Metabolism of lipids IX:

Plasma lipoproteins

Prof. Mamoun Ahram

Resources

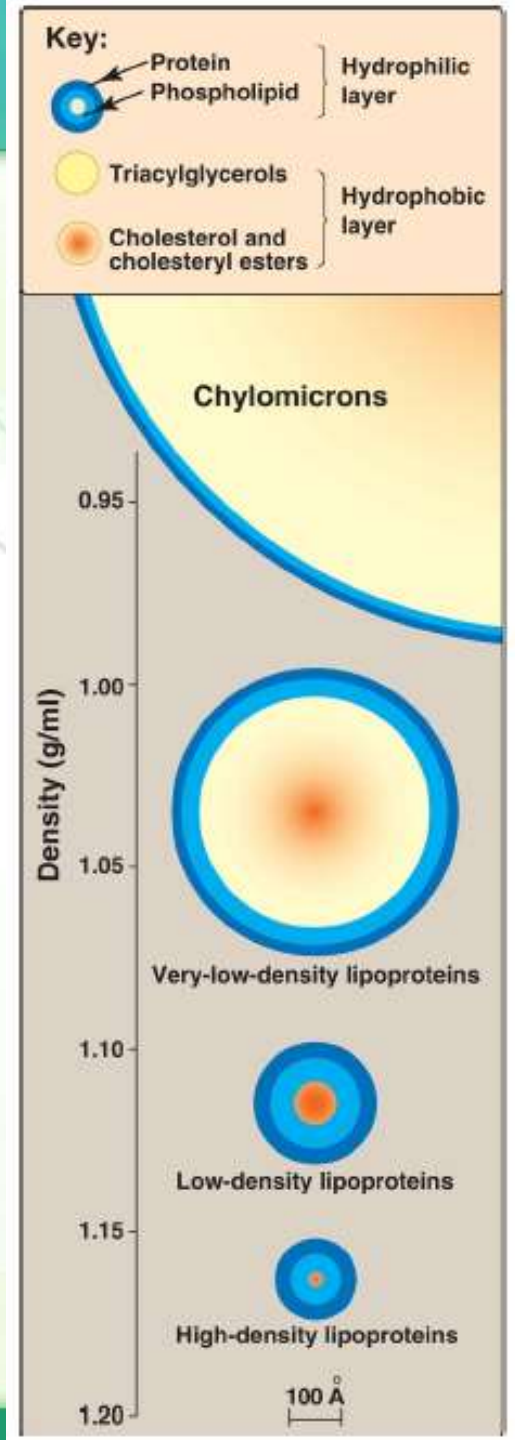
- This lecture
- Lippincott's Biochemistry, Ch. 18

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.

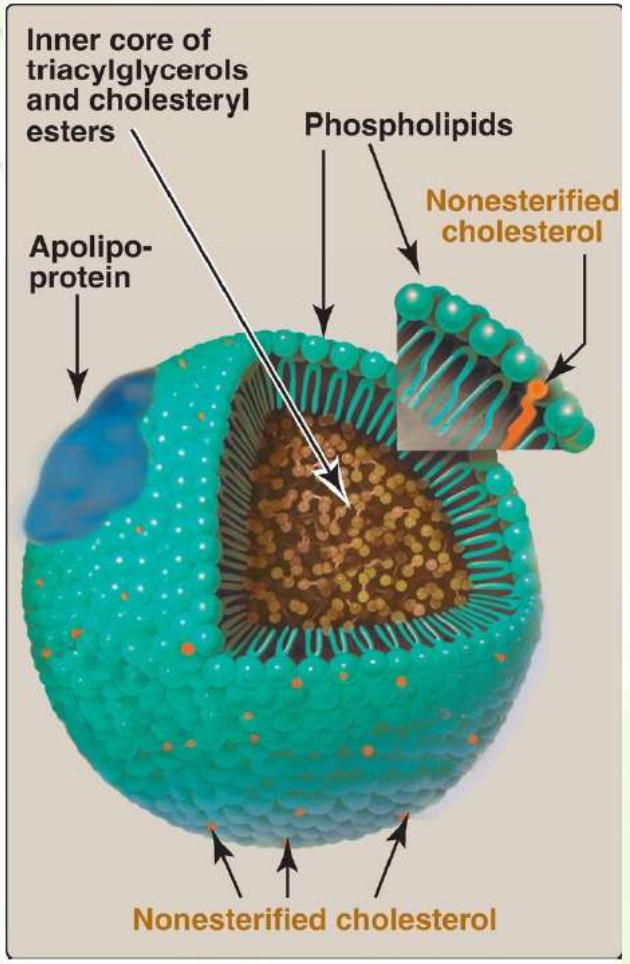
The higher the protein:lipid ratio, the higher the density



Lipid composition of lipoproteins

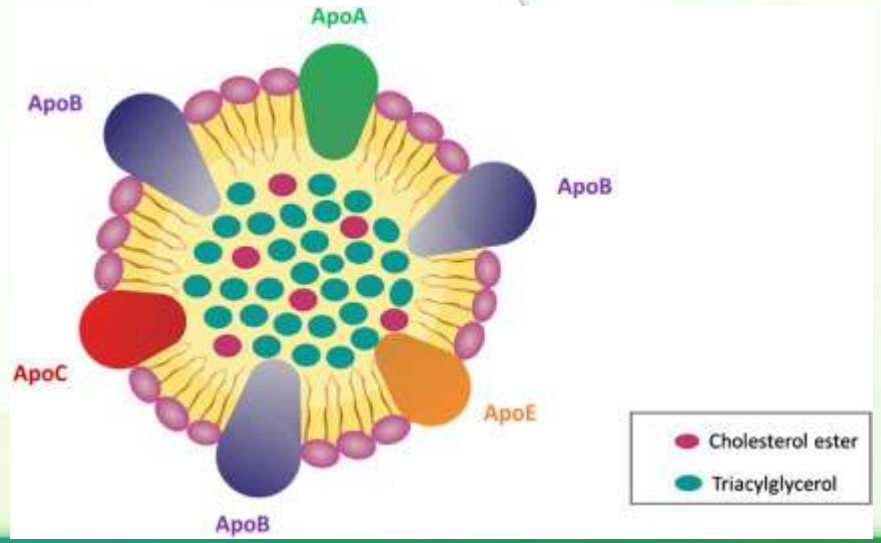
- A neutral lipid core (containing TAG and cholesteryl esters) surrounded by a shell of amphipathic apolipoproteins, phospholipid, and non-esterified (free) cholesterol.
  - These amphipathic compounds are oriented such that their polar portions are exposed on the surface of the lipoprotein.
- Sources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



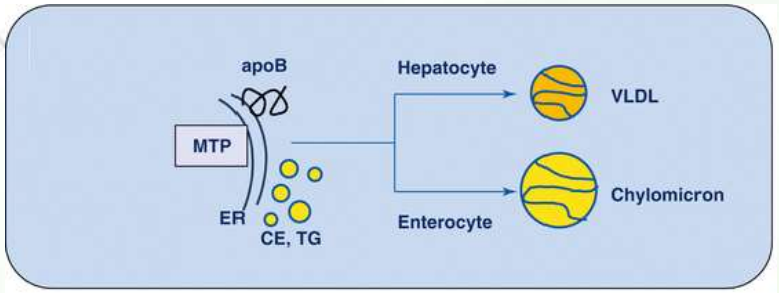
Protein composition of lipoproteins (Apolipoproteins)

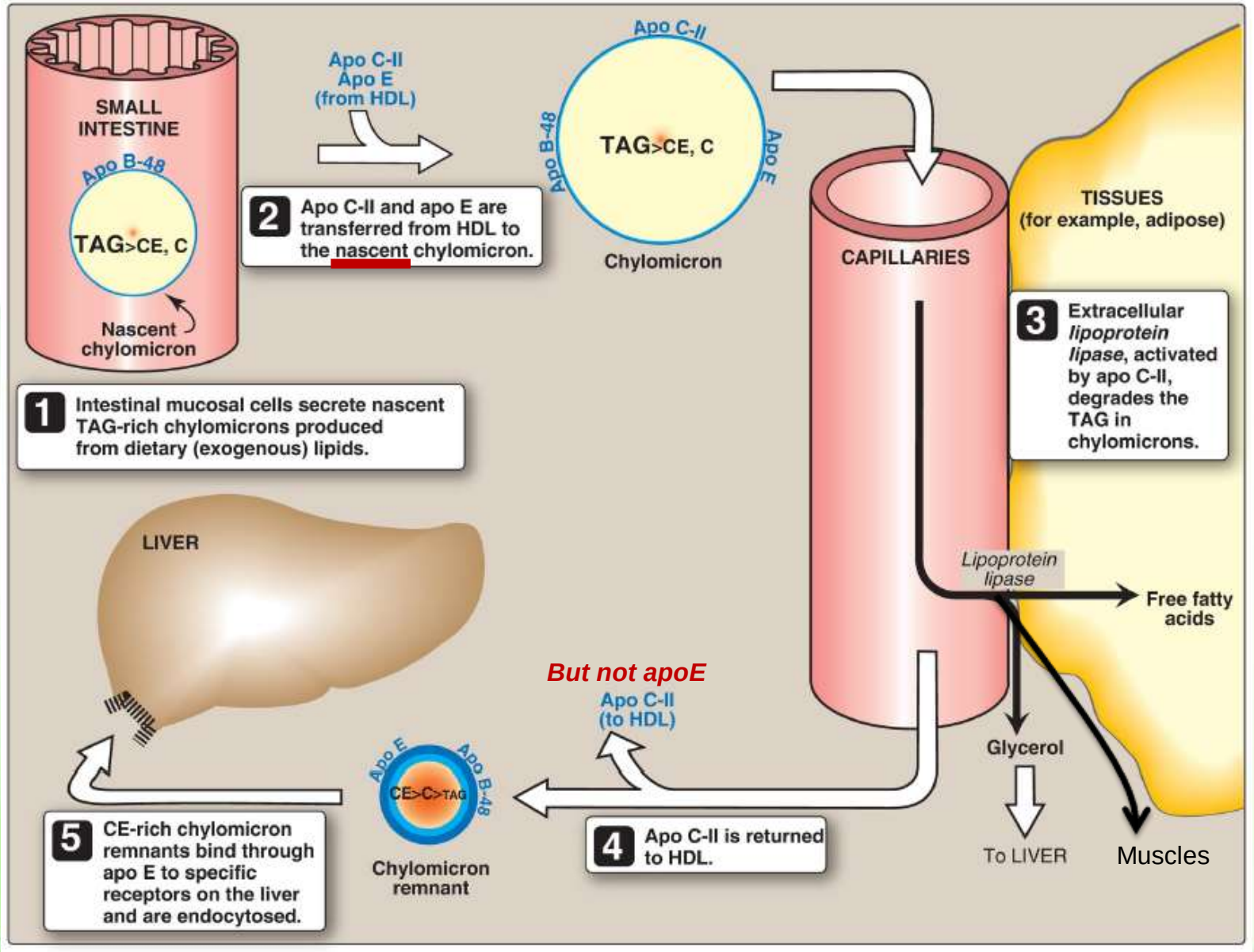
- Functions:
  - Structural (cannot be removed).
  - Recognition sites for cell-surface receptors
  - Activators or coenzymes for enzymes involved in lipoprotein metabolism.
- some are exchanged freely among lipoproteins.
- Classes of apolipoproteins are denoted by letters, and subclasses are designated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



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.



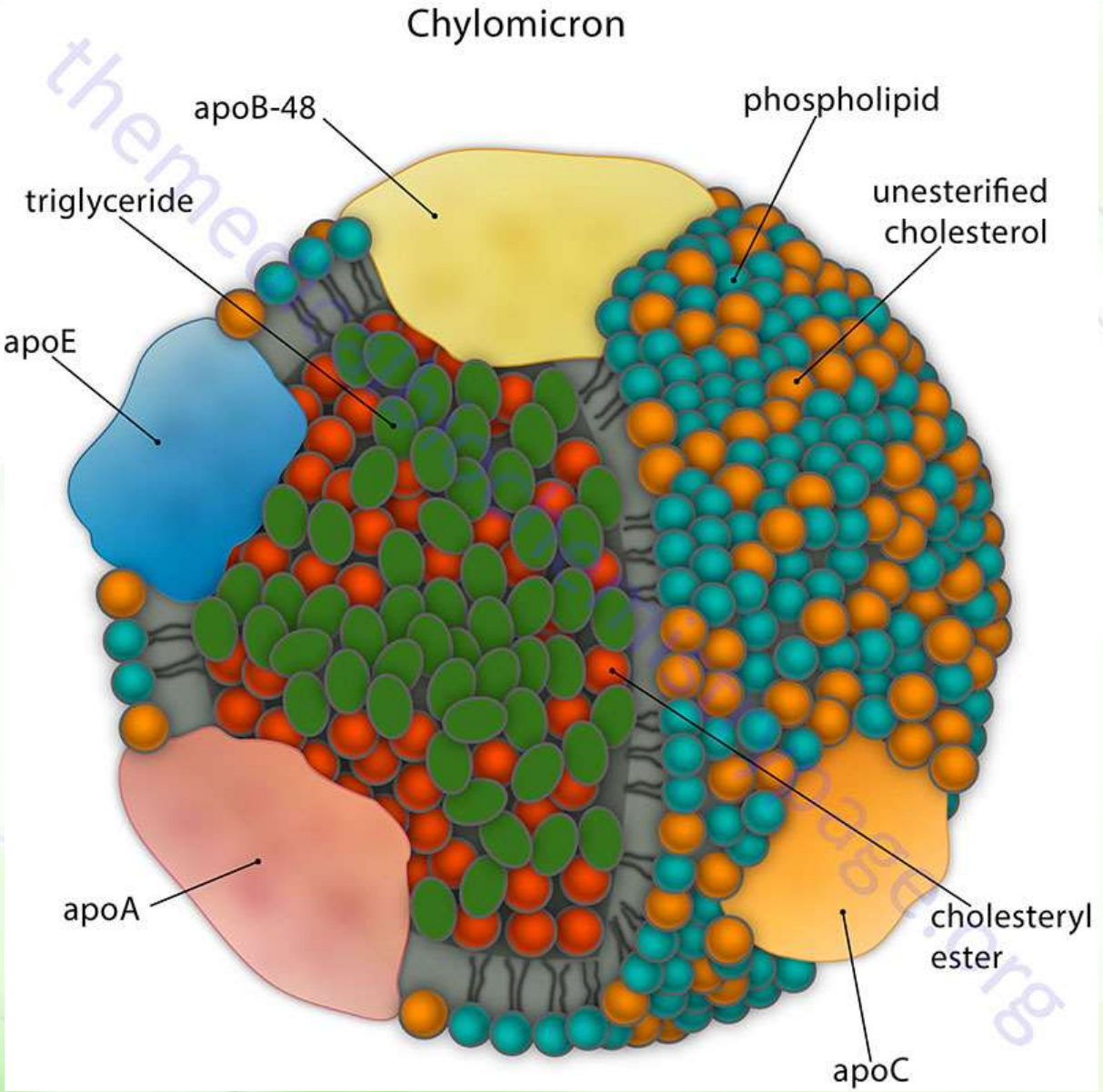


Apolipoproteins

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

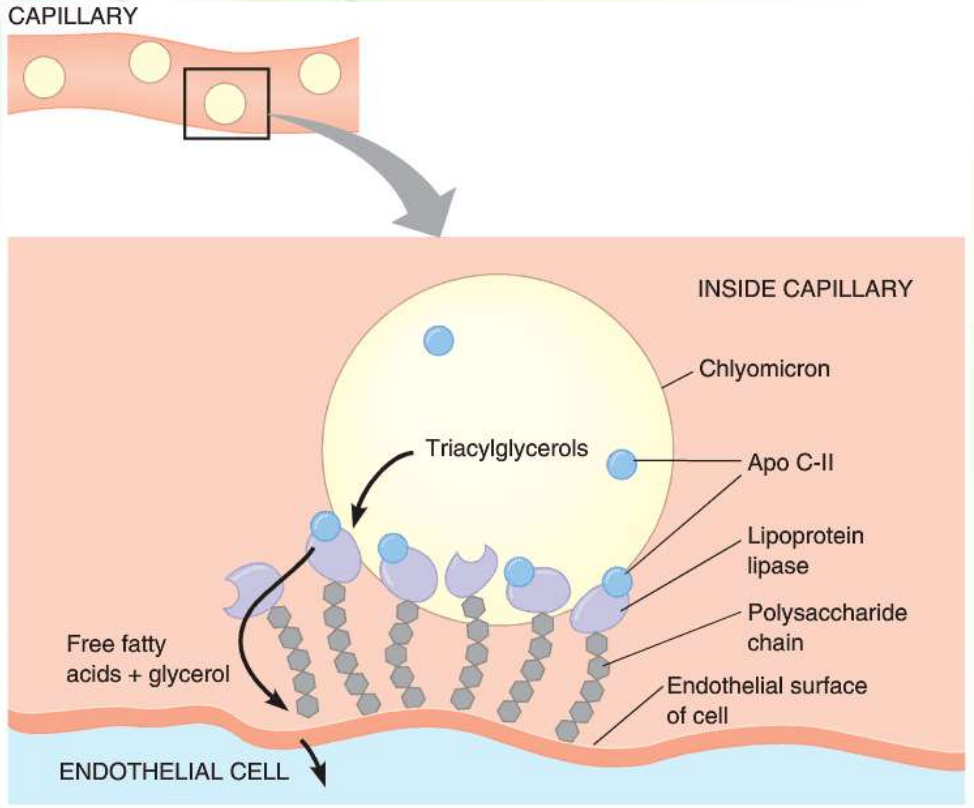
*B48 is exclusive to chylomicrons and chylomicrons remnants. St, structural apolipoprotein; Ex, exchangeable apolipoprotein. Other apolipoproteins (AIV, AV, D, F, G, H, J, (a)) are beyond the scope of this review.

Structure of chylomicrons



Function of apo CII

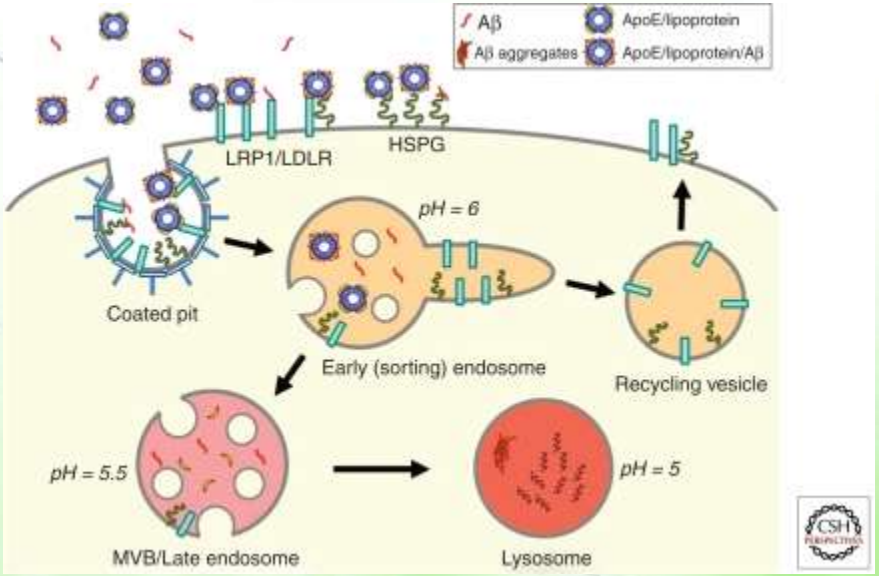
- ApoCII interacts with the lipoprotein lipase, which exists on the cell surface of endothelial cells, activating it.
- Lipoprotein lipase degrades TAG releasing fatty acids and glycerol, which enter the tissues.
- When TAGs are removed, chylomicron remnants are formed, which contain cholesteryl esters,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

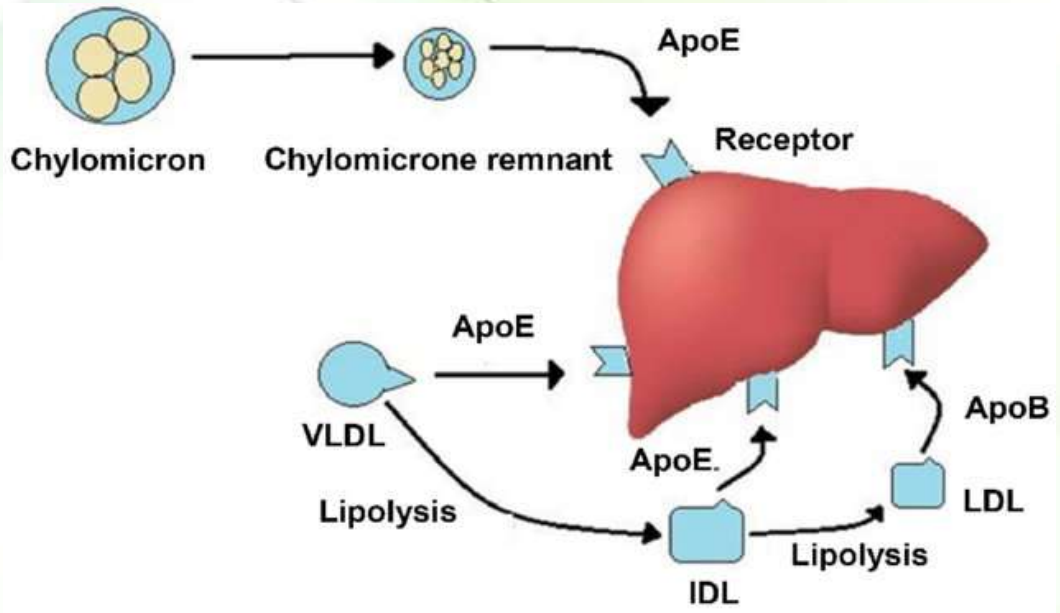


- **Type I hyperlipoproteinemia, familial chylomicronemia, hypertriacylglycerolemia: Deficiency of LPL or apo C-II leading to the accumulation of chylomicron-TAG in the Plasma.**

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.





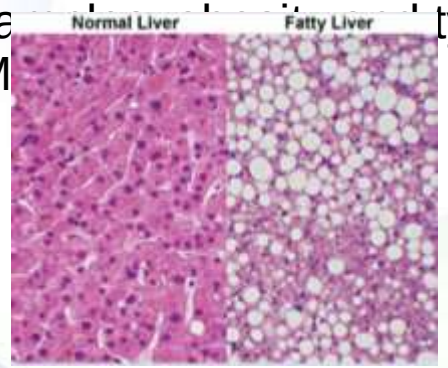
Type III hyperlipoproteinemia: mutations in apoE gene leading to decreased clearance of chylomicron remnants.

Very-low-density lipoprotein

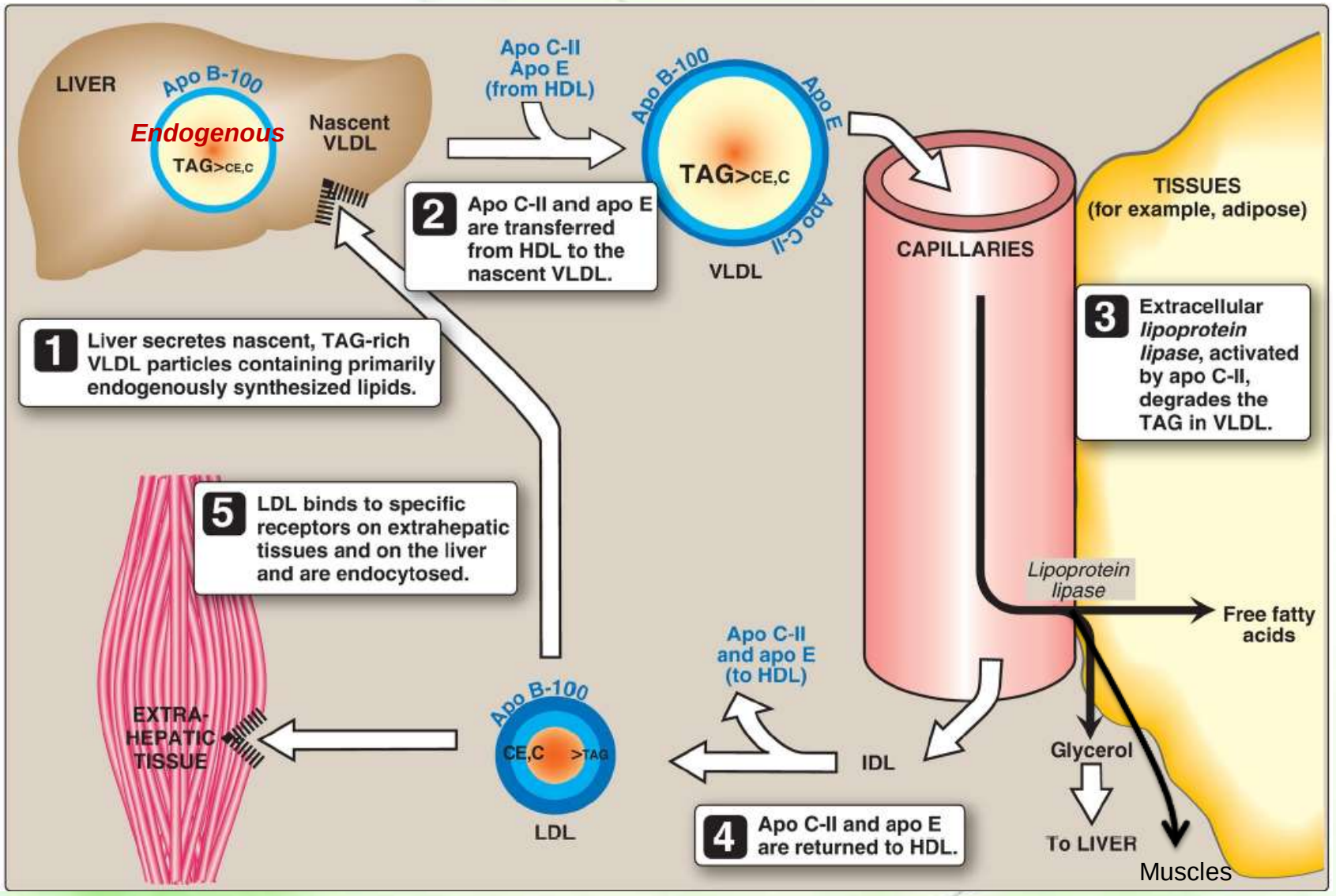
- Nonalcoholic fatty liver (hepatic steatosis):

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

- Exa[illegible]type 2 DM

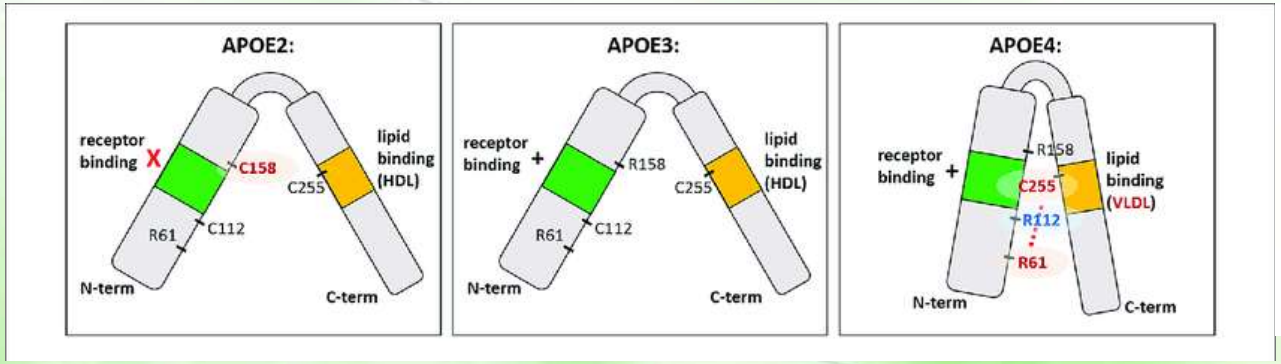


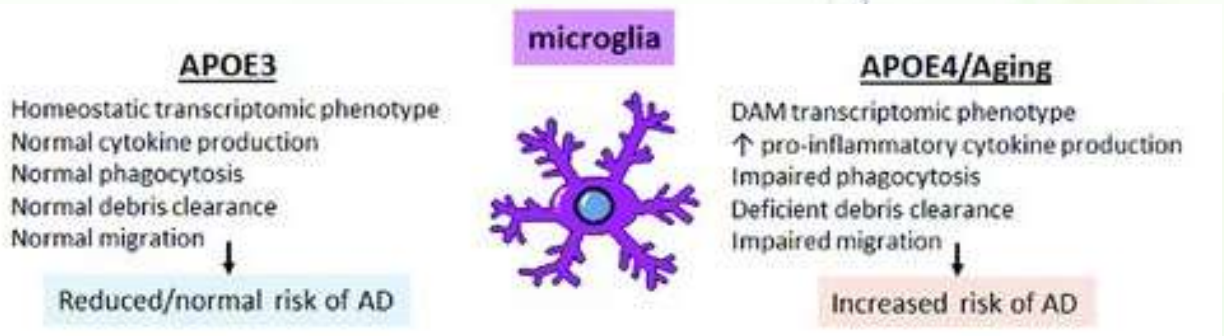
- **Abetalipoproteinemia**: a rare hypolipoproteinemia caused by defective MTP, leading to low VLDL or chylomicrons and TAG accumulates in the liver and intestine.
  - Deficient fat-soluble vitamins



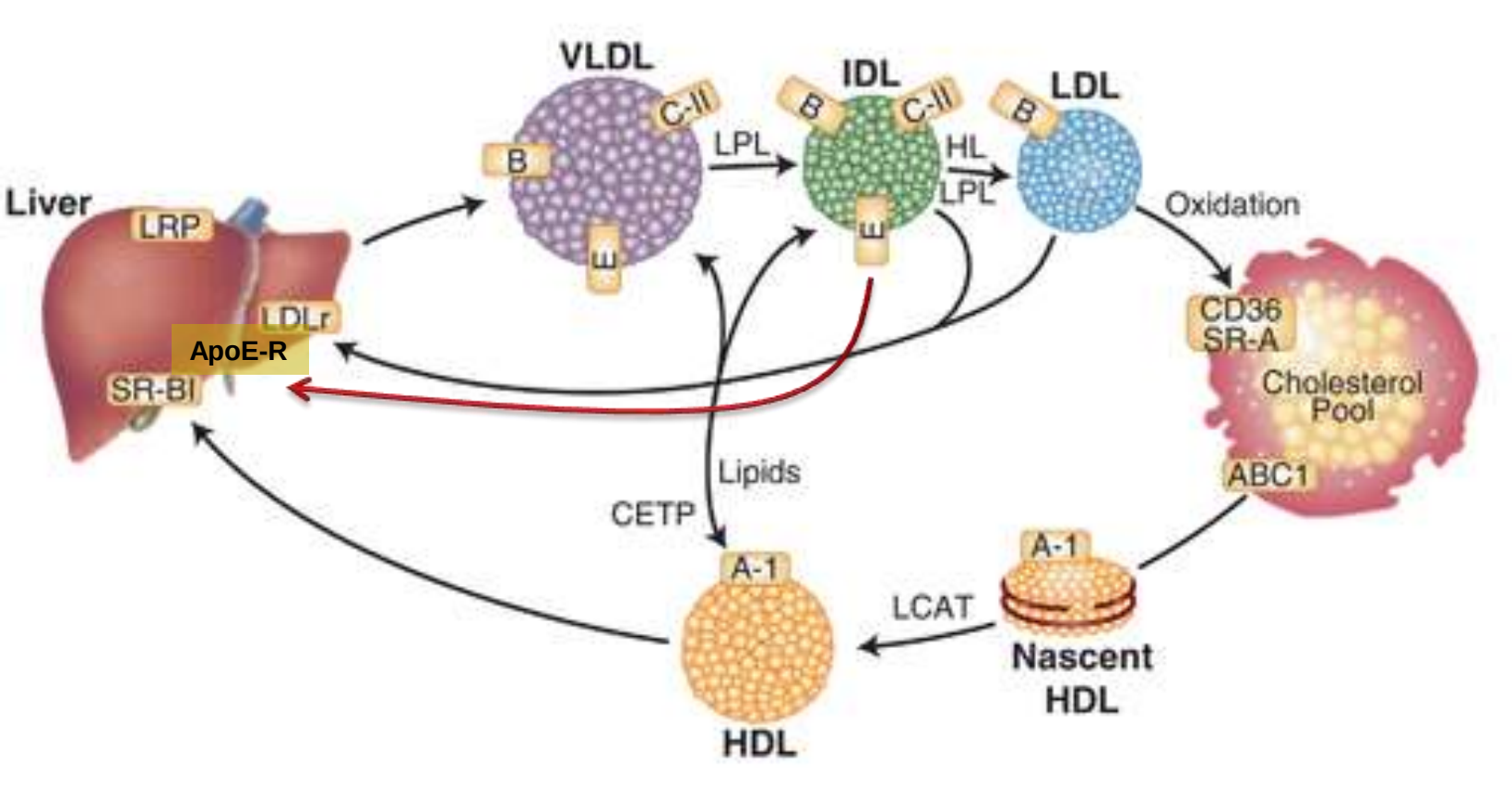
A note about apoE

- ApoE is present in three isoforms, E-2 (the least common), E-3 (the most common), and E-4.
  - ApoE-2 binds poorly to receptors.
    - patients who are homozygotic for apoE-2 are deficient in the clearance of IDL and chylomicron remnants.
    - These individuals have familial type III hyperlipoproteinemia (familial dysbetalipoproteinemia or broad beta disease), with hypercholesterolemia and premature atherosclerosis.
  - The apoE-4 isoform confers increased susceptibility to an earlier age of onset of the late-onset form of Alzheimer's disease.
    - Homozygotes are at the greatest risk.





Relation of VLDL to HDL, IDL, and LDL

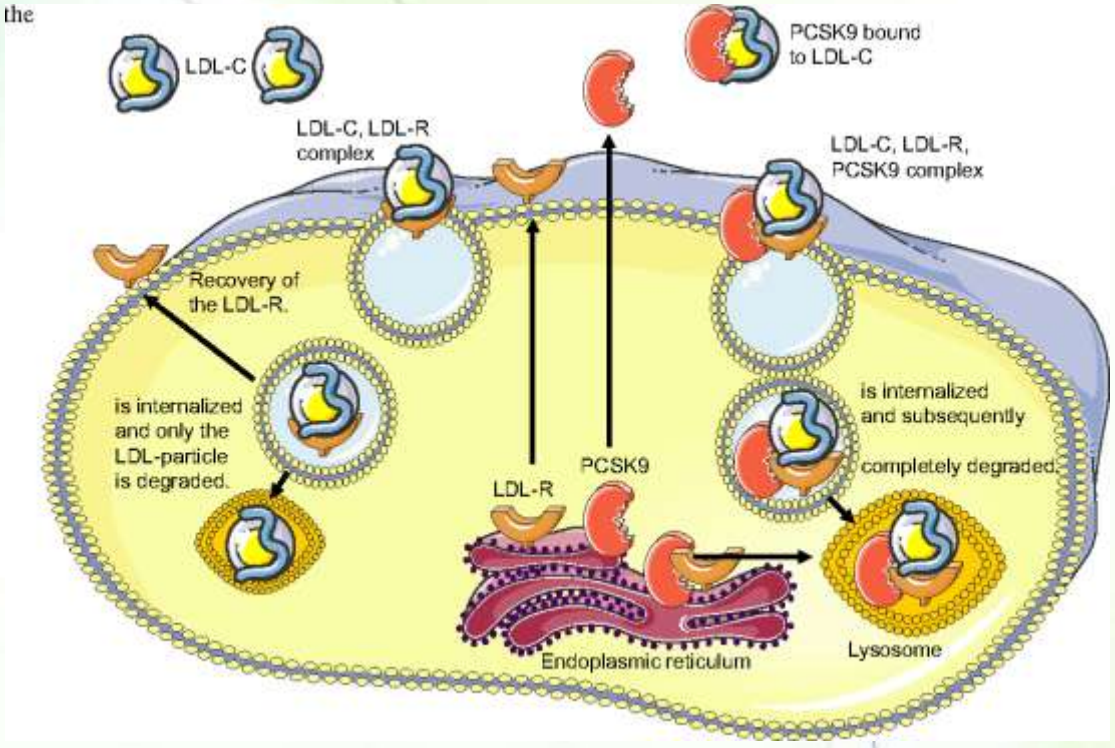


Regulation of lipoprotein lipase

- LPL is synthesized by adipose tissue and by cardiac and skeletal muscle.
  - The highest concentration of LPL is in the cardiac muscle.
- Expression of the tissue-specific isozymes is regulated by nutritional state and hormonal level.
  - In the fed state (elevated insulin levels), LPL synthesis is increased in adipose tissue but decreased in muscle tissue.
  - Fasting (decreased insulin) favors LPL synthesis in muscle.

Low density lipoprotein

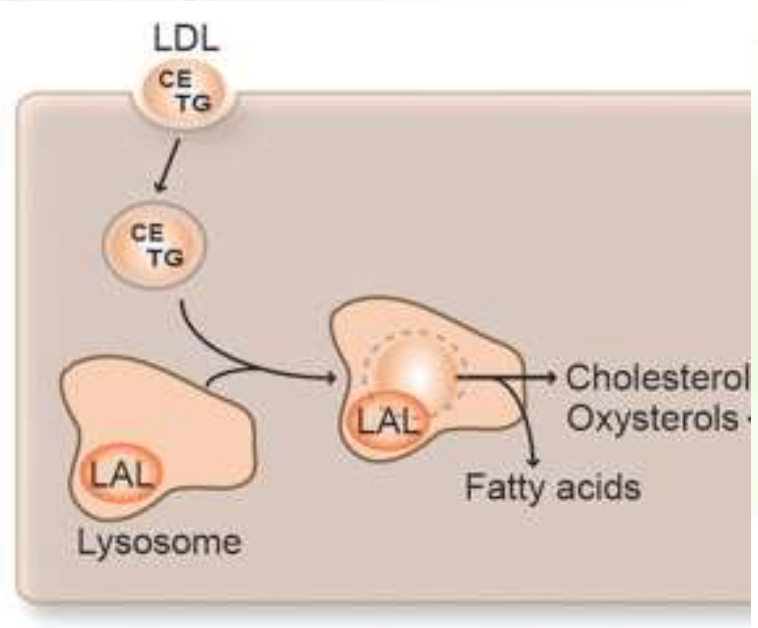
- Primary lipoprotein is B-100.
- Plasma cholesterol, ~70% of LDL content, is taken to peripheral tissues.
- Receptor-mediated endocytosis
- Type IIa hyperlipidemia (familial hypercholesterolemia [FH]): reduced synthesis of functional LDL receptor leading to premature atherosclerosis.
- Defective apo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

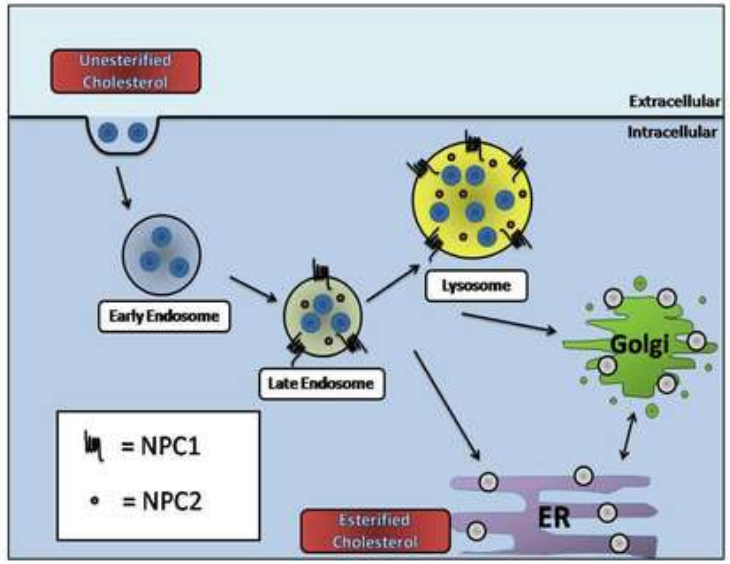


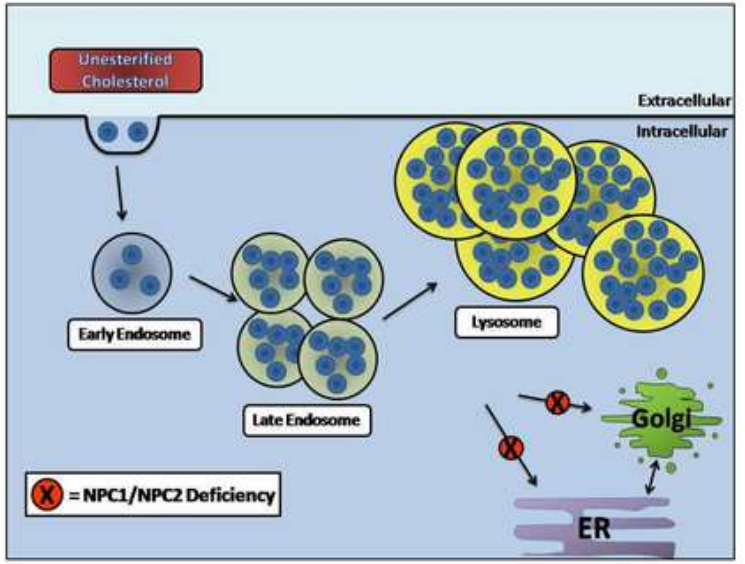
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes internalization and lysosomal degradation of the receptor.
  - PCSK9 inhibitors are now available for the treatment of hypercholesterolemia.

Lysosomal storage diseases

- Lysosomal acid lipase hydrolyzes cholesterol esters and TAG, which are then transported out.
- Wolman disease: a severe, autosomal-recessive deficiency of lysosomal acid lipase leading to massive intracellular accumulation of cholesteryl esters and triglycerides.
- Niemann-Pick disease, type C: autosomal-recessive deficiency in the transport of free cholesterol out of the lysosome.

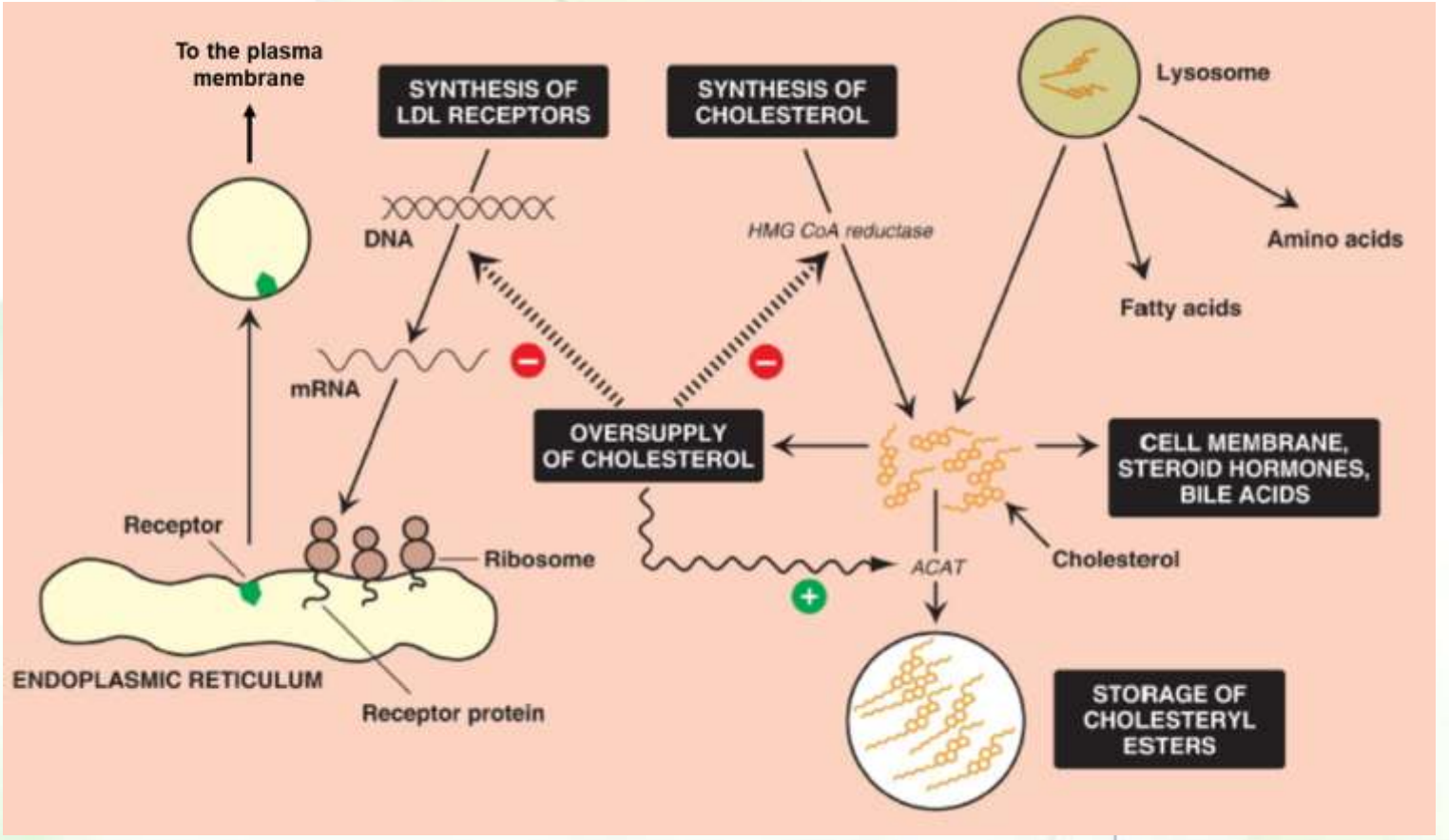






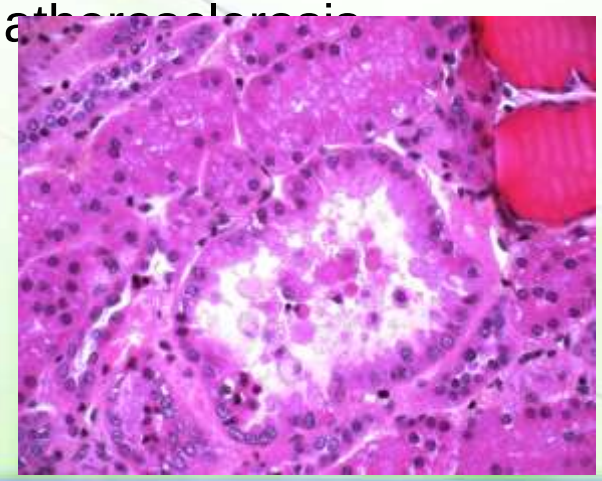
Fate and effects of cholesterol

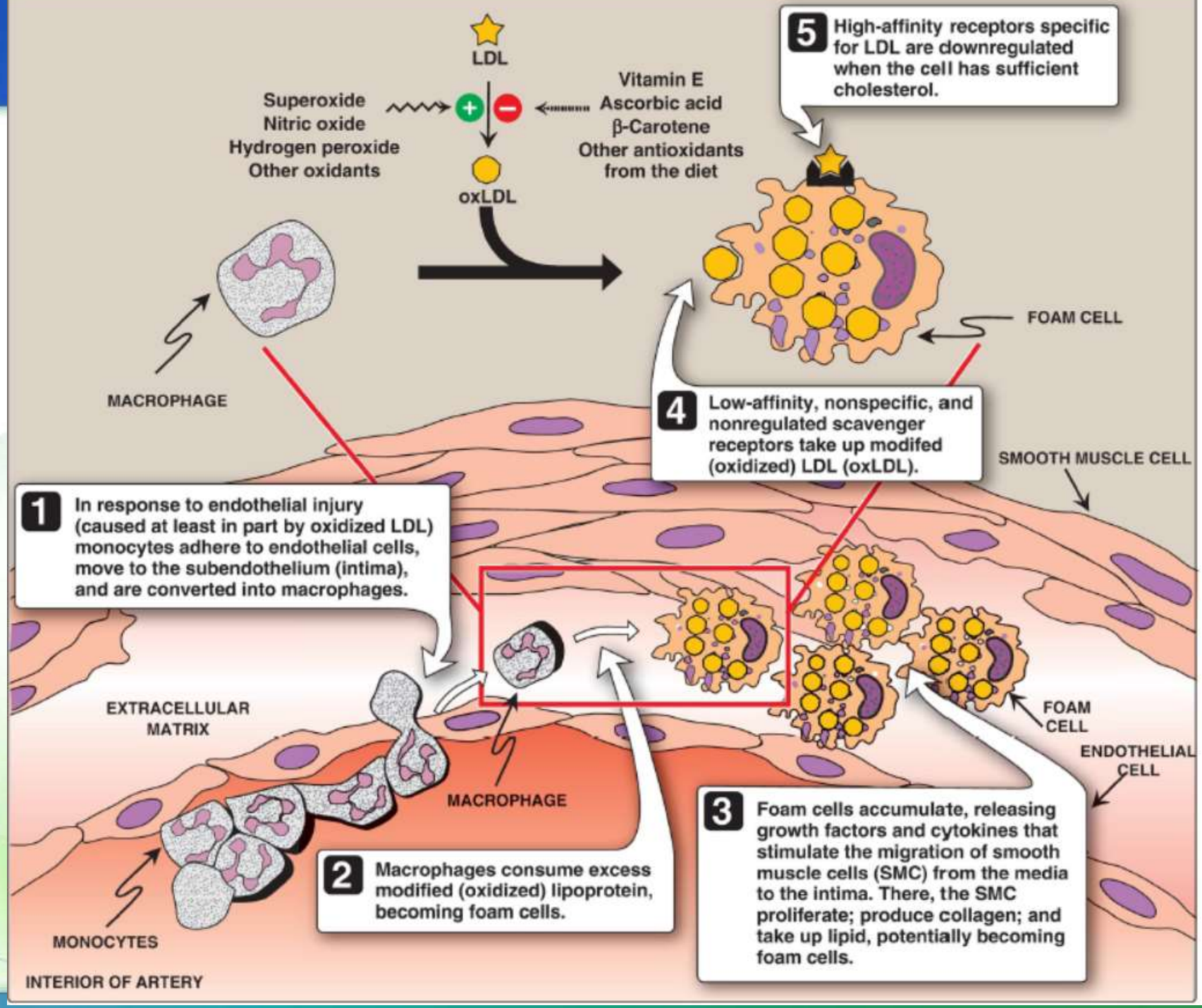
- High intracellular cholesterol levels
  - inhibit de novo cholesterol synthesis
  - induce the degradation of HMG CoA reductase.
  - decrease the synthesis of LDL receptor through the negative regulation of SREBP-2.
- Excess cholesterol is esterified by *acyl CoA:cholesterol acyltransferase* (*ACAT)*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



Foam cells

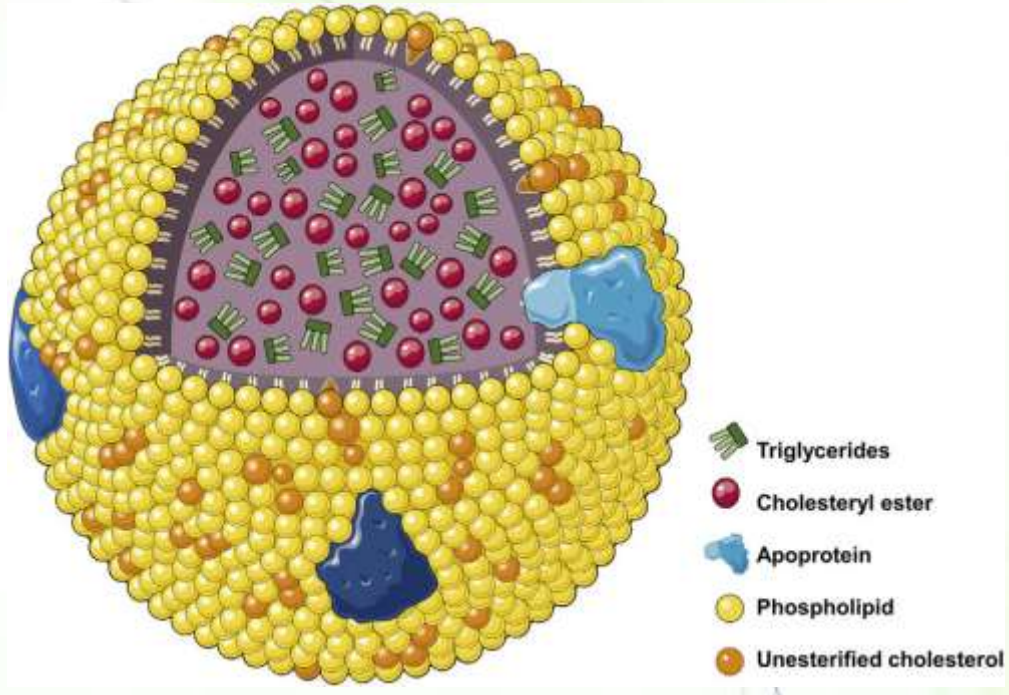
- Macrophages possess high levels of unregulated scavenger receptor class A (SR-A) that can bind and endocytose LDL particles carrying oxidized lipids.
- Cholesteryl esters accumulate in macrophages, which transform into “foam” cells that form atherosclerotic plaque.
- LDL-Cholesterol is the primary cause of a





High-density lipoprotein

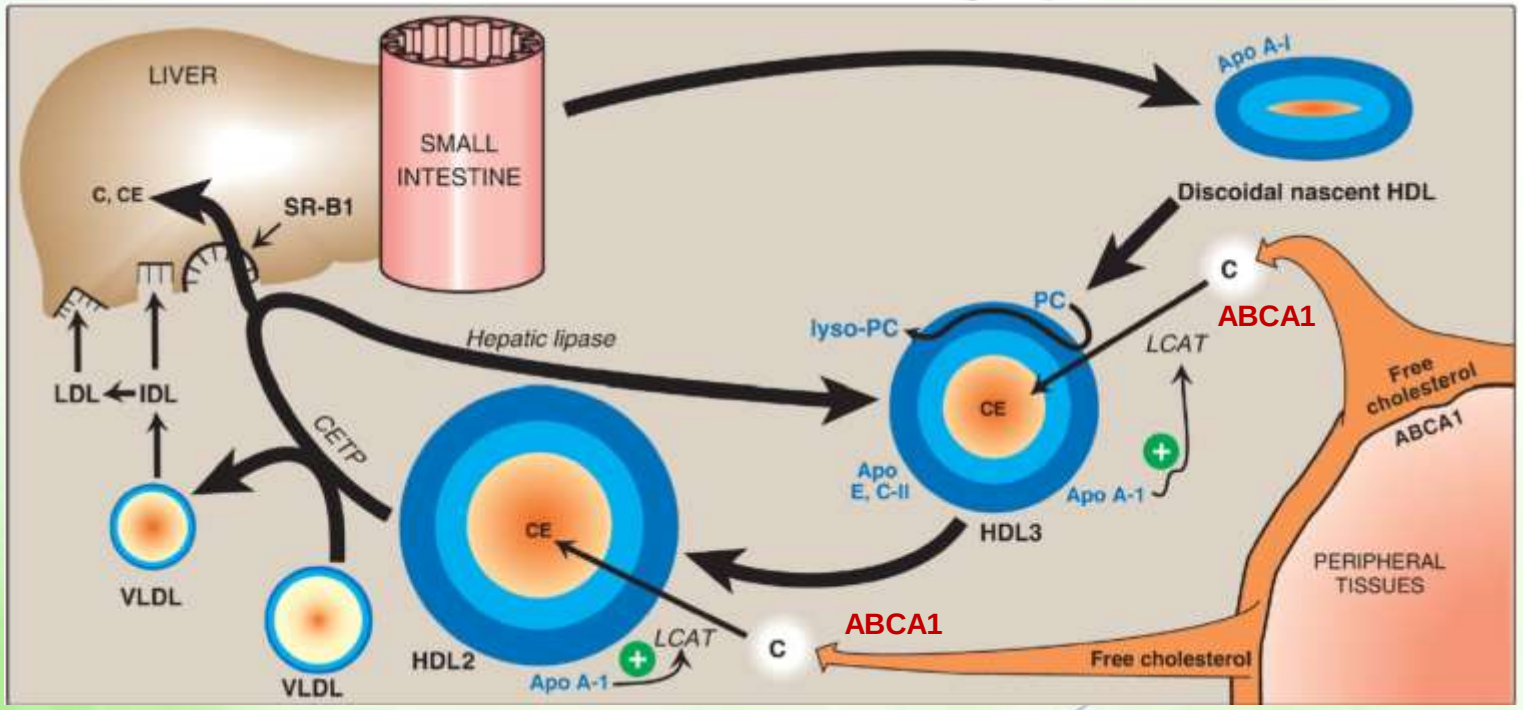
- HDL particles are formed by the addition of lipid to apo A-1 (~70% of lipoproteins in HDL), which is synthesized by the liver and intestine.
- Functions:
  - HDL provides apo CII and E to VLDL and chylomicron remnants.
  - They take up non-esterified cholesterol from peripheral tissues and return it to the liver as cholesteryl esters.



Transport of cholesterol by HDL

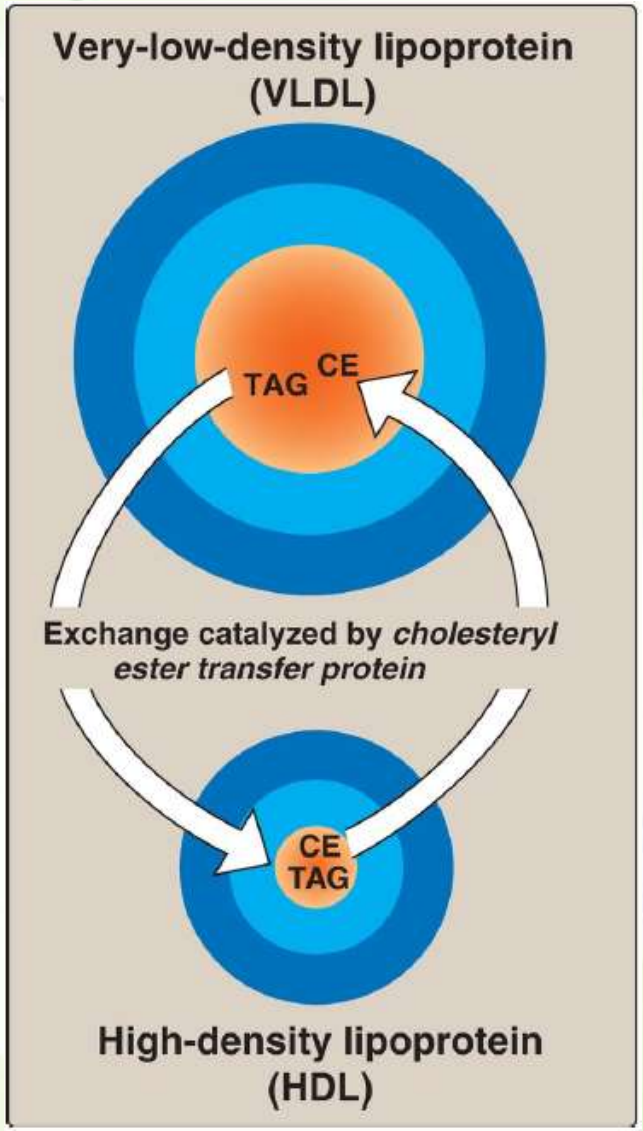
- The liver-synthesized, nascent, HDL-bound plasma enzyme lecithin:cholesterol acyltransferase (LCAT or PCAT) esterifies the HDL-carried cholesterol by transferring the FA of carbon 2 of PC and the CE is sequestered in the HDL core.
- Lysophosphatidylcholine is carried by albumin.
- LCAT is activated by apo A-I and inhibited by cholesterol ester.
- Hepatic lipase, which degrades TAG and phospholipids, participates in the conversion of HDL2 to HDL3.

Note:
Lecithin = phosphatidylcholine



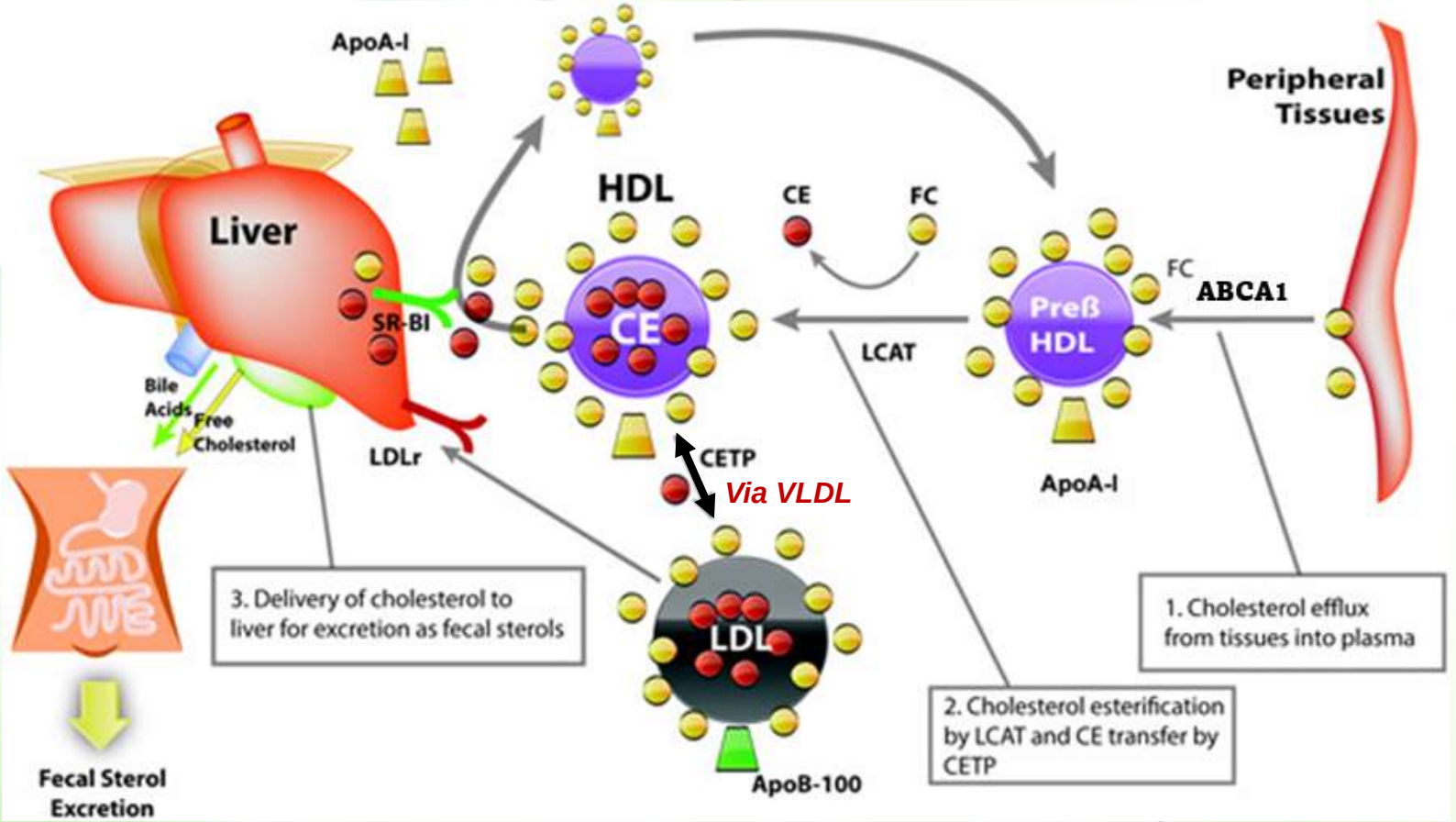
VLDL ↔ HDL through CETP

- Some TAGs are transferred from VLDL to HDL in an exchange reaction that concomitantly transfers cholesteryl esters from HDL to VLDL.
- This exchange is accomplished by cholesteryl ester transfer protein (CETP).
- End-result is relieving product inhibition of LCAT.
- VLDL can then be converted to IDL and LDL.



Reverse cholesterol transport

- The efflux of cholesterol from peripheral cells is mediated primarily by the transport protein ABCA1.
  - Tangier disease: no ABCA1, no HDL particles, degradation of apo A-1.
- Cholesteryl ester uptake by the liver is mediated by scavenger receptor class B type 1 (SR-B1).



Defective ABCA1 causes sitosterolemia, cystic fibrosis, X-linked adrenoleukodystrophy, respiratory distress syndrome, and liver disease.