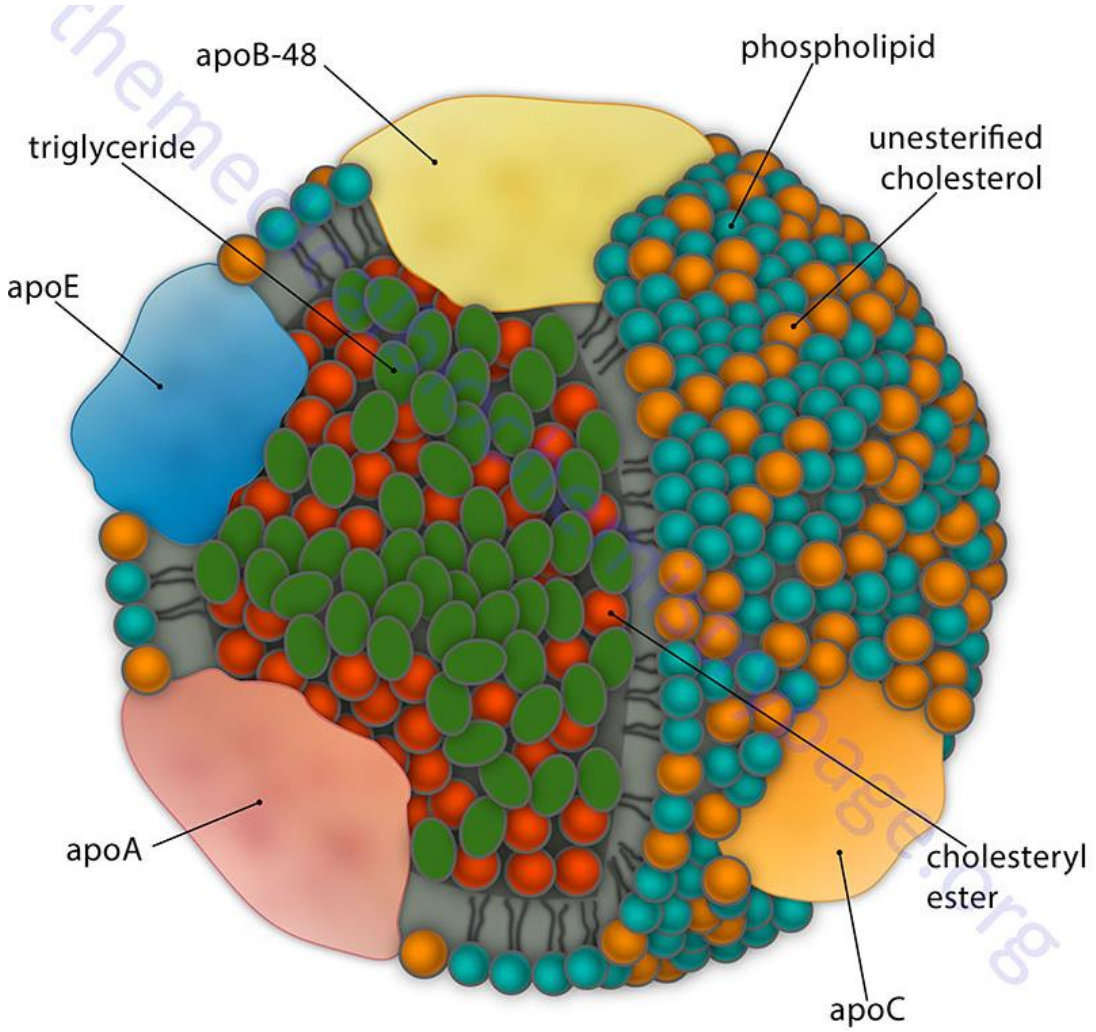
Plasma lipoproteins



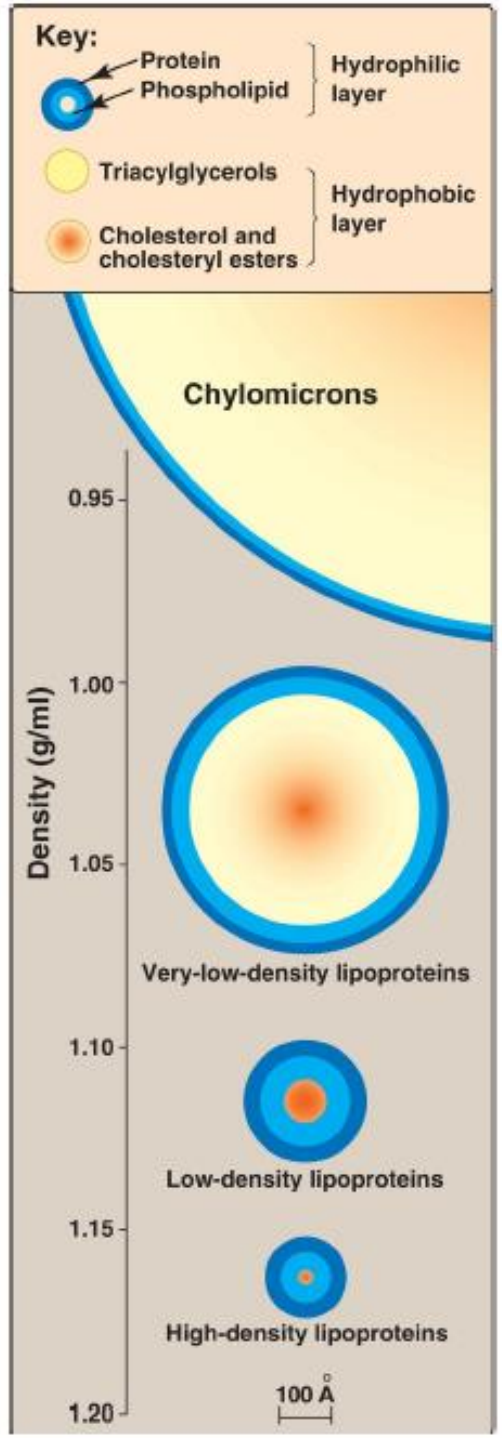
Lippincott's Biochemistry, Ch. 18

Characteristics of lipoproteins

- Lipoproteins function to
  - Solubilize and carry plasma lipids
  - Transport lipids to (and from) the tissues

- They range in size and density and have variable purposes and lipid and protein composition.

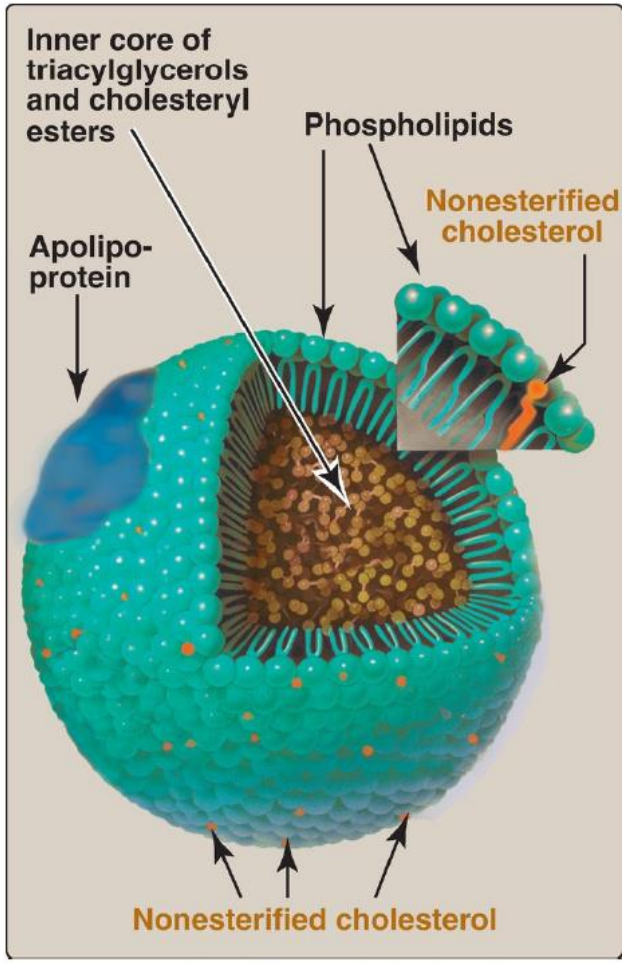
The higher the protein: lipid ratio, the higher the density



Lipid composition of lipoproteins

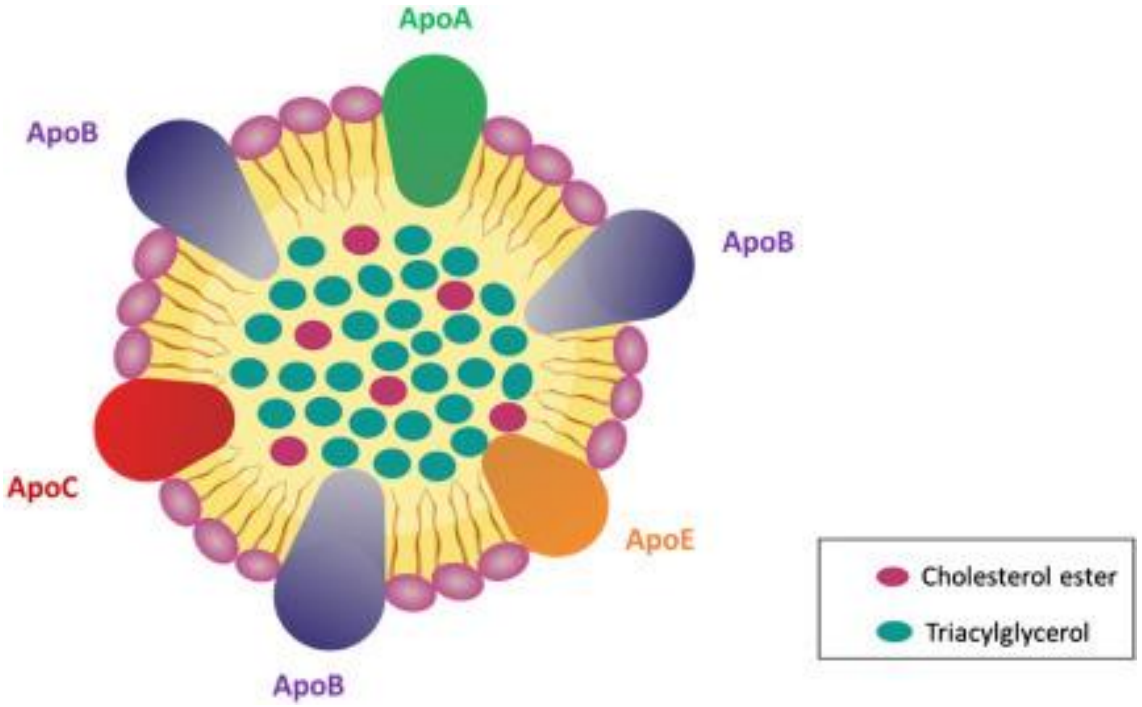
- A neutral lipid core (containing TAG and cholesteryl esters) surrounded by a shell of amphipathic apolipoproteins, phospholipid, and non-esterified (free) cholesterol.
  - These amphipathic compounds are oriented such that their polar portions are exposed on the surface of the lipoprotein.
- Sources of the lipid cargo: diet (exogenous source) or de novo synthesis (endogenous source).

- Total cholesterol=LDL-C + HDL-C + VLDL-C
  - VLDL-C is calculated by dividing TAG by 5 because the TAG/cholesterol ratio is 5/1 in VLDL.
    - The goal value for total cholesterol is <200 mg/dl.



Protein composition of lipoproteins (Apolipoproteins)

- Functions:
  - Structural (cannot be removed).
  - Recognition sites for cell-surface receptors
  - Activators or coenzymes for enzymes involved in lipoprotein metabolism.
- some are exchanged freely among lipoproteins.
- Classes of apolipoproteins are denoted by letters, and subclasses are designated by Roman numbers.
  - Example: apoC-I, apoC-II, and apoC-III.



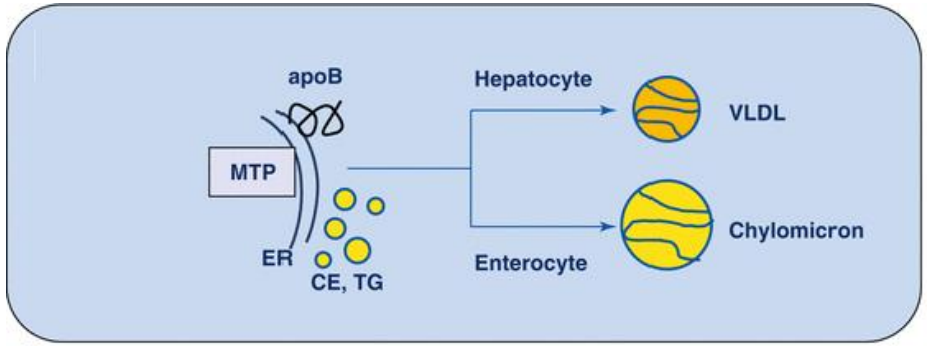
Apolipoproteins

Apolipo-protein	Molecular Weight	Chylomicron (CM)	VLDL	IDL/CM remnants	LDL	HDL
AI	28,016	Ex	Ex			St
AII	17,414	Ex	Ex			Ex
B100	515,000		St	St	St	
B48	241,000	St*		St*		
CI	6600	Ex	Ex			Ex
CII	8800	Ex	Ex			
CIII	8750	Ex	Ex	Ex		Ex
E	34,100	Ex	Ex	Ex		Ex

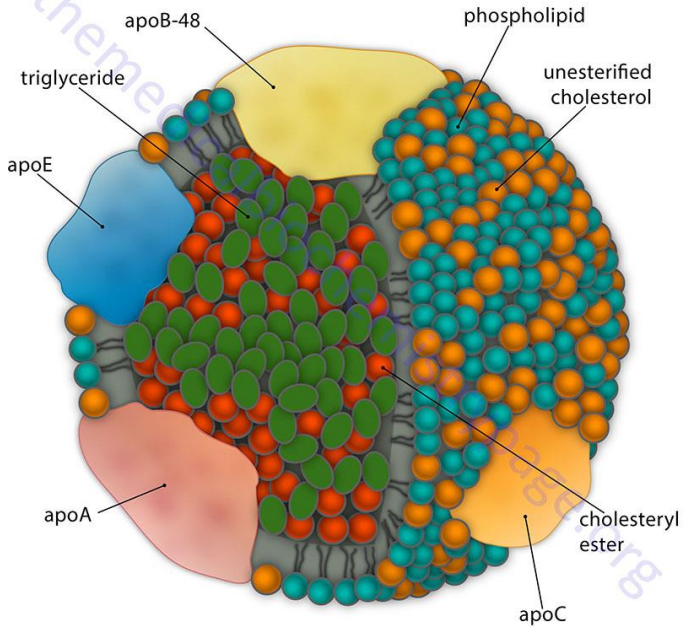
*B48 is exclusive to chylomicrons and chylomicrons remnants. St, structural apolipoprotein; Ex, exchangeable apolipoprotein. Other apolipoproteins (AIV, AV, D, F, G, H, J, (a)) are beyond the scope of this review.

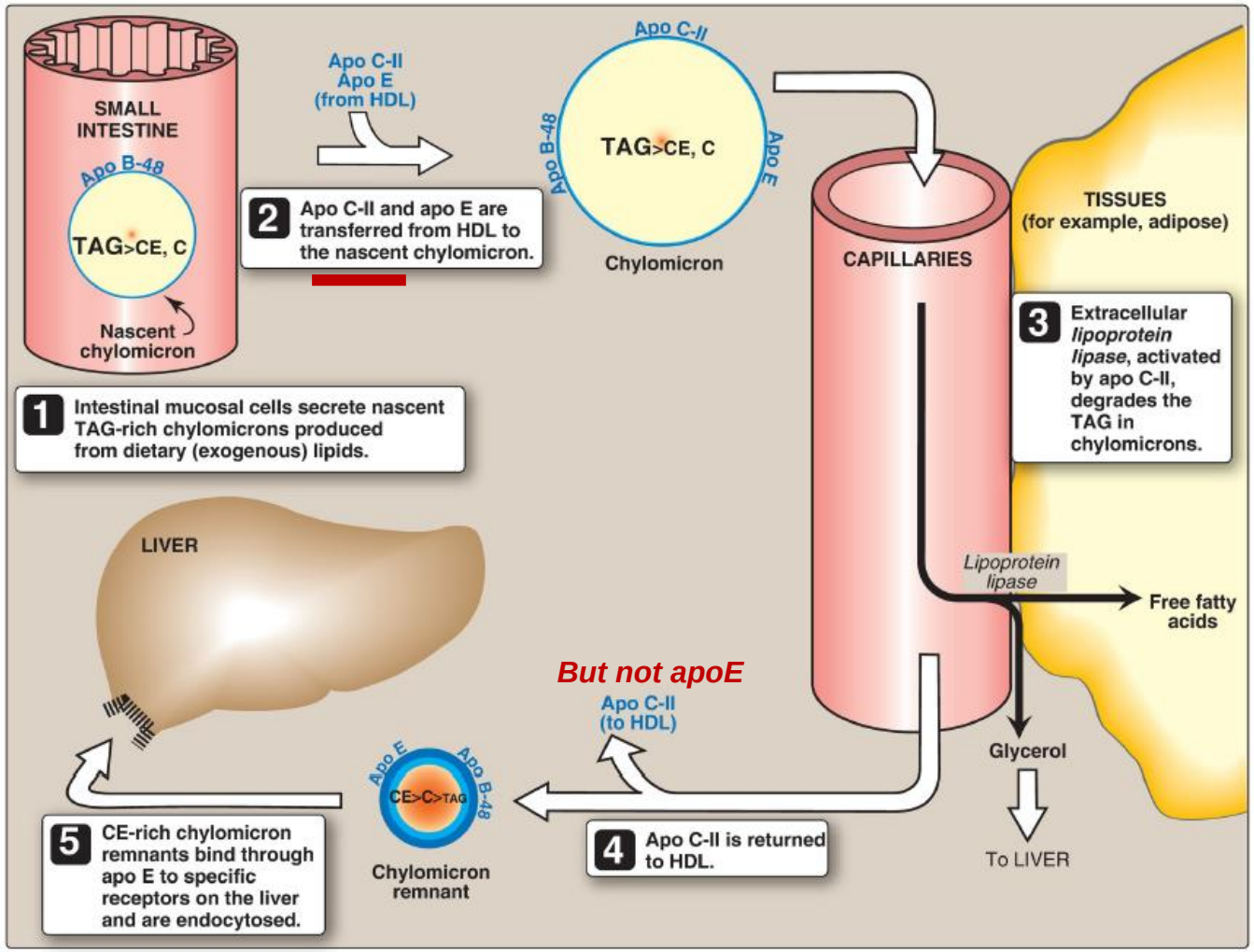
Chylomicrons

Microsomal triglyceride transfer protein (MTP) assembles the apoB protein with the lipids in the ER before transition to the Golgi, where the particles are packaged in secretory vesicles.



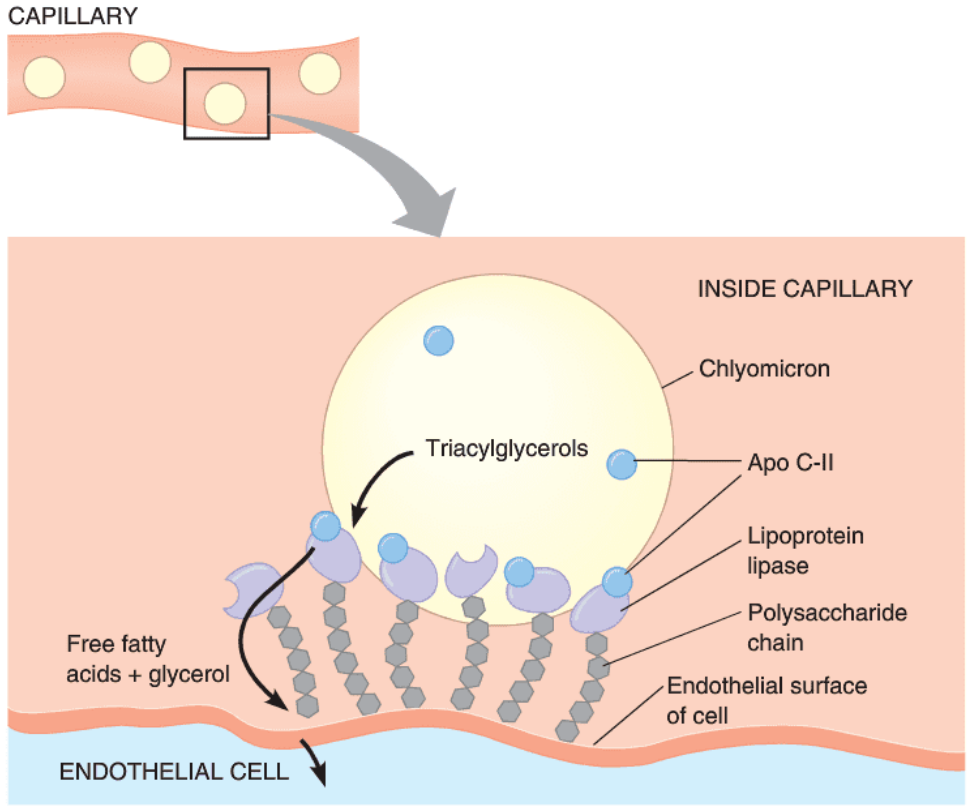
Chylomicron





Function of apo CII

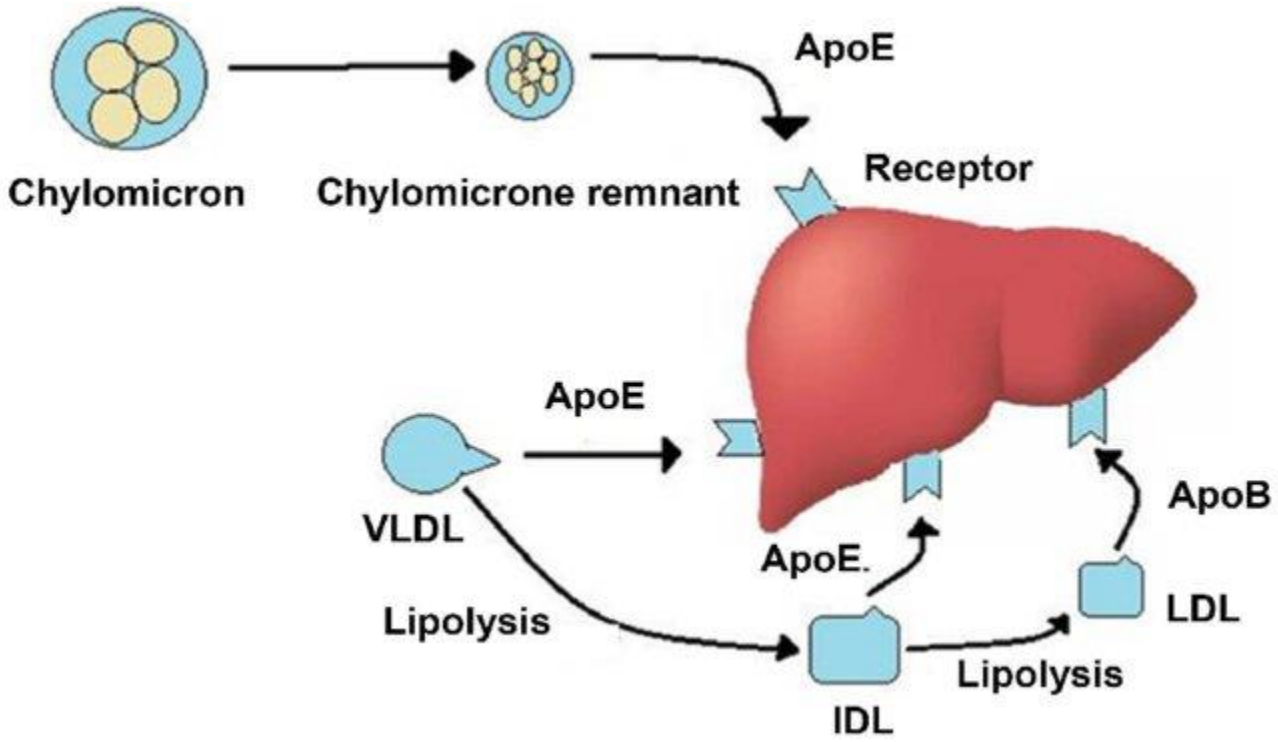
- ApoCII interacts with the lipoprotein lipase, which exists on the cell surface of endothelial cells, activating it.
- Lipoprotein lipase degrades TAG releasing fatty acids and glycerol, which enter the tissues.
- When TAGs are removed, chylomicron remnants are formed, which contain cholesteryl esters, phospholipids, apolipoproteins, fat-soluble vitamins, and a small amount of TAGs.



- **Type I hyperlipoproteinemia, familial chylomicronemia, hypertriacylglycerolemia: Deficiency of LPL or apo C-II leading to the accumulation of chylomicron-TAG in the Plasma.**

Fate of chylomicron remnant

- Chylomicron remnants bind to apoE receptors on the cell surface of hepatocytes and are taken into the by receptor-mediated endocytosis.
- The intracellular remnants are hydrolyzed to their component parts.



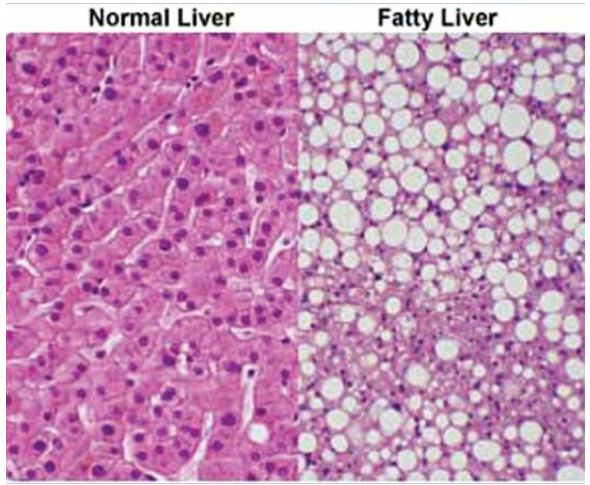
Type III hyperlipoproteinemia: mutations in apoE gene leading to decreased clearance of chylomicron remnants.

Very-low-density lipoprotein (VLDL)

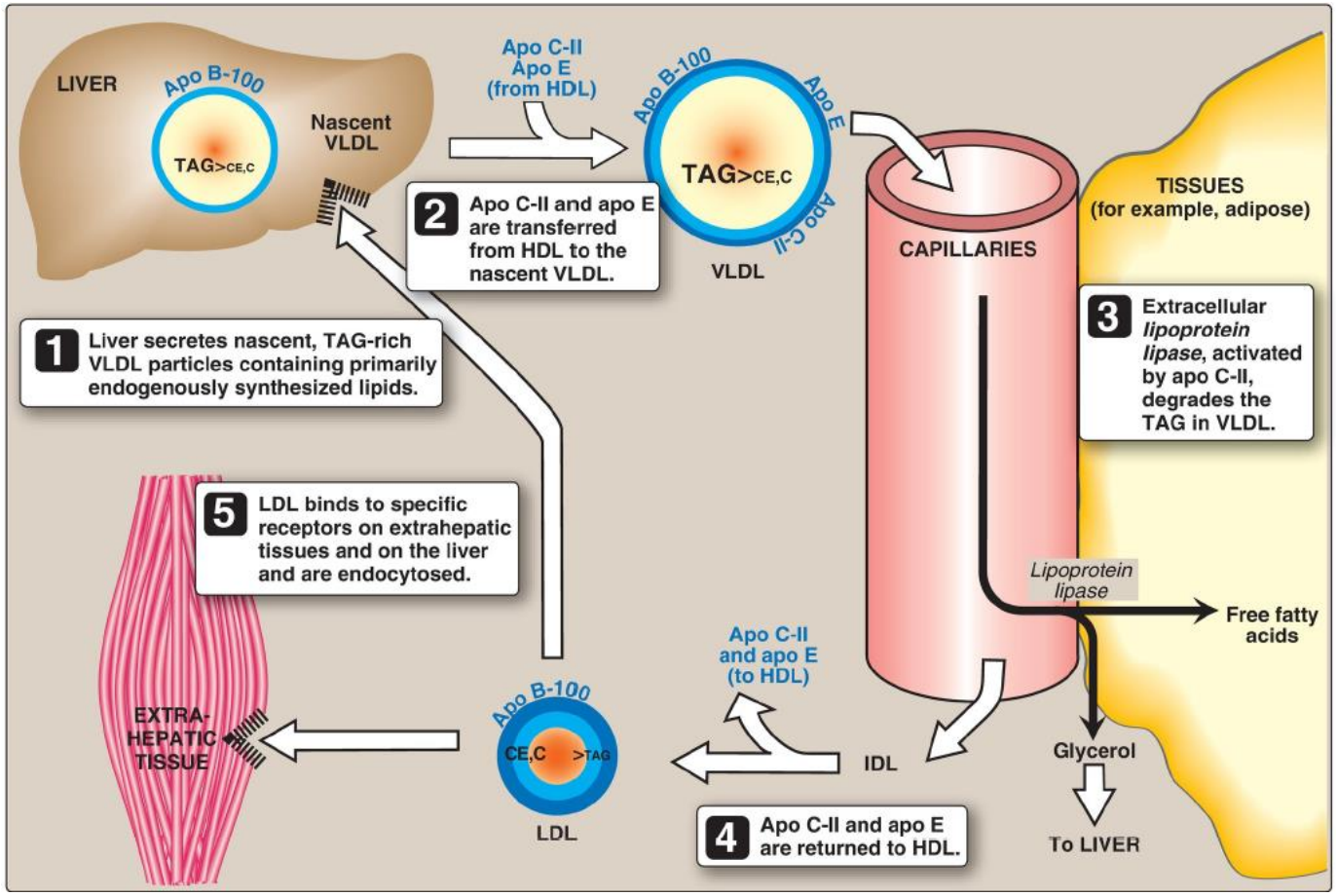
- Nonalcoholic fatty liver (hepatic steatosis):

<u>hepatic TAG synthesis >> VLDL release</u>

  - Examples: obesity and type 2 DM



- **Abetalipoproteinemia**: a rare hypolipoproteinemia caused by <u>defective MTP</u>, leading to low VLDL or chylomicrons and TAG accumulates in the liver and intestine.
  - Deficient fat-soluble vitamins



Low density lipoprotein (LDL)

- Primary lipoprotein is B-100.
- Plasma cholesterol, ~70% of LDL content, is taken to peripheral tissues.
- Receptor-mediated endocytosis
- Type IIa hyperlipidemia (familial hypercholesterolemia [FH]): reduced synthesis of functional LDL receptor leading to premature atherosclerosis.
- Defective apo B-100: autosomal dominant hypercholesterolemia with reduced binding to LDL receptor.

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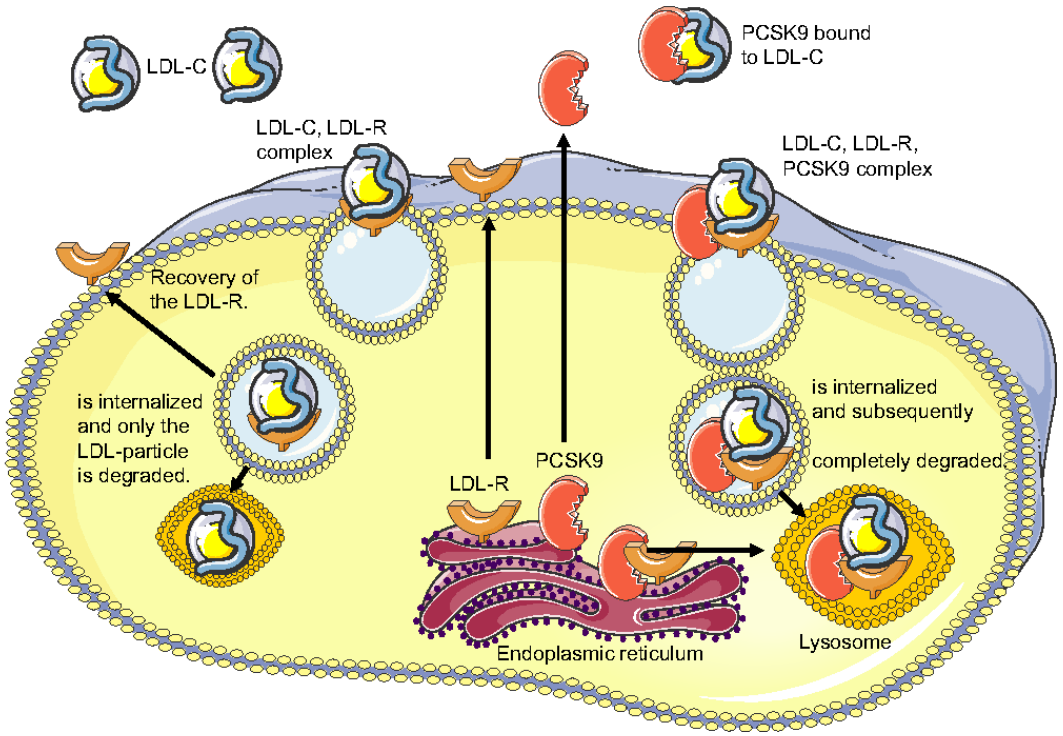
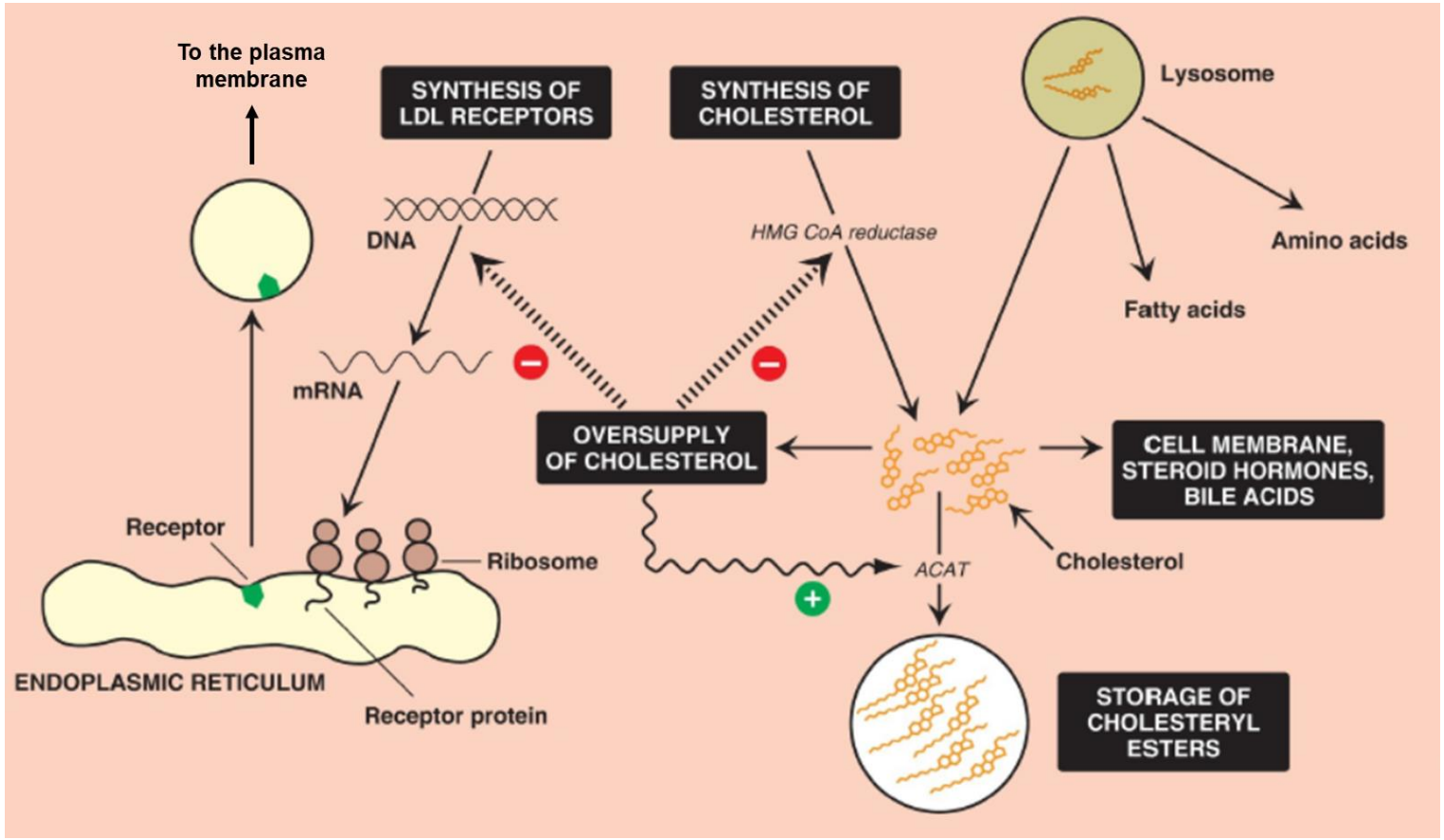


- Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes internalization and lysosomal degradation of the receptor.
  - PCSK9 inhibitors are now available for the treatment of hypercholesterolemia.

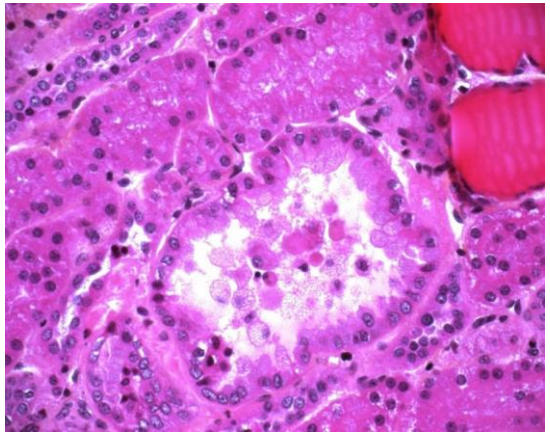
Fate and effects of cholesterol

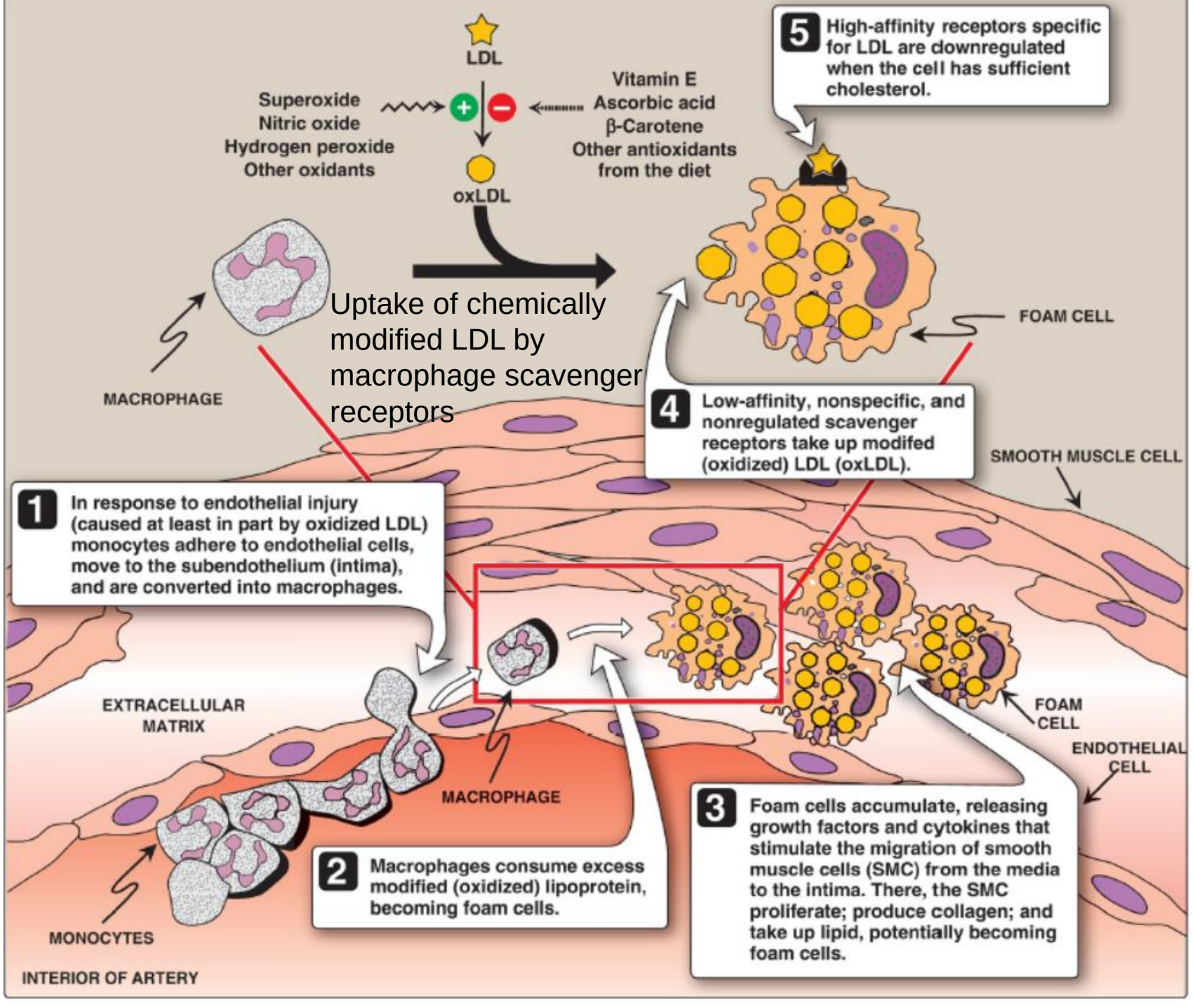
- High intracellular cholesterol levels
  - inhibit de novo cholesterol synthesis
  - induce the degradation of HMG CoA reductase.
  - decrease the synthesis of LDL receptor through the negative regulation of SREBP-2.
- Excess cholesterol is esterified by *acyl CoA:cholesterol acyltransferase* (*ACAT)* and stored in the cells.
  - The activity of ACAT is enhanced by the increased intracellular cholesterol.



Foam cells

- Macrophages possess high levels of unregulated scavenger receptor class A (SR-A) that can bind and endocytose LDL particles carrying oxidized lipids.
- Unlike the LDL receptor, the scavenger receptor is not down-regulated in response to increased intracellular cholesterol.
- Cholesteryl esters accumulate in macrophages, which transform into “foam” cells that form atherosclerotic plaque.
- LDL-Cholesterol is the primary cause of atherosclerosis.





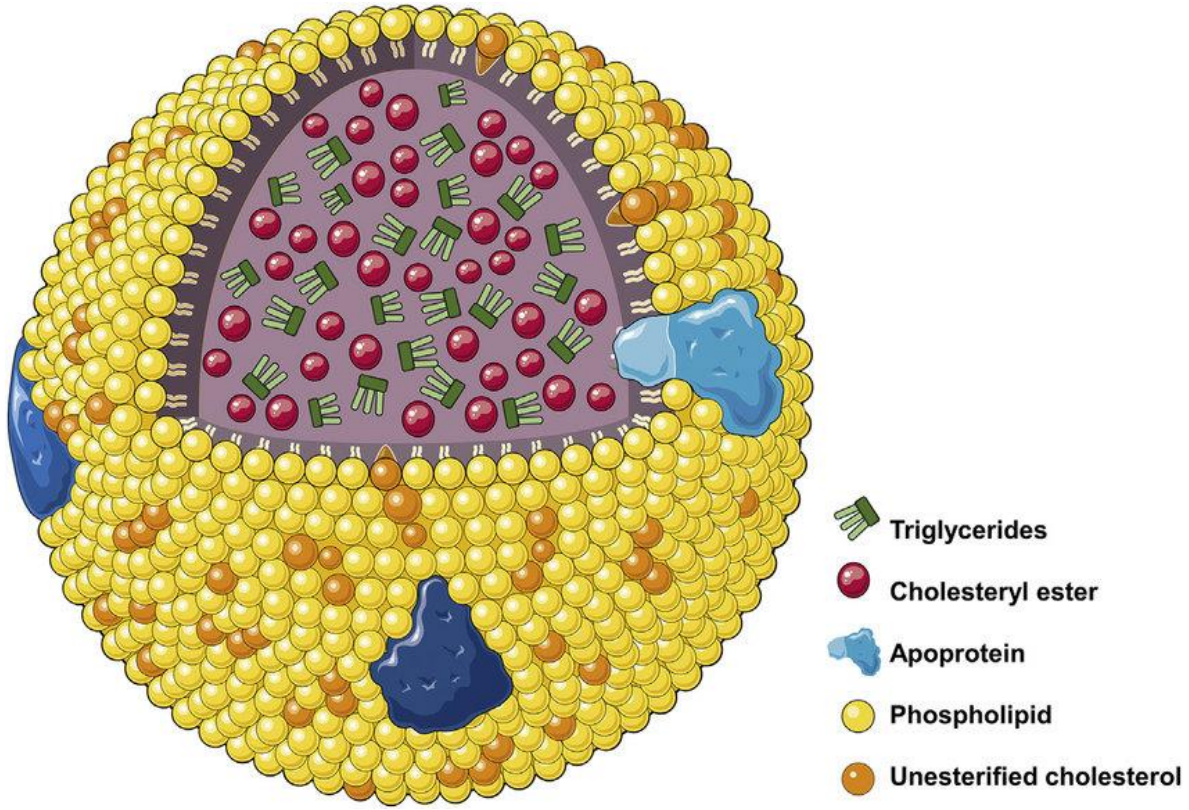
High-density lipoprotein (HDL)

- HDL particles are formed by the addition of lipid to apo A-1 (~70% of lipoproteins in HDL), which is synthesized by the liver and intestine.
- Functions:

1. HDL is a reservoir of apolipoproteins: HDL particles serve as a circulating reservoir of apo C-II (transferred to VLDL and chylomicrons, and is an activator of lipoprotein lipase), and apo E (required for the receptor-mediated endocytosis of IDLs and chylomicron remnants).

2. HDL uptake of unesterified cholesterol: Nascent HDL are disk-shaped particles containing primarily phospholipid (PC) and apo-A, C, and E. They take up cholesterol from non-hepatic (peripheral) tissues and return it to the liver as cholesteryl esters

3. Esterification of cholesterol by LCAT



Transport of cholesterol by HDL

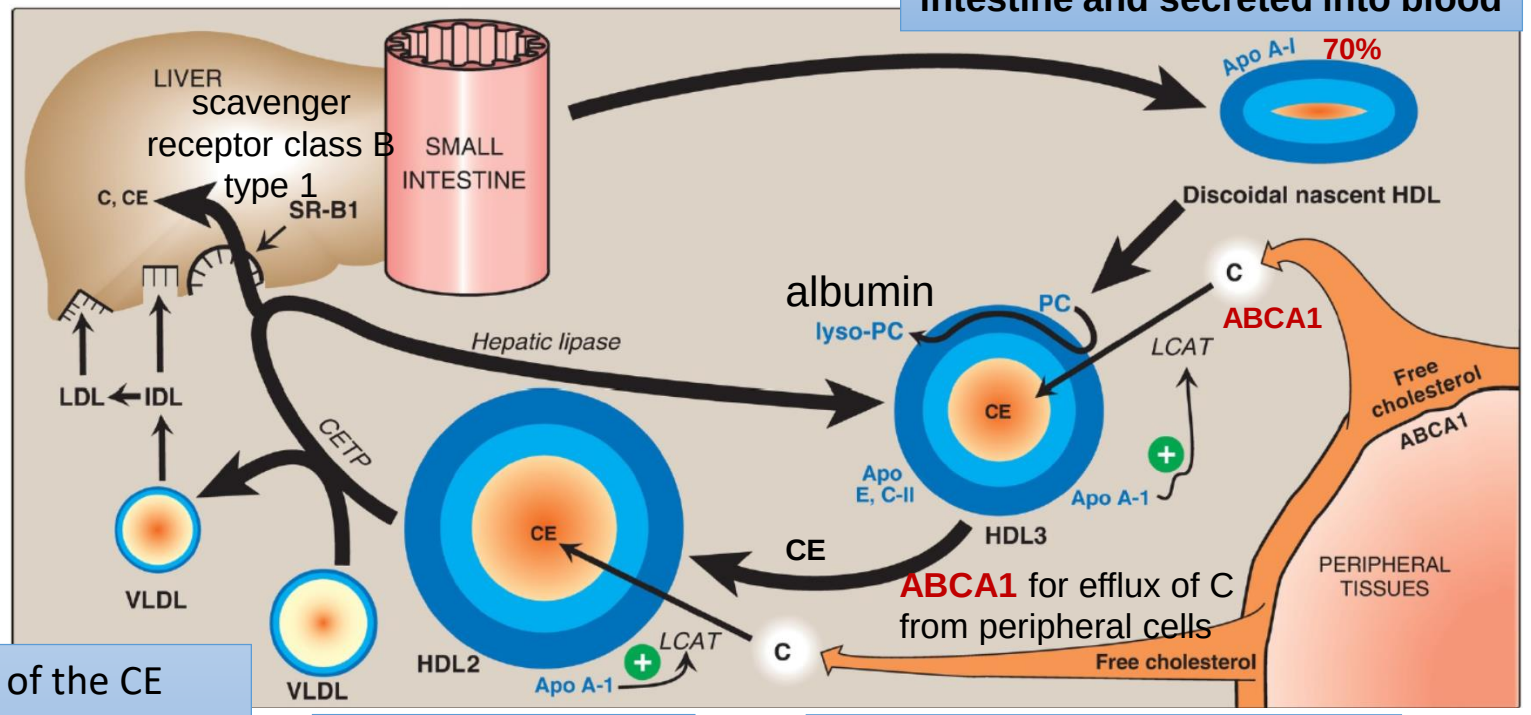
- HDL comprise a heterogeneous family of lipoproteins with a complex metabolism that is not completely understood.
- The liver-synthesized, nascent, HDL-bound plasma enzyme lecithin:cholesterol acyltransferase (LCAT or PCAT) esterifies the HDL-carried cholesterol by transferring the FA of carbon 2 of PC and the CE is sequestered in the HDL core.

✓ When C is taken up by HDL, it is immediately esterified by the plasma enzyme LCAT. LCAT binds to nascent HDL, and is activated by apo A-I but inhibited by CE. LCAT transfers the FA from C2 of PC to cholesterol producing CE, which is sequestered in the core of the HDL, and lyso-PC, which binds to albumin becoming spherical.

➢ Hepatic lipase, which degrades TAG and phospholipids, helps in the conversion of HDL2 to HDL3.

Lecithin = phosphatidylcholine (PC)

Apo A-1 is made by the liver and intestine and secreted into blood



CETP moves some of the CE from HDL to VLDL in exchange for TAGs, relieving product inhibition of LCAT

HDL2 is CE-rich and carries CE to the liver

Tangier disease: no ABCA1, no HDL particles, degradation of apo A-1.