRANSPORT (15-17,22,23,38,39)

esterified. LCAT, an HDL associated enzyme catalyzes the transfer of a fatty acid from phospholipids to free cholesterol resulting in the formation of cholesterol esters. The cholesterol ester formed is then able to move from the surface of the HDL particle to the core. Apo A-I is an activator of LCAT and facilitates this esterification process. LCAT activity is required for the formation of large HDL particles. LCAT deficiency in humans results in decreased HDL cholesterol and Apo A-I levels and a higher percentage of small HDL particles.

HDL Metabolism

Lipases and transfer proteins play an important role in determining the size and composition of HDL particles. The cholesterol ester carried in the core of HDL particles may be transferred to Apo B containing particles in exchange for triglyceride. This transfer is mediated by CETP and results in HDL enriched in triglycerides which may then be metabolized by lipases. Humans deficient in CETP activity have very high HDL cholesterol levels and large HDL particles. CETP also impacts LDL cholesterol levels and the absence of CETP results in a decrease in LDL cholesterol. Mice do not have CETP and have relatively high HDL cholesterol levels and low LDL cholesterol levels. Hepatic lipase hydrolyzes both triglycerides and phospholipids in HDL. The triglycerides that are transferred to HDL by CETP activity are catabolized by hepatic lipase resulting in the formation of small HDL particles, the release of Apo A-I, and increased Apo A-I degradation. Genetic deficiency of hepatic lipase results in a modest elevation in HDL cholesterol levels and larger HDL particles. Hepatic lipase activity is increased in insulin resistant states and this is associated with reduced HDL cholesterol levels. Endothelial cell lipase is a phospholipase that hydrolyzes the phospholipids carried in HDL particles. In mice increased endothelial lipase activity results in decreased HDL cholesterol levels while decreased endothelial lipase activity increases HDL cholesterol levels.

The cholesterol carried on HDL is primarily delivered to the liver. The uptake of HDL cholesterol by the liver is mediated by SR-BI, which promotes the selective uptake of HDL cholesterol. The HDL particle binds to SR-BI and the cholesterol in HDL is transported into the liver without internalization of the HDL particle. A smaller cholesterol depleted HDL particle is formed, which is then released back into the circulation. In SR-BI deficient mice there is a marked increase in HDL cholesterol levels. Interestingly the risk of atherosclerosis is increased in these SR-BI deficient despite an increase in HDL cholesterol levels. Notably, while HDL cholesterol levels are increased in SR-BI deficient mice the reverse cholesterol transport pathway is actually reduced. While in mice the physiological importance of the hepatic SR-BI pathway is clear, the role in humans is uncertain. In humans' polymorphisms in the SR-BI gene influence HDL cholesterol levels but the effect on atherosclerosis is minimal. In mice, the movement of cholesterol from peripheral tissues to the liver is dependent solely on SR-BI while in humans CETP can facilitate the transport of cholesterol from HDL to Apo B containing lipoproteins, which serves as an alternative pathway for the transport cholesterol to the liver.

Apo A-I is metabolized independently of HDL cholesterol. Most of the Apo A-I is catabolized by the kidneys with the remainder catabolized by the liver. Lipid free or lipid poor Apo A-I is filtered by the kidneys and then taken up by the renal tubules. The size of the Apo A-I particle determines whether it can be filtered by the kidneys and hence the degree of lipidation of Apo A-I determines the rate of catabolism. Conditions or disease states (for example Tangiers disease, which is due to a mutation in ABCA1 or LCAT deficiency) that result in lipid poor HDL lead to the accelerated catabolism of Apo A-I by the kidney. Apo A-I binds to cubilin, which in conjunction with megalin, a member of the LDL receptor gene family, leads to the uptake and degradation of filtered Apo A-I by renal tubular cells. While the liver is also involved in the catabolism of Apo A-I, the mechanisms are poorly understood. HDL particles may contain Apo E and it is therefore possible that Apo E containing HDL particles are taken up via the LDL receptor and other Apo E receptors in the liver and degraded.

Reverse Cholesterol Transport (40-44)

Peripheral cells accumulate cholesterol through the uptake of circulating lipoproteins and de novo cholesterol synthesis. Most cells do not have a mechanism for catabolizing cholesterol. Cells that synthesize steroid hormones can convert cholesterol to glucocorticoids, estrogen, testosterone, etc. Intestinal cells, sebocytes, and keratinocytes can secrete cholesterol into the intestinal lumen or onto the skin surface thereby eliminating cholesterol. However, in order for most cells to decrease their cholesterol content reverse cholesterol transport is required. From a clinical point of view, the ability of macrophages to efficiently efflux cholesterol into the reverse cholesterol transport pathway may play an important role in the prevention of atherosclerosis.

As noted earlier ABCA1 plays an important role in the efflux of cholesterol to lipid poor pre-beta Apo A-I particles (Figure 9). ABCG1 plays an important role in the efflux of cholesterol from cells to mature HDL particles. In some studies, SR-B1 also plays a role in the efflux of cholesterol to mature HDL particles. Additionally, passive diffusion of cholesterol from the plasma membrane to HDL may also contribute to cholesterol efflux. The levels of both ABCA1 and ABCG1 are increased by LXR activation. LXR is a nuclear hormone transcription factor that is activated by oxysterols. As the cholesterol levels in a cell increase the formation of oxysterols increases leading to the activation of LXR resulting in an increase in ABCA1 and ABCG1 expression, which will result in the enhanced efflux of cholesterol from the cell to HDL. Additionally, ABCA1 and ABCG1 mRNAs are targeted for degradation by miR-33, a microRNA that is embedded within the SREBP2 gene. An increase in cellular cholesterol decreases the expression of SREBP2 leading to a decrease in miR-33 resulting in enhanced LXR expression. Thus, the decrease in SREBP2 transcription will lead to a decrease in LDL receptor activity and a reduction in cholesterol uptake, while simultaneously, a decrease in miR-33 will lead to an increase in LXR activity stimulating the expression of ABCA1 and ABCG1 resulting in increased cholesterol efflux. Conversely a decrease in cellular cholesterol levels will increase SREBP2 expression resulting in an increase in LDL receptor activity and an increase in miR-33, which will result in a decrease in LXR activity, decreased expression of ABCA1 and ABCG1, and a reduction in cholesterol efflux. Together changes in cholesterol uptake mediated by the LDL receptor and cholesterol efflux mediated by ABCA1 and ABCG1 will maintain cellular cholesterol homeostasis.

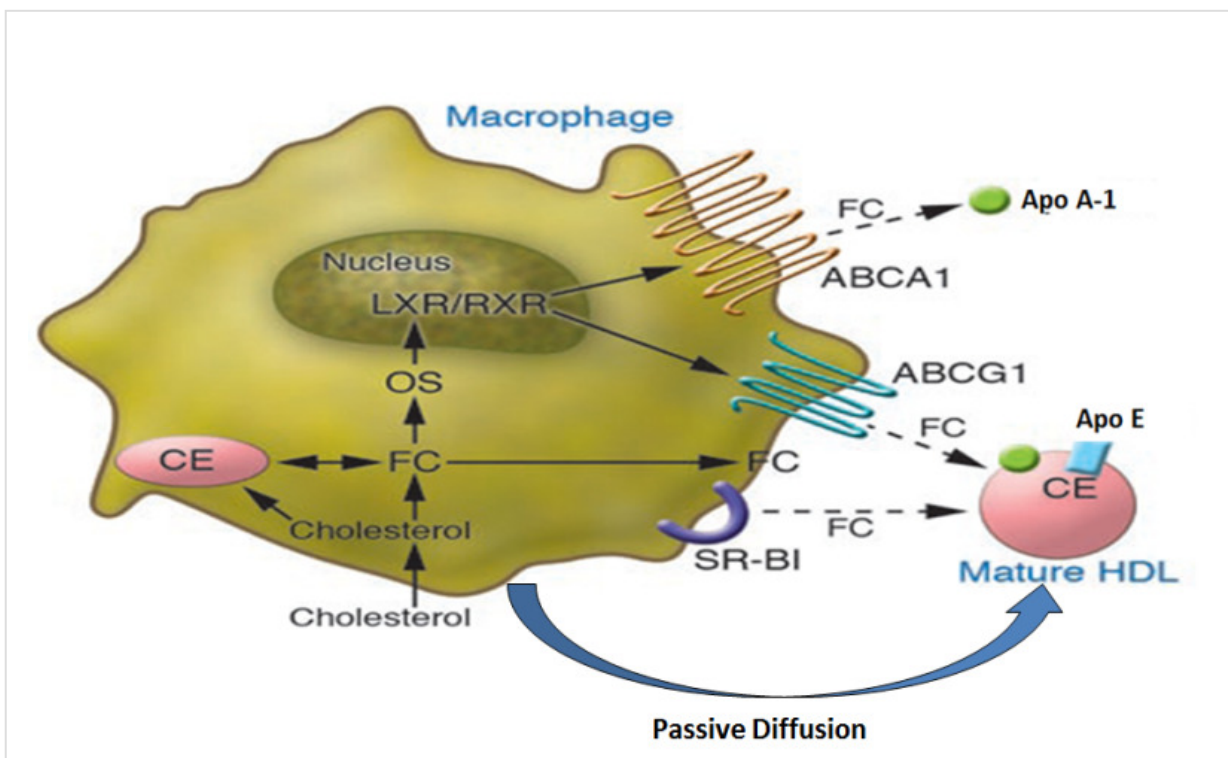


Figure 9.

Once cholesterol is transferred from cells to HDL there are two pathways for the cholesterol to be taken up by the liver. As discussed earlier, HDL can interact with hepatic SR-BI receptors resulting in the selective uptake of cholesterol from HDL particles. Alternatively, CETP can transfer cholesterol from HDL particles to Apo B containing particles with the subsequent uptake of Apo B containing lipoproteins by the liver. After the delivery of cholesterol to the liver there are several pathways by which the cholesterol can be eliminated. Cholesterol can be converted to bile acids and secreted in the bile. Alternatively, cholesterol can be directly secreted into the bile. ABCG5 and ABCG8 promote the transport of cholesterol into the bile and the expression of these genes is enhanced by LXR activation. Thus, an increase in hepatic cholesterol levels leading to increased oxysterol production will activate LXR resulting in the increased expression of ABCG5 and ABCG8 facilitating the secretion of cholesterol in the bile.

Evidence suggests that reverse cholesterol transport plays an important role in protecting from the development of atherosclerosis. It should be noted that HDL cholesterol levels may not be indicative of the rate of reverse cholesterol transport. As described above reverse cholesterol transport involves several steps and the level of HDL cholesterol may not accurately reflect these steps. For example, studies have shown that the ability of HDL to promote cholesterol efflux from macrophages can vary. Thus, the same level of HDL cholesterol may not have equivalent abilities to mediate the initial step of reverse cholesterol transport.

LIPOPROTEIN (a) (11,45,46)

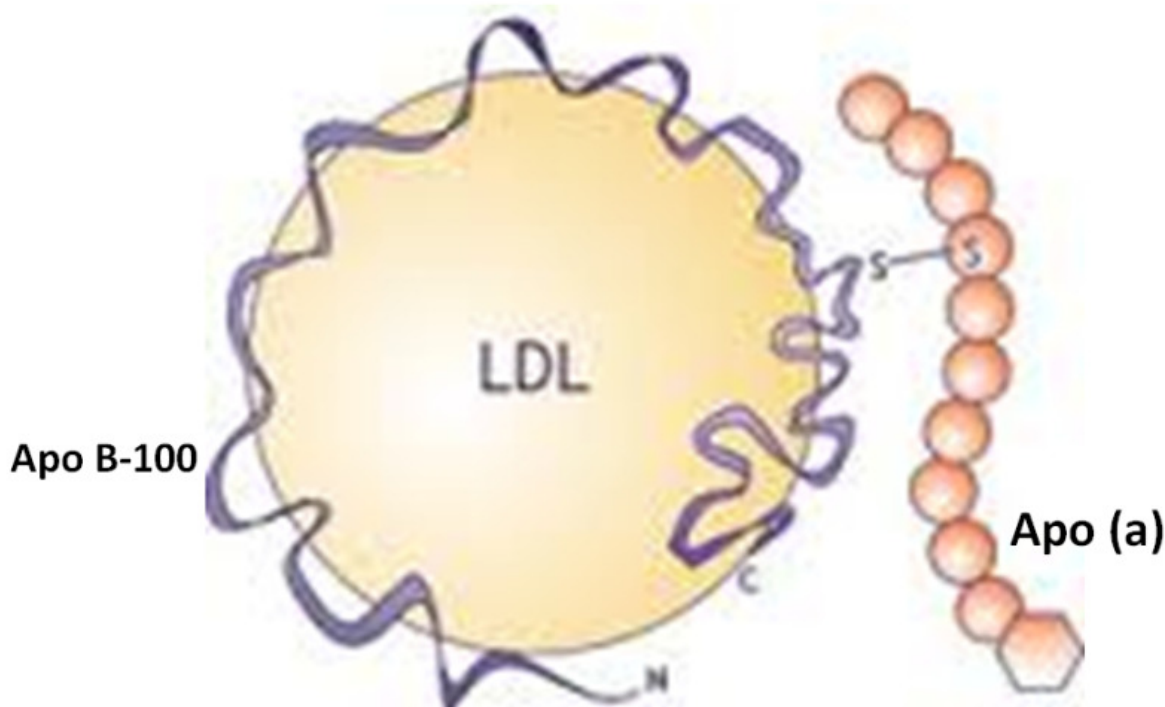


Figure 10.

Lp (a)

Lp (a) consists of an LDL molecule and a unique apolipoprotein (a), which is attached to the Apo B-100 of the LDL via a single disulfide bond. Lp (a) contain Apo (a) and Apo B-100 in a 1:1 molar ratio. Like Apo B-100, apo (a) is also made by hepatocytes. Apo (a) contains multiple kringle motifs that are similar to the kringle repeats in plasminogen. The number of kringle

repeats can vary and thus the molecular weight of apo (a) can range from 250,000 to 800,000. The levels of Lp (a) in plasma can vary more than a 1000-fold ranging from undetectable to greater than 100mg/dl. Lp (a) levels largely reflect Lp (a) production rates, which are primarily genetically regulated. Individuals with high molecular weight Apo (a) proteins tend to have lower levels of Lp (a) while individuals with low molecular weight Apo (a) tend to have higher levels. It is hypothesized that the liver is less efficient in secreting high molecular weight Apo (a). The mechanism of Lp (a) clearance is uncertain but does not appear to involve LDL receptors. Elevated plasma Lp(a) levels are associated with an increased risk of atherosclerosis. Therapies that accelerate LDL clearance and lower LDL levels do not lower Lp (a) levels (for example statin therapy). The kidney appears to play an important role in Lp (a) clearance as kidney disease is associated with delayed clearance and elevations in Lp (a) levels.

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