Lipid and Lipoprotein Metabolism

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KEYWORDS

• Chylomicrons • VLDL • LDL • HDL • Lipoprotein (a) • Apolipoproteins
• Reverse cholesterol transport

KEY POINTS

- Chylomicrons are triglyceride-rich lipoproteins synthesized in the intestine. In the circulation, the triglycerides are removed by lipoprotein lipase (LPL) leading to the formation of chylomicron remnants which are taken up by the liver.
- Very low-density lipoprotein particles (VLDL) are triglyceride-rich lipoproteins synthesized in the liver. In the circulation, the triglycerides are removed by LPL leading to the formation of VLDL remnants (intermediate density lipoproteins) which may be taken up by the liver or further metabolized to low-density lipoprotein (LDL).
- The plasma level of LDL cholesterol is primarily determined by hepatic LDL receptor activity, which regulates both the production and clearance of LDL.
- High-density lipoprotein (HDL) are cholesterol and phospholipid-rich particles that mediate the transport of cholesterol and other compounds from peripheral tissues to the liver (ie, reverse cholesterol transport), which is one of the several potential mechanisms by which HDL may be anti-atherogenic.
- Chylomicron remnants, VLDL, VLDL remnants, LDL, and lipoprotein (a) are pro-atherogenic particles while HDL is anti-atherogenic.

INTRODUCTION

Lipids are insoluble in water and therefore cholesterol and triglycerides need to be transported in association with proteins (ie, lipoproteins) in the bloodstream. Lipoproteins play a crucial role in the transport of dietary lipids from the small intestine to the liver, muscle, and adipose tissue, in the transport of hepatic lipids to peripheral tissues, and the transport of cholesterol from peripheral tissues to the liver and intestine (ie, reverse cholesterol transport). Lipoproteins may have additional functions and studies have suggested that they may play a role in protection from disease.[1] For example, lipoproteins bind endotoxin (LPS) from gram-negative bacteria and lipoteichoic acid from gram-positive bacteria thereby reducing their toxic effects.[1] In addition, apolipoprotein L1, associated with HDL particles, has lytic activity against the

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parasite *Trypanosoma brucei* and lipoproteins can neutralize viruses.[2,3] Thus, while this article will focus on the transport properties of lipoproteins the reader should recognize that lipoproteins may have other important functions.

LIPOPROTEIN STRUCTURE

The surface of lipoproteins is a hydrophilic membrane consisting of phospholipids, free cholesterol, and apolipoproteins which surrounds a central hydrophobic core of nonpolar lipids, primarily cholesteryl esters and triglycerides (**Fig. 1**).[4] Lipoprotein particles are divided into 7 classes based on size, apolipoprotein composition, and lipid composition (**Fig. 2**, **Table 1**).

ANTI-ATHEROGENIC LIPOPROTEIN PARTICLES

High-Density Lipoprotein Particles

High-density lipoprotein particles are enriched in cholesterol and phospholipids and apolipoproteins A-I, A-II, A-IV, C-I, C-II, C-III, and E are associated with HDL particles.[5,6] The core structural protein is Apo A-I and each HDL particle may contain multiple Apo A-I proteins. In addition, using mass spectrometry proteins involved in proteinase inhibition, complement activation, and the acute-phase response have been found associated with HDL particles.[7] HDL particles may be classified based on density, size, charge, and apolipoprotein composition and are very heterogeneous (**Table 2**). HDL particles mediate the transport of cholesterol and other compounds from peripheral tissues to the liver (ie, reverse cholesterol transport), which is one of the several potential mechanisms by which HDL may be anti-atherogenic. In addition, HDL particles have

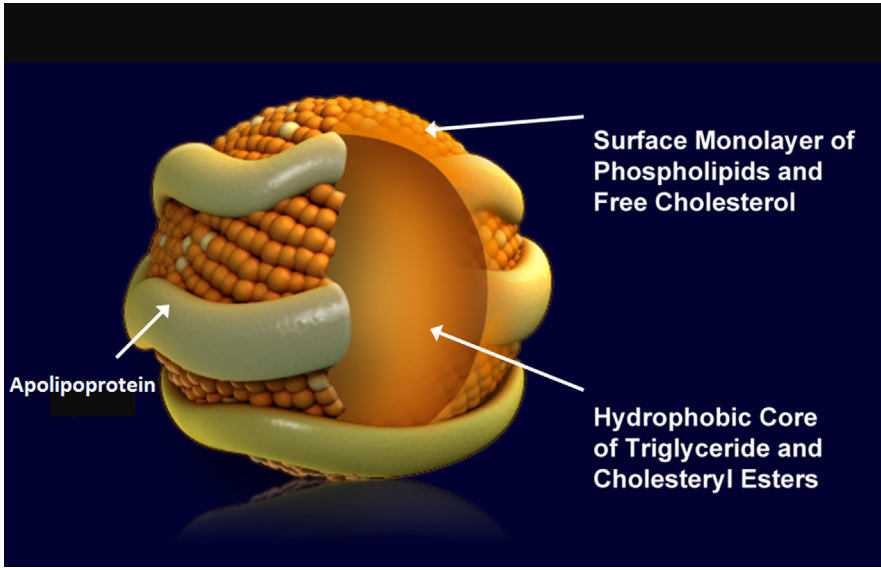

Fig. 1. Lipoprotein structure. (*From* Feingold KR. Introduction to Lipids and Lipoproteins. 2021 Jan 19. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–.)

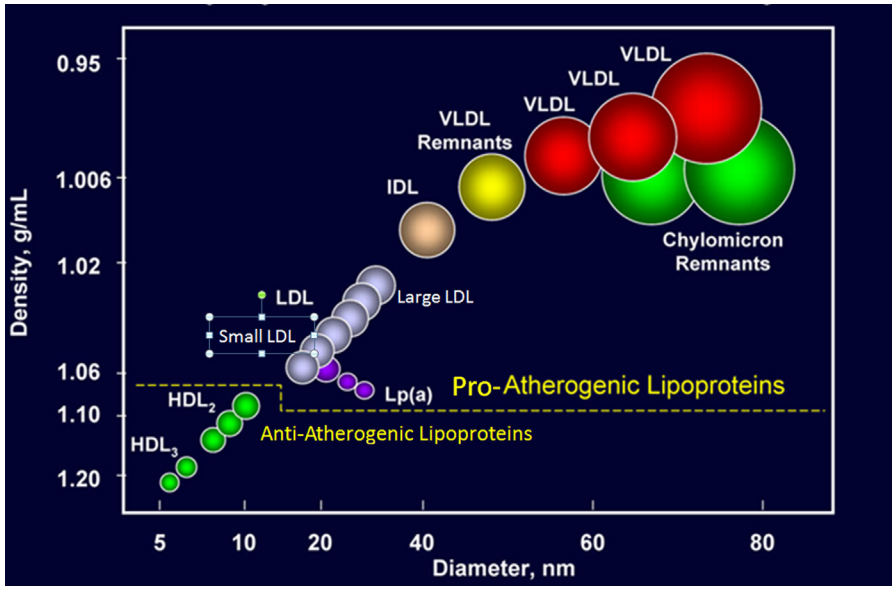

Fig. 2. Classes of lipoproteins. (*From* Feingold KR. Introduction to Lipids and Lipoproteins. 2021 Jan 19. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 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 VLDL remnants	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)

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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

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anti-oxidant, anti-inflammatory, anti-thrombotic, and anti-apoptotic properties, which may also contribute to their ability to prevent atherosclerosis.

PRO-ATHEROGENIC LIPOPROTEIN PARTICLES

Chylomicron Particles

Chylomicrons are large triglyceride-rich particles secreted by the small intestine, which play a key role in the transport of dietary triglycerides and cholesterol to peripheral tissues and liver.[8] Each chylomicron particle contains one Apo B-48 molecule, which is the core structural protein. In addition, chylomicron particles also contain A-I, A-II, A-IV, A-V, B-48, C-II, C-III, and E. Chylomicrons vary in size depending on the amount of fat ingested with a high-fat meal leading to the formation of large chylomicron particles with an increased quantity of triglyceride, whereas in the fasting state or with the consumption of a low-fat meal the chylomicron particles are small carrying decreased quantities of triglyceride. Similarly, the amount of cholesterol transported in chylomicrons can also vary.

Chylomicron Remnant Particles

Chylomicron remnants are formed by the removal of triglyceride from chylomicrons by muscle and adipose tissue lipoprotein lipase (LPL) resulting in smaller particles.[8,9] These particles are enriched in cholesterol and are pro-atherogenic.

Very Low-Density Lipoprotein Particles

Very low-density lipoprotein particles are produced by the liver and contain apolipoprotein B-100, C-I, C-II, C-III, and E. The core structural protein is Apo B-100 and each VLDL particle contains one Apo B-100 protein. The size of the VLDL particles varies and when triglyceride production in the liver is increased the secreted VLDL particles are large.

Intermediate-Density Lipoprotein Particles; Very Low-Density Lipoprotein Remnant Particles

Intermediate-density lipoprotein particles are formed by the removal of triglycerides from VLDL by muscle and adipose tissue LPL resulting in the formation of IDL particles which are enriched in cholesterol and are pro-atherogenic.[9] These IDL particles contain apolipoprotein B-100 and E.

Low-Density Lipoprotein Particles

Low-density lipoprotein particles are derived from the metabolism of VLDL and IDL particles and are enriched in cholesterol. Each LDL particle contains one Apo B-100 protein. The majority of the cholesterol and Apo B in the circulation is typically carried on LDL particles. LDL vary in size and density. The levels of small dense LDL particles are increased in association with hypertriglyceridemia, low HDL levels, obesity, type 2 diabetes (ie, in patients with metabolic syndrome). These small dense LDL particles are more pro-atherogenic than large LDL particles for several reasons.[10]

1. Small LDL particles have a decreased affinity for the LDL receptor leading to prolonged retention time in the circulation.
2. Small LDL particles more easily enter the arterial wall than large LDL particles.
3. Small LDL particles bind more avidly than large LDL to intra-arterial proteoglycans, which trap these particles in the arterial wall.
4. Small LDL particles are more easily oxidized, which would allow macrophages to more efficiently take up these particles leading to cholesterol accumulation.

Lipoprotein (a) Particles

Lipoprotein (a) is an LDL particle that has apolipoprotein (a) attached to Apo B-100 via a single disulfide bond.[11–13] Lp (a) contain Apo (a) and Apo B-100 in a 1:1 M ratio. Apo (a) is made in the liver. The size of Lp(a) particles can vary greatly based on the size of apolipoprotein (a). Apo (a) contains multiple kringle motifs that are similar to the kringle repeats in plasminogen. The number of kringle repeats can vary greatly and thus the molecular weight of apo (a) can range from approximately 250,000 to 800,000. The levels of Lp (a) in plasma can vary 1000-fold ranging from undetectable to greater than 100 mg/dl. Lp (a) levels. The levels of Lp (a) largely reflect Lp (a) production rates, which are primarily genetically regulated. Individuals with low molecular weight Apo (a) proteins tend to have higher levels of Lp (a) while individuals with high molecular weight Apo (a) tend to have lower levels. It is thought that the secretion of high molecular weight Apo (a) by the liver is less efficient. LDL receptors do not seem to play a major role in Lp (a) clearance while the kidney seems to play an important role as kidney disease is associated with delayed clearance and elevations in Lp (a) levels. Apo (a) is an inhibitor of fibrinolysis and enhances the uptake of lipoproteins by macrophages, both of which could account for the increased risk of atherosclerosis in individuals with elevated Apo (a) levels. Additionally, Lp (a) is the major lipoprotein carrier of oxidized phospholipids, which could also increase the risk of atherosclerosis. The physiologic function of Apo (a) is unknown. Apo (a) is found in primates but not in other species.

APOLIPOPROTEINS

Apolipoproteins play an essential role in lipoprotein metabolism (**Table 3**). They have 4 key functions.[14,15]

1. Guiding the synthesis of lipoproteins
2. Serving in a structural role
3. Serving as ligands for lipoprotein receptors
4. Activating or inhibiting enzymes involved in the metabolism of lipoproteins

Apolipoprotein A-I

Apo A-I is the major structural protein of HDL accounting for approximately 70% of HDL protein.[16] Apo A-I is an activator of lecithin: cholesterol acyltransferase (LCAT),

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	6600	Liver	Chylomicrons, VLDL, HDL	Activates LCAT
Apo C-II	8800	Liver	Chylomicrons, VLDL, HDL	Cofactor for LPL
Apo C-III	8800	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

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an enzyme that converts free cholesterol into cholesteryl ester, and interacts with receptors and transporters including ATP-binding cassette protein A1 (ABCA1), ABCG1, and class B, type I scavenger receptor (SR-B1). Apo A-1 is synthesized in both the liver and intestine. High levels of Apo A-I are associated with a decreased risk of atherosclerosis.

Apolipoprotein A-II

Apo A-II is the second most abundant protein carried on HDL accounting for approximately 20% of HDL protein.[17] The role of Apo A-II in lipid metabolism is not well understood. Apo A-II is synthesized in the liver and high levels are a strong predictor of an increased risk for atherosclerosis.

Apolipoprotein A-IV

Apo A-IV is associated with chylomicrons and HDL, but is also found in the lipoprotein-free fraction.[18] The role of Apo A-IV in lipoprotein metabolism remains to be determined but it may have a role in regulating food intake. Apo A-IV is synthesized in the intestine during fat absorption.

Apolipoprotein A-V

Apo A-V is carried on triglyceride-rich lipoproteins and is an activator of LPL-mediated lipolysis and thus plays an important role in the clearance of triglyceride-rich lipoproteins.[19,20] Apo A-V is synthesized in the liver.

Apolipoprotein B-48

Apo B-48 is the major structural protein of chylomicrons and chylomicron remnants and there is a single apo B-48 protein per chylomicron or chylomicron remnant particle.[21] Apo B-48 is synthesized in the intestine and a single apolipoprotein B gene is expressed in both the liver and intestine. The intestinal Apo B protein is approximately ½ the size of the liver due to mRNA editing. The apobec-1 editing complex, which edits mRNA, is expressed in the intestine and edits a specific cytidine to uracil in Apo B mRNA resulting in a stop codon that leads to the cessation of protein translation and a shorter Apo B protein (Apo B-48). The portion of Apo-B that is recognized by the LDL receptor is not contained in Apo-B48 and Apo B-48 is not recognized by the LDL receptor.

Apolipoprotein B-100

Apo B-100 is the major structural protein of VLDL, IDL, and LDL and there is a single molecule of Apo B-100 per VLDL, IDL, LDL, and Lp(a) particle. Apo B-100 is synthesized in the liver. Apo B-100 is recognized by the LDL receptor and therefore plays an important role in the clearance of Apo B-100 containing lipoprotein particles. Certain mutations in Apo B-100 result in decreased binding to the LDL receptor and familial hypercholesterolemia. Elevated levels of Apo B-100 are associated with an increased risk of developing atherosclerosis.

Apolipoprotein C

The C apolipoproteins are synthesized primarily in the liver. Apo C apolipoproteins are found in association with chylomicrons, VLDL, and HDL and freely exchange between these particles.[22–24]

Apo C-II is a cofactor for LPL and stimulates triglyceride hydrolysis and the clearance of triglyceride-rich lipoproteins.[22,25] Individuals who are homozygous for loss of function mutations in Apo C-II have markedly elevated triglyceride levels due to a failure to clear triglyceride-rich lipoproteins.

Apo C-III inhibits the activity of LPL[26] and inhibits the interaction of triglyceride-rich lipoproteins with their receptors.[23] Loss of function mutations in Apo C-III result in decreases in serum triglyceride levels and a decreased risk of cardiovascular disease. Furthermore, inhibition of Apo C-III leads to a decrease in serum triglyceride levels even in patients deficient in LPL, indicating that the ability of Apo C-III to decrease serum triglyceride levels is not entirely mediated by regulating LPL activity.[27]

Apolipoprotein E

The liver and intestine are the primary sources of circulating Apo E but Apo E is synthesized in many tissues.[28] Apo E is associated with chylomicrons, chylomicron remnants, VLDL, IDL, and a subgroup of HDL particles and exchanges between lipoprotein particles. There are 3 common genetic variants of Apo E (Apo E2, E3, and E4) and Apo E3 is the most common form. Apo E2 differs from Apo E3, by a single amino acid substitution whereby cysteine substitutes for arginine at residue 158 and Apo E4 differ from Apo E3 at residue 112 whereby arginine substitutes for cysteine. Apo E3 and E4 are recognized by the LDL receptor while Apo E2 is poorly recognized.

Individuals who are homozygous for Apo E2 can develop familial dysbetalipoproteinemia. Individuals with Apo E4 have an increased risk of both Alzheimer's disease and atherosclerosis.

TRANSFER PROTEINS AND ENZYMES: KEY ROLES IN LIPOPROTEIN METABOLISM

Cholesteryl Ester Transfer Protein

In the plasma, cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl esters from HDL to VLDL, chylomicrons, and LDL and the linked transfer of triglycerides from these particles to HDL.[29] CETP is synthesized in the liver. Inhibition of CETP activity leads to a decrease in LDL cholesterol and an increase in HDL cholesterol.

Lecithin: Cholesterol Acyltransferase

LCAT catalyzes the synthesis of cholesteryl esters in HDL particles by facilitating the transfer of fatty acid from position 2 of lecithin to cholesterol.[30] The formation of cholesteryl esters allows for the transfer of the free cholesterol from the surface of the HDL particle to the core of the HDL particle. This decrease in the free cholesterol concentration on the surface of HDL particles allows for the uptake of free cholesterol by HDL particles facilitating the efflux of cholesterol from cells. LCAT is synthesized in the liver. Patients with decreased LCAT activity have decreased HDL cholesterol levels.

Lipoprotein Lipase

LPL is synthesized in muscle, heart, and adipose tissue, then secreted and attached to the endothelium of capillaries.[31] LPL hydrolyzes the triglycerides carried in triglyceride-rich lipoproteins, chylomicrons, and VLDL, to fatty acids, which are then taken up by adipocytes or muscle cells. The removal of triglycerides results in the conversion of chylomicrons into chylomicron remnants and VLDL into IDL (VLDL remnants). Apo C-II is an essential cofactor for LPL activity and Apo A-V also plays an important role in the activation of LPL. In contrast, Apo C-III and Apo A-II inhibit LPL activity. LPL expression is stimulated by insulin and in patients with poorly controlled diabetes LPL activity is reduced, which can decrease the clearance of triglyceride-rich lipoproteins leading to hypertriglyceridemia. Patients who are homozygotes for loss of function mutations In LPL have marked elevations in plasma triglyceride levels.

Hepatic Lipase

Hepatic lipase is synthesized in the liver and localized at the sinusoidal surface of hepatocytes.[32] Hepatic lipase catalyzes the hydrolysis of triglycerides and phospholipids in IDL and LDL producing smaller lipoprotein particles (IDL is converted to LDL; large LDL is converted to small LDL). Hepatic lipase also catalyzes the hydrolysis of triglycerides and phospholipids in HDL producing smaller HDL particles.

Endothelial Lipase

Endothelial lipase plays a key role in hydrolyzing the phospholipids in HDL.[33]

Microsomal Triglyceride Transfer Protein

Microsomal triglyceride transfer protein is expressed primarily in the liver and small intestine and plays a crucial role in the synthesis of lipoproteins in these tissues. MTP mediates the transfer of triglycerides to apolipoprotein B-100 in the liver to form VLDL and to apolipoprotein B-48 in the intestine to form chylomicrons.[34] Patients homozygous for loss of function mutations in MTP have very low plasma lipid levels (abetalipoproteinemia).

LIPOPROTEIN RECEPTORS AND LIPID TRANSPORTERS: KEY ROLES IN LIPOPROTEIN METABOLISM

Low-Density Lipoprotein Receptor

The LDL receptor is present in most tissues but the expression of LDL receptors in the liver plays a key role in determining plasma LDL levels.[35] A low number of hepatic LDL receptors is associated with high plasma LDL levels while a high number of hepatic LDL receptors is associated with low plasma LDL levels. The LDL receptor recognizes Apo B-100 and Apo E and thereby mediates not only the uptake of LDL but also chylomicron remnants and VLDL remnants (IDL). Lipoprotein particle uptake occurs via endocytosis of the LDL receptor and the attached lipoprotein particle (**Fig. 3**). After internalization, the lipoprotein particle is degraded in lysosomes and the cholesterol is released. The number of LDL receptors is regulated by cellular cholesterol levels.[36] When cellular cholesterol levels are low the transcription factor SREBP is transported from the endoplasmic reticulum to the Golgi whereby proteases cleave and activate SREBP, which then migrates to the nucleus and stimulates the expression of LDL receptors and many of the enzymes that synthesize cholesterol including HMGCoA reductase. Conversely, when cellular cholesterol levels are increased 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. Loss of function mutation in the LDL receptor is the most common cause of familial hypercholesterolemia.

Low-Density Lipoprotein Receptor-Related Protein 1

Lipoprotein receptor-related protein (LRP-1) is expressed in multiple tissues including the liver and is a member of the LDL receptor family.[37] Apo E is a ligand for LRP-1. LRP-1 mediates the hepatic uptake of Apo E containing lipoproteins (chylomicron remnants and VLDL remnants (IDL)).

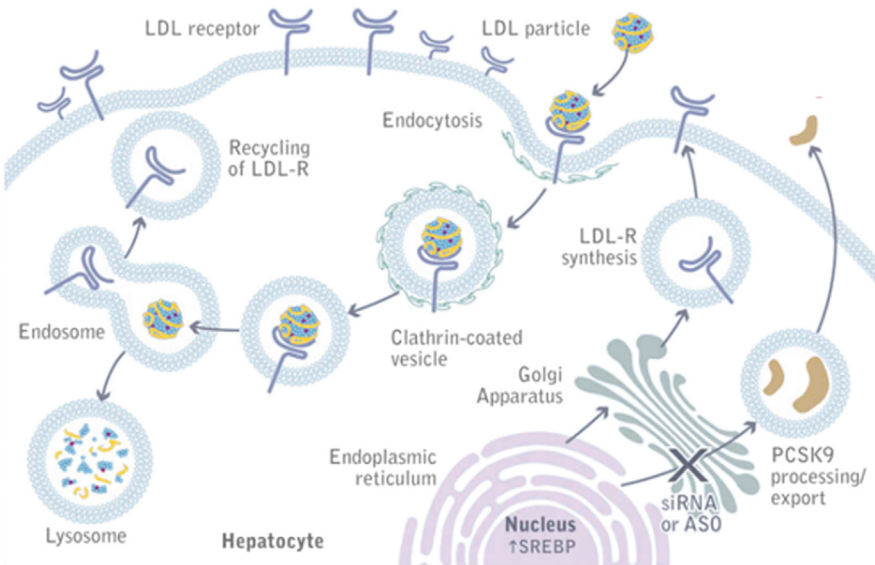

Fig. 3. Ldl receptor pathway. (*Adapted from* Lambert G, Sjouke B, Choque B, Kastelein JJ, Hovingh GK. The PCSK9 decade. J Lipid Res. 2012 Dec;53(12):2515-24.)

Niemann-Pick C1-like 1

Niemann-Pick C1-like 1 (NPC1L1) is expressed in the small intestine and mediates the uptake of dietary cholesterol and plant sterols from the intestinal lumen into the intestinal cell.[38] NPC1L1 is also expressed in the liver whereby it mediates the movement of cholesterol from hepatocytes into the bile.

Class B Scavenger Receptor B1

Scavenger receptor B1 (SR-B1) is expressed in many cells including the liver, adrenal glands, ovaries, testes, and macrophages.[39] In the liver and steroid producing cells (adrenal glands, ovaries, testes), it facilitates the selective uptake of cholesteryl esters from HDL particles. In macrophages and other cells, it mediates the efflux of cholesterol from the cell to HDL particles.

ATP-Binding Cassette Transporter A1

ATP-binding cassette transporter A1 (ABCA1) is expressed in hepatocytes, intestinal cells, macrophages, and many other cells.[40] It mediates the efflux of cholesterol and phospholipids from cells to small lipid-poor HDL particles (pre–beta-HDL).

ATP-Binding Cassette Transporter G1

ATP-binding cassette transporter G1 (ABCG1) is expressed in many different cell types and mediates the efflux of cholesterol from cells to mature HDL particles.[41]

ATP-Binding Cassette Transporter G5 and G8

ATP-binding cassette transporter G5 and G8 (ABCG5 and ABCG8) form a heterodimer and are expressed in the liver and intestine.[42] In the intestine, ABCG5/ABCG8 facilitates the movement of cholesterol and plant sterols from inside the enterocyte into the intestinal lumen thereby decreasing the absorption of cholesterol and limiting the uptake of dietary plant sterols. In the liver, ABCG5/ABCG8 facilitates the movement of cholesterol and plant sterols into the bile resulting in the transport of plant sterols and cholesterol to the intestine.

EXOGENOUS LIPOPROTEIN PATHWAY

Absorption of Dietary Fat

The exogenous lipoprotein pathway is initiated in the small intestine (**Fig. 4**).[43–46] Intestinal lipases hydrolyze dietary triglycerides (approximately 100 g per day) to free fatty acids and monoacylglycerol and these are emulsified with bile acids, plant sterols, cholesterol, and fat-soluble vitamins to form micelles. The fatty acids in the intestinal lumen are mainly from the diet while the cholesterol in the intestinal lumen is mainly derived from bile (approximately 800–1200 mg of cholesterol from bile vs 200–500 mg from diet). Approximately 100 to 150 mg of plant sterols are ingested per day. The cholesterol, plant sterols, fatty acids, monoacylglycerol, and fat-soluble vitamins contained in the micelles are transported into the intestinal cells. NPC1L1 facilitates the uptake of cholesterol and plant sterols from the intestinal lumen into intestinal cells (**Fig. 5**). Ezetimibe binds to NPC1L1 and inhibits the absorption of cholesterol and plant sterols. Cholesterol and plant sterols in the intestinal cell may be converted to sterol esters by acyl-CoA cholesterol acyltransferase (ACAT), which attaches a fatty acid to the sterol or be transported back into the intestinal lumen, a process mediated by ABCG5 and ABCG8. The synthesis of plant sterol esters does not occur as efficiently as the synthesis of cholesteryl esters because plant sterols are poor substrates for ACAT compared with cholesterol. In humans, less than 5%

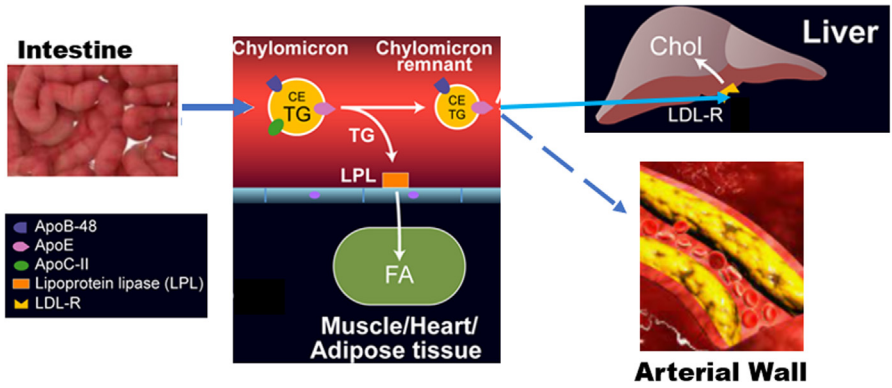

Fig. 4. Exogenous lipoprotein pathway. (*Modified from* Feingold KR. Introduction to Lipids and Lipoproteins. 2021 Jan 19. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–.)

of dietary plant sterols are absorbed. Mutations in either ABCG5 or ABCG8 result in increased absorption of dietary plant sterols (20%–30% absorbed vs < 5% in normal subjects) resulting in sitosterolemia. Thus, ACAT and ABCG5 and ABCG8 serve as gatekeepers and block the uptake of plant sterols and likely also play an important role in determining cholesterol absorption (humans absorb approximately 50% of dietary cholesterol with a range of 25%–75%).

The absorption of free fatty acids is not well understood but it is likely that both passive diffusion and specific transporters play a role. CD36, a fatty acid transporter, is strongly expressed in the proximal third of the intestine and is localized to the villi. This transporter likely plays a role in fatty acid uptake by intestinal cells but is not essential as humans and mice deficient in this protein do not have fat malabsorption.

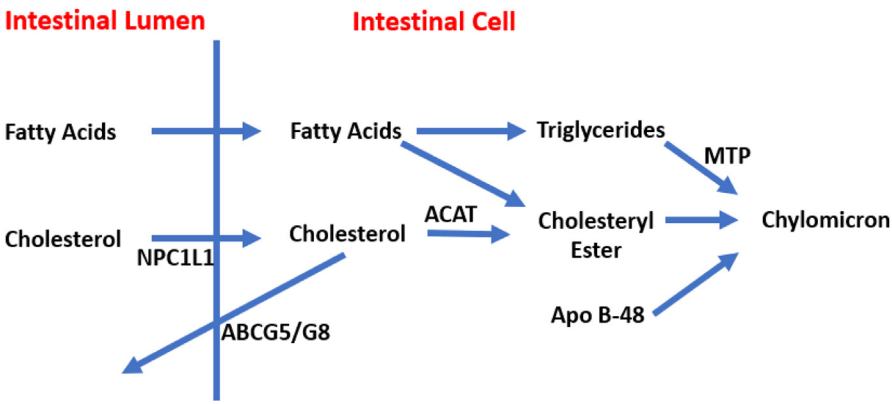

Fig. 5. Formation of chylomicrons by intestinal cells. (*Adapted from* Feingold KR. Introduction to Lipids and Lipoproteins. 2021 Jan 19. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–.)

In CD36 deficient mice the absorption of fatty acids is enhanced in the distal intestine, suggesting that other pathways compensate for the absence of CD36. Fatty acid transport protein 4 (FATP4), another fatty acid transporter, is also highly expressed in the intestine but mice deficient in FATP4 do not have abnormalities in fat absorption. It is likely that there are multiple pathways for the absorption of fatty acids. The pathways by which monoacylglycerols are absorbed by intestinal cells are unknown.

Formation of Chylomicron Particles

The fatty acids and monoacylglycerols that are absorbed are used in intestinal cells to synthesize triglycerides.[43,46] Monoacylglycerol acyltransferase (MGAT) and diacylglycerol transferase (DGAT) are the key enzymes in triglyceride synthesis. 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. The cholesterol in the intestine is esterified to cholesteryl esters by ACAT. In the endoplasmic reticulum of intestinal cells, the triglycerides and cholesteryl esters are packaged into chylomicrons. The formation of chylomicrons in the endoplasmic reticulim requires the synthesis of Apo B-48 (see **Fig. 5**). The movement of lipid in the endoplasmic reticulum to Apo B-48 is mediated by MTP. The absence of MTP activity results in the failure to form chylomicrons and VLDL (abetalipoproteinemia). Lomitapide inhibits MTP activity and is approved to treat patients with homozygous Familial Hypercholesterolemia.

Metabolism of Chylomicron Particles

The chylomicrons synthesized in the intestine are secreted into the lymph and delivered via the thoracic duct to the systemic circulation, rather than to the liver via the portal vein.[22,26,31,47–51] This enhances the delivery of the nutrients to muscle and adipose tissue. LPL is synthesized in myocytes and adipocytes and transported to the luminal surface of capillaries. The stabilization and movement of LPL from muscle cells and adipocytes to the capillary endothelial cell surface is facilitated by Lipase maturation factor 1. Glycosylphosphatidylinositol anchored high-density lipoprotein binding protein 1 (GPIHBP1) binds LPL and transports LPL to the capillary lumen and anchors it to the capillary endothelium. Apo C-II, carried on the chylomicrons, activates LPL, leading to the hydrolysis of the triglycerides in the chylomicrons resulting in the formation of free fatty acids, which are taken up by muscle cells and adipocytes and used for either energy production or storage. The uptake of fatty acids into adipocytes and muscle cells is facilitated by fatty acid transport proteins (FATPs) and CD36. A portion of the free fatty acids released from the hydrolysis of triglycerides in chylomicrons bind to albumin and can be transported to other tissues. Apo A-V also plays a role in activating LPL activity. Mutations in LPL, Apo C-II, GPIHPB1, lipase maturation factor 1, and Apo A-V can result in marked hypertriglyceridemia (familial chylomicronemia syndrome). In addition, 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, also regulate LPL activity. Loss of function mutations in angiopoietin-like protein 3 and 4 are associated with decreases in plasma triglyceride levels.

The hydrolysis of the triglycerides carried in the chylomicrons results in a marked decrease in the size of the chylomicrons resulting in the formation of chylomicron remnants, which are enriched in cholesteryl esters and acquire Apo E. As chylomicrons decrease in size phospholipids and apolipoproteins (Apo A and C) on the surface of the chylomicrons are transferred to other lipoproteins, primarily HDL. The transfer of Apo C-II from chylomicrons to HDL decreases the ability of LPL to further breakdown triglycerides. The liver is the primary site whereby chylomicrons are removed from

circulation. The Apo E carried on the chylomicron remnants bind to the LDL receptor and other hepatic receptors such as LRP-1 and syndecan-4 and the entire particle is taken up by the hepatocytes. Apo E is important for this process and polymorphisms in Apo E (for example the Apo E2 isoform) can result in decreased chylomicron remnant clearance and elevations in plasma cholesterol and triglyceride levels (familial dysbetalipoproteinemia).

The exogenous lipoprotein pathway results in the efficient transfer of dietary triglycerides (fatty acids) to muscle and adipose tissue for energy utilization and storage. In individuals with normal lipid metabolism, this pathway can transfer large amounts of dietary fat from the intestine to muscle and adipose tissue (100 g or more per day) without resulting in marked increases in plasma triglyceride levels. Dietary cholesterol is primarily delivered to the liver whereby it can be used in the synthesis of VLDL or bile acids, or secreted back to the intestine via secretion into the bile.

ENDOGENOUS LIPOPROTEIN PATHWAY

Formation of Very Low-Density Lipoprotein Particles Particles

In the liver, MTP mediates the transfer of cholesterol and triglycerides to newly synthesized Apo B-100 in the endoplasmic reticulum, a process that is similar to the formation of chylomicron particles in the intestine (**Fig. 6**).[34,52,53] The rate of VLDL particle formation is determined by the supply of triglycerides and when the supply of

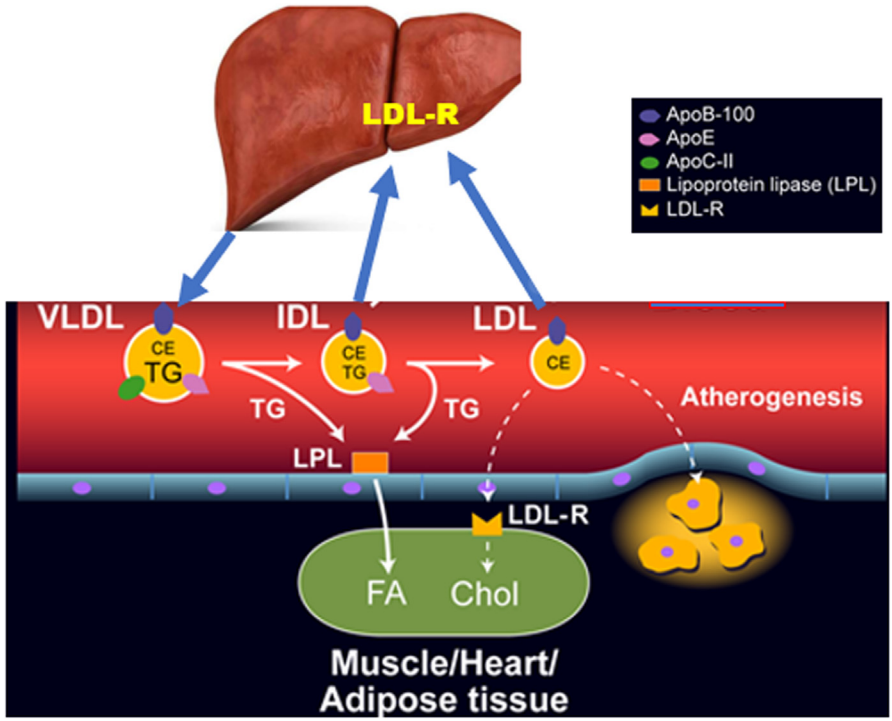

Fig. 6. Endogenous lipoprotein pathway. (*Adapted from* Feingold KR. Introduction to Lipids and Lipoproteins. 2021 Jan 19. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–.)

triglycerides is not abundant the newly synthesized Apo B-100 is rapidly degraded. When the supply of triglycerides is abundant the Apo B-100 is protected from degradation. Thus, the rate of formation and secretion of VLDL particles is determined by the availability of triglycerides and not the rate of synthesis of Apo B-100. Additionally, the size of the VLDL particles is determined by the availability of triglycerides. When triglycerides are abundant the VLDL particles are large.

The levels of fatty acids available for the synthesis of triglycerides are the main determinant of the number of triglycerides in the liver. The major sources of fatty acids are (a) de novo fatty acid synthesis, (b) the hepatic uptake of triglyceride-rich lipoproteins, and (c) the flux of fatty acids from adipose tissue to the liver. Diabetes, obesity, and metabolic syndrome are common causes of an increase in hepatic triglyceride levels and the increased secretion of VLDL.

The early addition of lipid to Apo B-100 particles is mediated by MTP while other pathways that do not require MTP add additional lipid. The details by which newly synthesized VLDL particles are secreted by the liver remain to be elucidated.

Metabolism of Very Low-Density Lipoprotein Particles Particles

In peripheral tissues, the triglycerides carried on the VLDL particles are hydrolyzed by LPL and fatty acids are released, a process that is very similar to that described above for chylomicrons (see **Fig. 6**).[9,47] VLDL and chylomicron particles compete for clearance by the LPL system. The removal of triglycerides by LPL from VLDL particles results in the formation of VLDL remnants (IDL), which are enriched in cholesteryl esters. VLDL remnant particles are removed from the circulation by the liver via binding of Apo E to LDL and LRP-1 receptors similar to the removal of chylomicron remnants. In contrast to chylomicron remnants where the vast majority are rapidly cleared from the circulation by the liver only a portion of VLDL remnant particles are removed (approximately 50% but varies). The residual triglycerides in the VLDL remnant particles are hydrolyzed by hepatic lipase leading to the formation of LDL particles. LDL particles contain mainly cholesteryl esters and Apo B-100 as the vast majority of triglycerides have been removed and exchangeable apolipoproteins are transferred from the VLDL remnant particles to other lipoproteins. Thus, VLDL metabolism results in the formation of LDL.

Metabolism of Low-Density Lipoprotein Particles

The rate of LDL clearance and the rate of LDL production are primarily regulated by the number of hepatic LDL receptors and thus the number of hepatic LDL receptors is the main determinant of plasma LDL levels.[35,54–56] High LDL receptor activity decreases the conversion of VLDL remnants to LDL while low LDL receptor activity increases the conversion of VLDL remnants to LDL (ie, increased LDL production). Additionally, approximately 70% of circulating LDL is cleared by LDL receptors in the liver with the remainder taken up by extrahepatic tissues. Thus, an increase in LDL receptors in the liver will increase LDL clearance resulting in a decrease in plasma LDL levels, whereas a decrease in liver LDL receptors will decrease LDL clearance resulting in an increase in plasma LDL levels. Thus, the number of LDL receptors in the liver plays a major role in regulating plasma LDL levels. Many of the drugs used to lower plasma LDL levels, such as statins, ezetimibe, PCSK9 inhibitors, and bempedoic acid lower plasma LDL levels by increasing the number of hepatic LDL receptors.

The cholesterol content of the liver is the primary regulator of the number of hepatic LDL receptors. Low cholesterol levels in the liver lead to the transport of inactive sterol regulatory element-binding proteins (SREBPs), which are transcription factors that stimulate the expression of LDL receptors and other key genes involved in cholesterol

and fatty acid metabolism, from the endoplasmic reticulum to the Golgi whereby proteases cleave the SREBPs into active transcription factors. These active SREBPs transfer to the nucleus whereby they increase the transcription of LDL receptor mRNA and upregulate other genes, including HMG-CoA reductase and other proteins required for cholesterol synthesis. When hepatic cholesterol is high inactive SREBPs remain in the endoplasmic reticulum and the synthesis of LDL receptors is not increased. Thus, LDL receptor activity is regulated by cellular cholesterol levels with high cellular cholesterol levels leading to decreased LDL receptor activity and decreased clearance of LDL particles from the circulation and low cellular cholesterol levels leading to increased LDL receptor activity and the increased clearance of LDL particles from the circulation. Statins, ezetimibe, and bempedoic acid decrease hepatic cholesterol levels thereby increasing LDL receptor levels and decreasing plasma LDL levels.

Finally, PCSK9 is a secreted protein that binds to the LDL receptor and increases LDL receptor degradation in the lysosomes. Gain of function mutations in PCSK9 lead to decreased LDL receptor activity and elevations in LDL levels while loss of function mutations in PCSK9 result in increased LDL receptor activity and decreased LDL levels. Drugs that inhibit PCSK9 decrease LDL receptor degradation leading to an increase in hepatic LDL receptors resulting in a decrease in plasma LDL levels.

METABOLISM OF HIGH-DENSITY LIPOPROTEIN PARTICLES AND REVERSE CHOLESTEROL TRANSPORT

Formation of High-Density Lipoprotein Particles

The formation of mature HDL particles requires several steps (**Fig. 7**).[30,39–41,57–59] The initial step is the synthesis of Apo A-I, the main structural protein of HDL, in the liver and intestine. The liver and intestine secrete Apo A-1 which then acquires cholesterol and phospholipids that are effluxed from hepatocytes and enterocytes leading to the formation of pre–beta-HDL. ABCA1 facilitates the efflux of cholesterol and phospholipids and patients with loss of function mutations in ABCA1 are unable to add lipid to the newly secreted Apo A-I resulting in the rapid degradation of Apo A-I and very low HDL levels. In mice, targeted knock-outs of ABC1 in the liver result in an 80% decrease in HDL levels while targeted knock-outs in the intestine result in a 30% decrease in HDL levels. ABCA1 is expressed in numerous tissues allowing these tissues to also contribute cholesterol and phospholipids to lipid-poor Apo A-I particles.

During the metabolism of triglyceride-rich lipoproteins cholesterol and phospholipids may be transferred from chylomicrons and VLDL to newly formed HDL, which explains the observation that patients with high plasma triglyceride levels due to decreased metabolism of triglyceride-rich lipoprotein often also have low HDL levels. The metabolism of triglyceride-rich lipoproteins also results in the transfer of apolipoproteins to HDL from these triglyceride-rich lipoproteins. The movement of phospholipids between lipoproteins is facilitated by phospholipid transfer protein (PLTP) and mice lacking PLTP have a large reduction in HDL and Apo A-I levels.

High-Density Lipoprotein Cholesteryl Esterification

As noted earlier free cholesterol is localized on the surface of lipoprotein particles including HDL while the bulk of the cholesterol is in the core of HDL in the form of cholesteryl esters. Free cholesterol is effluxed from cells to HDL and to form mature large spherical HDL particles, this free cholesterol must be esterified. LCAT is an HDL-associated enzyme that catalyzes the transfer of fatty acid from phospholipids to free cholesterol resulting in the synthesis of cholesteryl esters which migrate from

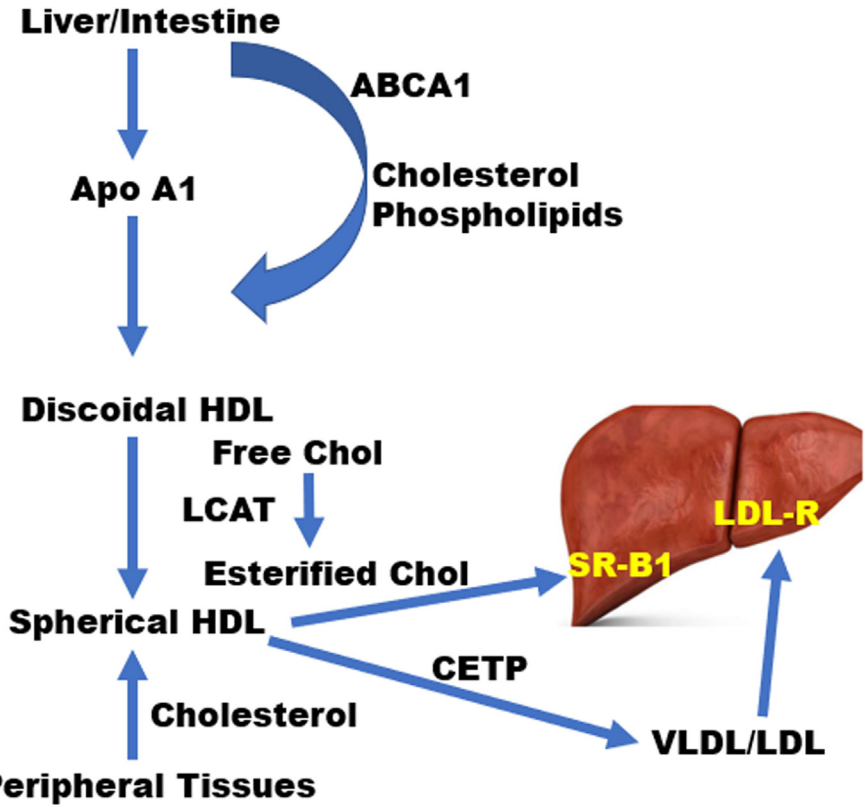

Fig. 7. Hdl metabolism. (*Adapted from* Feingold KR. Introduction to Lipids and Lipoproteins. 2021 Jan 19. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–.)

the surface of HDL particles into the core. Apo A-I is an activator of LCAT. In humans, LCAT deficiency leads to very low HDL cholesterol and Apo A-I levels and a large number of small HDL particles.

Metabolism of High-Density Lipoprotein Particles

The size and composition of HDL particles are determined by lipases and transfer proteins. CETP mediates the transfer of cholesteryl esters in the core of HDL particles to Apo B containing lipoproteins in exchange for triglycerides. The triglycerides transferred to HDL may be metabolized by hepatic lipase resulting in small HDL particles. Apo A-I more easily disassociates from small HDL resulting in increased Apo A-I degradation. Humans deficient in CETP activity have large HDL particles and very high HDL cholesterol levels. As one would expect the absence of CETP also results in a decrease in LDL cholesterol levels. Genetic deficiency of hepatic lipase results in larger HDL particles and a modest elevation in HDL cholesterol levels. The phospholipids carried on HDL particles are hydrolyzed by endothelial cell lipase. In mice decreased endothelial lipase activity results in increased HDL cholesterol levels while increased endothelial lipase activity results in decreased HDL cholesterol levels.

HDL cholesterol is primarily delivered to the liver. SR-B1, which promotes the selective uptake of HDL cholesterol mediates the uptake of HDL cholesterol by the liver. HDL particles bind to hepatic SR-BI and the cholesterol in HDL is transported into the liver without the internalization of the HDL particle. This results in a cholesterol depleted smaller HDL particle, which is then released back into the circulation. Mice deficient in SR-B1 have a marked increase in HDL cholesterol levels and interestingly, the risk of atherosclerosis is increased despite the increase in HDL cholesterol levels due to a decrease in reverse cholesterol transport. In mice, the importance of the hepatic SR-BI pathway is well defined but the role in humans is less certain. In mice, the transport of cholesterol from peripheral tissues to the liver is dependent solely on SR-BI while in humans CETP transports cholesterol from HDL to Apo B containing lipoproteins, which can serve as an alternative pathway for the transport cholesterol to the liver. In humans' polymorphisms in the SR-BI gene influence HDL cholesterol levels but have only a minimal effect on atherosclerosis.

Apo A-I is metabolized independently of HDL cholesterol with most of the Apo A-I catabolized by the kidneys with the remainder catabolized by the liver. The kidney filters lipid-free or lipid-poor Apo A-I which is 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 metabolism. Lipid-poor HDL lead to the rapid catabolism of Apo A-1 by the kidney. Conditions or disease states that result in lipid-poor HDL are associated with low HDL and Apo A-I levels. In the renal tubule, Apo A-I binds to cubilin, which in association with megalin, a member of the LDL receptor gene family, results in the uptake and degradation of filtered Apo A-I by renal tubular cells. The mechanisms by which the liver catabolizes Apo A-I are poorly defined. Apo E containing HDL particles may be taken up by the LDL receptor and other Apo E receptors in the liver and degraded.

Reverse Cholesterol Transport

Peripheral cells accumulate cholesterol via de novo cholesterol synthesis and the uptake of cholesterol from circulating lipoproteins.[60–65] Only a few specialized cells have mechanisms to decrease cellular cholesterol levels. Intestinal cells can secrete cholesterol into the intestinal lumen and sebocytes and keratinocytes can secret cholesterol onto the skin surface. Adrenal, testicular, and ovarian cells can convert cholesterol into steroid hormones. Other cells can only decrease cellular cholesterol via reverse cholesterol transport. The ability of macrophages in the arterial wall to efficiently remove cholesterol by reverse cholesterol transport pathway may play an important role in the prevention of atherosclerosis.

The efflux of cellular cholesterol to lipid-poor pre–beta-HDL particles is mediated by ABCA1 while efflux of cellular cholesterol to mature HDL particles is mediated by ABCG1 (**Fig. 8**). SR-B1 and passive diffusion may also contribute to the efflux of cellular cholesterol to mature HDL particles. ABCA1 and ABCG1 are upregulated by the activation of LXR, a nuclear hormone transcription factor that is activated by oxysterols. As cellular cholesterol rises the formation of oxysterols is enhanced resulting in the activation of LXR which stimulates the expression of ABCA1 and ABCG1 resulting in an increase in the efflux of cholesterol from cells to HDL.

miR-33 is a microRNA that is embedded within the SREBP2 gene which targets ABCA1 and ABCG1 mRNA for degradation. As the cellular cholesterol levels increase the expression of SREBP2 decreases resulting in a decrease in LDL receptor and cholesterol synthesis and a decrease in miR-33 levels. The decrease in miR-33 will lead to an increase in the expression of ABCA1 and ABCG1 resulting in increased cholesterol efflux which coupled with the decrease in LDL receptor activity and

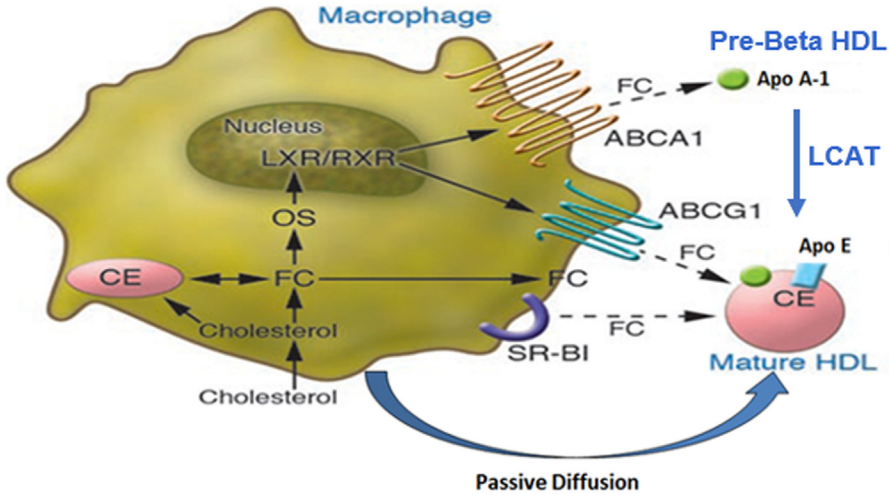

Fig. 8. Cholesterol efflux from macrophages. (*Modified from* Rader DJ. Molecular regulation of HDL metabolism and function: implications for novel therapies. J Clin Invest. 2006 Dec;116(12):3090-100.)

cholesterol synthesis will decrease cellular cholesterol levels. Conversely, a decrease in cellular cholesterol levels will increase SREBP2 expression resulting in an increase in LDL receptor activity and cholesterol synthesis increasing cholesterol accumulation, and an increase in miR-33, resulting in the decreased expression of ABCA1 and ABCG1 and a reduction in cholesterol efflux. Together these changes in cholesterol accumulation mediated by the LDL receptor and cholesterol synthesis and cholesterol efflux mediated by ABCA1 and ABCG1 will maintain cellular cholesterol homeostasis.

There are 2 pathways for cholesterol carried on HDL to be transported to the liver. HDL can interact with hepatic SR-BI receptors resulting in the selective uptake of cholesterol from HDL particles into the liver or CETP can transfer cholesterol from HDL particles to Apo B lipoprotein particles with the subsequent uptake of Apo B containing lipoproteins by the liver. The cholesterol delivered to the liver can be eliminated from the body by 2 pathways. First, cholesterol can be secreted into the bile, a process facilitated by ABCG5 and ABCG8. ABCG5 and ABCG8 expression is increased by the activation of LXR and therefore an increase in hepatic cholesterol levels results in an increase in oxysterol production thereby increasing LXR activation and the secretion of bile acid. Second, cholesterol can be converted to bile acids and secreted in the bile.

Studies have suggested that reverse cholesterol transport plays an important role in protecting from the development of atherosclerosis. HDL cholesterol levels may not be indicative of the rate of reverse cholesterol transport as reverse cholesterol transport involves multiple steps and HDL cholesterol levels may not accurately reflect these steps. For example, the ability of HDL to promote cholesterol efflux from macrophages can vary and the same level of HDL cholesterol may not have equivalent abilities to mediate the first step of reverse cholesterol transport.

CLINICS CARE POINTS

- Low HDL-C levels are often due to decreased metabolism of triglyceride-rich lipoproteins, which explains the association of low HDL-C with hypertriglyceridemia

- Hepatic LDL receptors are the major regulator of LDL-C levels and drugs such as statins, ezetimibe, PCSK9 inhibitors, and bempedoic acid lower LDL-C levels by increasing the number of hepatic LDL receptors
- Reverse cholesterol transport is a complex process and the levels of HDL-C may not accurately indicate the activity of reverse cholesterol transport.

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REFERENCES

1. Feingold KR, Grunfeld C. Lipids: a key player in the battle between the host and microorganisms. J Lipid Res 2012;53:2487–9.
2. Nielsen LB, Nielsen MJ, Moestrup SK. Lipid metabolism: an apolipoprotein-derived weapon combating trypanosoma infection. Curr Opin Lipidol 2006;17:699–701.
3. Feingold KR. The bidirectional link between HDL and COVID-19 infections. J Lipid Res 2021;62:100067.
4. Smith LC, Pownall HJ, Gotto AM Jr. The plasma lipoproteins: structure and metabolism. Annu Rev Biochem 1978;47:751–7.
5. Asztalos BF, Niisuke K, Horvath KV. High-density lipoprotein: our elusive friend. Curr Opin Lipidol 2019;30:314–9.
6. Thakkar H, Vincent V, Sen A, et al. Changing perspectives on hdl: from simple quantity measurements to functional quality assessment. J Lipids 2021;2021:5585521.
7. Vaisar T, Pennathur S, Green PS, et al. Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of HDL. J Clin Invest 2007;117:746–56.
8. Julve J, Martin-Campos JM, Escola-Gil JC, et al. Advances in biology, pathology, laboratory testing, and therapeutics. Clin Chim Acta 2016;455:134–48.
9. Chait A, Ginsberg HN, Vaisar T, et al. Remnants of the triglyceride-rich lipoproteins, diabetes, and cardiovascular disease. Diabetes 2020;69:508–16.
10. Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Res 2002;43:1363–79.
11. Kostner KM, Kostner GM. Lipoprotein (a): a historical appraisal. J Lipid Res 2017;58:1–14.
12. Schmidt K, Noureen A, Kronenberg F, et al. Structure, function, and genetics of lipoprotein (a). J Lipid Res 2016;57:1339–59.
13. Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. J Lipid Res 2016;57:1953–75.
14. Mahley RW, Innerarity TL, Rall SC Jr, et al. Plasma lipoproteins: apolipoprotein structure and function. J Lipid Res 1984;25:1277–94.
15. Breslow JL. Human apolipoprotein molecular biology and genetic variation. Annu Rev Biochem 1985;54:699–727.
16. Frank PG, Marcel YL. Apolipoprotein A-I: structure-function relationships. J Lipid Res 2000;41:853–72.
17. Chan DC, Ng TW, Watts GF. Apolipoprotein A-II: evaluating its significance in dyslipidaemia, insulin resistance, and atherosclerosis. Ann Med 2012;44:313–24.

18. Wang F, Kohan AB, Lo CM, et al. Apolipoprotein A-IV: a protein intimately involved in metabolism. J Lipid Res 2015;56:1403–18.
19. Hubacek JA. Apolipoprotein A5 fifteen years anniversary: lessons from genetic epidemiology. Gene 2016;592:193–9.
20. Sharma V, Forte TM, Ryan RO. Influence of apolipoprotein A-V on the metabolic fate of triacylglycerol. Curr Opin Lipidol 2013;24:153–9.
21. Anant S, Davidson NO. Molecular mechanisms of apolipoprotein B mRNA editing. Curr Opin Lipidol 2001;12:159–65.
22. Wolska A, Dunbar RL, Freeman LA, et al. Apolipoprotein C-II: New findings related to genetics, biochemistry, and role in triglyceride metabolism. Atherosclerosis 2017;267:49–60.
23. Ramms B, Gordts P. Apolipoprotein C-III in triglyceride-rich lipoprotein metabolism. Curr Opin Lipidol 2018;29:171–9.
24. D'Erasmo L, Di Costanzo A, Gallo A, et al. A multifaceted protein in cardiometabolic disease. Metabolism 2020;113:154395.
25. Wolska A, Reimund M, Remaley AT. Apolipoprotein C-II: the re-emergence of a forgotten factor. Curr Opin Lipidol 2020;31:147–53.
26. Taskinen MR, Boren J. Why Is Apolipoprotein CIII emerging as a novel therapeutic target to reduce the burden of cardiovascular disease? Curr Atheroscler Rep 2016;18:59.
27. Witztum JL, Gaudet D, Freedman SD, et al. Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome. N Engl J Med 2019;381:531–42.
28. Mahley RW. Apolipoprotein E: from cardiovascular disease to neurodegenerative disorders. J Mol Med (Berl) 2016;94:739–46.
29. Shrestha S, Wu BJ, Guiney L, et al. Cholesteryl ester transfer protein and its inhibitors. J Lipid Res 2018;59:772–83.
30. Ossoli A, Simonelli S, Vitali C, et al. Role of LCAT in Atherosclerosis. J Atheroscler Thromb 2016;23:119–27.
31. Olivecrona G. Role of lipoprotein lipase in lipid metabolism. Curr Opin Lipidol 2016;27:233–41.
32. Kobayashi J, Miyashita K, Nakajima K, et al. Hepatic lipase: a comprehensive view of its role on plasma lipid and lipoprotein metabolism. J Atheroscler Thromb 2015;22:1001–11.
33. Yasuda T, Ishida T, Rader DJ. Update on the role of endothelial lipase in high-density lipoprotein metabolism, reverse cholesterol transport, and atherosclerosis. Circ J 2010;74:2263–70.
34. Hooper AJ, Burnett JR, Watts GF. Contemporary aspects of the biology and therapeutic regulation of the microsomal triglyceride transfer protein. Circ Res 2015;116:193–205.
35. Goldstein JL, Brown MS. The LDL receptor. Arterioscler Thromb Vasc Biol 2009;29:431–8.
36. Goldstein JL, DeBose-Boyd RA, Brown MS. Protein sensors for membrane sterols. Cell 2006;124:35–46.
37. van de Sluis B, Wijers M, Herz J. News on the molecular regulation and function of hepatic low-density lipoprotein receptor and LDLR-related protein 1. Curr Opin Lipidol 2017;28:241–7.
38. Jia L, Betters JL, Yu L. Niemann-pick C1-like 1 (NPC1L1) protein in intestinal and hepatic cholesterol transport. Annu Rev Physiol 2011;73:239–59.
39. Trigatti BL. SR-B1 and PDZK1: partners in HDL regulation. Curr Opin Lipidol 2017;28:201–8.

40. Wang S, Smith JD. ABCA1 and nascent HDL biogenesis. Biofactors 2014;40:547–54.
41. Baldan A, Tarr P, Lee R, et al. ATP-binding cassette transporter G1 and lipid homeostasis. Curr Opin Lipidol 2006;17:227–32.
42. Patel SB, Graf GA, Temel RE. ABCG5 and ABCG8: more than a defense against xenosterols. J Lipid Res 2018;59:1103–13.
43. Abumrad NA, Davidson NO. Role of the gut in lipid homeostasis. Physiol Rev 2012;92:1061–85.
44. D'Aquila T, Hung YH, Carreiro A, et al. Recent discoveries on absorption of dietary fat: Presence, synthesis, and metabolism of cytoplasmic lipid droplets within enterocytes. Biochim Biophys Acta 2016;1861:730–47.
45. Hussain MM. Intestinal lipid absorption and lipoprotein formation. Curr Opin Lipidol 2014;25:200–6.
46. Kindel T, Lee DM, Tso P. The mechanism of the formation and secretion of chylomicrons. Atheroscler Suppl 2010;11:11–6.
47. Dallinga-Thie GM, Franssen R, Mooij HL, et al. The metabolism of triglyceride-rich lipoproteins revisited: new players, new insight. Atherosclerosis 2010;211:1–8.
48. Dijk W, Kersten S. Regulation of lipid metabolism by angiopoietin-like proteins. Curr Opin Lipidol 2016;27:249–56.
49. Fong LG, Young SG, Beigneux AP, et al. GPIHBP1 and Plasma Triglyceride Metabolism. Trends Endocrinol Metab 2016;27:455–69.
50. Peterfy M. Lipase maturation factor 1: a lipase chaperone involved in lipid metabolism. Biochim Biophys Acta 2012;1821:790–4.
51. Young SG, Fong LG, Beigneux AP, et al. GPIHBP1 and Lipoprotein Lipase, Partners in Plasma Triglyceride Metabolism. Cell Metab 2019;30:51–65.
52. Tiwari S, Siddiqi SA. Intracellular trafficking and secretion of VLDL. Arterioscler Thromb Vasc Biol 2012;32:1079–86.
53. Choi SH, Ginsberg HN. Increased very low density lipoprotein (VLDL) secretion, hepatic steatosis, and insulin resistance. Trends Endocrinol Metab 2011;22:353–63.
54. Brown MS, Radhakrishnan A, Goldstein JL. Retrospective on cholesterol homeostasis: the central role of scap. Annu Rev Biochem 2018;87:783–807.
55. Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. Cell 2015;161:161–72.
56. Horton JD, Cohen JC, Hobbs HH. Molecular biology of PCSK9: its role in LDL metabolism. Trends Biochem Sci 2007;32:71–7.
57. Rosenson RS, Brewer HB Jr, Davidson WS, et al. Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. Circulation 2012;125:1905–19.
58. Rye KA, Barter PJ. Cardioprotective functions of HDLs. J Lipid Res 2014;55:168–79.
59. Mabuchi H, Nohara A, Inazu A. Cholesteryl ester transfer protein (CETP) deficiency and CETP inhibitors. Mol Cells 2014;37:777–84.
60. Zhao Y, Van Berkel TJ, Van Eck M. Relative roles of various efflux pathways in net cholesterol efflux from macrophage foam cells in atherosclerotic lesions. Curr Opin Lipidol 2010;21:441–53.
61. Lee-Rueckert M, Escola-Gil JC, Kovanen PT. HDL functionality in reverse cholesterol transport–Challenges in translating data emerging from mouse models to human disease. Biochim Biophys Acta 2016;1861:566–83.

62. Tall AR. Cholesterol efflux pathways and other potential mechanisms involved in the athero-protective effect of high density lipoproteins. J Intern Med 2008;263:256–73.
63. Siddiqi HK, Kiss D, Rader D. HDL-cholesterol and cardiovascular disease: rethinking our approach. Curr Opin Cardiol 2015;30:536–42.
64. Moore KJ, Rayner KJ, Suarez Y, et al. The role of microRNAs in cholesterol efflux and hepatic lipid metabolism. Annu Rev Nutr 2011;31:49–63.
65. Ouimet M, Barrett TJ, Fisher EA. HDL and reverse cholesterol transport. Circ Res 2019;124:1505–18.