Lipoproteins

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Lipoproteins

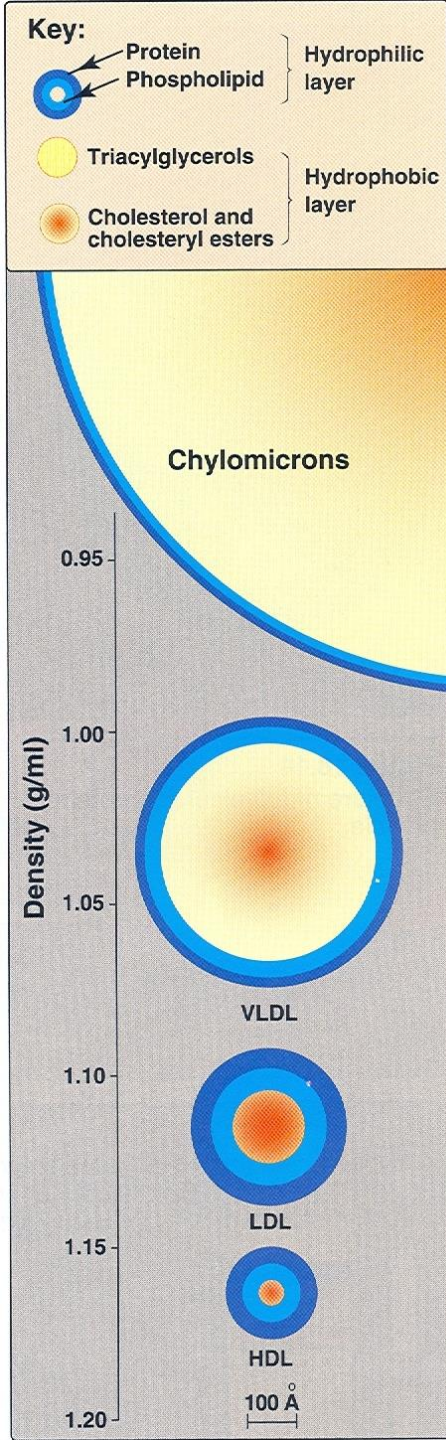
- Function: Transport of fat soluble substances

- Types:
  1) Chylomicron
  2) VLDL
  3) LDL
  4) HDL

How can lipoproteins Differ

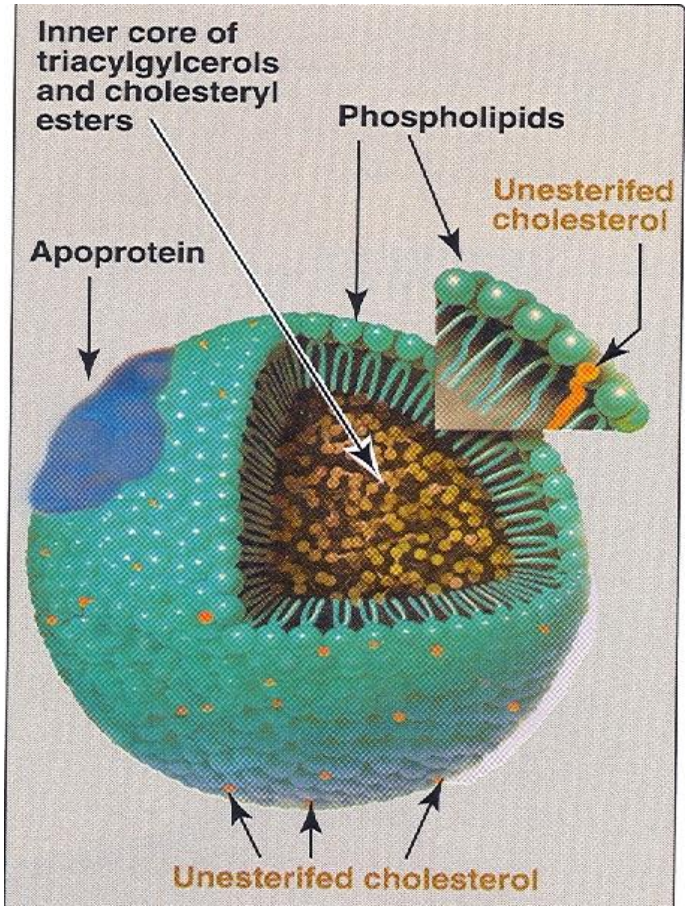
- They differ according to:

1. Composition of lipids to proteins
2. Size
3. Density



Composition of Plasma Lipoproteins

- Neutral core (TAG, exogenous or *de novo,* cholesterol esters)
- Amphipathic apolipoprotein
- Phospholipids
- Cholesterol



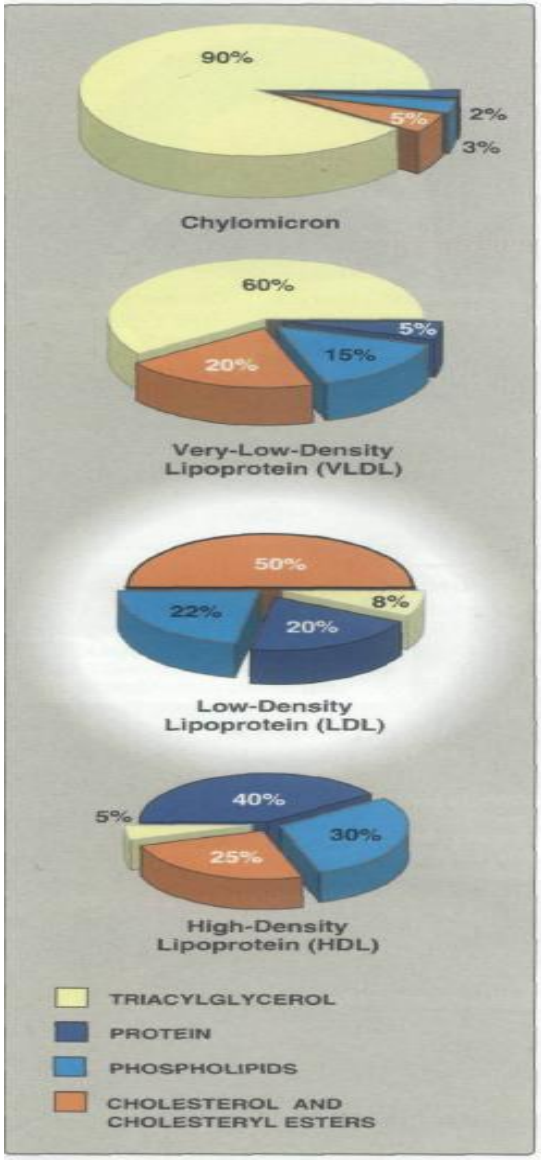


Figure 18.19
Composition of the plasma lipoproteins. Note high concentration of cholesterol and cholesteryl esters in LDL.

Classes of apolipoproteins

- A, B, C, D, E are major classes
- Subclasses: apo A-1, apo C-II
- N.B. function of all apolipoproteins are not yet known

Type	Association	Function
B48	Chylomicron	Carry cholesterol esters Lacks LDL receptor binding domain
B100	VLDL,IDL,LDL	Binds LDL recpt.
C-II	Chyl. VLDL, IDL, HDL	Activates LPL
C-III	Chyl. VLDL, IDL, HDL	Inhibits LPL
E	Chyl. Remnant, VLDL, IDL HDL	Binds LRP
A-1	HDL/Chylomicron	LCAT activator (lecithin:cholesterol acyltransferase)

Functions of Apo proteins

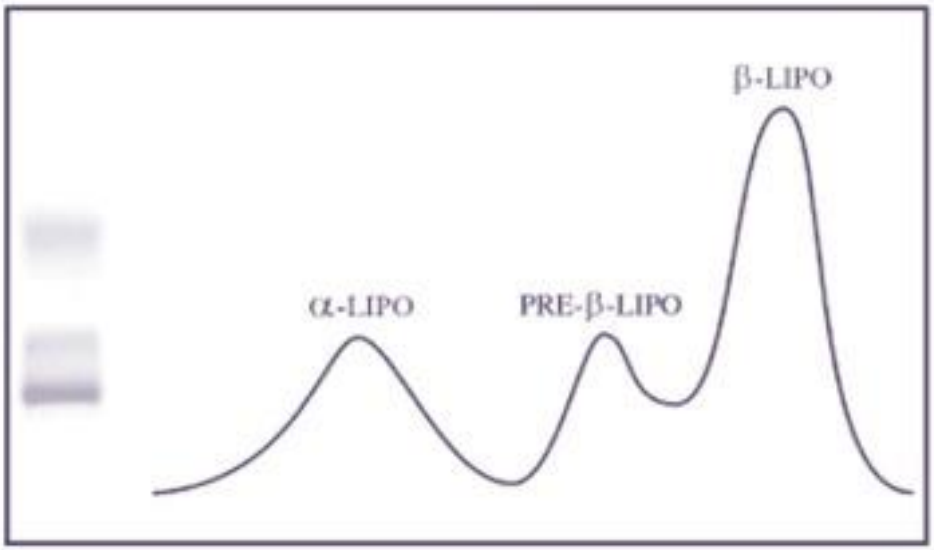
(1) They can form part of the structure of the lipoprotein, e.g. apo B, structural component of VLDL and Chylomicons

(2) They are enzyme cofactors, e.g. C-II for lipoprotein lipase, A-I for lecithin: cholesterol acyl transferase (LCAT), or enzyme inhibitors, eg, apo A-II and apo C-III for lipoprotein lipase, apo C-I for cholesteryl ester transfer protein

(3) They act as ligands for interaction with lipoprotein receptors in tissues, e.g. apo B-100 and apo E for the LDL receptor, apo A-I for the HDL receptor.

Classification of Lipoproteins

LIPOPROTEINS INTERPRETATION



Normal values range

Fraction	% Lipoproteine tot.
α-Lipo	20-48
Pre-β-Lipo	12-30
β-Lipo	45-70
Chilomicroni	0

Lipoproteins may be separated according to their electrophoretic properties into - **α, pre β, β,** and broad beta **lipoproteins.**

Classification of Lipoproteins

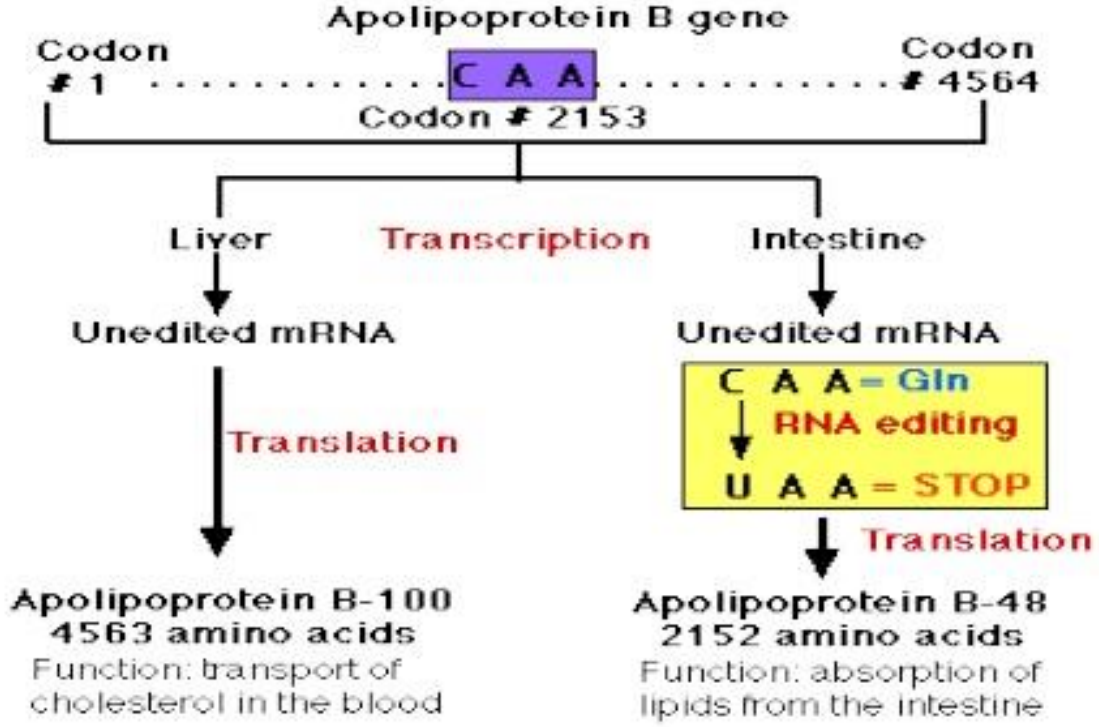
2) Based on electrophoretic mobilities (contd.)

- HDL are -α , VLDL pre- β, LDL-β , and IDL are broad beta lipoproteins.
- Free fatty acid and albumin complex although not a lipoprotein is an important lipid fraction in serum and is the fastest moving fraction.
- Chylomicrons remain at the origin since they have more lipid content.
- VLDLs with less protein content than LDL move faster than LDL, this is due to nature of apoprotein present.

Chylomicrons

- Made by: the small intestines in the fed state
- Absorbed into: the lymph vessels, then --> moves into the blood
- Rich in: TGs
- Function: Deliver TG's to body cells to be used as fuel

Synthesis of Chylomicrons



The synthesis of apo B48 is the result of RNA editing process.

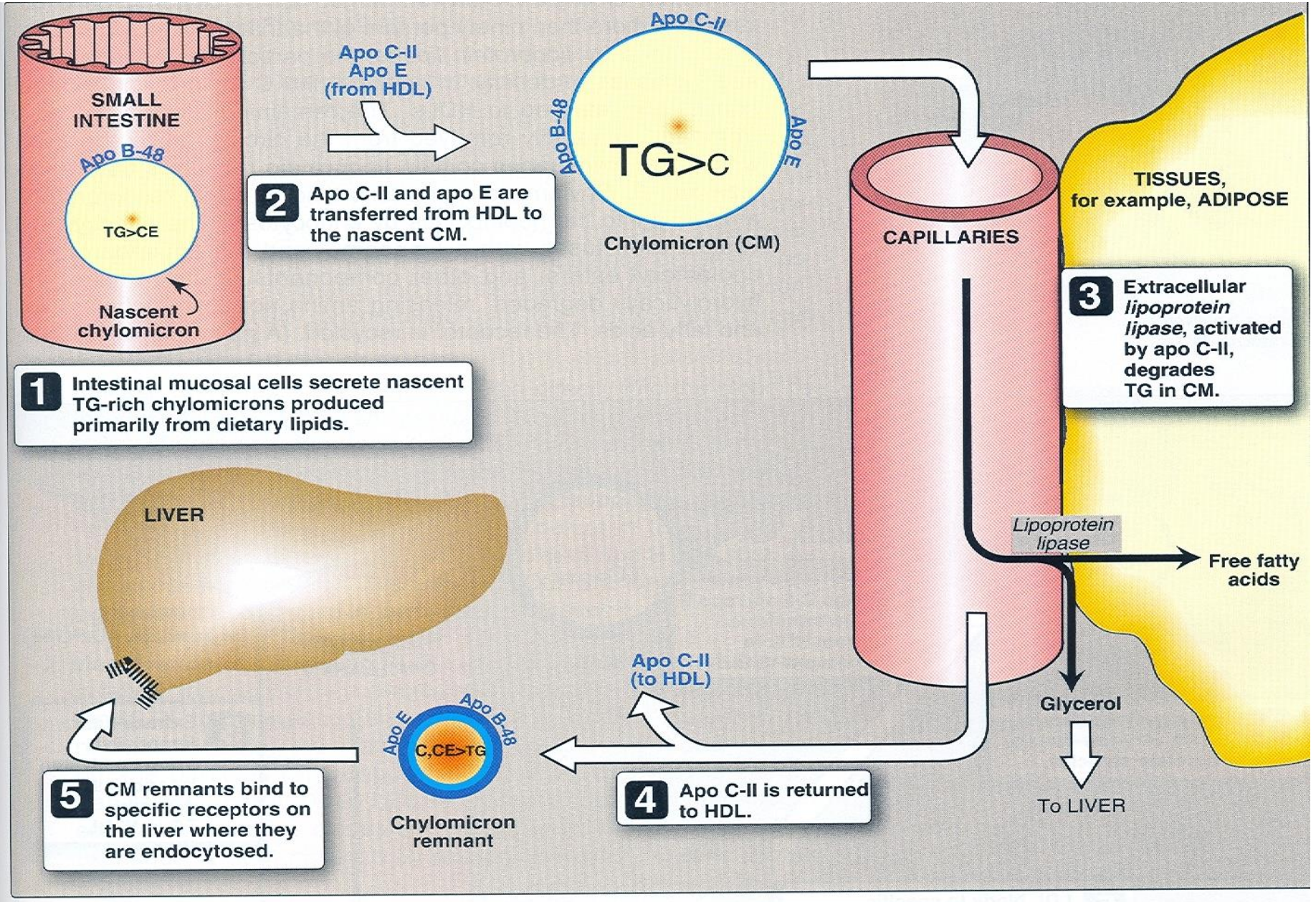
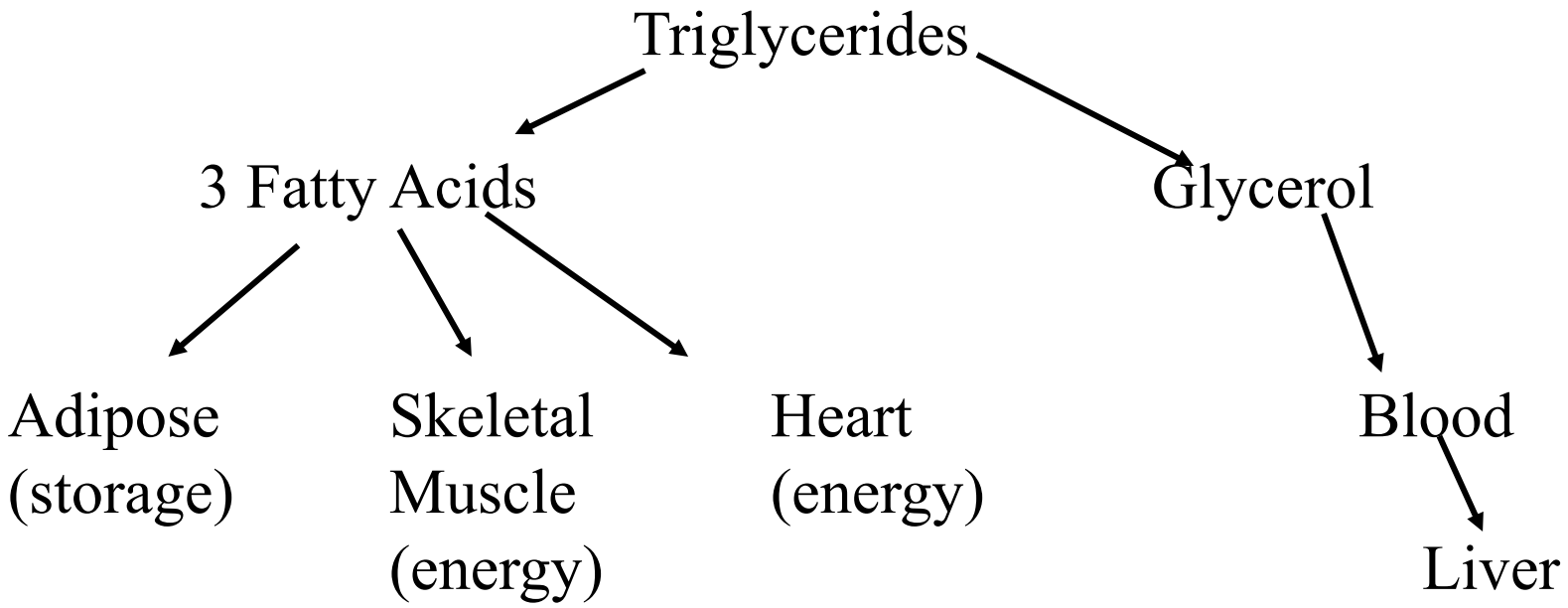


Figure 18.16
Metabolism of chylomicrons. CM = chylomicron; TG = triacylglycerol; C = cholesterol; CE = cholesteryl esters. Apo B-48, apo C-II, and apo E are apolipoproteins found as specific components of plasma lipoproteins. The lipoproteins are not drawn to scale (see Figure 18.13 for details of the size and density of lipoproteins).

Chylomicron



Chylomicron Remnant

↓

Liver

VLDL

- = Very Low Density Lipoprotein
- Made in: the liver from excess dietary carbohydrate and protein along with the Chylomicron remnant
- Secreted into: the bloodstream
- Rich in: TGs
- Function: Deliver TGs to body cells
- Contains apo B100
- Similar to Chylomicrons, but made by different tissues

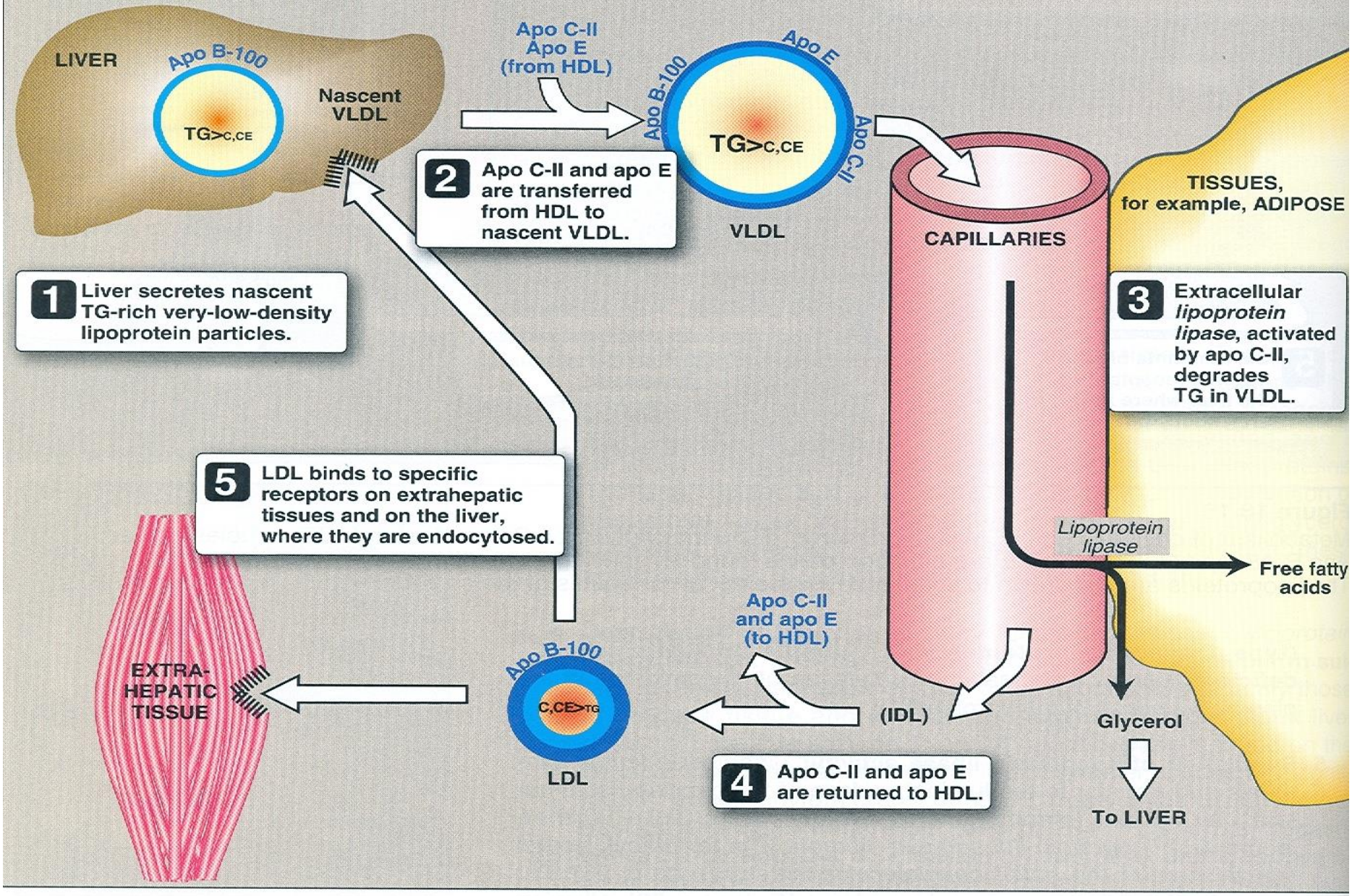


Figure 18.17

Metabolism of VLDL and LDL. TG = triacylglycerol; VLDL = very-low-density lipoprotein; LDL = low-density-lipoprotein; IDL = intermediate-density lipoprotein; C = cholesterol; CE = cholesterol esters. Apo B-100, apo C-II, and apo E are apolipoproteins found as specific components of plasma lipoproteins. Lipoproteins are not drawn to scale (see Figure 18.13 for details of the size and density of lipoproteins).

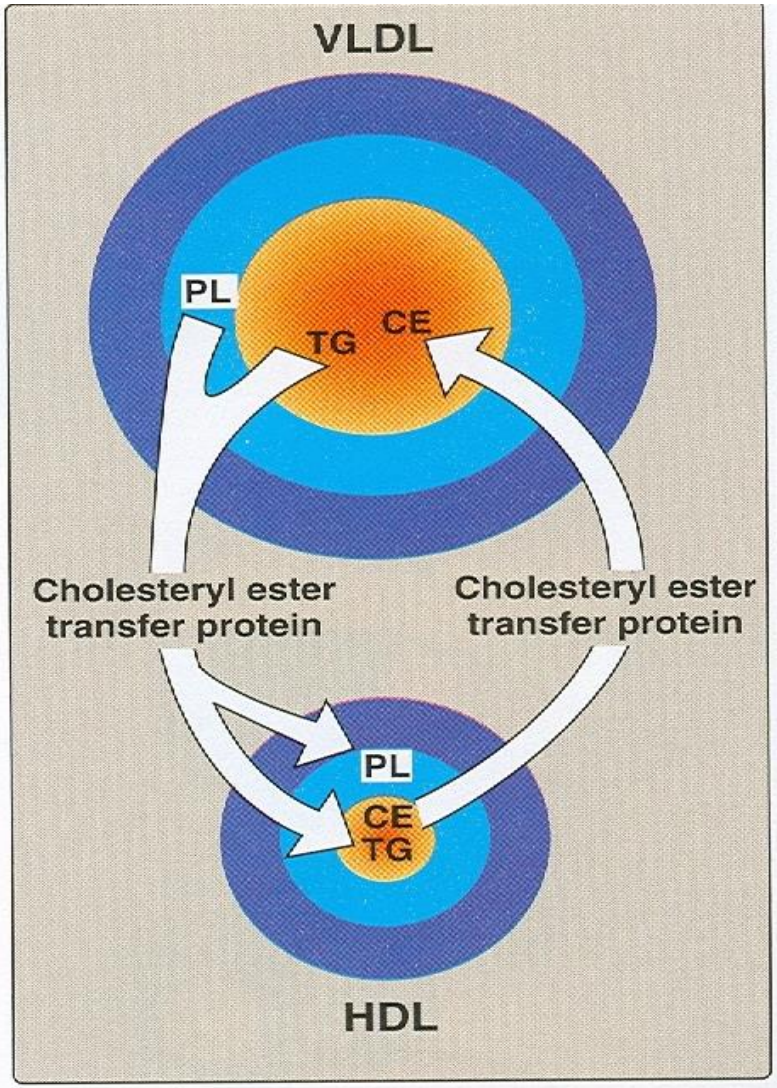
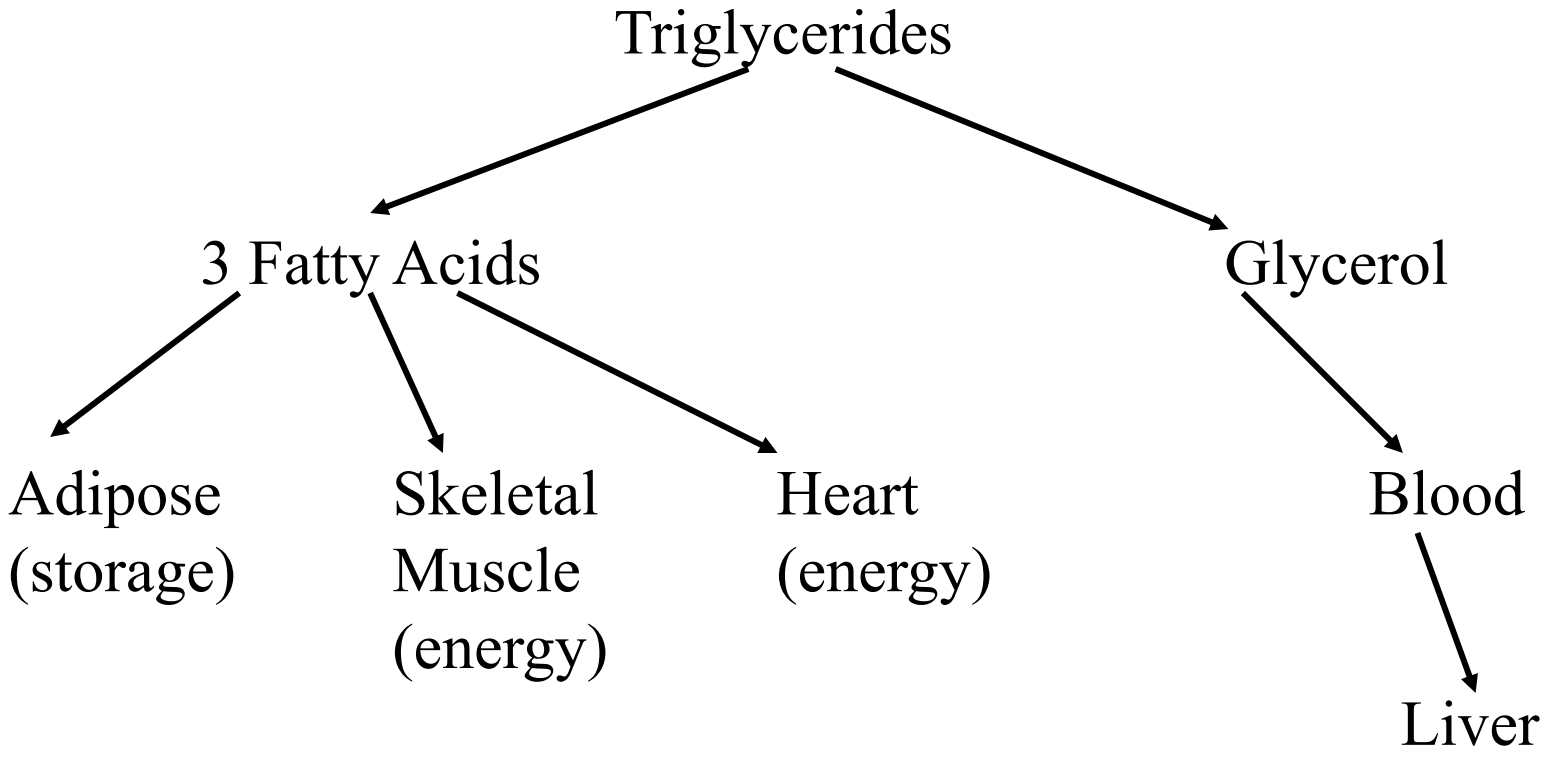


Figure 18.18
Transfer of cholesteryl esters (CE) from HDL to VLDL in exchange for triacylglycerol (TG) or phospholipids (PL).

VLDL



Once VLDL looses much of its TG's it becomes LDL

LDL

- = Low Density Lipoprotein
- Made in: the Liver as VLDL
- Arise from: VLDL once it has lost a lot of its TG's
- Secreted into: the bloodstream
- Rich in: Cholesterol
- Function: Deliver cholesterol to all body cells

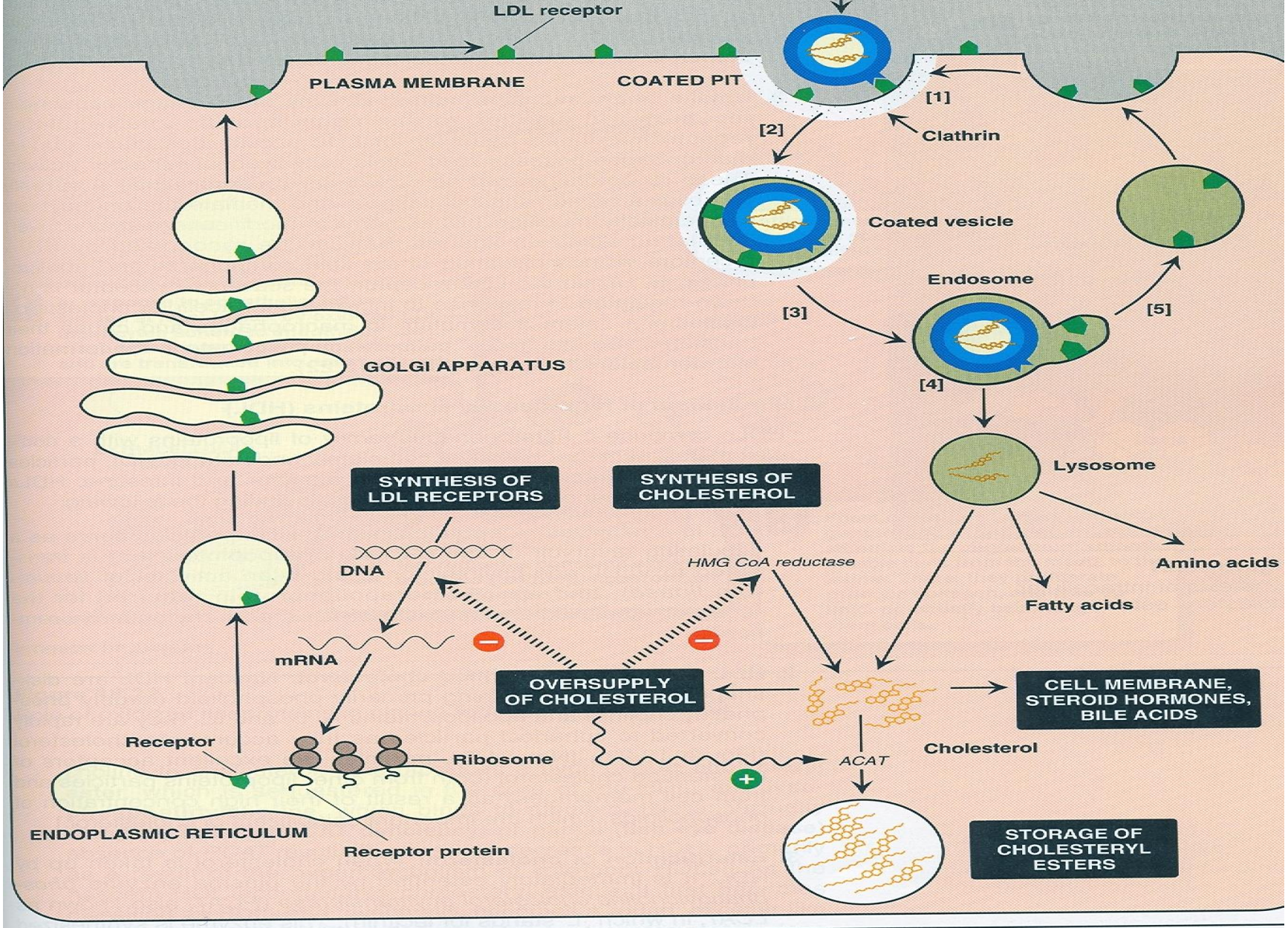


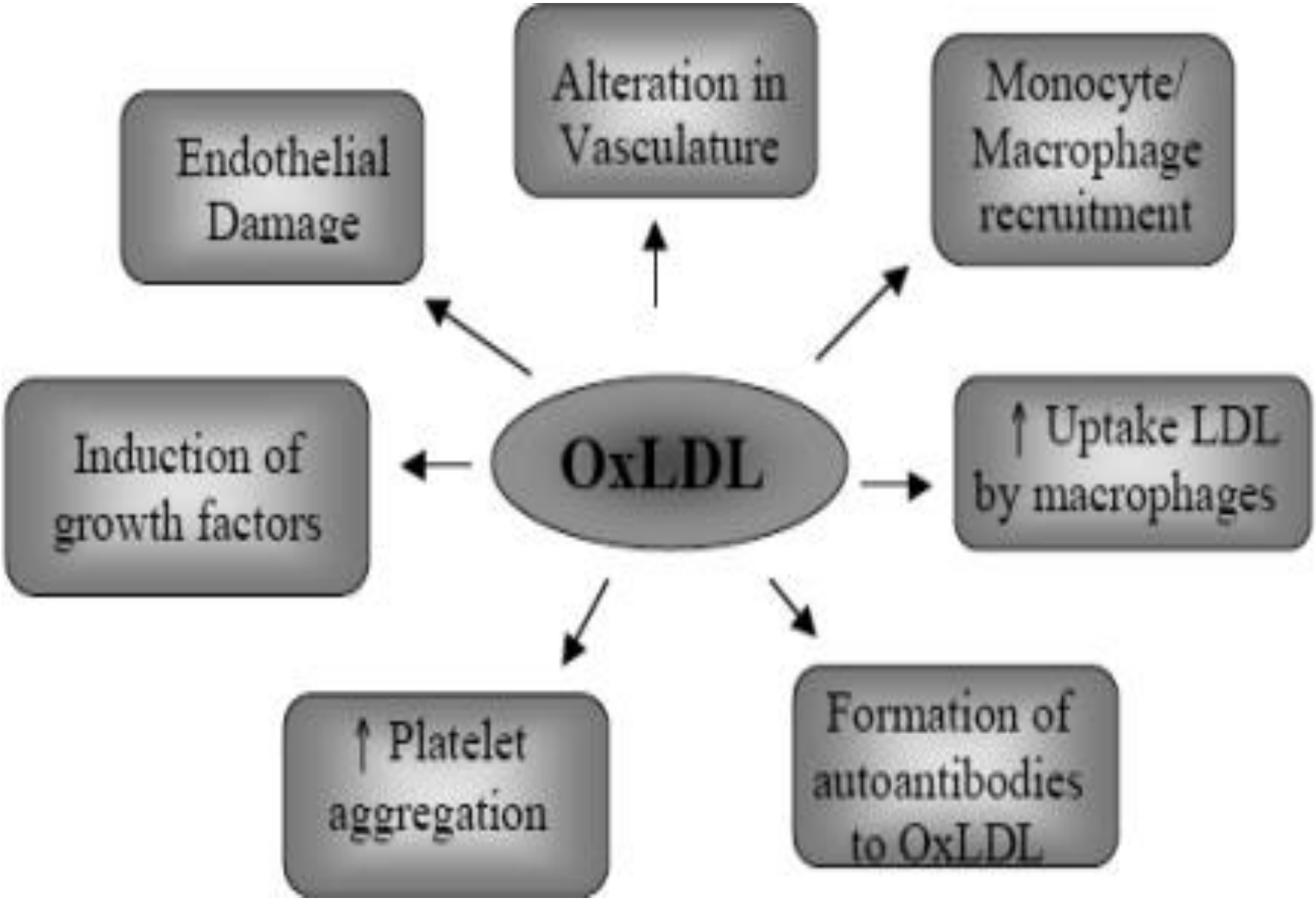
Figure 18.20
Cellular uptake and degradation of LDL. *ACAT = acyl CoA:cholesterol acyltransferase.*

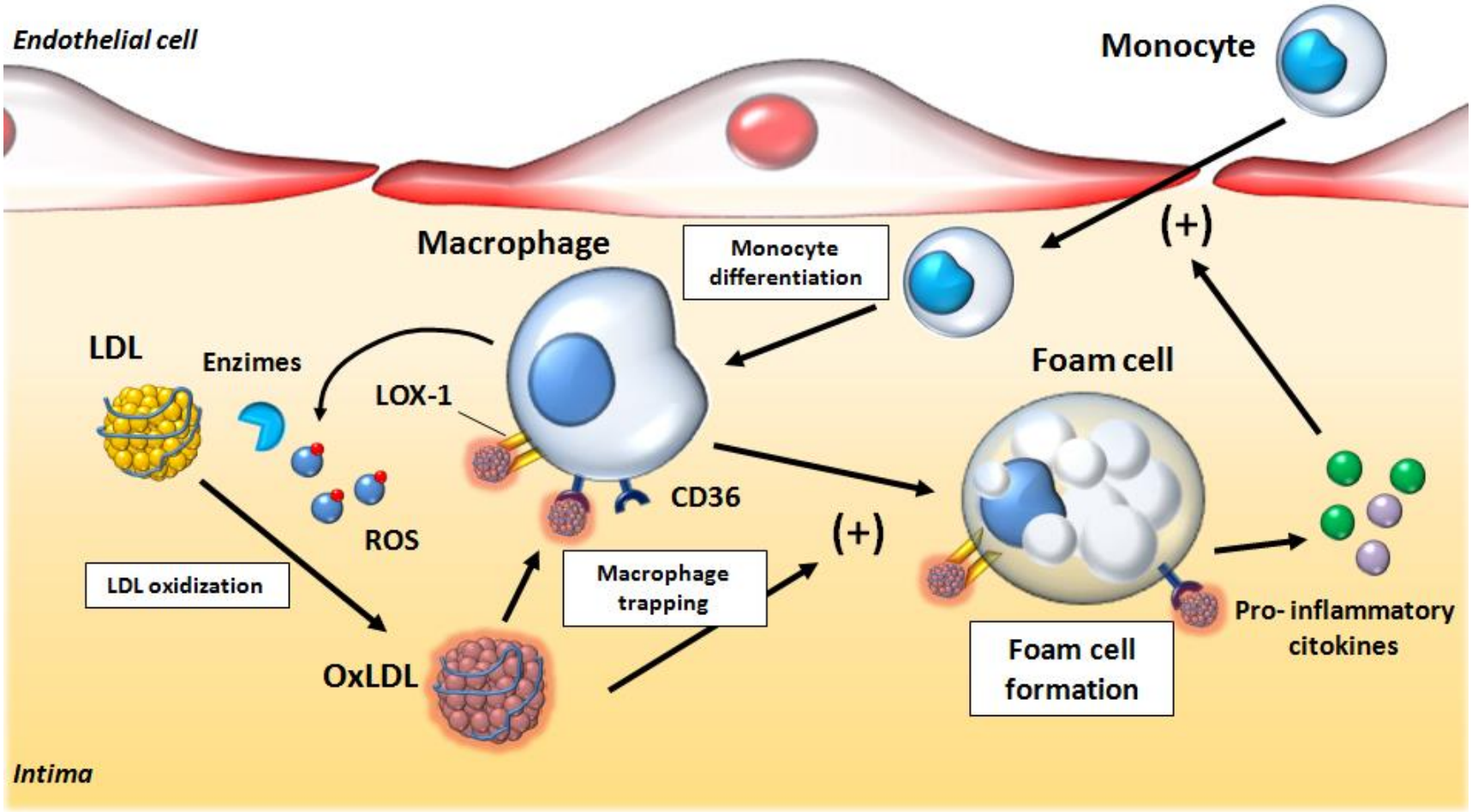
Oxidation of LDL (oxLDL)

- Oxidation = process by which free radicals (oxidants) attack and damage target molecules / tissues
- Targets of free radical attack:
  - DNA - carbohydrates
  - Proteins - PUFA's>>> MUFA's>>>>> SFA's

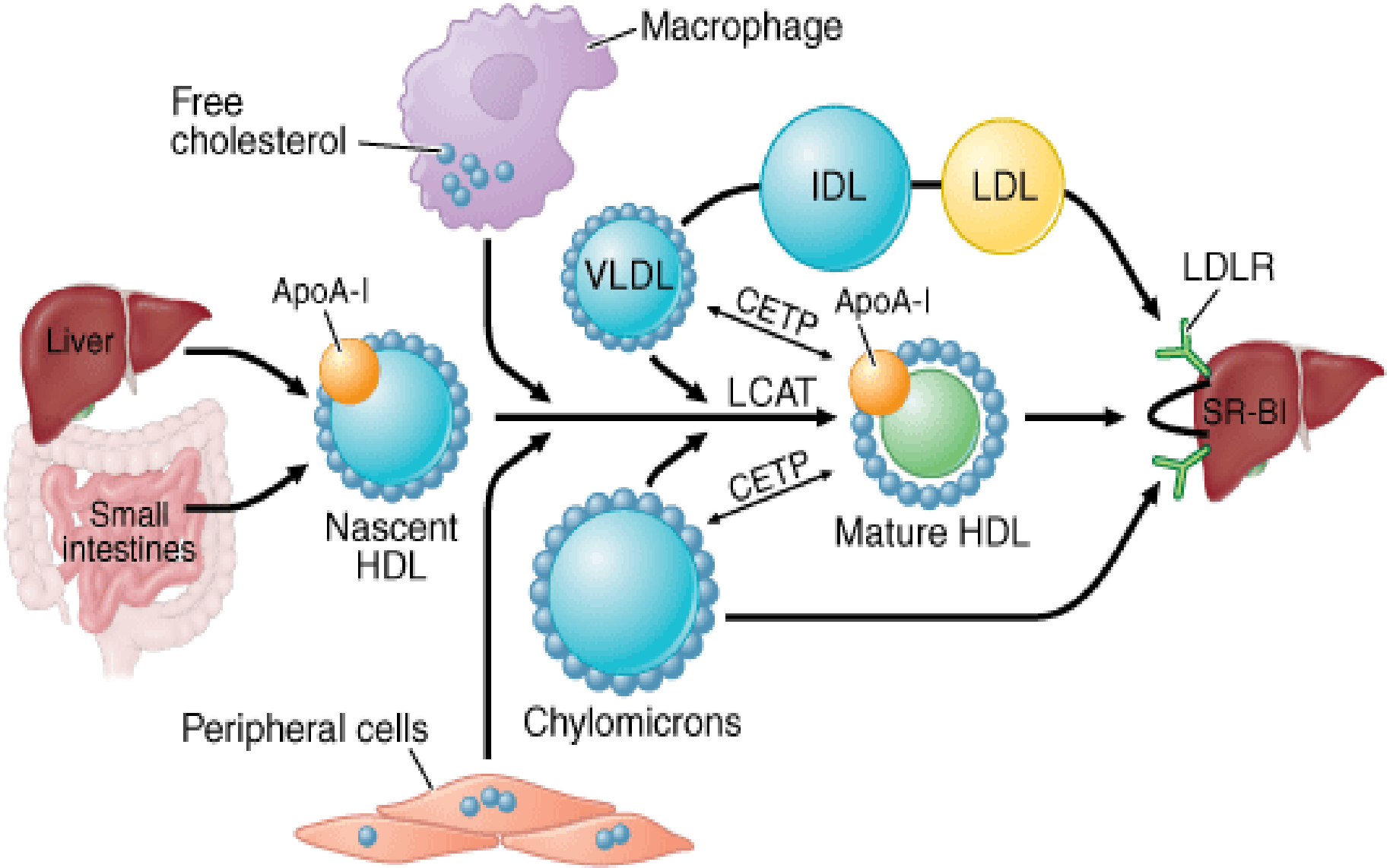
- LDL can be oxidatively damaged: PUFA's are oxidized and trigger oxidation of $apoB_{100}$ protein --> oxLDL

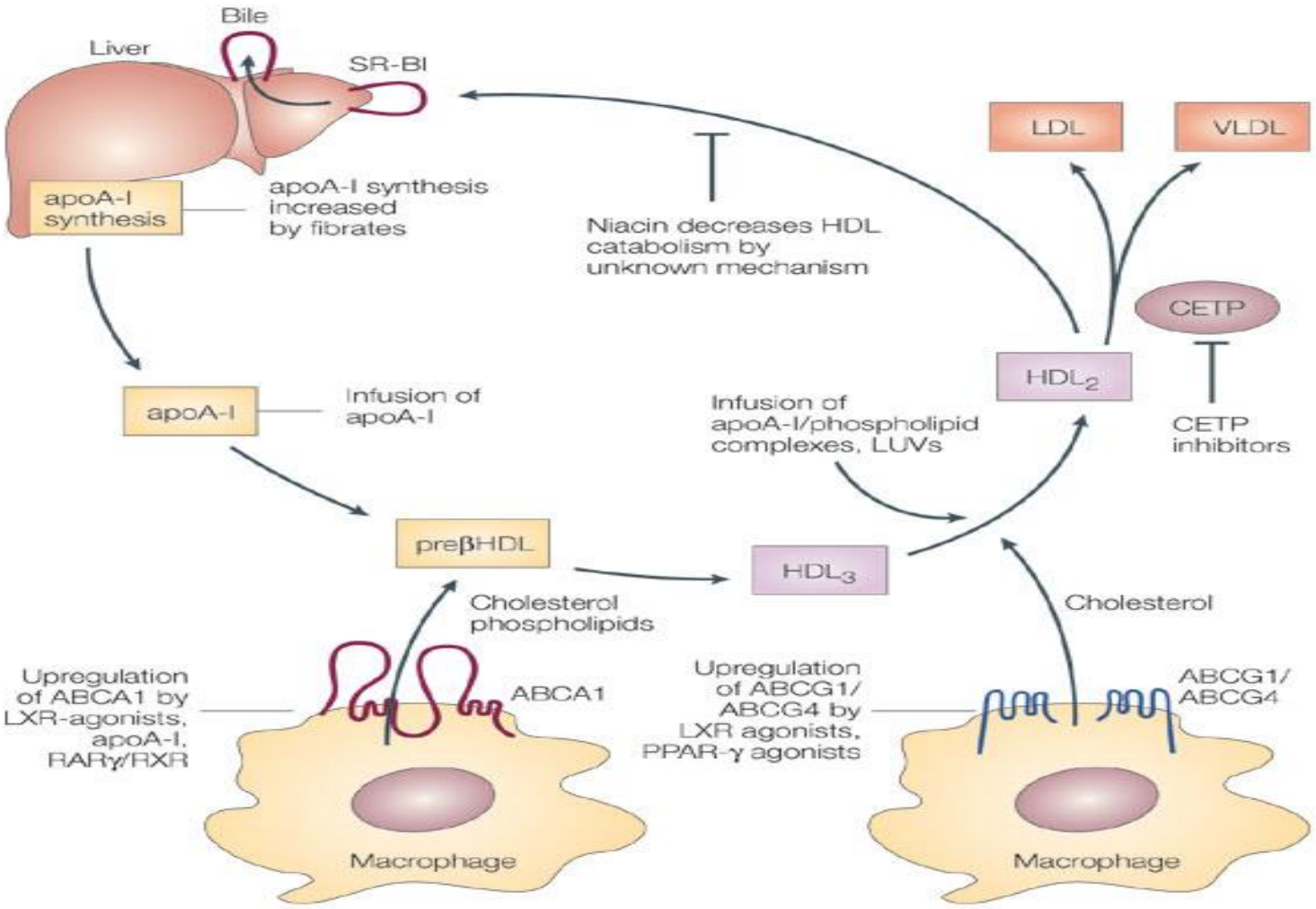
- OxLDL is engulfed by macrophages in subendothelial space


Alteration in Vasculature
Endothelial Damage
Monocyte/ Macrophage recruitment
Induction of growth factors
OxLDL
↑ Uptake LDL by macrophages
↑ Platelet aggregation
Formation of autoantibodies to OxLDL

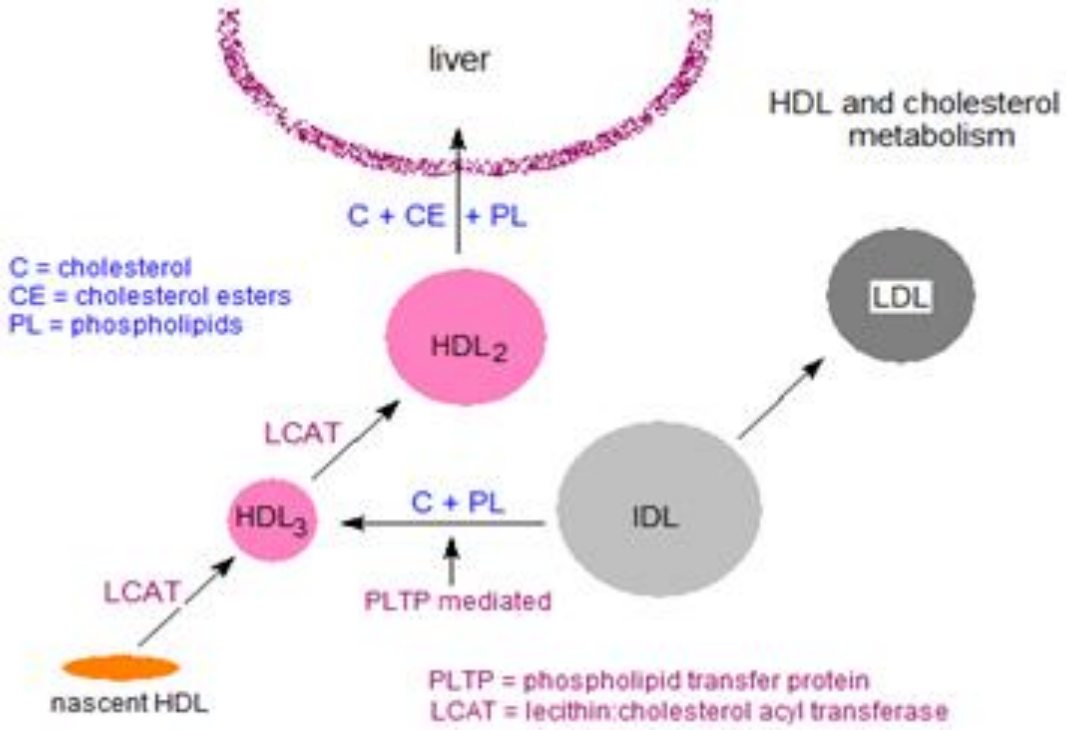

Endothelial cell
Monocyte
Macrophage
Monocyte differentiation
(+)
LDL
Enzimes
LOX-1
Foam cell
CD36
ROS
LDL oxidization
Macrophage trapping
(+)
Pro- inflammatory citokines
OxLDL
Foam cell formation
Intima

HDL


Macrophage
Free cholesterol
IDL
LDL
VLDL
CETP
ApoA-I
LDLR
Liver
ApoA-I
LCAT
SR-BI
Small intestines
Nascent HDL
CETP
Mature HDL
Chylomicrons
Peripheral cells



Nature Reviews | Drug Discovery


liver
HDL and cholesterol metabolism
C + CE + PL
C = cholesterol
CE = cholesterol esters
PL = phospholipids
LDL
HDL2
LCAT
HDL3
C + PL
IDL
LCAT
PLTP mediated
nascent HDL
PLTP = phospholipid transfer protein
LCAT = lecithin:cholesterol acyl transferase

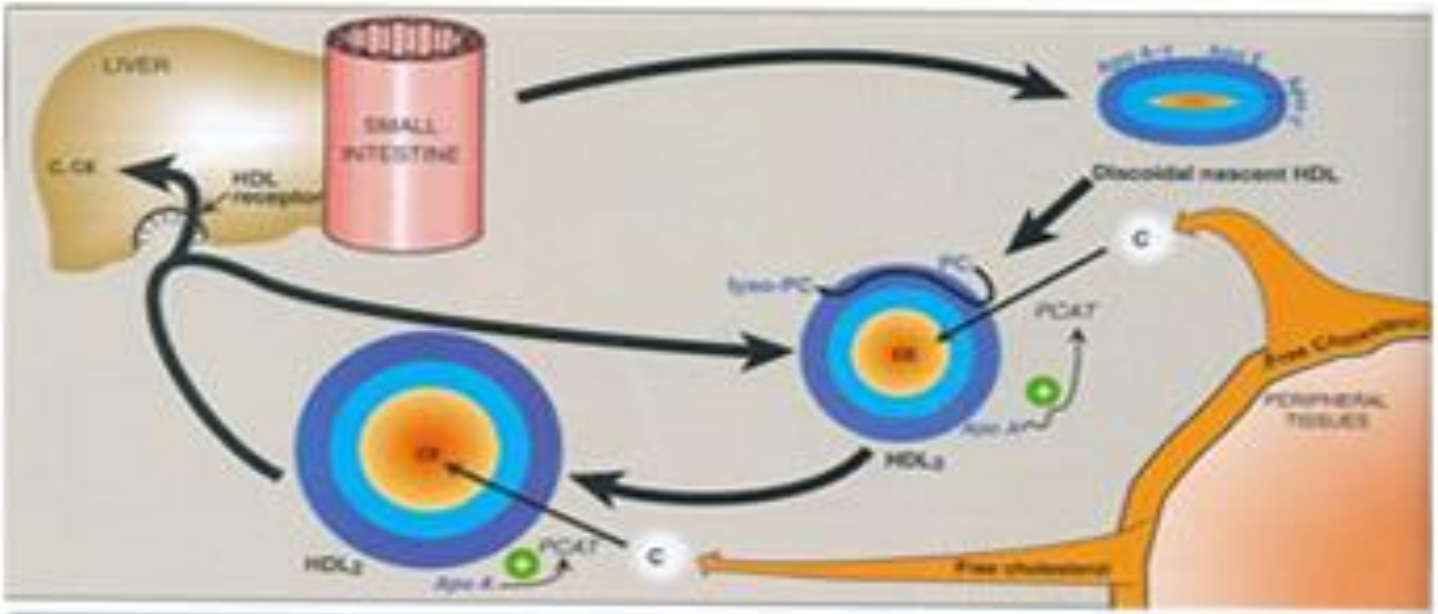


Figure 18.23
Metabolism of HDL. PC = phosphatidylcholine; lyso-PC = lysophosphatidylcholine. *PCAT = Phosphatidylcholine cholesterol transferase.*

Metabolism of HDL

Synthesis of HDL

- 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 bilayer containing apo A and free cholesterol.

Metabolism of HDL

- LCAT and the LCAT activator apo A-I—bind to the discoidal particles, 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.
- This aids the removal of excess unesterified cholesterol from lipoproteins and tissues .

Metabolism of HDL

Role of LCAT

- LCAT(Lecithin Cholesterol Acyl Transferase) enzyme catalyzes the esterification of cholesterol to form Cholesteryl ester. The reaction can be represented as follows-
- Lecithin + Cholesterol ⟶ Lysolecithin + Cholesteryl Ester

Metabolism of HDL

- The **class B scavenger receptor B1 (SR-B1)** has been identified as an **HDL receptor with a dual role in HDL metabolism.**
- In the liver and in steroidogenic tissues, it binds HDL via apo A-I, and cholesteryl ester is selectively delivered to the cells, although the particle itself, including apo A-I, is not taken up.
- In the tissues, on the other hand, SR-B1 mediates the acceptance of cholesterol from the cells by HDL, which then transports it to the liver for excretion via the bile (either as cholesterol or after conversion to bile acids) in the process known as **reverse cholesterol transport**

HDL- cycle

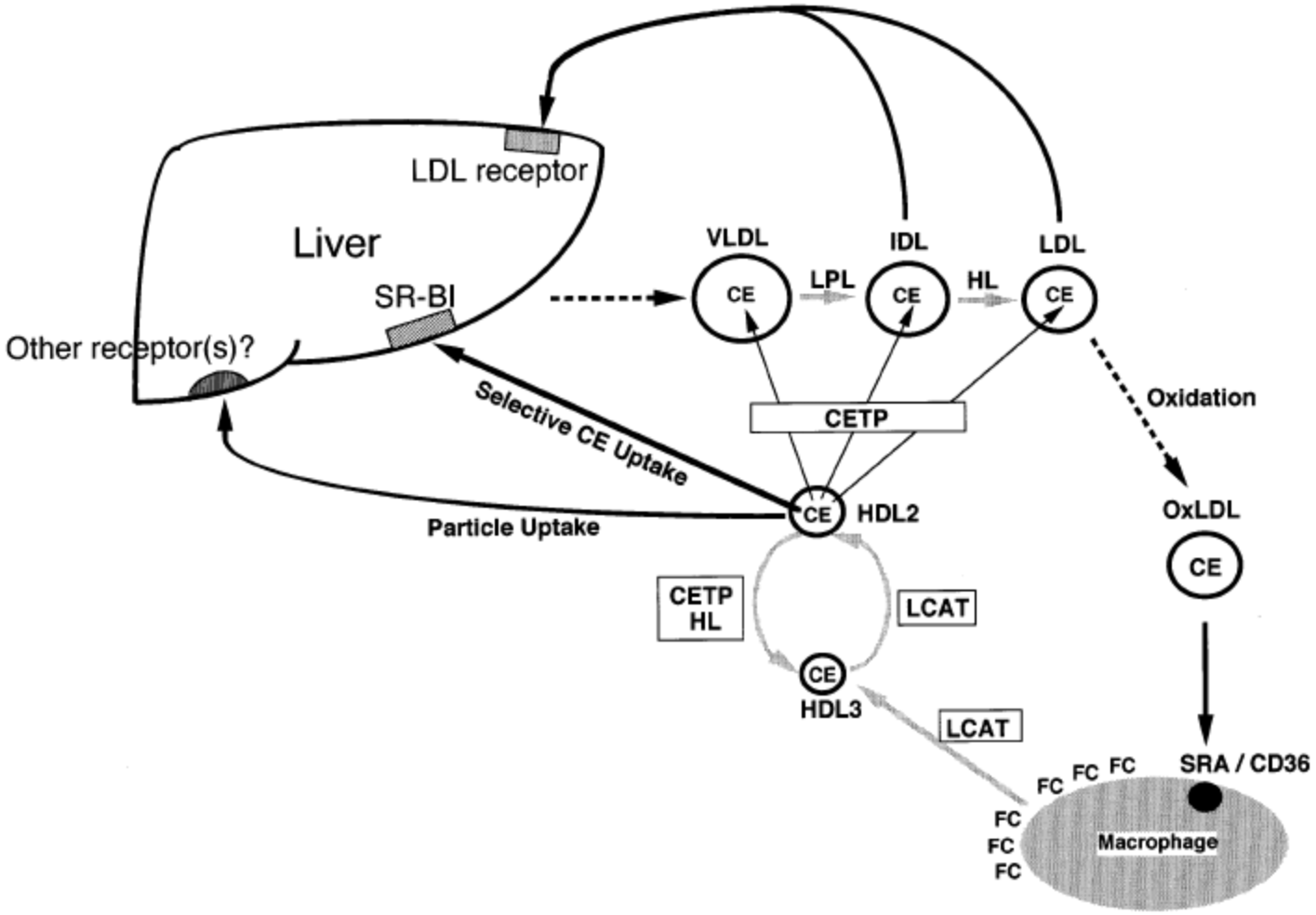
- HDL_3, generated from discoidal HDL by the action of LCAT, accepts cholesterol from the tissues via the **SR-B1** and the cholesterol is then esterified by LCAT, increasing the size of the particles to form the less dense HDL_2.
- HDL_3 is then reformed, either after selective delivery of cholesteryl ester to the liver via the SR-B1 or by hydrolysis of HDL_2 phospholipid and triacylglycerol by hepatic lipase. This interchange of HDL_2 and HDL_3 is called the HDL cycle.
- Free apo A-I is released by these processes and forms **pre -HDL** after associating with a minimum amount of phospholipid and cholesterol

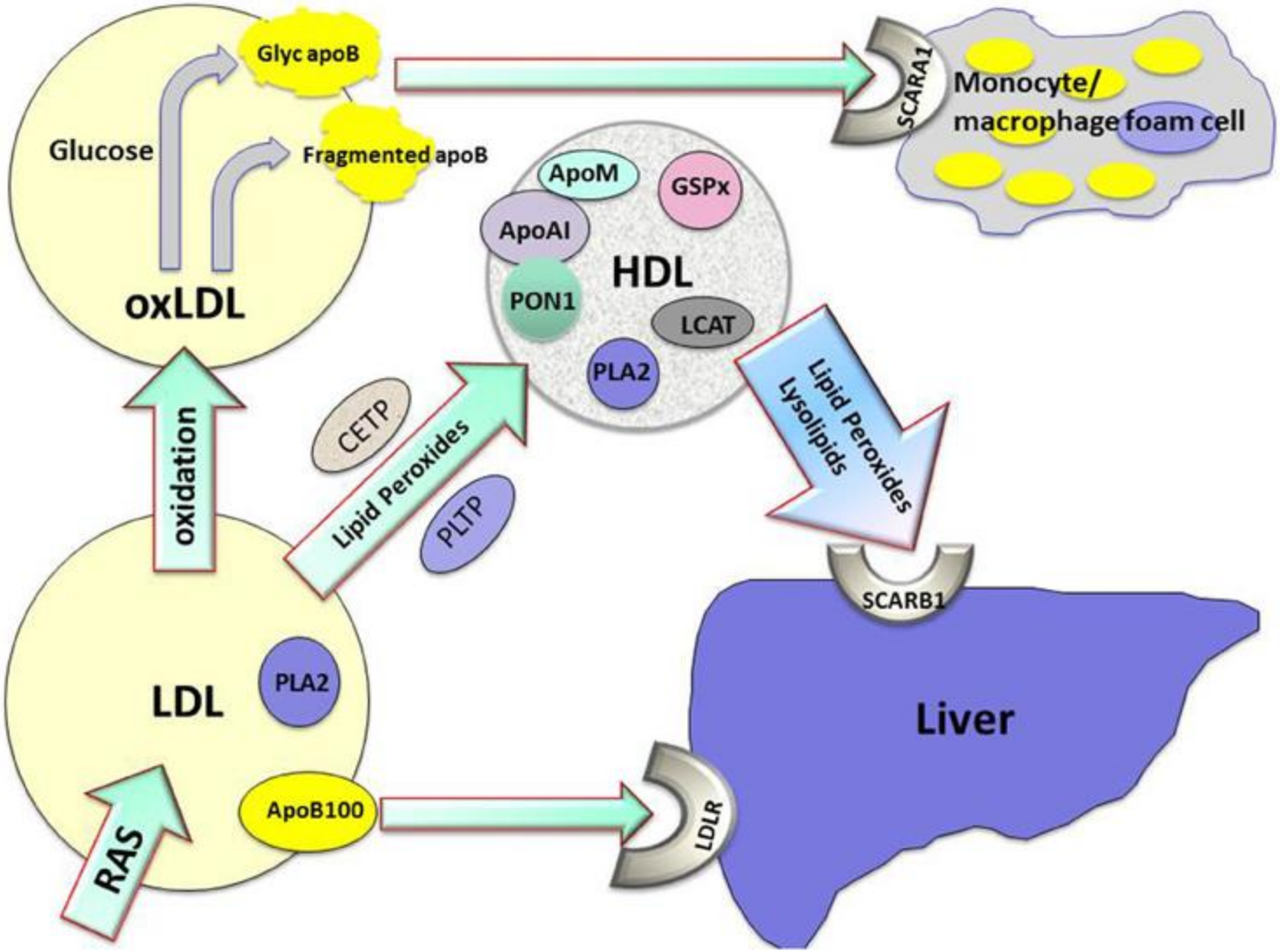
Metabolism of HDL

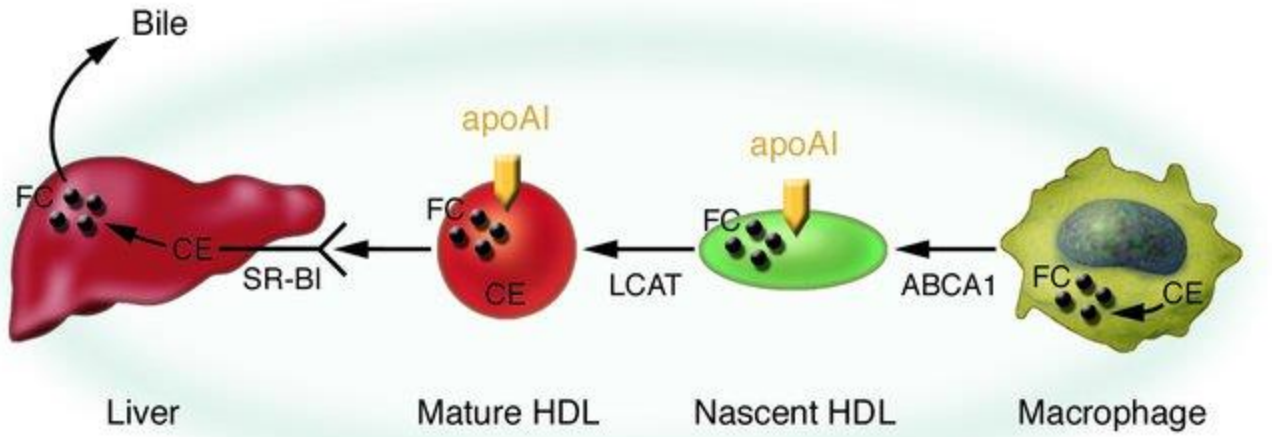
- A second important mechanism for reverse cholesterol transport involves the **ATP-binding cassette transporter A1 (ABCA1).**
- ABCA1 is a member of a family of transporter proteins that couple the hydrolysis of ATP to the binding of a substrate, enabling it to be transported across the membrane.
- ABCA1 preferentially transfer cholesterol from cells to poorly lipidated particles such as pre -HDL or apo A-1, which are then converted to HDL_3 via discoidal HDL
- Pre -HDL is the most potent form of HDL inducing cholesterol efflux from the tissues.

Functions of HDL

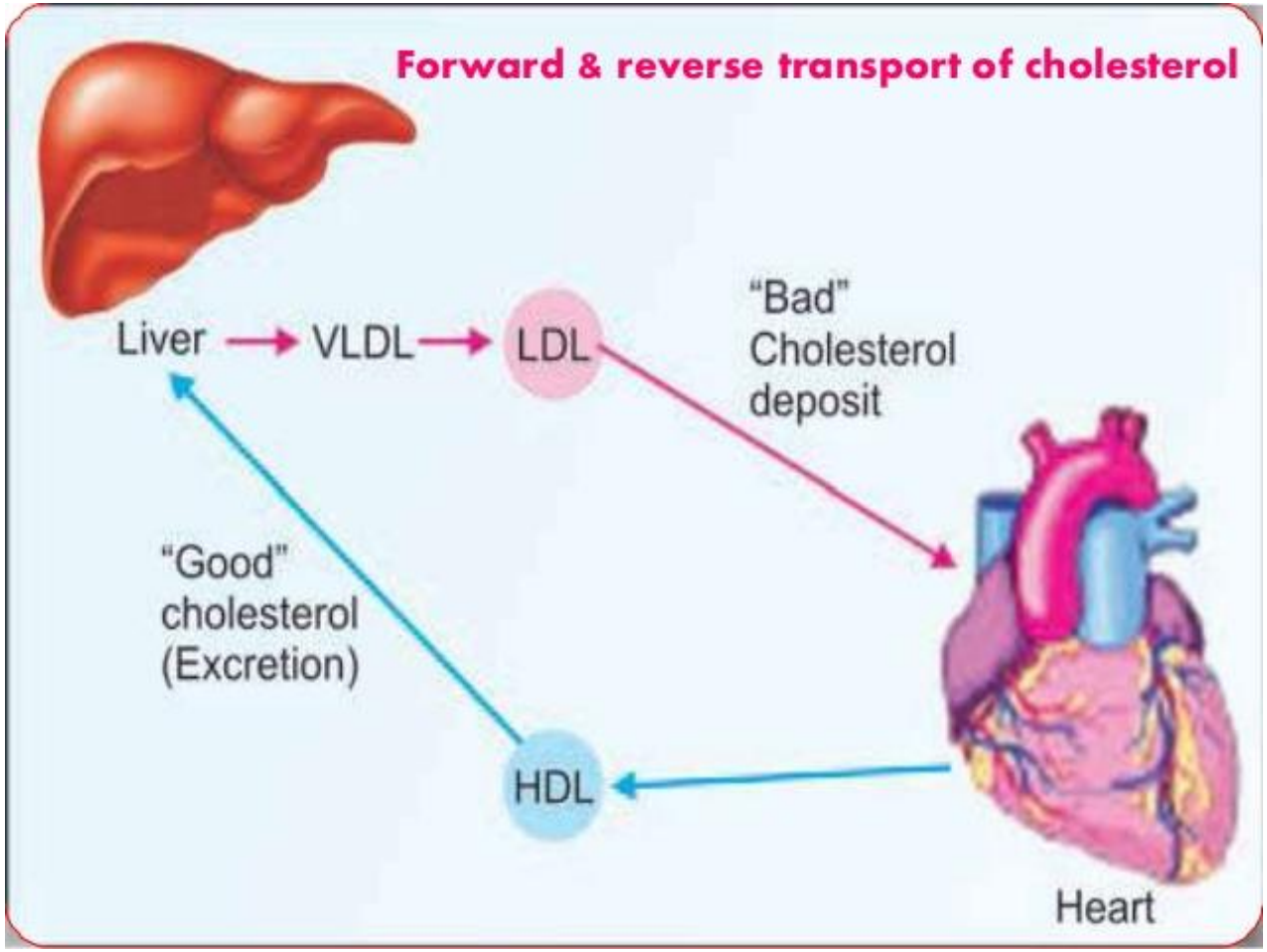
- Scavenging action- HDL scavenges extra cholesterol from peripheral tissues by reverse cholesterol transport
- HDL, with the help of apo E competes with LDL for binding sites on the membranes and prevents internalization of LDL cholesterol in the smooth cells of the arterial walls
- HDL contributes its apo C and E to nascent VLDL and chylomicrons for receptor mediated endocytosis
- HDL stimulated prostacyclin synthesis by the endothelial cells, which prevent thrombus formation
- HDL also helps in the removal of macrophages from the arterial walls .


LDL receptor
Liver
SR-BI
Other receptor(s)?
VLDL
IDL
LDL
CE
LPL
HL
CETP
Oxidation
Selective CE Uptake
Particle Uptake
HDL2
OxLDL
CETP
HL
LCAT
HDL3
LCAT
SRA / CD36
FC
Macrophage

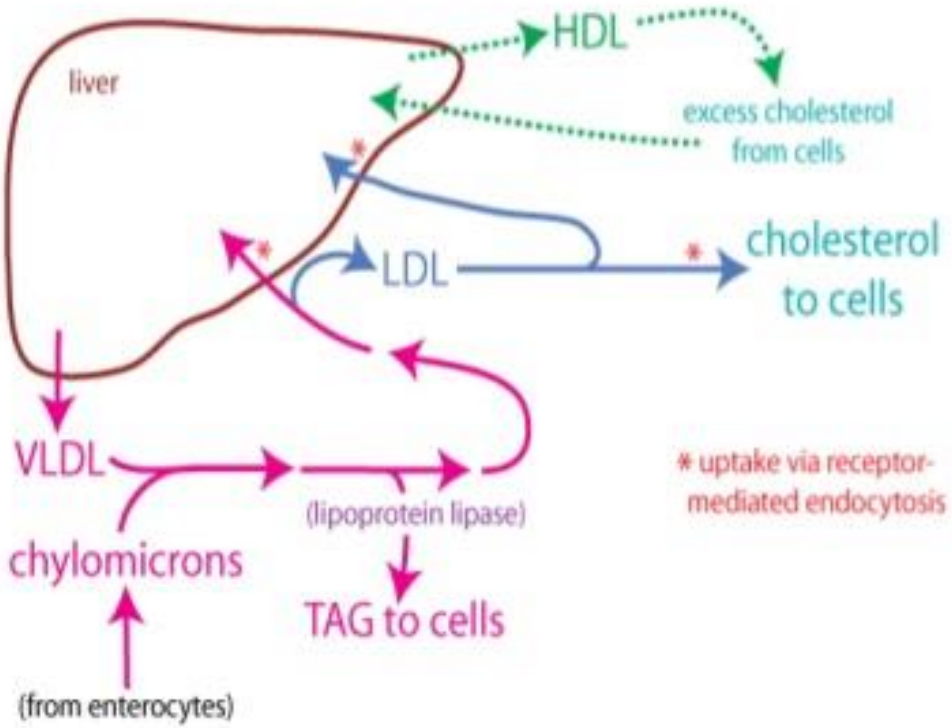

Glyc apoB
Glucose
Fragmented apoB
oxLDL
SCARA1
Monocyte/
macrophage foam cell
ApoM
GSPx
ApoAI
HDL
PON1
LCAT
PLA2
oxidation
CETP
Lipid Peroxides
PLTP
Lipid Peroxides
Lysolipids
SCARB1
LDL
PLA2
Liver
RAS
ApoB100
LDLR



Bruce Worden, *J. Clin. Invest.*


Forward & reverse transport of cholesterol
Liver
VLDL
LDL
"Bad"
Cholesterol
deposit
"Good"
cholesterol
(Excretion)
HDL
Heart

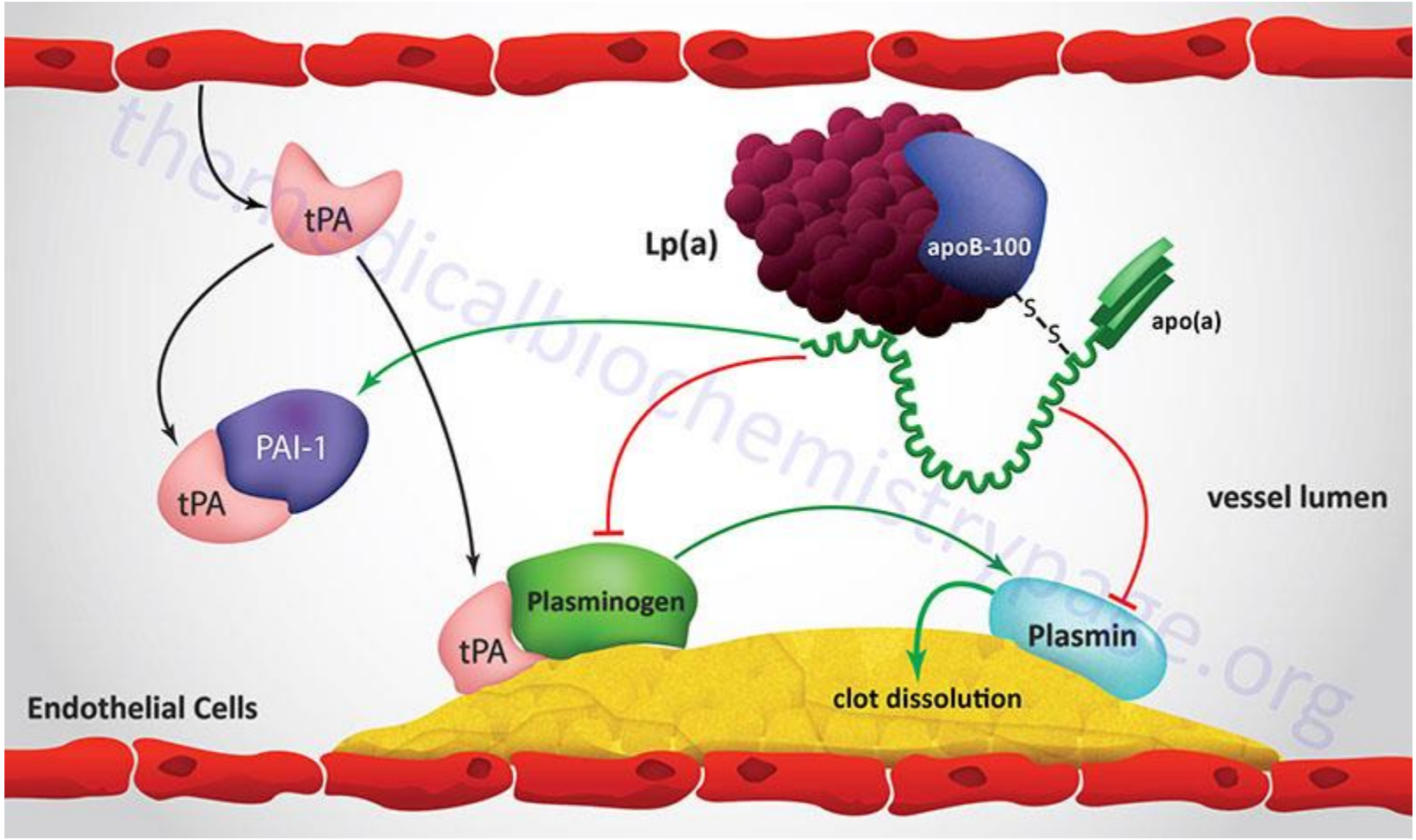
Summary of formation and fate of lipoproteins



- Chylomicrons is a transporter of dietary lipids whereas VLDL is a transporter of endogenous lipids(mainly TGs).
- LDL transports cholesterol to peripheral cells while HDL transports cholesterol from peripheral cells back to liver.

Lipoprotein a [Lp(a)]

- Composed of a common LDL nucleus linked to a molecule of apolipoprotein(a) by disulfide bond
- Synthesis of Lp(a) occurs in the liver
- The half-life of Lp(a) in the circulation is approximately 3–4 days


tPA
Lp(a)
apoB-100
apo(a)
PAI-1
tPA
vessel lumen
Plasminogen
tPA
Plasmin
clot dissolution
Endothelial Cells

- Decrease synthesis of tpA
- Increase synthesis of PAI (Plasminogen activator inhibitor)
- Interfer in binding of tPA to Plasminogen
- Interfer in binding of Plasmin to clot