دانشگاه کردستان
University of Kurdistan
زانکۆی کوردستان

Metabolism Regulation 7

Lipoprotein Metabolism

Ref: Keith N. Frayn. Metabolic Regulation: A Human Perspective. 3rd Edition. Wiley Blackwell, 2010. Chapter 10.

Introduction to Lipoprotein Metabolism

- Non-esterified fatty acids are carried in the plasma bound to albumin.
- The transport of both triacylglycerol and cholesterol occurs in specialized macromolecular structures known as **lipoproteins**. Because triacylglycerol and cholesterol are carried by the same system, the metabolism of these two lipids in the plasma is closely interrelated. Some fat-soluble vitamins are also transported by the lipoprotein system (especially Vitamin E).
- The lipoproteins have a lipid, highly hydrophobic interior (core) and a relatively hydrophilic outer surface. A typical lipoprotein particle (Figure 10.1) consists of a core of triacylglycerol and cholesteryl ester, with an outer surface monolayer of phospholipid and free cholesterol. Each lipoprotein particle has associated with it one or more protein molecules, the apolipoproteins. These proteins have hydrophobic domains, which "dip into" the core and anchor the protein to the particle, and also hydrophilic domains that are exposed at the surface.
- The chylomicron and VLDL particles are relatively rich in triacylglycerol and are often referred to together as the triacylglycerol-rich lipoproteins; they are mainly concerned with delivery of triacylglycerol to tissues. The smaller LDL and HDL particles, on the other hand, are more involved with transport of cholesterol to and from cells.

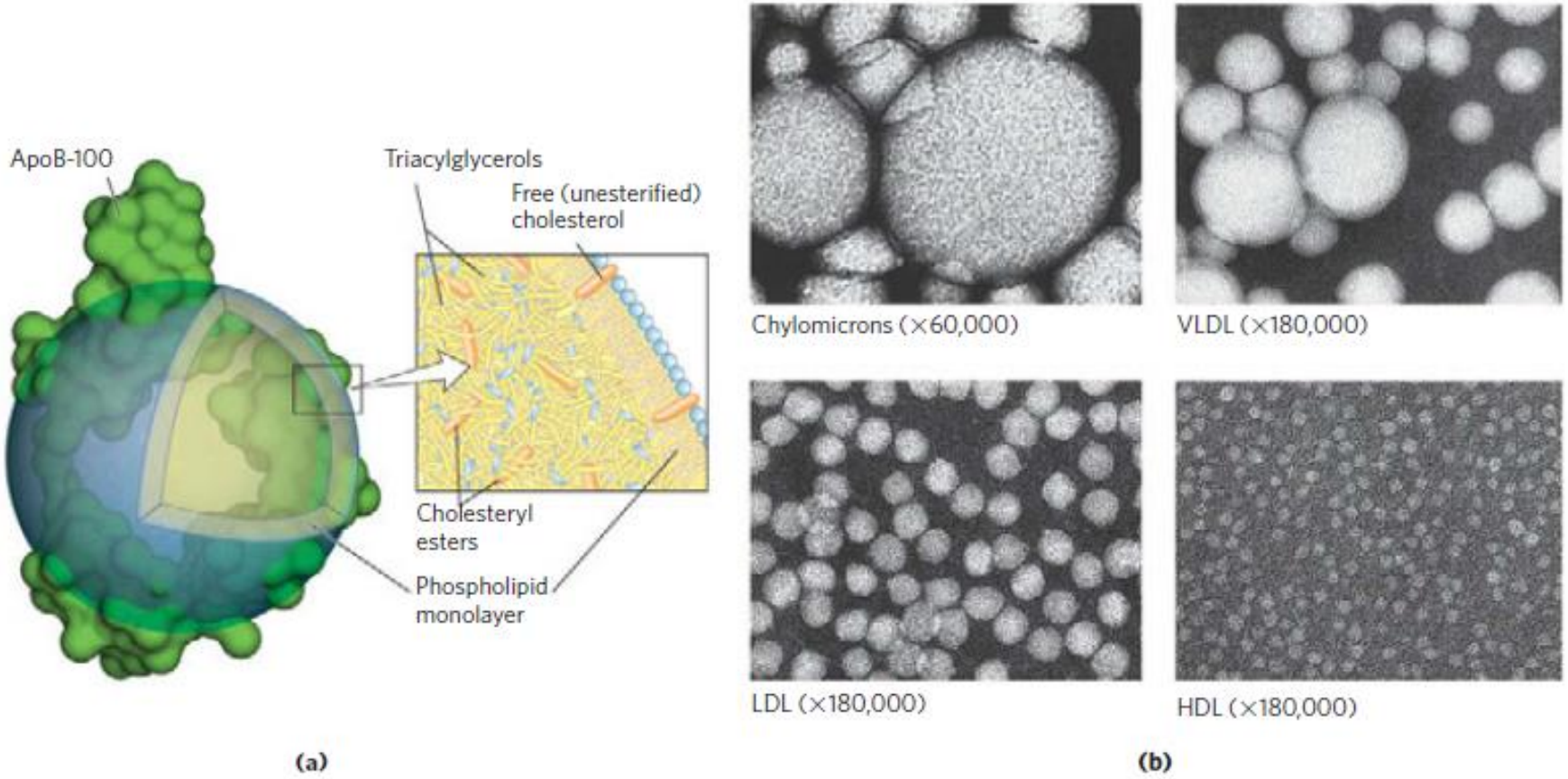
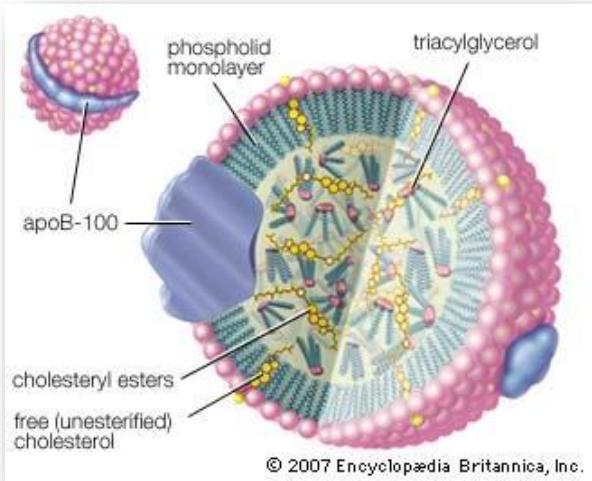


FIGURE 21–39 Lipoproteins. (a) Structure of a low-density lipoprotein (LDL). Apolipoprotein B-100 (apoB-100) is one of the largest single polypeptide chains known, with 4,636 amino acid residues (M_r 512,000). One particle of LDL contains a core with about 1,500 molecules of cholesteryl esters, surrounded by a shell composed of about 500 more molecules of cholesterol, 800 molecules of phospholipids, and one molecule of apoB-100. **(b)** Four classes of lipoproteins, visualized in the electron microscope after negative staining. Clockwise from top left: chylomicrons, 50 to 200 nm in diameter; VLDL, 28 to 70 nm; HDL, 8 to 11 nm; and LDL, 20 to 25 nm. The particle sizes given are those measured for these samples; particle sizes vary considerably in different preparations. For properties of lipoproteins, see Table 21–1.



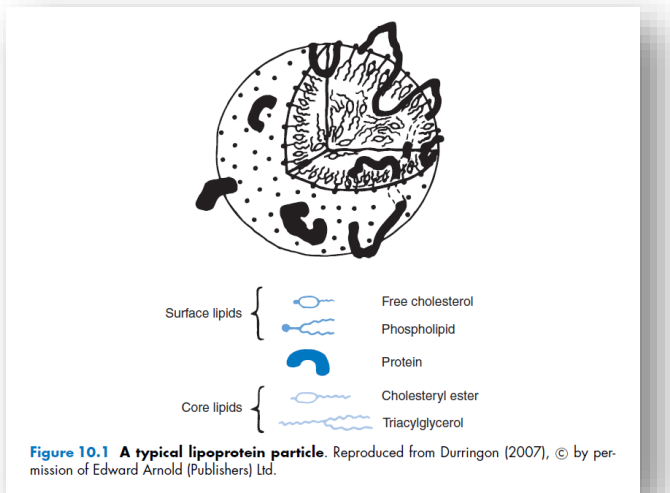


Figure 10.1 A typical lipoprotein particle. Reproduced from Durrington (2007), © by permission of Edward Arnold (Publishers) Ltd.

TABLE 21–1 Major Classes of Human Plasma Lipoproteins: Some Properties

Lipoprotein	Density (g/mL)	Composition (wt %)				
		Protein	Phospholipids	Free cholesterol	Cholesteryl esters	Triacylglycerols
Chylomicrons	<1.006	2	9	1	3	85
VLDL	0.95–1.006	10	18	7	12	50
LDL	1.006–1.063	23	20	8	37	10
HDL	1.063–1.210	55	24	2	15	4

Source: Modified from Kritchevsky, D. (1986) Atherosclerosis and nutrition. *Nutr. Int.* 2, 290–297.

TABLE 21–2 Apolipoproteins of the Human Plasma Lipoproteins

Apolipoprotein	Polypeptide molecular weight	Lipoprotein association	Function (if known)
ApoA-I	28,100	HDL	Activates LCAT; interacts with ABC transporter
ApoA-II	17,400	HDL	Inhibits LCAT
ApoA-IV	44,500	Chylomicrons, HDL	Activates LCAT; cholesterol transport/clearance
ApoB-48	242,000	Chylomicrons	Cholesterol transport/clearance
ApoB-100	512,000	VLDL, LDL	Binds to LDL receptor
ApoC-I	7,000	VLDL, HDL	
ApoC-II	9,000	Chylomicrons, VLDL, HDL	Activates lipoprotein lipase
ApoC-III	9,000	Chylomicrons, VLDL, HDL	Inhibits lipoprotein lipase
ApoD	32,500	HDL	
ApoE	34,200	Chylomicrons, VLDL, HDL	Triggers clearance of VLDL and chylomicron remnants

Source: Modified from Vance, D.E. & Vance, J.E. (eds) (2008) *Biochemistry of Lipids and Membranes*, 5th edn, Elsevier Science Publishing.

Some Important Enzymes Involved in Lipoprotein Metabolism

- Lipoprotein Lipase (LPL): This enzyme is found in a number of tissues outside the liver, particularly adipose tissue, skeletal muscle, and heart muscle. It is synthesized within the cells of the tissue (e.g., the adipocytes or the muscle fibers) and exported to the capillaries, where it is attached to the endothelial cells. Here it is bound (non-covalently) to highly negatively charged glycosaminoglycan chains, such as heparan sulfate. LPL acts on lipoprotein particles passing through the capillaries, hydrolyzing triacylglycerol molecules to release non-esterified fatty acids, which may be taken up into the tissue for esterification (and hence storage – mainly in adipose tissue) or oxidation (in muscle). It can only do this if the particles contain apolipoprotein CII. LPL activity in adipose tissue is stimulated by insulin, over a relatively long time (a few hours). In muscle it is slightly suppressed by insulin but its activity is increased by exercise (both acutely and by training).
- Lecithin-Cholesterol Acyl Transferase (LCAT): This enzyme comes from the liver and is found in the plasma. It associates with particles containing apolipoprotein AI (which activates it). It transfers a fatty acid from position 2 of the phospholipid phosphatidylcholine (present in HDL particles) to unesterified cholesterol, forming a cholesteryl ester. The remaining lysophosphatidylcholine is transferred to plasma albumin from which it is rapidly removed from blood and reacylated.
- Acyl-Coenzyme A: Cholesterol Acyltransferase (ACAT): There are two isoforms, ACAT1 and ACAT2. These are intracellular enzymes responsible for the synthesis of cholesteryl esters from cholesterol and acyl-CoA. They are responsible for esterification of dietary cholesterol within the enterocyte (for package into the chylomicron), formation of cholesteryl ester droplets for storage within cells, and providing cholesteryl esters for VLDL secretion from the liver. ACAT1 is widely expressed, whereas ACAT2 is mainly expressed in the enterocytes of the small intestine and in the liver. There has been considerable interest in the possibility of inhibition of ACAT2 by drugs to reduce cholesterol absorption.

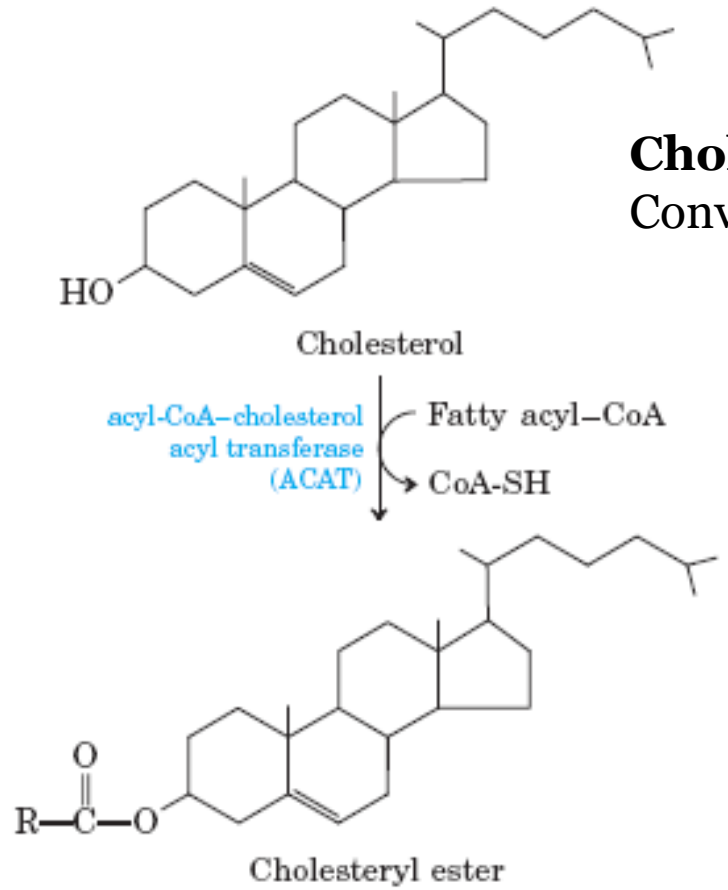


FIGURE 21–38 **Synthesis of cholesteryl esters.** Esterification converts cholesterol to an even more hydrophobic form for storage and transport.

Cholesterol Has Several Fates

Convert to Cholesteryl esters (CE): storage, transport

Lipoproteins

Cholesterol and Other Lipids Are Carried on Plasma Lipoproteins

Lipoprotein = Lipid + Protein

Lipid= phospholipid, cholestrol, cholesteryl ester (CE), TG

Protein = Apolipoprotein

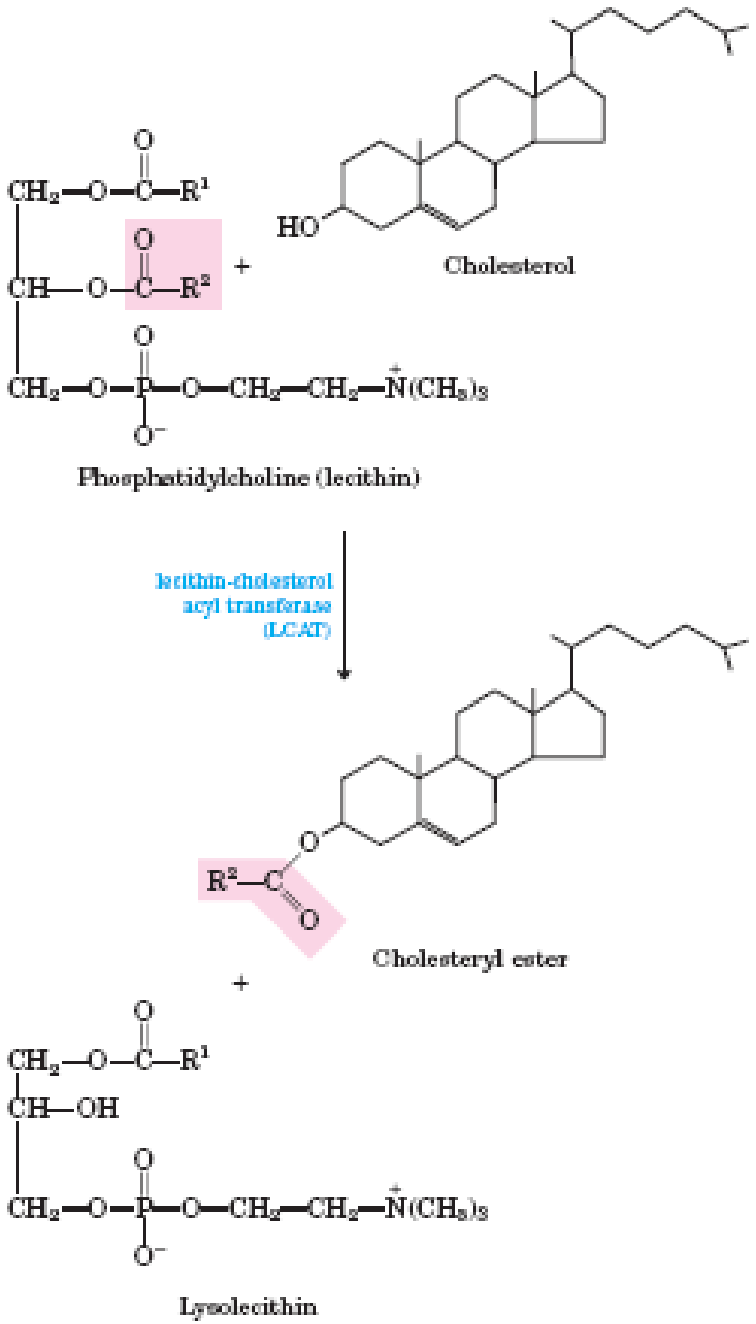
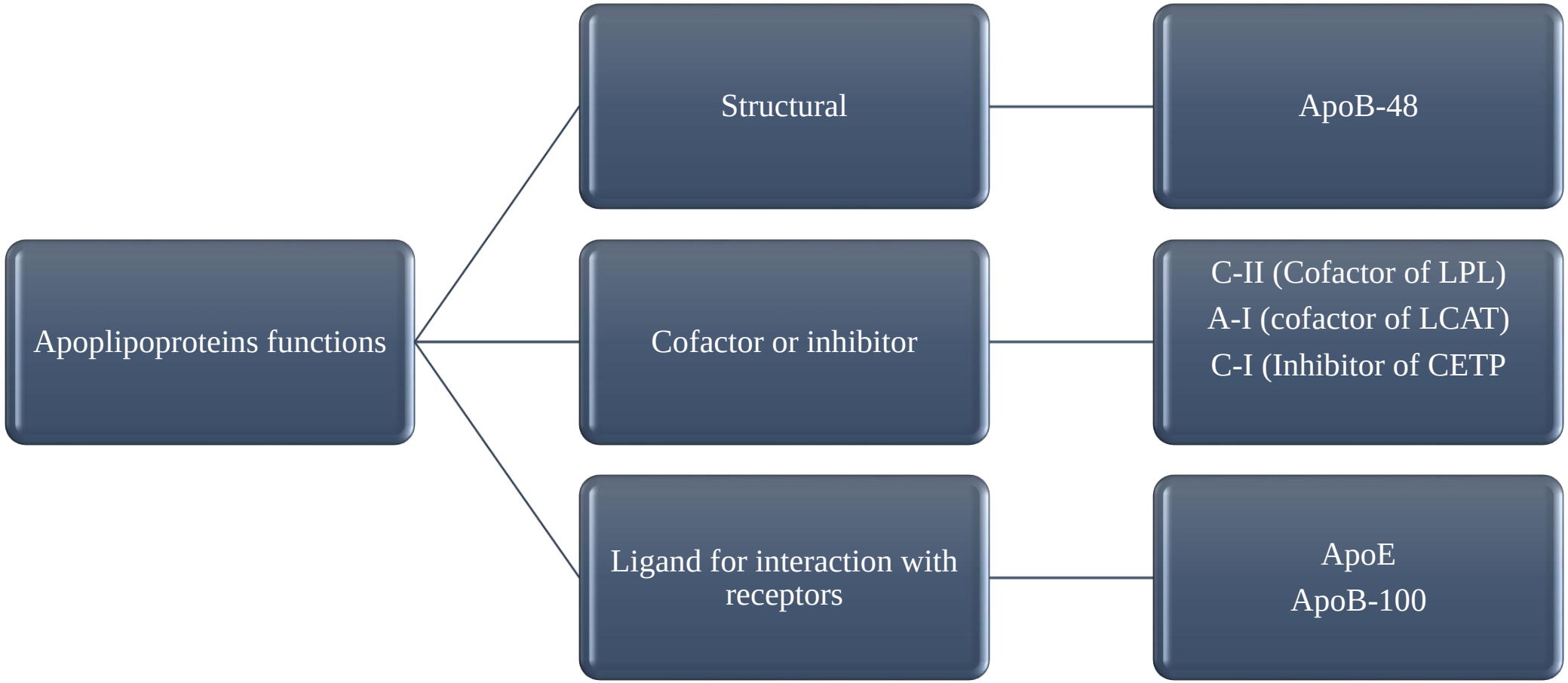


FIGURE 21–41 Reaction catalyzed by lecithin-cholesterol acyl transferase (LCAT). This enzyme is present on the surface of HDL and is stimulated by the HDL component apoA-I. Cholesteryl esters accumulate within nascent HDLs, converting them to mature HDLs.


Apoplipoproteins functions
Structural
ApoB-48
Cofactor or inhibitor
C-II (Cofactor of LPL)
A-I (cofactor of LCAT)
C-I (Inhibitor of CETP
Ligand for interaction with receptors
ApoE
ApoB-100

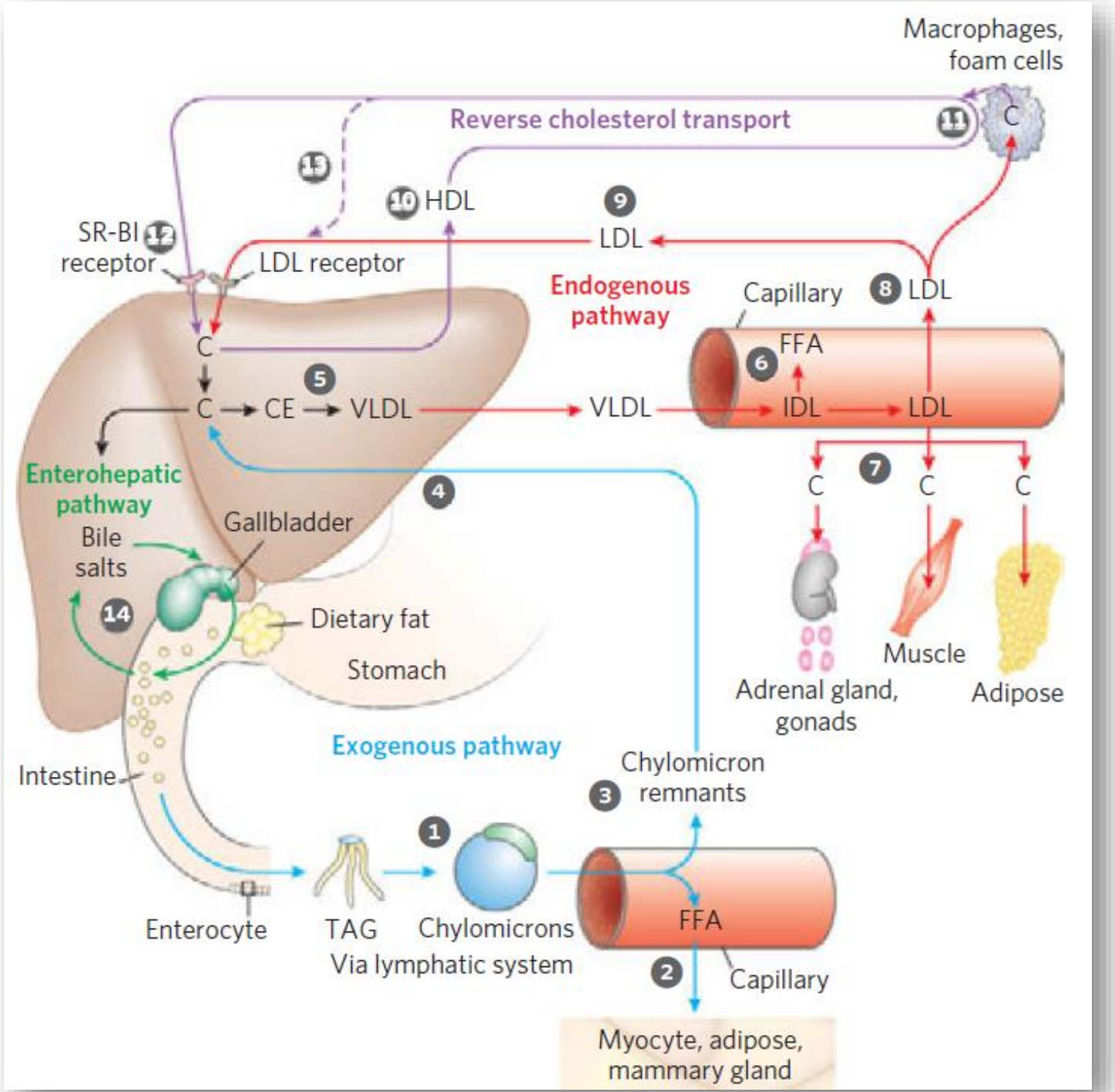
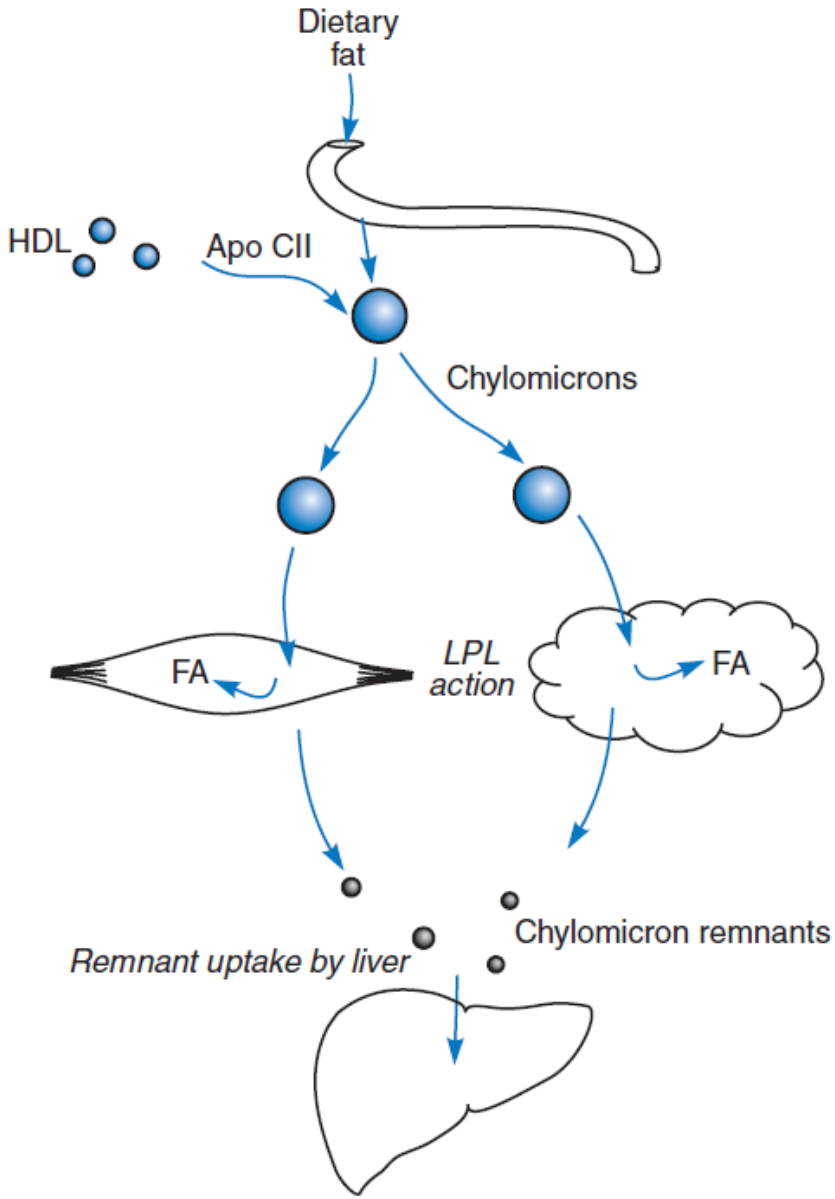


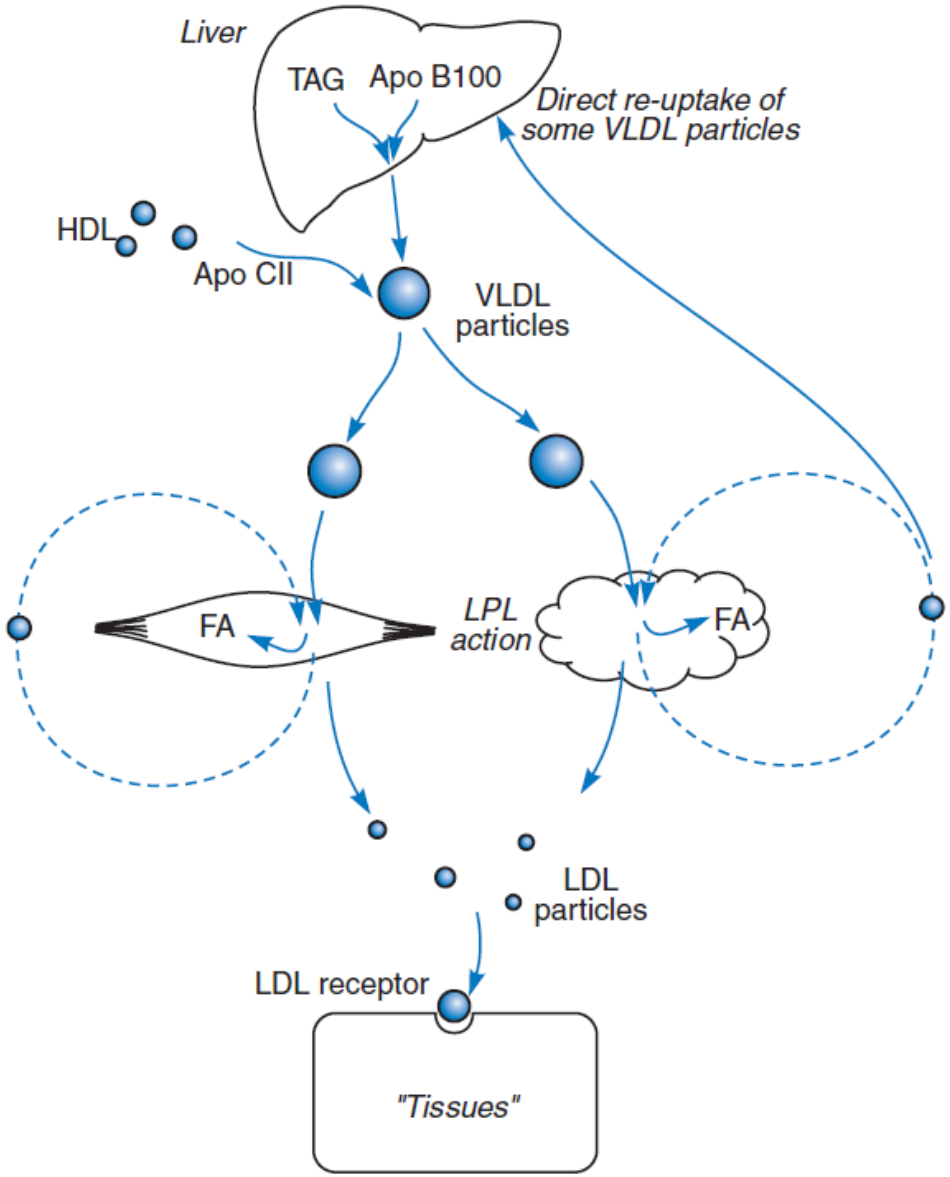
FIGURE 21-40 Lipoproteins and lipid transport. Lipids are transported in the bloodstream as lipoproteins, which exist as several variants that have different functions, different protein and lipid compositions, and thus different densities. Numbered steps are described in the text. In the exogenous pathway (blue arrows), dietary lipids are packaged into chylomicrons; fatty acids from triacylglycerol (TAG) are released by lipoprotein lipase to adipose and muscle tissues, during transport through capillaries. Chylomicron remnants (containing largely protein and cholesterol) are taken up by the liver. Bile salts produced in the liver aid in dispersing dietary fats and are then reabsorbed in the enterohepatic pathway (green arrows). In the endogenous pathway (red arrows), lipids synthesized or packaged in the liver are delivered to peripheral tissues by VLDL. Extraction of lipid from VLDL (along with loss of some apolipoproteins) gradually converts some of it to LDL, which delivers cholesterol to extrahepatic tissues or returns to the liver. Excess cholesterol in extrahepatic tissues is transported back to the liver as HDL in reverse cholesterol transport (purple arrows). C represents cholesterol; CE, cholesteryl ester.

Chylomicrons, are the largest of the lipoproteins and the least dense, containing a high proportion of triacylglycerols. **1** Chylomicrons are synthesized from dietary fats in the ER of enterocytes, epithelial cells that line the small intestine. The chylomicrons then move through the lymphatic system and enter the bloodstream via the left subclavian vein. The apolipoproteins of chylomicrons include apoB-48 (unique to this class of lipoproteins), apoE, and apoC-II. **2** ApoC-II activates lipoprotein lipase in the capillaries of adipose, heart, skeletal muscle, and lactating mammary tissues, allowing the release of free fatty acids (FFA) to these tissues. Chylomicrons thus carry dietary fatty acids to tissues where they will be consumed or stored as fuel. **3** The remnants of chylomicrons, depleted of most of their triacylglycerols but still containing cholesterol, apoE, and apoB-48, move through the bloodstream to the liver. Receptors in the liver bind to the apoE in the chylomicron remnants and mediate uptake of these remnants by endocytosis. **4** In the liver, the remnants release their cholesterol and are degraded in lysosomes. This pathway from dietary cholesterol to the liver is the exogenous pathway (blue arrows in Fig. 21-40). When the diet contains more fatty acids and cholesterol than are needed immediately as fuel or precursors to other molecules, **5** they are converted to triacylglycerols or cholesteryl esters in the liver and packaged with specific apolipoproteins into very-low-density lipoprotein (VLDL). Excess carbohydrate in the diet can also be converted to triacylglycerols in the liver and exported as VLDL. In addition to triacylglycerols and cholesteryl esters, VLDL contains apoB-100, apoC-I, apoC-II, apoC-III, and apoE. VLDL is transported in the blood from the liver to muscle and adipose tissue. **6** In the capillaries of these tissues, apoC-II activates lipoprotein lipase, which catalyzes the release of free fatty acids from triacylglycerols in the VLDL. Adipocytes take up these fatty acids, reconvert them to triacylglycerols, and store the products in intracellular lipid droplets; myocytes, in contrast, primarily oxidize the fatty acids to supply energy. When the insulin level is high (after a meal), VLDL serves primarily to convey lipids from the diet to adipose tissue for storage. In the fasting state between meals, the fatty acids used to produce VLDL in the liver originate primarily from adipose tissue, and the principal VLDL target is myocytes of the heart and skeletal muscle.

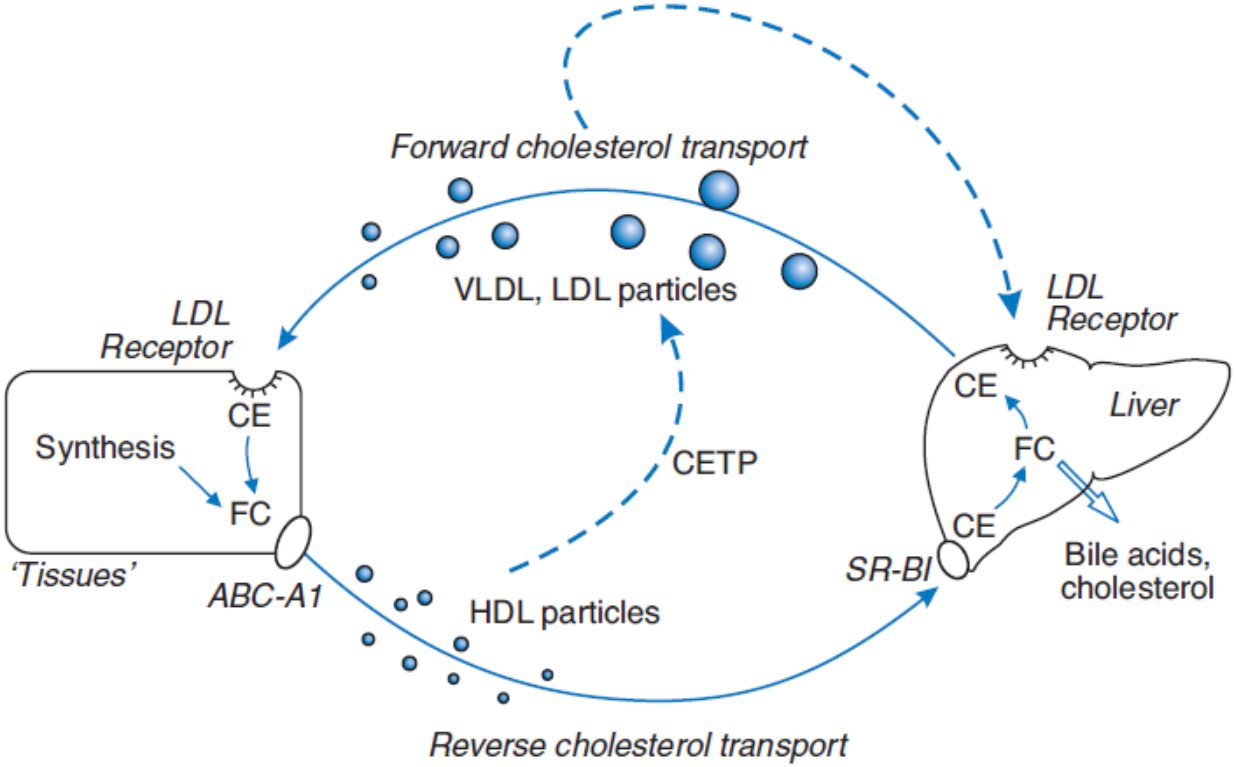
- The loss of triacylglycerol converts some VLDL to VLDL remnants, also called intermediate-density lipoprotein (IDL). Further removal of triacylglycerol from IDL (remnants) produces low-density lipoprotein (LDL). Rich in cholesterol and cholesteryl esters, and containing apoB-100 as its major apolipoprotein, **7** LDL carries cholesterol to extrahepatic tissues such as muscle, adrenal glands, and adipose tissue. These tissues have plasma membrane LDL receptors that recognize apoB-100 and mediate uptake of cholesterol and cholesteryl esters. **8** LDL also delivers cholesterol to macrophages, sometimes converting them into foam cells. **9** LDL not taken up by peripheral tissues and cells returns to the liver and is taken up via LDL receptors in the hepatocyte plasma membrane. Cholesterol that enters hepatocytes by this path may be incorporated into membranes, converted to bile acids, or reesterified by ACAT for storage within cytosolic lipid droplets. This pathway, from VLDL formation in the liver to LDL return to the liver, is the endogenous pathway of cholesterol metabolism and transport (red arrows). Accumulation of excess intracellular cholesterol is prevented by reducing the rate of cholesterol synthesis when sufficient cholesterol is available from LDL in the blood. Regulatory mechanisms to accomplish this are described below.



The exogenous pathway of lipoprotein metabolism. Apo, apolipoprotein; FA, fatty acids; LPL, lipoprotein lipase.



The endogenous pathway of lipoprotein metabolism. Particles may undergo several cycles of hydrolysis by lipoprotein lipase (LPL) in capillary beds (dashed lines), forming smaller particles which may be taken up directly by receptors in the liver; others remain in the circulation as low-density-lipoprotein (LDL) particles. These are eventually removed by uptake into tissues via the LDL receptor



Forward and reverse cholesterol transport. Cholesterol is secreted by the liver in VLDL particles; these become LDL particles after hydrolysis of their triacylglycerol by lipoprotein lipase and hepatic lipase and are taken up by tissues via the LDL receptor. A proportion of the particles will be taken up again by the liver. Cholesterol is removed from peripheral tissues by HDL particles via interaction with the receptor ABC-A1. This cholesterol is transferred to the liver by interaction with the receptor SR-BI and may be excreted in the bile. An alternative fate for the cholesterol in HDL particles is transfer via the action of cholesteryl ester transfer protein (CETP) to triacylglycerol-rich particles whose remnants thus become cholesterol-enriched. They may be taken up by receptors in the liver. This alternative route (dashed arrows) for transfer of cholesterol to the liver might be the major route in humans. CE, cholesteryl ester; FC, free cholesterol.

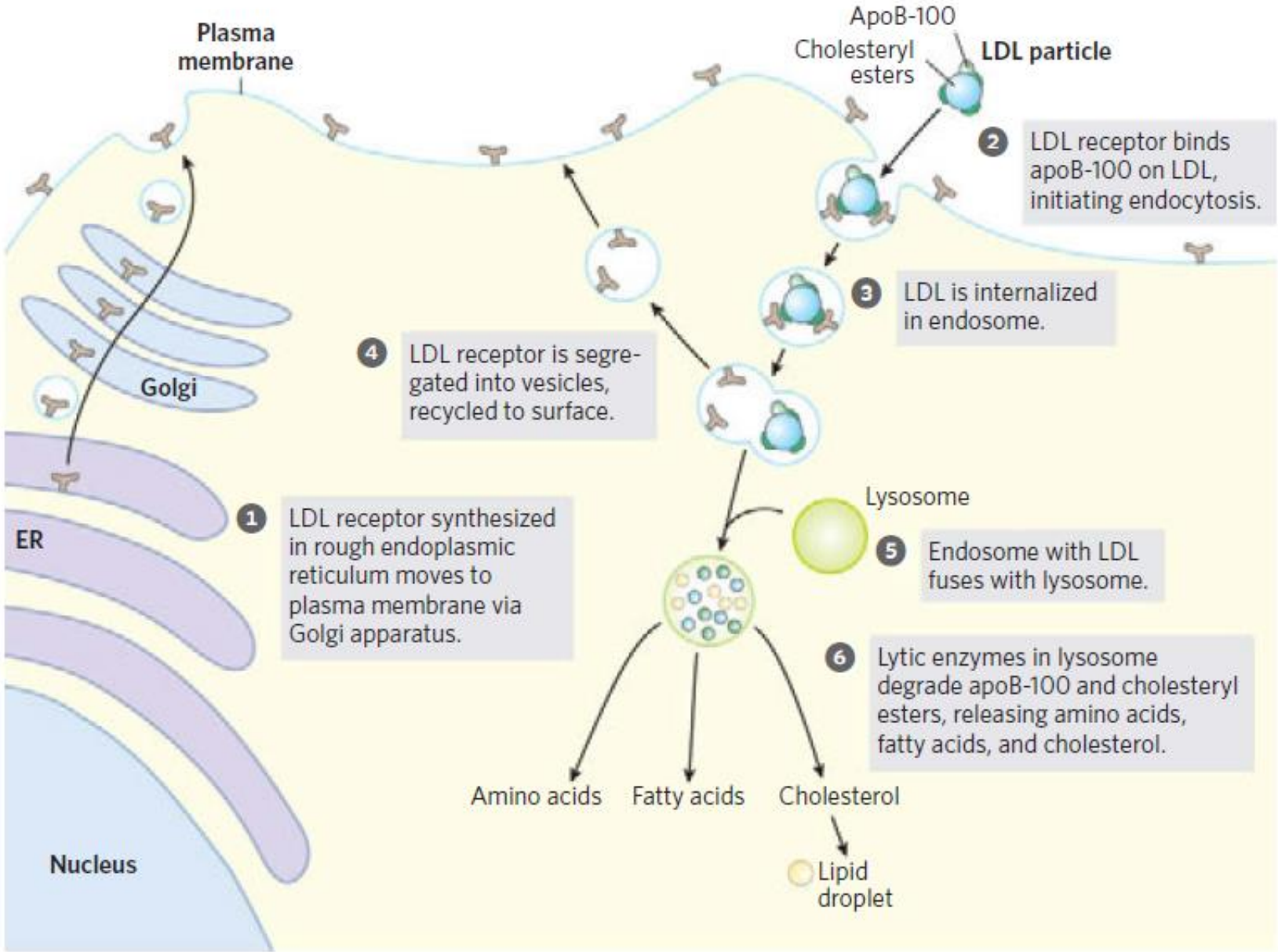
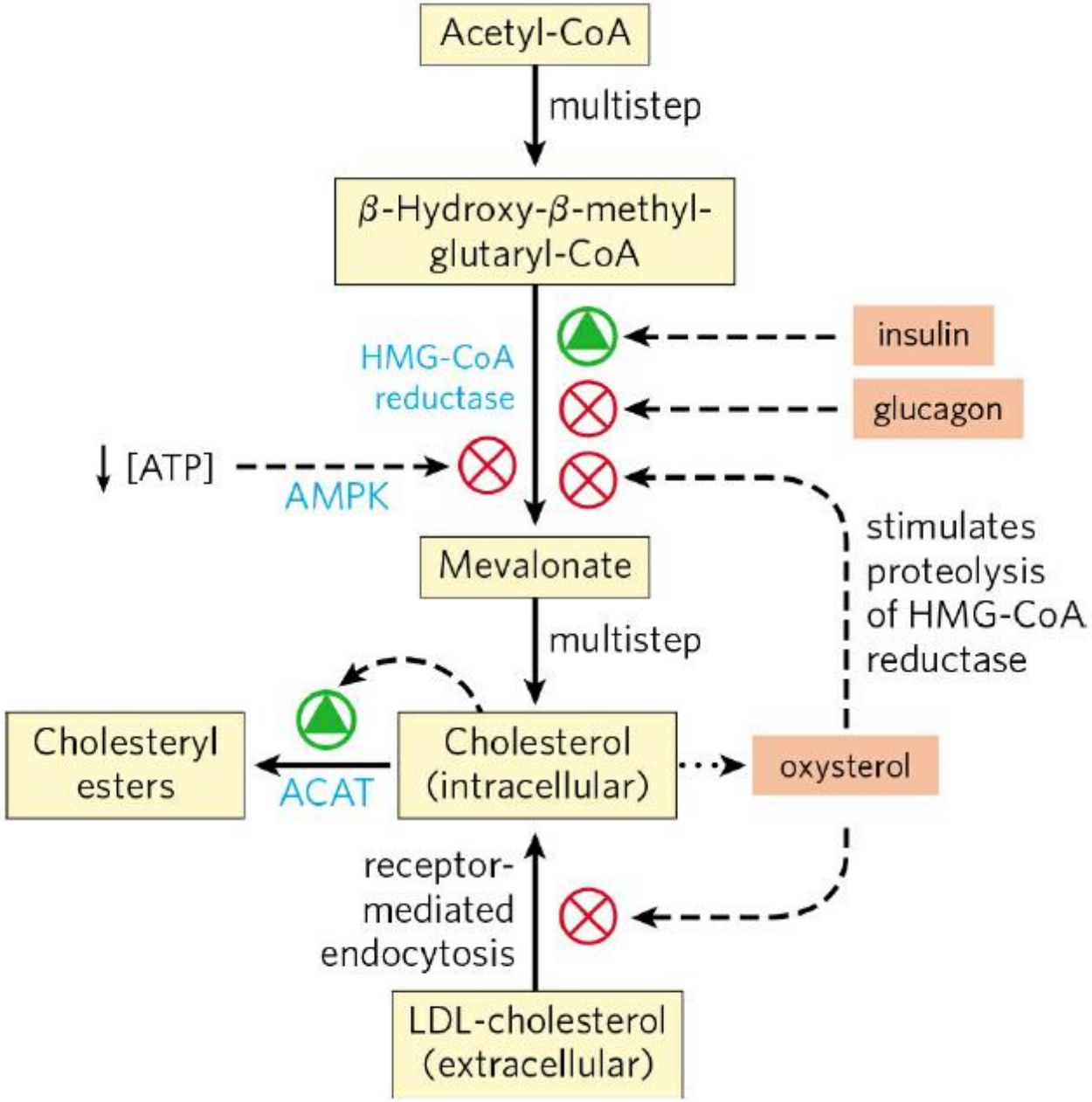
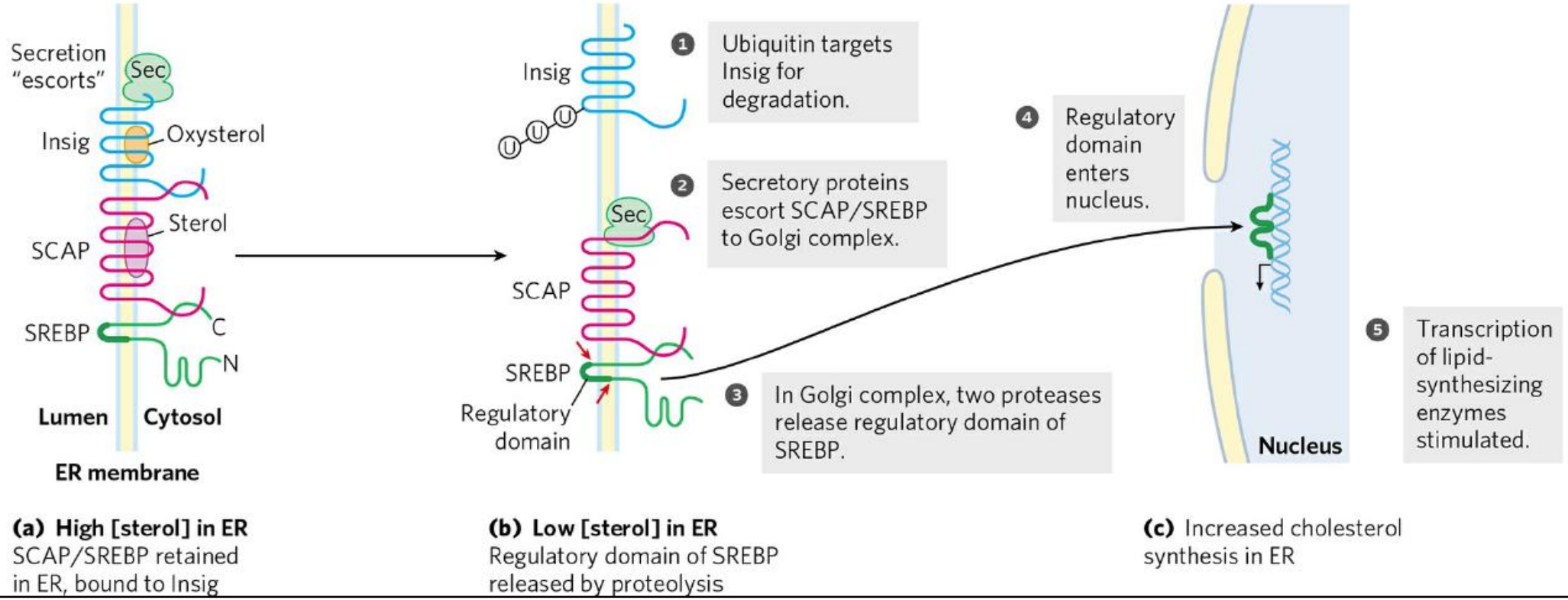


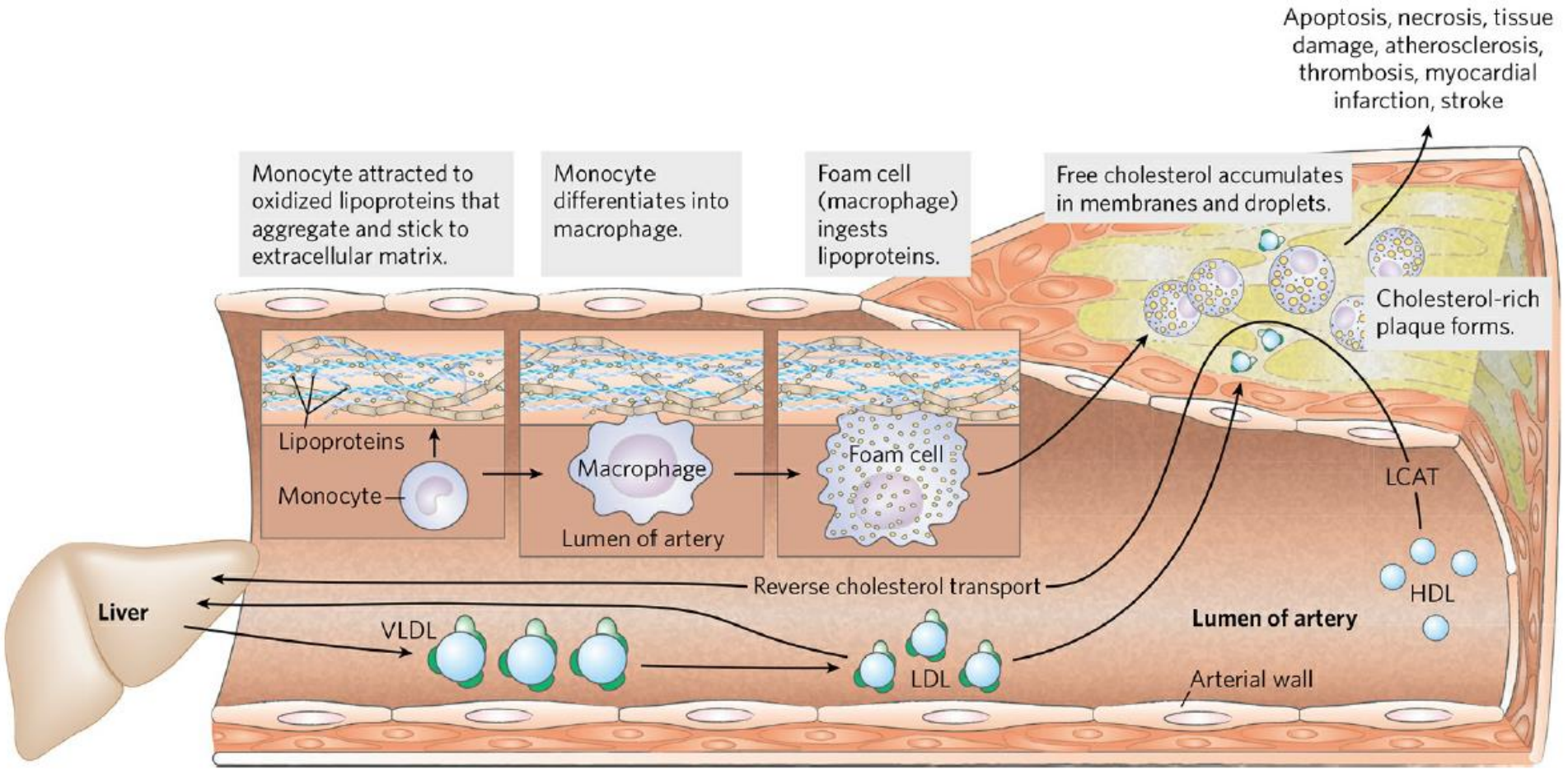
FIGURE 21–41 Uptake of cholesterol by receptor-mediated endocytosis.



Regulation of cholesterol formation balances synthesis with dietary uptake and energy state. Insulin promotes dephosphorylation (activation) of HMG-CoA reductase; glucagon promotes its phosphorylation (inactivation); and the AMP-dependent protein kinase AMPK, when activated by low [ATP] relative to [AMP], phosphorylates and inactivates HMG-CoA reductase. Oxysterol metabolites of cholesterol (for example, 24(S)-hydroxycholesterol) stimulate proteolysis of HMG-CoA reductase.



Regulation of cholesterol synthesis by SREBP. Sterol regulatory element-binding proteins (SREBPs, shown in green) are embedded in the ER when first synthesized, in a complex with the protein SREBP cleavage-activating protein (SCAP, red), which is in turn bound to Insig (blue). (N and C represent the amino and carboxyl termini of the proteins.) (a) When bound to SCAP and Insig, SREBPs are inactive. (b) When sterol levels decline, sterol-binding sites on Insig and SCAP are unoccupied, the complex migrates to the Golgi complex, and SREBP is cleaved (red arrows) to produce a regulatory domain fragment. (c) This domain acts in the nucleus to increase the transcription of sterol-regulated genes. Insig is targeted for degradation by the attachment of several ubiquitin molecules.



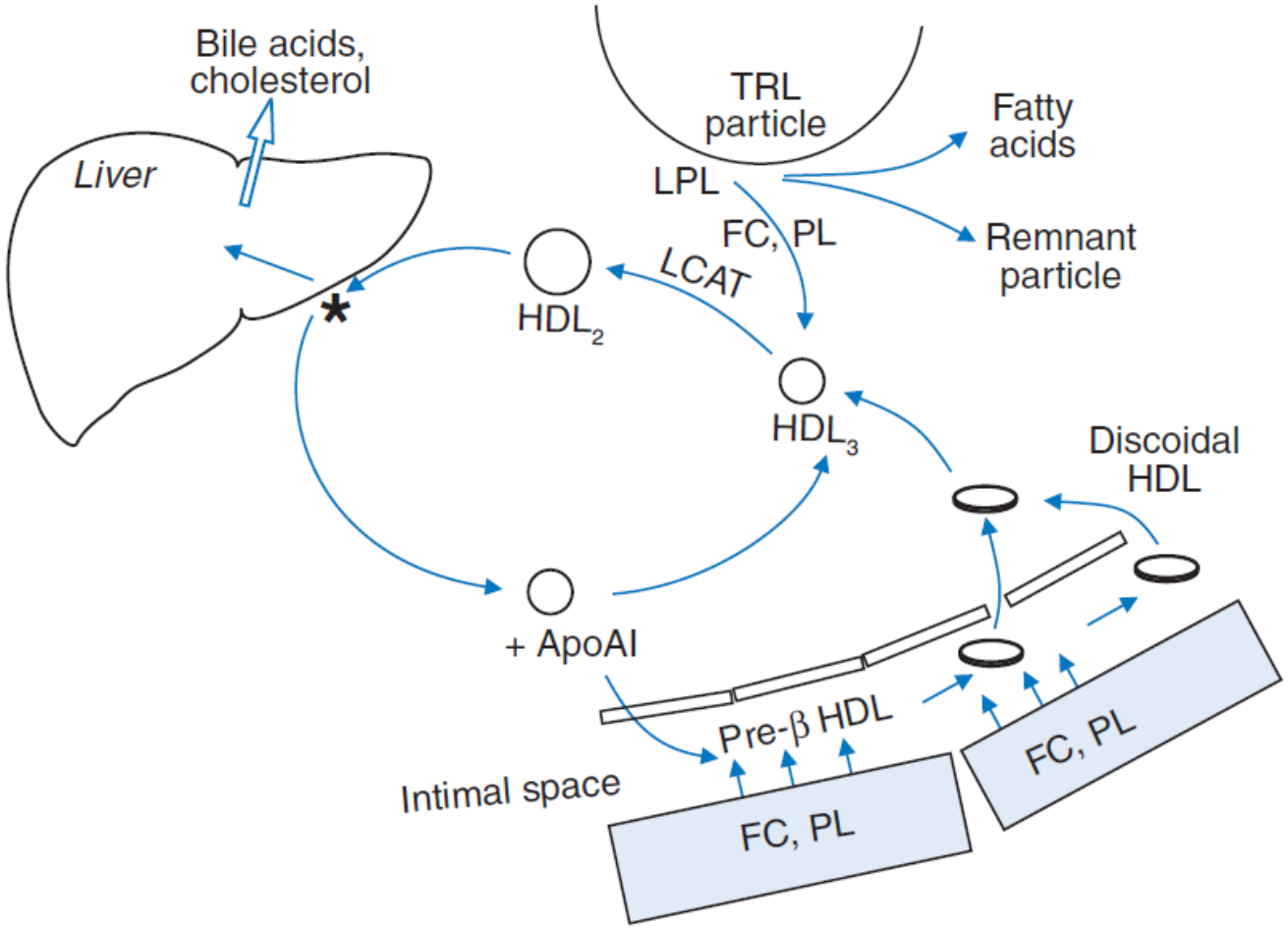
Formation of atherosclerotic plaques. Excess lipid derived from the diet is deposited on arterial walls, a process facilitated by the conversion of monocytes to foam cells and incorporation of foam cells into growing plaques. Some of this deposition is countered by HDL and reverse cholesterol transport.

- Newly secreted or “nascent” chylomicrons and VLDL contain only a small amount of apolipoproteins C and E, and the full complement is acquired from HDL in the circulation.
- Apo B is essential for chylomicron and VLDL formation. In abetalipoproteinemia (a rare disease), lipoproteins containing apo B are not formed and lipid droplets accumulate in the intestine and liver.
- The clearance of labeled chylomicrons from the blood is rapid, the half-time of disappearance being under **1 hour** in humans. Larger particles are catabolized more quickly than smaller ones.
- Fatty acids originating from *chylomicron triacylglycerol* are delivered mainly to *adipose tissue*, *heart*, and *muscle* (80%), while about 20% goes to the *liver*. However, the liver does not metabolize native chylomicrons or VLDL significantly; thus, the fatty acids in the liver must be secondary to their metabolism in extrahepatic tissues.
- *Triacylglycerols of Chylomicrons & VLDL Are Hydrolyzed by Lipoprotein Lipase*. Lipoprotein lipase is located on the walls of blood capillaries, anchored to the endothelium by negatively charged proteoglycan chains of heparan sulfate. It has been found in *heart*, *adipose tissue*, *spleen*, *lung*, *renal medulla*, *aorta*, *diaphragm*, and *lactating mammary gland*, though it is not active in adult liver. It is not normally found in blood; however, following injection of heparin, lipoprotein lipase is released from its heparin sulfate binding into the circulation. **Hepatic lipase** is bound to the sinusoidal surface of liver cells and is released by heparin. This enzyme, however, does not react readily with chylomicrons or VLDL but is concerned with chylomicron remnant and HDL metabolism.

- Both phospholipids and apo C-II are required as cofactors for lipoprotein lipase activity, while apo A-II and apo C-III act as inhibitors.
- *The Action of Lipoprotein Lipase Forms Remnant Lipoproteins.* Reaction with lipoprotein lipase results in the loss of approximately 90% of the triacylglycerol of chylomicrons and in the loss of apo C (which returns to HDL) but not apo E, which is retained. The resulting chylomicron remnant is about half the diameter of the parent chylomicron and is relatively enriched in cholesterol and cholesteryl esters because of the loss of triacylglycerol. Similar changes occur to VLDL, with the formation of VLDL remnants or IDL (intermediate-density lipoprotein).
- *The Liver Is Responsible for the Uptake of Remnant Lipoproteins.* Chylomicron remnants are taken up by the liver by receptor-mediated endocytosis, and the cholesteryl esters and triacylglycerols are hydrolyzed and metabolized. Uptake is mediated by a receptor specific for apo E, and both the LDL (apo B-100, E) receptor and the LRP (LDL receptor-related protein) are believed to take part. *VLDL is the precursor of IDL, which is then converted to LDL*. Only one molecule of apo B-100 is present in each of these lipoprotein particles, and this is conserved during the transformations. Thus, each LDL particle is derived from only one VLDL particle. Two possible fates await IDL. It can be taken up by the liver directly via the LDL (apo B-100, E) receptor, or it is converted to LDL. In humans, a relatively large proportion forms LDL, accounting for the increased concentrations of LDL in humans compared with many other mammals.

- LDL IS METABOLIZED VIA THE LDL RECEPTOR. The liver and many extrahepatic tissues express the LDL (B-100, E) receptor. It is so designated because it is specific for apo B-100 but not B-48, which lacks the carboxyl terminal domain of B-100 containing the LDL receptor ligand, and it also takes up lipoproteins rich in apo E. This receptor is defective in familial hypercholesterolemia. Approximately 30% of LDL is dedegraded in extrahepatic tissues and 70% in the liver. A positive correlation exists between the incidence of coronary atherosclerosis and the plasma concentration of LDL cholesterol.
- HDL takes part in both lipoprotein triacylglycerol & cholesterol metabolism. HDL is synthesized and secreted from both liver and intestine. However, apo C and apo E are synthesized in the liver and transferred from liver HDL to intestinal HDL when the latter enters the plasma. *A major function of HDL is to act as a repository for the apo C and apo E required in the metabolism of chylomicrons and VLDL*. Nascent HDL consists of discoid phospholipid bilayers containing apo A and free cholesterol. These lipoproteins are similar to the particles found in the plasma of patients with a deficiency of the plasma enzyme lecithin:cholesterol acyltransferase (LCAT) and in the plasma of patients with obstructive jaundice. LCAT—and the LCAT activator apo A-I—bind to the disk, and the surface phospholipid and free cholesterol are converted into cholesteryl esters and lysolecithin. The nonpolar cholesteryl esters move into the hydrophobic interior of the bilayer, whereas lysolecithin is transferred to plasma albumin. Thus, a nonpolar core is generated, forming a spherical, pseudomicellar HDL covered by a surface film of polar lipids and apolipoproteins. In this way, the LCAT system is involved in the removal of excess unesterified cholesterol from lipoproteins and tissues.

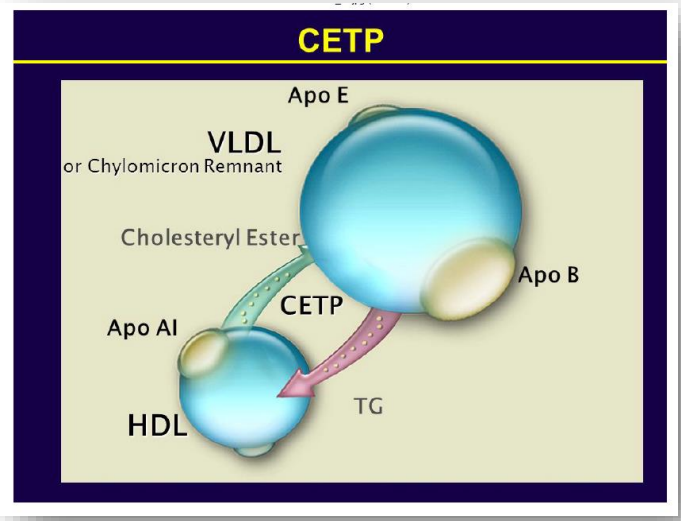
- The class B scavenger receptor B1 (SR-B1) has recently been identified as an HDL receptor in the liver and in steroidogenic tissues. HDL binds to the receptor via apo A-I and cholesteryl ester is selectively delivered to the cells, but the particle itself, including apo A-I, is not taken up.
- The transport of cholesterol from the tissues to the liver is known as reverse cholesterol transport and is mediated by an HDL cycle. The smaller HDL3 accepts cholesterol from the tissues via the ATP-binding cassette transporter-1 (ABC-1). After being accepted by HDL3, the cholesterol is then esterified by LCAT, increasing the size of the particles to form the less dense HDL2. The cycle is completed by the re-formation of HDL3, either after selective delivery of cholesteryl ester to the liver via the SR-B1 or by hydrolysis of HDL2 phospholipid and triacylglycerol by hepatic lipase. In addition, free apo A-I is released by these processes and forms preβ-HDL after associating with a minimum amount of phospholipid and cholesterol. Preβ-HDL is the most potent form of HDL in inducing cholesterol efflux from the tissues to form discoidal HDL. Surplus apo A-I is destroyed in the kidney.
- HDL concentrations vary reciprocally with plasma triacylglycerol concentrations and directly with the activity of lipoprotein lipase. This may be due to surplus surface constituents, eg, phospholipid and apo A-I being released during hydrolysis of chylomicrons and VLDL and contributing toward the formation of preβ-HDL and discoidal HDL. HDL2 concentrations are inversely related to the incidence of coronary atherosclerosis, possibly because they reflect the efficiency of reverse cholesterol transport.



HDL metabolism. Pre-β HDL is apolipoprotein AI (apoAI) associated with some phospholipid. It acquires free cholesterol (FC) and further phospholipid (PL) by interaction with cells and forms discoidal HDL particles, which acquire further FC and PL that is shed from triacylglycerolrich lipoprotein (TRL) particles as lipoprotein lipase (LPL) acts upon them. Lecithin-cholesterol acyltransferase (LCAT) esterifies the FC the HDL particles have acquired and by this means they mature into spherical, cholesterol-rich HDL2 particles. These may give up their cholesterol and some phospholipid to the liver from where the cholesterol can be excreted in the bile, marked by '*'.

- **Cholesteryl Ester Transfer Protein**: A circulating protein known as cholesteryl ester transfer protein (CETP) catalyzes the exchange of hydrophobic lipids – cholesteryl esters and triacylglycerol – between lipoprotein particles. They exchange by facilitated diffusion along concentration gradients, but the exchange is also dependent on the numbers of particles in the circulation (more particles means more "collisions" between them and opportunities for exchange). When the plasma concentration of triacylglycerol is high, especially when this reflects large numbers of VLDL particles present, CETP will catalyze the movement of cholesteryl ester from HDL to the triacylglycerol-rich lipoproteins, while triacylglycerol moves in the opposite direction. This will also tend to occur after a meal, when triacylglycerol-laden chylomicrons are present. The cholesteryl esters remain with the triacylglycerol-rich lipoprotein particle until it is taken up by the liver as a remnant. The HDL has now become enriched with triacylglycerol. This HDL-triacylglycerol can be hydrolyzed by hepatic lipase, leaving smaller, cholesteryl ester-depleted HDL3 particles, which can then pick up further cholesterol from cells.

- This **remodeling of HDL** is accompanied by the dissociation from the HDL of lipid-poor, preβ-migration ApoA-1, the fraction that has been reported to be the preferred plasma acceptor of cell cholesterol.



Our understanding of the relevance of this system to cardiovascular disease has been challenged in recent years. Some species – such as the rat – do not have CETP activity and they do not suffer from atherosclerosis. Some Japanese families have been described in whom CETP is lacking; they have high HDL-cholesterol concentrations and some reports suggest that they have exceptional longevity, although early suggestions that they are protected against atherosclerosis have not always been confirmed. Recently, inhibitors of CETP have been tested in humans. The idea is that inhibition of CETP will raise HDL-cholesterol concentrations, a change which, in epidemiological terms, should be associated with a decreased risk of atherosclerosis. One such agent, torcetrapib, was tested in a large trial. It very effectively raised HDL-cholesterol concentrations. However, mortaility in the patients taking torcetrapib was increased compared with those taking a placebo. This could imply that in humans CETP is, in fact, an important part of the route for reverse cholesterol transport. Blocking that route would raise HDL-cholesterol concentrations, but without beneficial effect because cholesterol excretion would be reduced. Alternatively, for some reason torcetrapib had other, unwanted effects; for instance, it was found to raise blood pressure, and that in itself would be harmful. Other CETP inhibitors are being developed. Clinical trials of these agents may well aid our fundamental understanding of reverse cholesterol transport in humans.