

Review of Lipoproteins

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Lipids by definition are insoluble in water. In order to transport lipids such as fatty acids, triacylglycerols, steroids and fat soluble vitamins in the blood plasma, a carrier protein is required. Fatty acids are carried from the adipose tissue to the muscle, heart and liver tissues by serum albumin. Vitamin A is carried by the retinol binding protein. There are steroid carrier proteins that carry steroids to the target cells. The bulk of the body's lipids (cholesterol, phospholipids and triacylglycerols), are transported in the plasma by large complexes called **lipoproteins**. These lipoproteins consist of a core of hydrophobic lipids surrounded by a shell of phosphatidyl glycerols and proteins. The protein components of lipoproteins solubilize the hydrophobic lipids and contain the cell targeting signals. Lipoproteins are classified according to their density. The lowest density lipoproteins are the **chylomicrons** followed by the **chylomicron remnants**, very low density lipoproteins **VLDLs**, intermediate density lipoproteins, **IDLs**, low density lipoproteins, **LDLs**, and high density lipoproteins, **HDLs**. The densities of these lipoproteins are related to the relative amounts of lipids to proteins in the complex. The higher the protein content the higher the density of the lipoprotein.

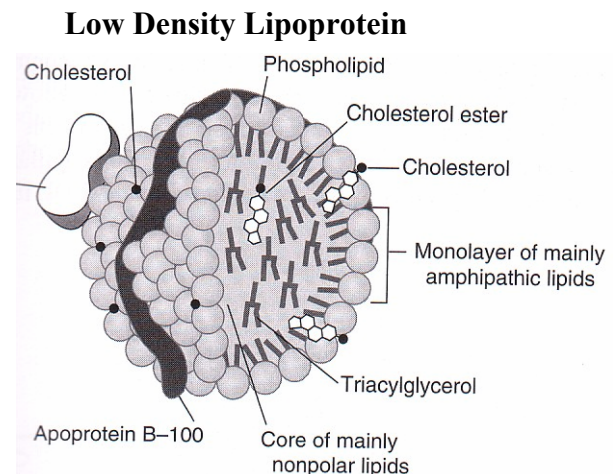
Shown to the left is a low density lipoprotein. The core of the LDL is composed of triacylglycerols and cholesteryl esters. This lipid core is surrounded by a layer of amphipathic phospholipids and unesterified cholesterol. The lone hydroxyl group of cholesterol molecules is oriented towards the outer surface shown here as black dots. The lipoproteins also contain apoproteins in their outer shell.

The **apoproteins** have important roles in lipid transport and metabolism. They have specific structural domains that are recognized by cell receptors. All of the apoproteins have amphipathic α -helices with the hydrophobic side chains facing the lipid interior of the lipoprotein and the hydrophilic residues interacting with the polar head groups of the phospholipids or interacting with the aqueous solvent.

The affinities of the apoproteins for the surface components of the lipoprotein change during lipoprotein metabolism. Apoproteins often diffuse from one lipoprotein and bind to another. Only apoprotein B maintains its association with the lipoprotein during the cycle of lipoprotein metabolism.

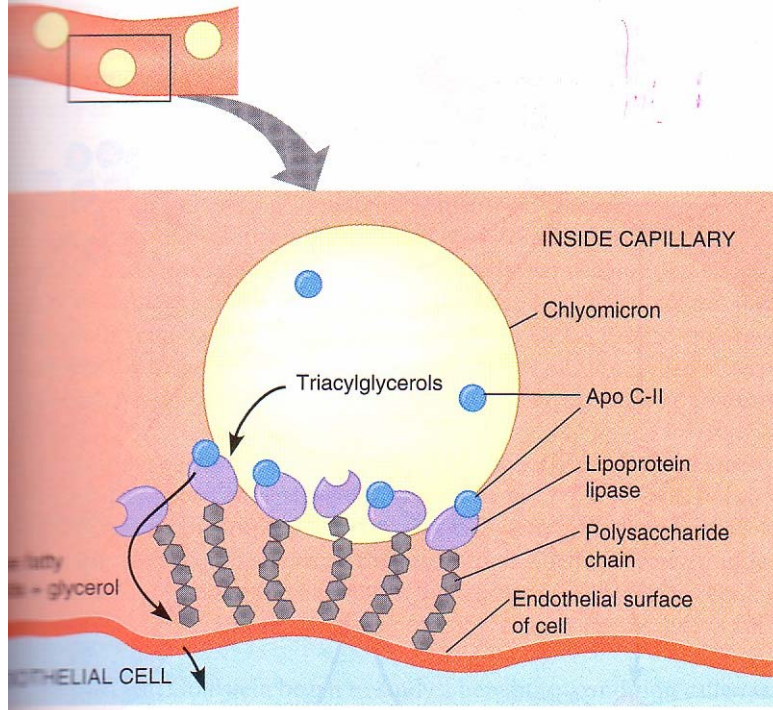
Chylomicrons

Dietary lipids are carried from the intestinal mucosa cells to other tissues by lipoproteins called chylomicrons. Chylomicrons are large and have the lowest protein to lipid ratio and hence have the lowest density of all the lipoproteins. Chylomicrons contain phospholipids and proteins on the surface so that the hydrophilic surfaces are in contact with water. The hydrophobic molecules are enclosed in the interior. The principle apoproteins of nascent chylomicrons are apo B-48, apo A-I, apo A-II and apo A-IV. In circulation, the nascent chylomicrons acquire apo-C and apo-E from plasma HDL in exchange for phospholipids. The acquisition of apo-CII from HDL is essential to activate lipoprotein lipase, LPL. Chylomicrons bind to membrane bound lipoprotein lipases (LPLs) located on adipose and muscle tissues where the triacylglycerols are hydrolyzed into fatty acids. The fatty acids are transported into the adipose



cell where they are once again resynthesized into triacylglycerols and stored. In the muscle, the fatty acids are oxidized to provide energy. As the tissues absorb the fatty acids, the chylomicrons progressively shrink until they are reduced down to cholesterol enriched remnants. As the chylomicron shrinks it transfers a substantial portion of its phospholipids and apoproteins A and C to HDL. The apo C proteins are continuously recycled between chylomicrons and HDL. The remnants lacking apo A and C proteins do not bind to the LPLs in the capillaries. The remnants are rapidly absorbed by the liver.

Lipoprotein Lipases



Chylomicrons bind to Lipoprotein Lipases located in the capillaries of the tissues. Apo-CII is required to activate the LPLs. The LPLs hydrolyze the fatty acid ester bonds liberating glycerol and free fatty acids. The fatty acids are absorbed by the endothelial cells that line the capillary.

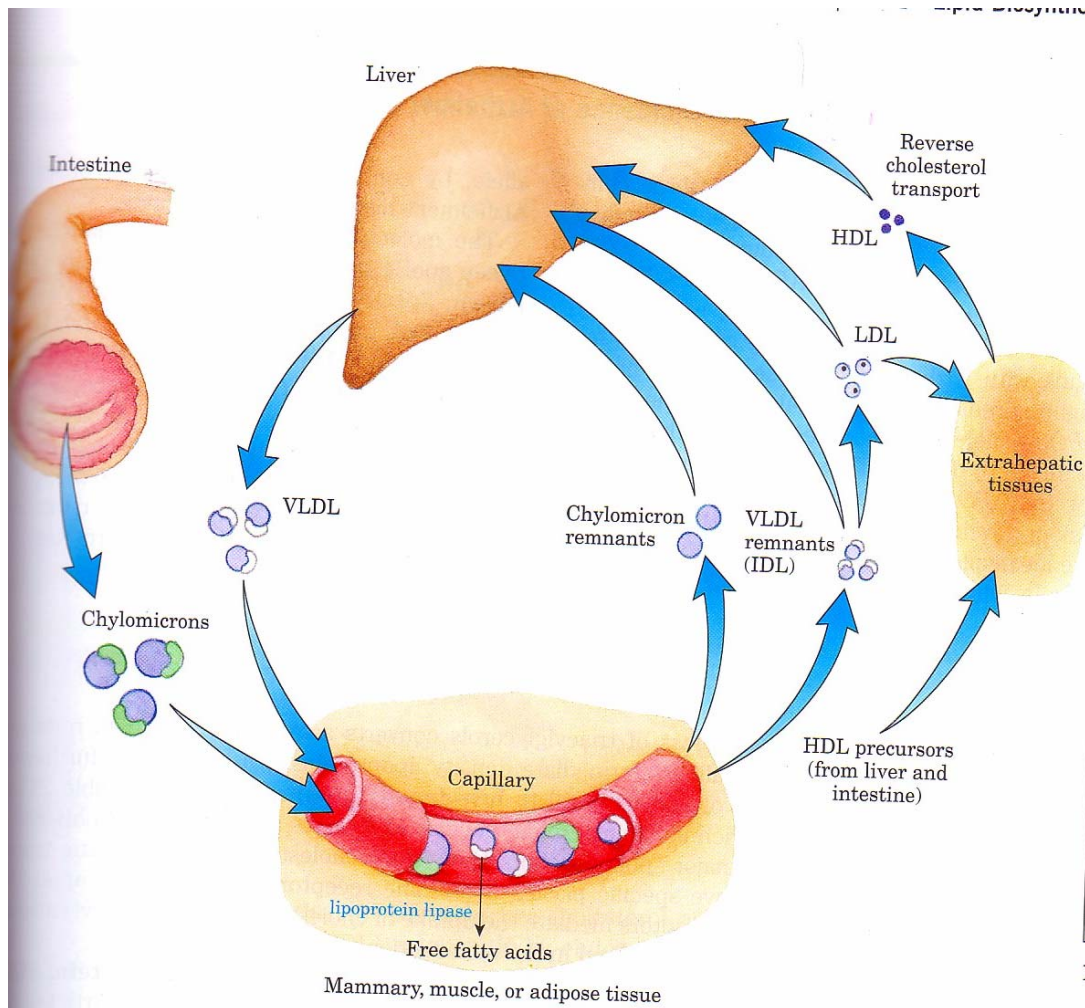
LPL is serine esterase that is found primarily in muscle and adipose tissue.

LPL is secreted out of the cell and is translocated to the luminal surface of the endothelial cells lining the capillary where it is attached to heparin sulfate.

LPL is the major enzyme involved in the processing of chylomicrons and VLDLs.

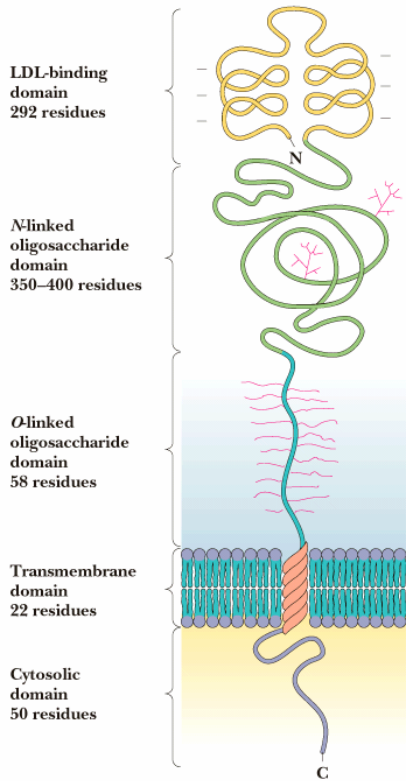
Human Apoproteins

Apoprotein	Lipoprotein Classes	Function
A-I	Chylomicrons, HDL	Activates LCAT
A-II	Chylomicrons, HDL	Inhibits LCAT, enhances hepatic lipase activity.
A-IV	Chylomicron	Unknown function
B-100	VLDL, IDL, LDL	Necessary for binding to cell receptors, LPLs.
B-48	Chylomicron	Necessary for binding to cell receptors, LPLs.
C-I	Chylomicron, VLDL, HDL	Cofactor for LCAT
C-II	Chylomicron, VLDL, HDL	Activates LPL
C-III	Chylomicron, VLDL, HDL	Regulates LPL
D	HDL	Essential for LCAT activity and Cholesteryl ester transfer.
E	All	Binds to specific cell receptors.



Very Low Density Lipoproteins

The liver synthesizes fatty acids and cholesterol and packages them for transport in the blood plasma in VLDLs. Normally the cholesterol is unesterified and found as a surface component of the lipoprotein. A high cholesterol diet alters the composition of the VLDL with cholesteryl esters substituting for triacylglycerols as the primary constituent of the lipid core. The primary apoprotein is B-100. The liver secretes VLDLs via exocytosis. Like chylomicrons, VLDLs undergo constant changes in the plasma. First, the nascent VLDL acquires apo C and E from HDL. VLDLs bind to the same membrane bound lipoprotein lipases (LPLs) located on adipose and muscle tissues where the triacylglycerols are hydrolyzed into fatty acids. The fatty acids are transported into the adipose cell where they are once again resynthesized into triacylglycerols and stored. In the muscle, the fatty acids are oxidized to provide energy. As the tissues absorb the fatty acids and monoacylglycerols, the VLDLs progressively shrink forming IDLs. As the VLDL shrinks it transfers a substantial portion of its phospholipids and apoprotein C to HDL. IDLs can bind to receptors of liver cells where they are absorbed in an analogous manner to chylomicrons, or they can be further catabolized by LPLs, eventually losing apo-E to form LDL. LDL is a cholesterol rich lipoprotein which contains almost exclusively apo B-100. LDL is the principal plasma cholesterol carrier. The concentration of LDLs positively correlates with the incidence of coronary heart disease. Hence, LDL is commonly called the **bad cholesterol** when LDL is actually the carrier of plasma cholesterol to the tissues. LDL serves as a source of cholesterol for most tissues of the body. High levels of LDL are associated with the formation of atherosclerotic plaques that occlude blood vessels causing heart attacks and strokes.

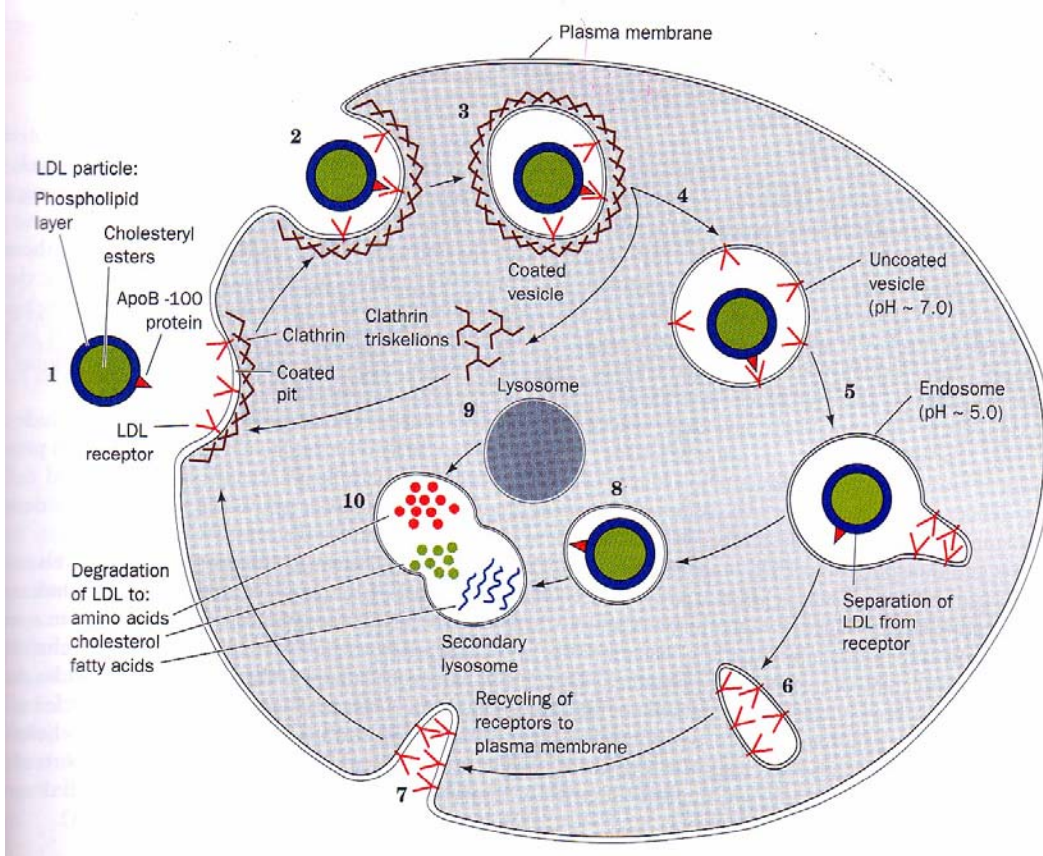


Low Density Lipoproteins

LDLs bind to specific cell receptors located on the plasma membrane of target cells. The LDL receptor (Shown to the left) is a glycoprotein which contains a domain with negatively charged residues. This LDL binding domain has electrostatic interactions with the positively charged arginine and lysine residues of apo-B100.

The LDL receptors migrate to areas of the plasma membrane specialized for endocytosis called coated pits. They are called coated pits because of the **clathrin protein** coat on the cytoplasmic side of the membrane. Once the LDL binds to the receptor, the clathrin proteins promote endocytosis. Once the vesicle is inside of the cell, the clathrin spontaneously dissociates from the endosomal vesicle. The pH of the vesicle is lowered such that LDL dissociates from the receptor. The LDL receptors are recycled to the cell surface. The vesicle fuses with a lysosome which then degrades the lipoprotein to its primary components, fatty acids, glycerol, cholesterol and amino acids. The cholesterol is incorporated into the intracellular cholesterol pool which is used for membrane

or steroid synthesis.



The liver also absorbs LDLs by the same endocytosis mechanism. Approximately 75% of the LDLs are absorbed by the liver.

Hypercholesterolemias

Familial hypercholesterolemia is a genetic disease caused by a defective LDL-receptor. There are five classes of mutations that have been identified with the disease.

1. The receptor is not synthesized at all.
2. The receptor is not transported to the surface of the cell.
3. The receptor fails to bind LDL.
4. The receptor fails to cluster in the clathrin coated pits.
5. The receptor may fail to release LDL in the endosome.

Deficiencies of the LDL receptor results in increased concentration of LDL.

Having one gene that produces an abnormal LDL receptor is called **heterozygous** familial hypercholesterolemia. One out of every 500 individuals has heterozygous familial hypercholesterolemia. Heterozygous familial hypercholesterolemia results in half of the LDL receptors being defective. Individuals with heterozygous familial hypercholesterolemia have normal concentrations of triacylglycerols and HDL levels, but their LDL cholesterol levels are typically between 320 -500 mg/dL which is more than 3 times normal (100 – 120 mg/dL). More than half of these individuals will experience coronary artery disease in their thirties or forties. One out of every one million individuals is homozygous for familial hypercholesterolemia (Both genes defective). In these cases, the cholesterol levels are between 600 to 1,200 mg/dL. The onset of coronary heart disease for these individuals occurs before the age of 10.

High Density Lipoproteins

HDLs are secreted by liver and intestinal cells. The nascent HDLs are disk shaped, but they become spherical as they acquire free cholesterol from cell membranes and triacylglycerols from other lipoproteins. The primary function of HDLs is to remove excess cholesterol and carry the excess to the liver to be metabolized into bile salts. This function of cholesterol removal from the tissues underlies the inverse relationship between the plasma concentration of HDLs and the incidence of heart diseases. HDL is commonly called the **good cholesterol** when HDL is actually the transporter of plasma cholesterol back to the liver. HDL contains enzymes that either esterify cholesterol or transfer cholesteryl esters.

Lechithin-cholesterol transferase (LCAT) is a peripheral enzyme that circulates with HDL. LCAT catalyzes the transfer of long chain fatty acids from phospholipids to cholesterol to form cholesteryl esters. Cholesteryl esters occupy the lipid core of the HDL. LCAT thus facilitates the storage and transport of excess cholesterol. LCAT is activated by apo A-I. Cholesteryl esters are exchanged between lipoproteins via a process that is mediated by **cholesteryl ester transfer protein (CETP)** which is another peripheral protein that circulates with HDL.

CETP promotes the net transfer of cholesterol esters from HDL to LDL, IDL and VLDL in exchange triacylglycerols. This process transforms VLDLs and IDLs into LDLs. As the HDLs grow in size they acquire apo-E which increases the binding affinity of the HDL towards receptors in the liver. The HDL is then absorbed and catabolized by the liver.

Functions of HDL

- Transfers apoproteins to other lipoproteins.
- Picks up lipids from other lipoproteins.
- Picks up cholesterol from cell membranes.
- Converts cholesterol to cholesteryl esters via the LCAT reaction.

- Transfers cholesteryl esters to other lipoproteins via CETP. These other lipoproteins transport the cholesteryl esters to the liver.

TABLE 26.1 Properties of plasma lipoproteins

Lipoproteins	Major core lipids	Apoproteins	Mechanism of lipid delivery
Chylomicron	Dietary triacylglycerols	B-48, C, E	Hydrolysis by lipoprotein lipase
Chylomicron remnant	Dietary cholesterol esters	B-48, E	Receptor-mediated endocytosis by liver
Very low density lipoprotein (VLDL)	Endogenous triacylglycerols	B-100, C, E	Hydrolysis by lipoprotein lipase
Intermediate-density lipoprotein (IDL)	Endogenous cholesterol esters	B-100, E	Receptor-mediated endocytosis by liver and conversion into LDL
Low-density lipoprotein (LDL)	Endogenous cholesterol esters	B-100	Receptor-mediated endocytosis by liver and other tissues
High-density lipoprotein (HDL)	Endogenous cholesterol esters	A	Transfer of cholesterol esters to IDL and LDL

Source: After M. S. Brown and J. L. Goldstein, *The Pharmacological Basis of Therapeutics*, 7th ed., A. G. Gilman, L. S. Goodman, T. W. Rall, and F. Murad, Eds. (Macmillan, 1985), p. 828.

Typical values for HDL, LDL

for males, females 15-29

- Cholesterol: females - 157-167, males - 150-174
- HDL: females - 52-55, males 45
- LDL: females - 100-106, males 97-116
- However, with age, total cholesterol rises, and HDLs may fall, so exercise and diet become keys.
- **Regular, vigorous exercise** raises HDLs and **a low fat diet** that avoids red meat reduces serum cholesterol levels.