

*Lipoproteins and Their Metabolism:
Understanding Hyperlipoproteinemia*

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Lipoproteins

Complex lipids →

- These are complex lipids formed of ^① lipids conjugated ^{+ ②} with protein.

- They are present in ^① cell membrane, ^② mitochondria and ^③ plasma

(plasma lipoproteins)

① Lipoprotein قلمد تتواجد ك
structural component
cell membrane بالسي

fluidity and تحافظ على
integrity

تعتبر cell membrane

② Lipoprotein قلمد تتواجد ك

في mitochondria - أيضا

تتواجد في membrane ك

تتبع Structural and
metabolic roles .

③ تتواجد في دسي
plasma lipoproteins

circulating lipoprotein عباقة

Blood يتحرك في

هي سولة عن عملية

Transporting of cholesterol

and Triglycerides and other

Lipids from tissue to another.

لذلك أمد ك function ك Lipoproteins

Serve as a transporter system
of lipids.

Lipid لا يذوب
insoluble in
water
↓
لذلك تتلاصق بـ
aqueous environment
of the body ex: plasma
↓
تحتاج إلى
transporters
↓
Lipoproteins عباقة

Plasma Lipoproteins

- Plasma lipoproteins convert water insoluble lipids into water soluble

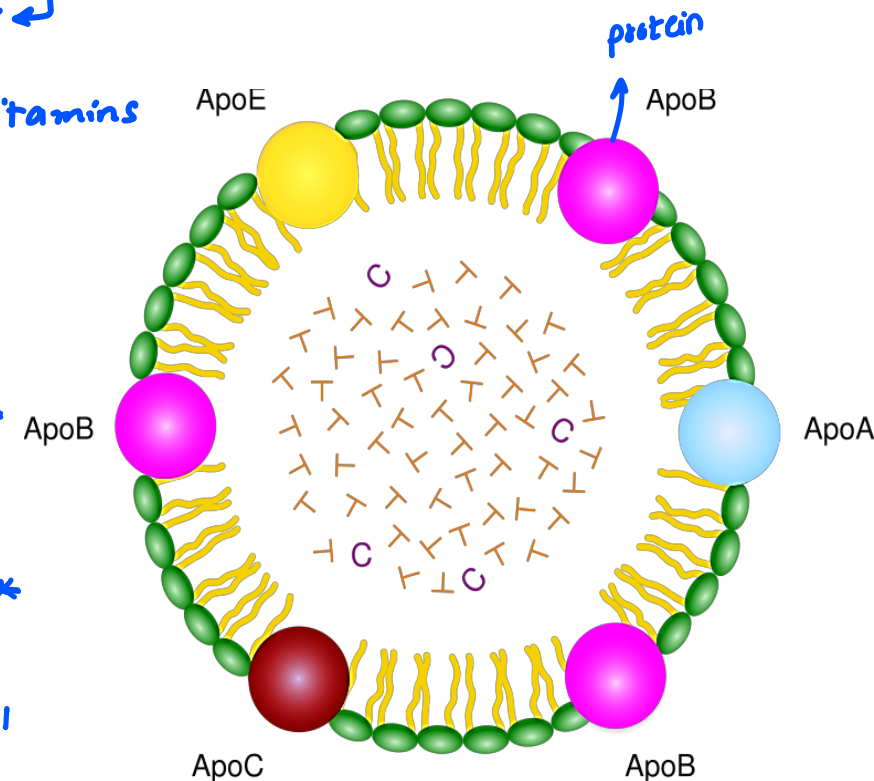
complexes. *ہائڈروفوبک مالیکیولز* *hydrophobic molecule* *جس میں* *plasma water* *موجود ہے* *جس میں* *lipids* *موجود ہیں* *جس میں* *triglycerides* *موجود ہیں* *جس میں* *cholesterol* *موجود ہیں* *جس میں* *fat soluble vitamins* *موجود ہیں*

Function of lipoprotein:

This facilitates transport of lipids between blood and different tissues.

* عند ارتباط Lipids بال proteins
(Lipoprotein) Structure

* Lipoprotein بتخل encapsulate lipids
داخل shell مشابہہ قدر صندل shell تتحرك عبر
ال plasma بالتي



Plasma Lipoproteins

The lipids present in plasma (total range: 360–820 mg/dL) include the following components:

- The plasma lipids (360-820 mg/dl) are ^①phospholipids, ^②cholesterol (free and esterified) and lipids between ^③triacylglycerols, ^④free fatty acids.

normal range of plasma lipid

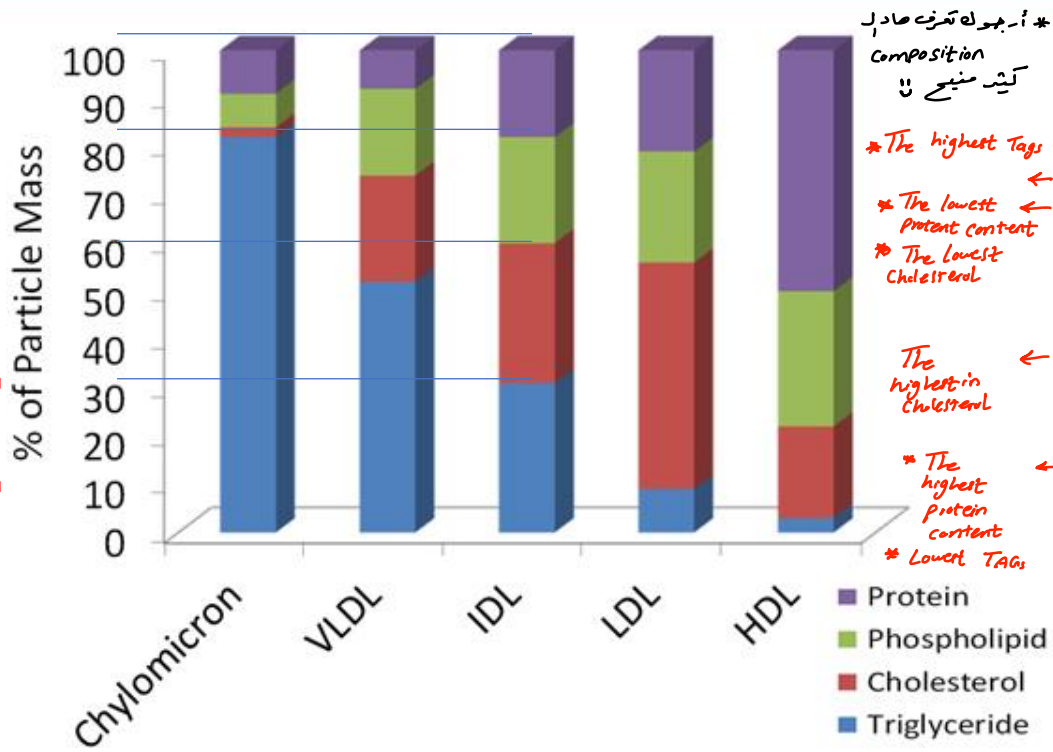
1-Cholesterol :	140 -220 mg/dl 70% Cholesteryl esters 30% Free cholesterol
2-Phospholipids :	150-200 mg/dl
3-Triacylglycerols :	40-160 mg/dl
4-Free fatty acids :	6-16 mg/dl

Plasma Lipoproteins

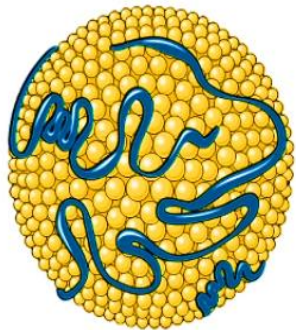
- The plasma lipoproteins are ^{كروية} spherical macromolecular complexes of lipids and proteins ^{مستط} (apolipoproteins).
- The lipoprotein particles ^{أنواع} include ^① chylomicrons, ^② very-low-density lipoproteins (VLDLs), ^③ intermediate-density lipoproteins (IDLs), ^④ low-density lipoproteins (LDLs), and ^⑤ high-density lipoproteins (HDLs).
- They differ in lipid and protein composition, ^{التركيب} size, density, and site of origin. ^① ^② ^③ ^④

Synthesis ←
تخليق

Composition of lipoproteins



Lipoprotein	Density (g/mL)	Composition (wt %)				
		Protein	Phospholipids	Free cholesterol	Cholesteryl esters	Triacylglycerols TAGs
Chylomicrons	<1.006	2	9	1	85	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
Data from D. Kritchevsky, Nutr. Int. 2:290, 1986.						
IDL	1.006-1.019	15	20-25	free + ester cholesterol	25	35



Chylomicron



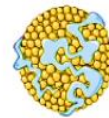
VLDL



IDL



LDL



HDL

* Notes

1. HDL : - The highest density
- The highest protein content
- The lowest triglycerides content
2. Chylomicron: - The lowest protein content
- The lowest cholesterol content
- The highest Triglycerides content
3. LDL : The highest cholesterol content

The density and diameter of different lipoproteins

← سلسلہ ترتیب سے بڑھتا جا رہا ہے

Lipoprotein	Density (g/dL)	Diameter (nm)
Chylomicrons	0.95 < 1.006	75-1200
VLDL (very low-density lipoproteins)	<u>0.95-1.006</u>	30-80
IDL (intermediate-density lipoproteins)	<u>1.006-1.019</u>	25-35
LDL (low-density lipoproteins)	<u>1.019-1.063</u>	18-25
HDL (high-density lipoproteins)	<u>1.063-1.21</u>	5-12

تعداد سے
انجینئرنگ
HDL



Chylomicrons

Chylomicrons ← Lipids + Solubility ← Protein composition

- **Chylomicrons** (TAG= 90%) are highly soluble in both lymphatic fluid and blood.

- **Function** in the transport of dietary triacylglycerol, cholesterol, and cholesteryl esters to other tissues.
* بعد امتصاص Lipids ← يتم نقل Chylomicron
Ex: - adipose tissue
- muscle
- liver

Combination of absorbed lipids from diet with Apo B48 lipoprotein
From intestine → peripheral tissues
عناقة ربط الجزيء
عناقة ربط الجزيء
يتركب
or = immature chylomicron
يتركب
↓
Lymphatic system
↓
blood stream
↓
Secretion
↓
نقل

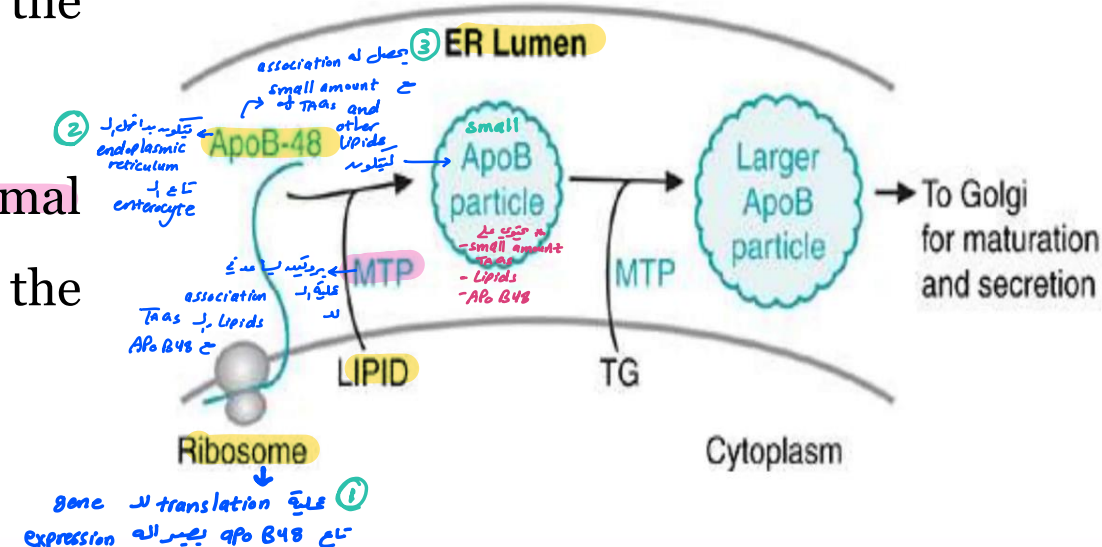
• **Assembly of chylomicrons** occurs in the intestinal lining cells and results in a nascent chylomicron that contains lipids and apolipoproteins.

Chylomicron assembly in enterocytes

1. Initial Assembly:

- A. The synthesis begins with the translation of the apoB-48 protein.
- B. Lipid association occurs next, where small amounts of triglycerides and other lipids associate with the apoB-48 protein.
- C. This process is catalyzed by **microsomal triglyceride transfer protein (MTP)**, leading to the formation of small apoB-containing particles.

This process occurs within the endoplasmic reticulum (ER).

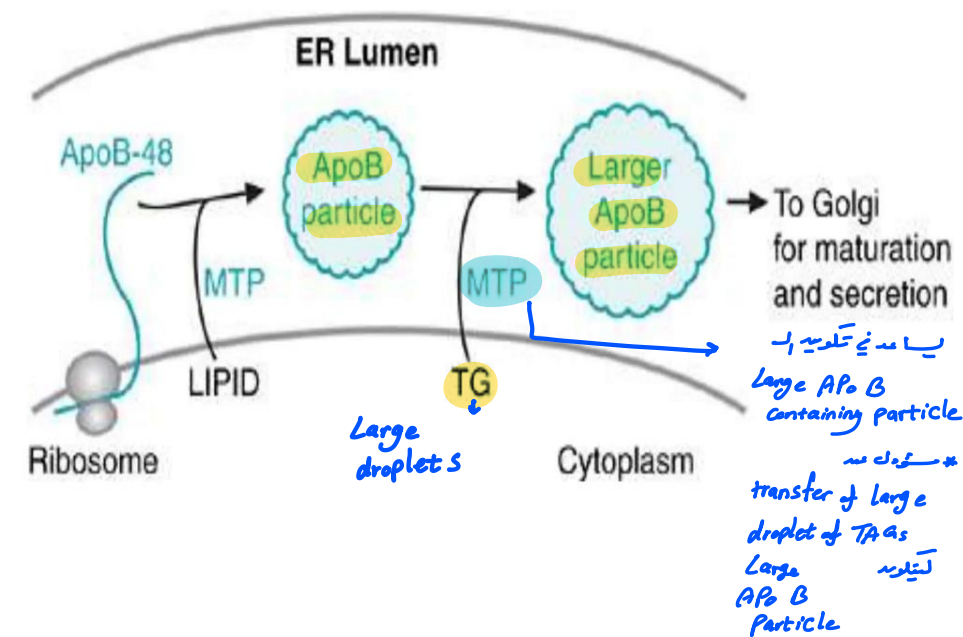


Chylomicron assembly in enterocytes

← تکبيرد Small particle

B. Particle Expansion:

- Large triacylglycerol droplets fuse with the initial ^{= small} apoB-containing particles.
- MTP also facilitates the transfer of additional triacylglycerol from the cytoplasm into the ER lumen, where it forms lipid droplets that are incorporated ^{تم دججا} into the growing chylomicron.



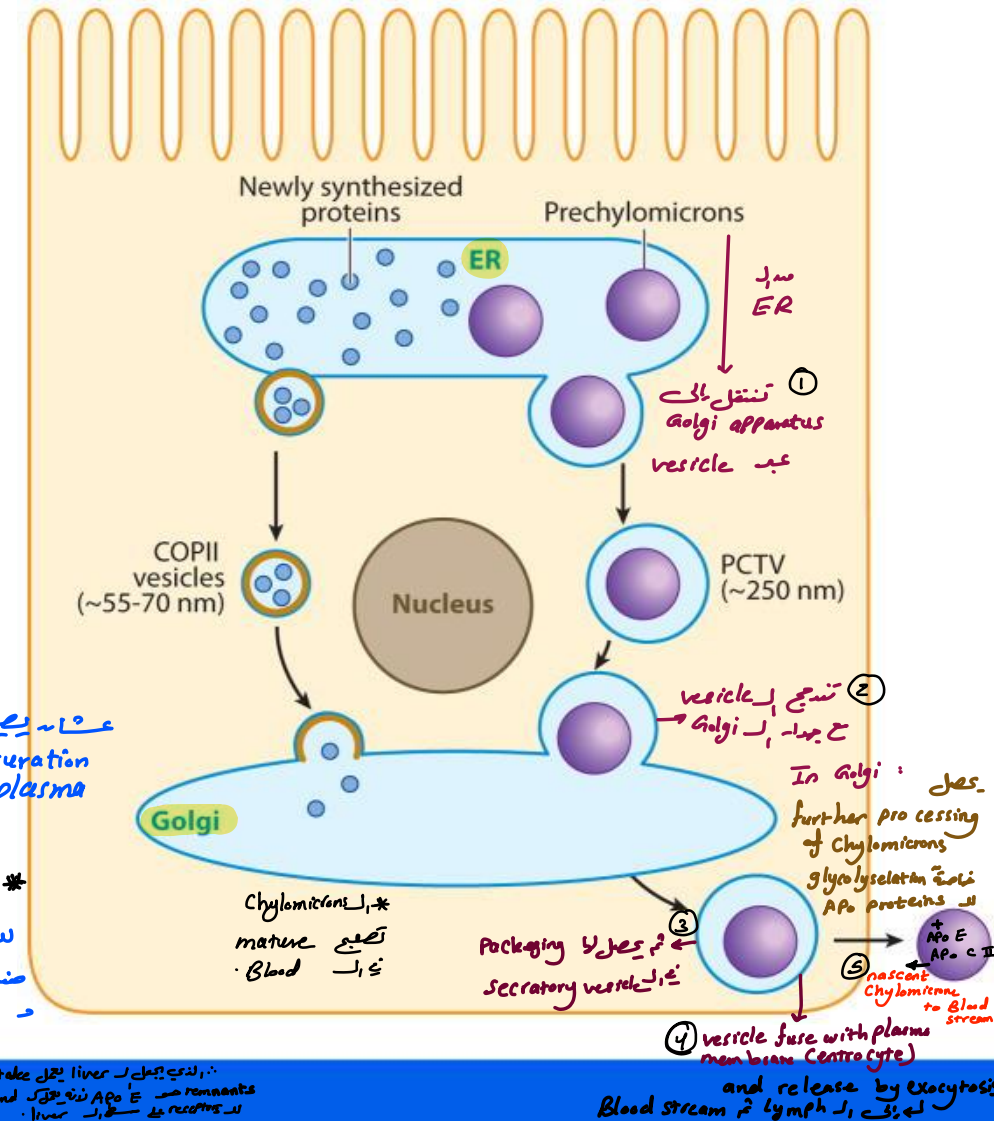
Chylomicron assembly in enterocytes

* بعد تكوينه، pre-chylomicron (immature chylomicron) في Endoplasmic reticulum

1. Transition of the chylomicrons to Golgi, From ER where the particles are packaged in secretory vesicles.

2. These fuse with the plasma membrane releasing the lipoproteins to the blood.

3. When it reaches the plasma, the particle is rapidly modified, receiving apo E and apo C-II (The source of these apolipoproteins is circulating HDL).



: Apo C II
بروتينه مهم جداً لأنه يحفز
activation of LPL
(Lipoprotein Lipase)

لأنه يحفز
Chylomicrons
Fatty acids + glycerol

M. ELEYAN

Tissues
- muscle
- adipose tissue

liver uptake
Chylomicrons remnants

Legend: Apo E
receptors
uptake
Chylomicrons remnants

processing
fatty acids + glycerol

uptake
liver
receptors

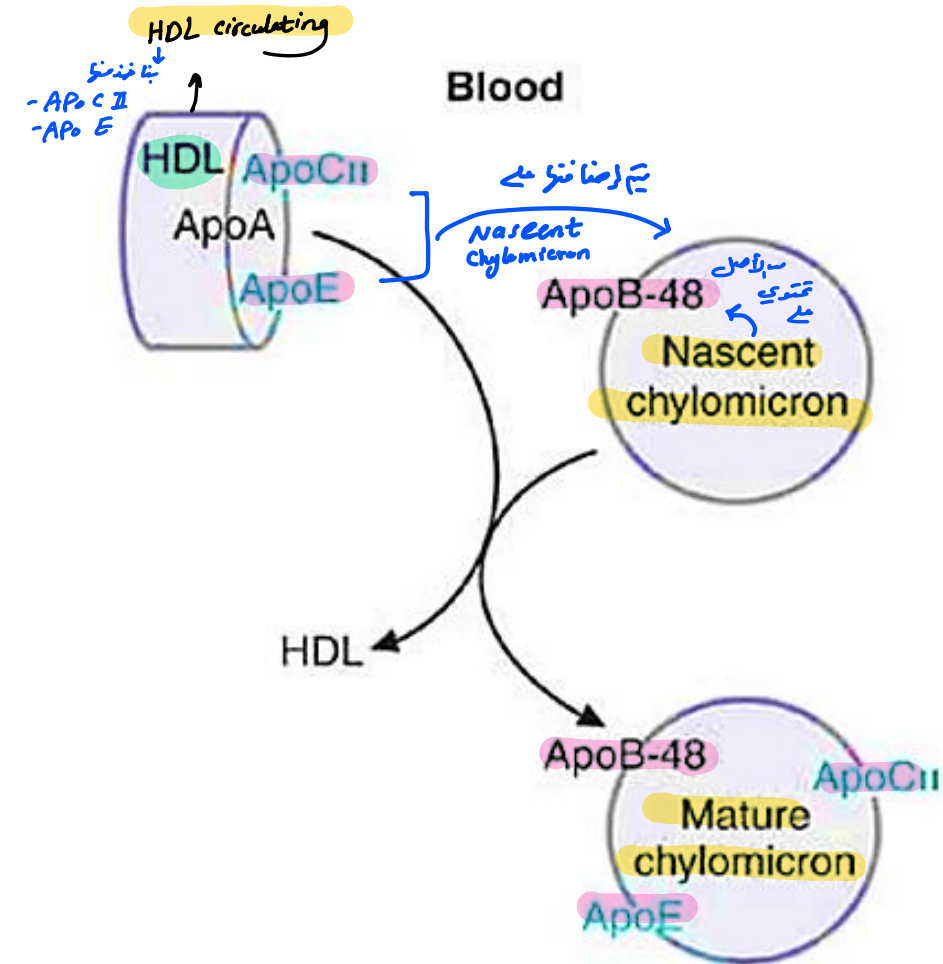
vesicle fuse with plasma membrane
and release by exocytosis
Blood stream

Transfer of proteins from HDL to chylomicrons

- Newly synthesized chylomicrons (nascent chylomicrons) mature as they receive apoC-II and apoE from HDL.

• Roles of ApoC-II and ApoE:

- ApoC-II:** Essential for the activation of lipoprotein lipase (LPL), the enzyme responsible for hydrolyzing triglycerides in chylomicrons into free fatty acids and glycerol for uptake by tissues (e.g., muscle, adipose tissue).
- ApoE:** Serves as a ligand for receptors that mediate the uptake and clearance of chylomicron remnants by the liver.



* نئے ایسے enterocyte

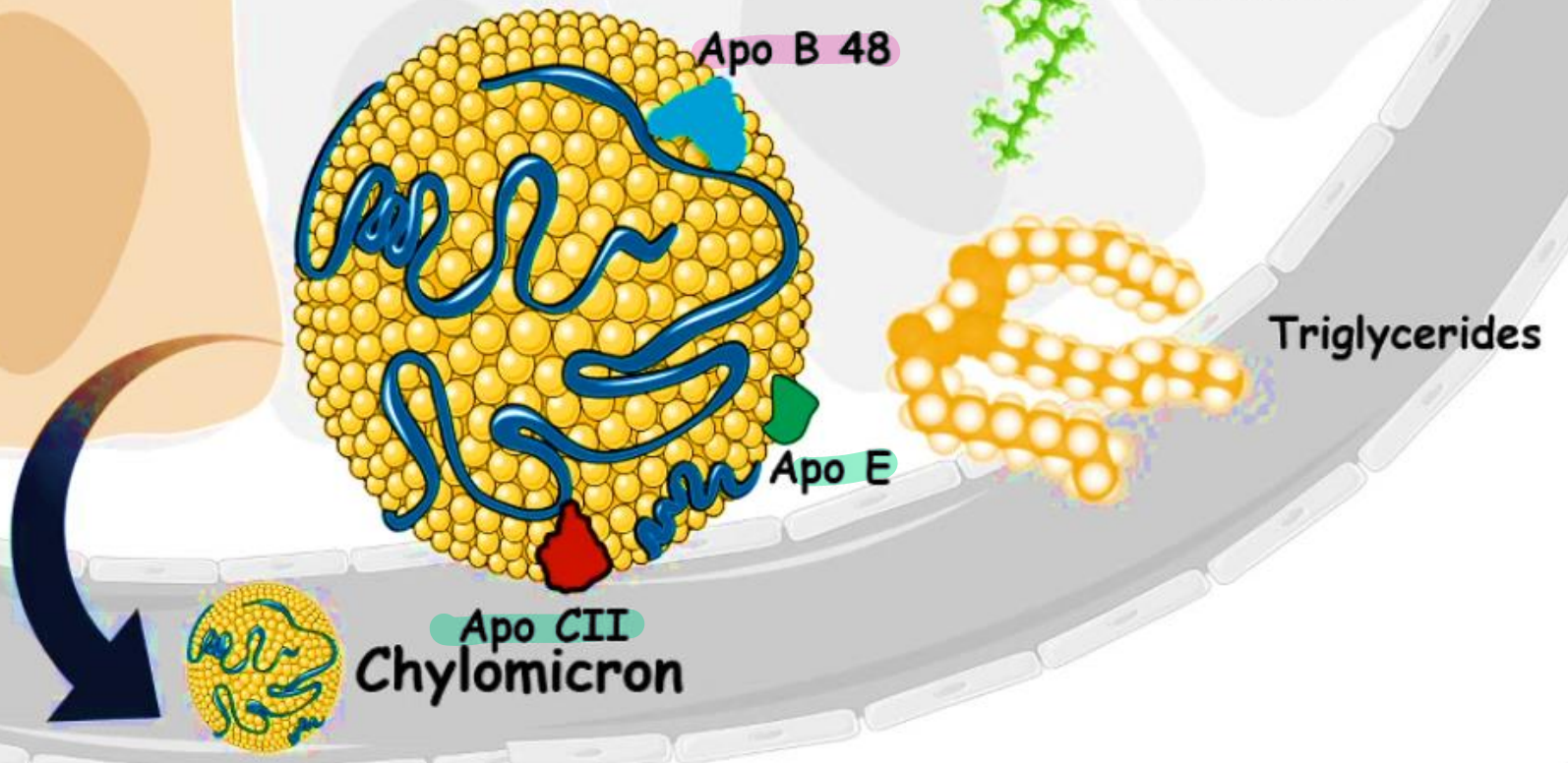
- Premature chylomicrosome
- immature chylomicron
- nascent chylomicron

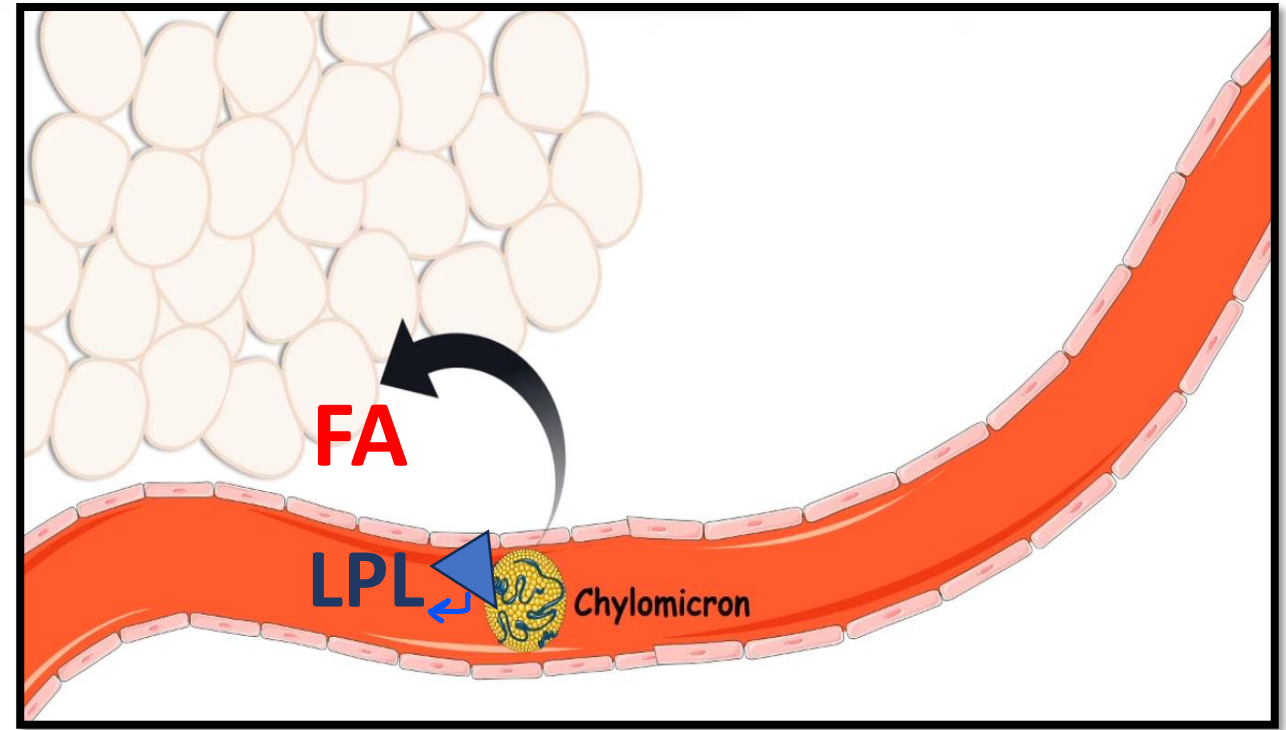
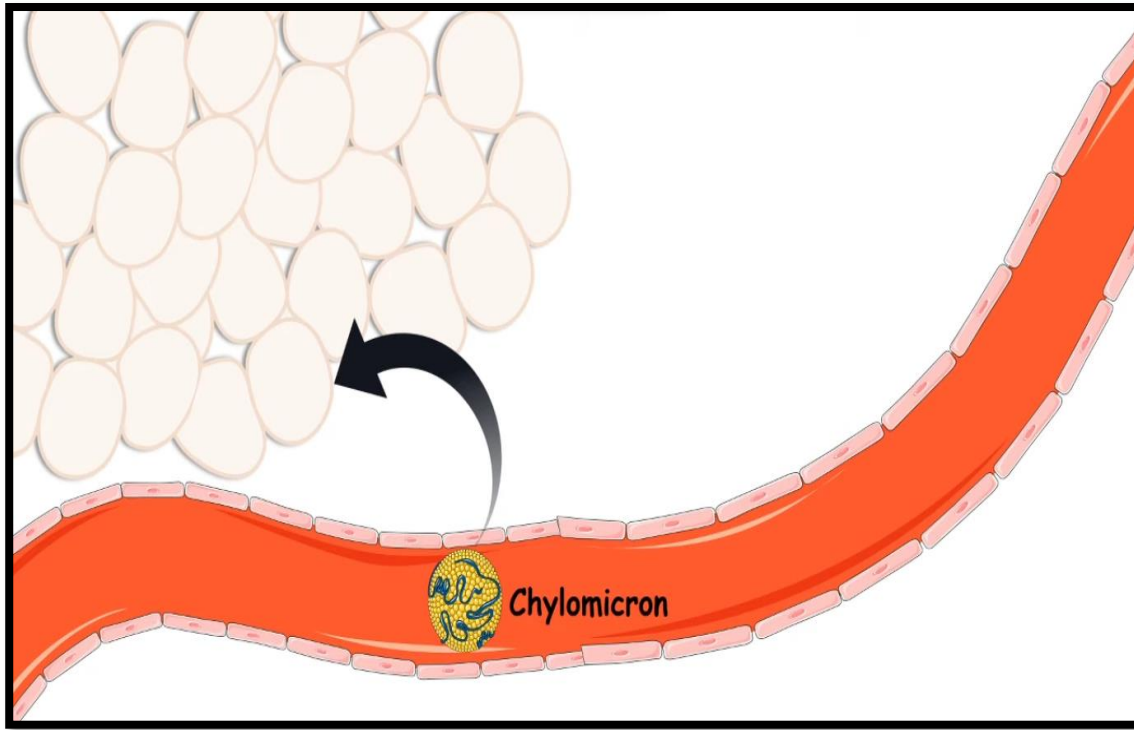
other lipids , TAGs
مع APo B 48

releasing in circulation

APo E
APo C II

Chylomicrons





• Hydrolysis of chylomicron ← التحلل المائي للكيلوميكرون

- **Lipoprotein lipase (LPL)** is an extracellular enzyme that is ^{غالباً} anchored to the **capillary walls** of most tissues but predominantly ^{ملاحظة} those of **adipose tissue** and **cardiac and skeletal muscle**.

Fate of Chylomicron

- LPL, activated by apo C-II on chylomicrons, ^{LPL}hydrolyzes the TAG in these ^{chylomicrons} particles to ^①FA and ^②glycerol.
_{Fatty acid}
- The FA are ^①stored (in adipose) or ^②used for energy (in muscle).
- The glycerol is taken up by the liver, converted to dihydroxyacetone phosphate (an intermediate of glycolysis),
↓
and used in lipid synthesis or gluconeogenesis. _{glucose from protein.}

Fate of Chylomicron

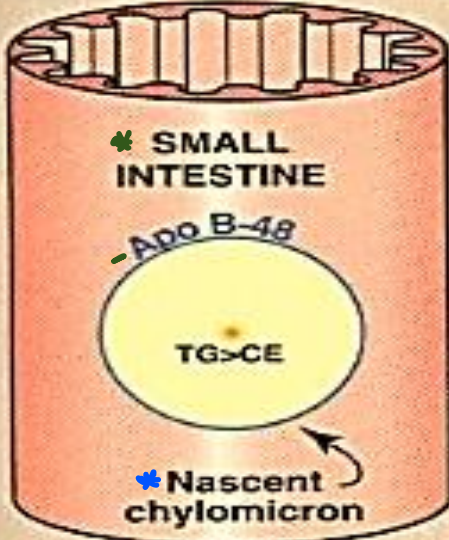
* بعد اخذ کھانا کے آپل Chylomicrons سے آپل glycerol - fatty acids
[تبعی]

- The remaining particle (remnant) is rapidly removed from the circulation by the liver, whose cell membranes contain lipoprotein receptors that recognize apo E and then taken into the hepatocytes by endocytosis.
liver آپل
remnant chylomicron آپل موجود ہے
liver آپل remnant chylomicron آپل

- ① In the lysosome: the apolipoproteins, cholesteryl esters, and
③ other components of the remnant are hydrolytically degraded,
Hydrolysis of Apo proteins آپل سے آپل
releasing amino acids, free cholesterol, and FA.

آسٹمبلی of chylomicron آپل
fatty acid + glycerol آپل

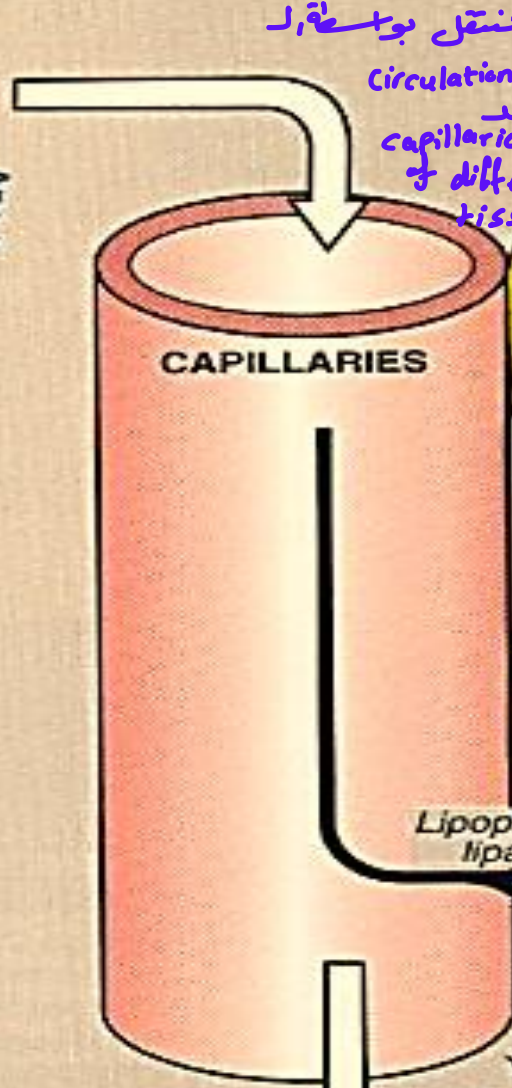
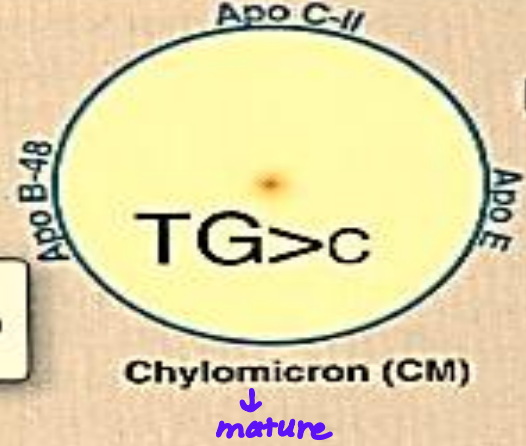
cholesterol
hydrolysis آپل سے آپل



1 Intestinal mucosal cells secrete nascent TG-rich chylomicrons produced primarily from dietary lipids.



2 Apo C-II and apo E are transferred from HDL to the nascent CM.



3 Extracellular lipoprotein lipase, activated by apo C-II, degrades TG in CM.

TISSUES, for example, ADIPOSE

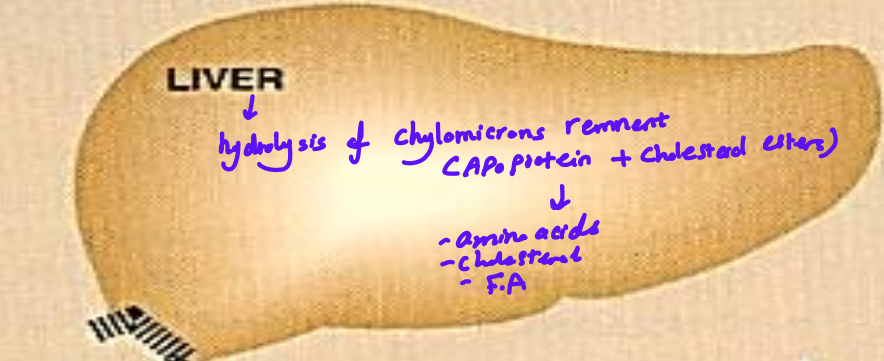
Free fatty acids

muscles → energy

adipose tissue → storage

Glycerol

To LIVER



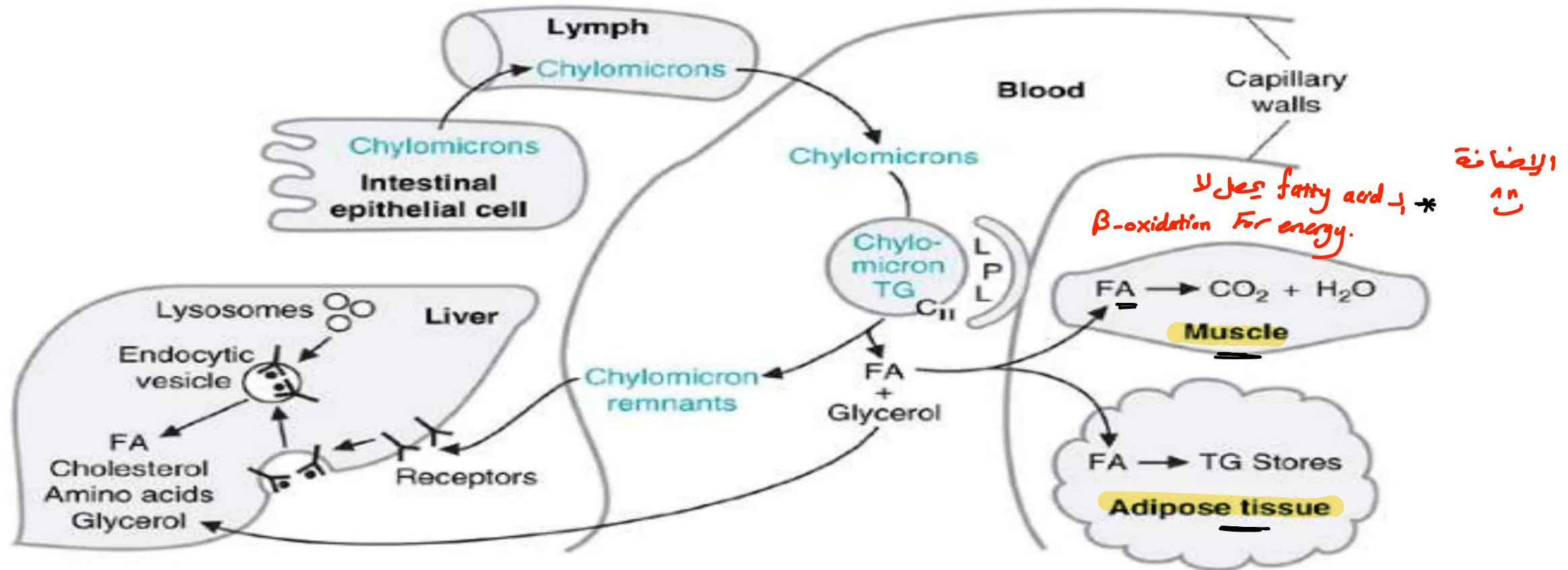
5 CM remnants bind to specific receptors on the liver where they are endocytosed.



4 Apo C-II is returned to HDL.

Legend: Apo E is the receptor

Fate of chylomicrons. Chylomicrons are synthesized in intestinal epithelial cells, secreted into the lymph, pass into the blood, and become mature chylomicrons (see Fig.). On capillary walls in adipose tissue and muscle, lipoprotein lipase (LPL) activated by ApoC-II digests the triacylglycerols (TG) of chylomicrons to fatty acids and glycerol. Fatty acids (FA) are oxidized in muscle or stored in adipose cells as triacylglycerols. The remnants of the chylomicrons are taken up by the liver by receptor-mediated endocytosis. Lysosomal enzymes within the hepatocyte digest the remnants, releasing the products into the cytosol.



* clinical correlate to chylomicrons:

Type I Hyperlipoproteinemia (Familial Hyperchylomicronemia):

genetic/inheritance pattern

- Type I hyperlipoproteinemia is a rare autosomal recessive disorder characterized by the abnormal accumulation of chylomicrons in the plasma.

- Causes:
 - glycerol + F.A ← TAGs hydrolysis in chylomicrons
 - بالتالي ما في تحليل لـ chylomicrons وتتراكم في plasma

2-

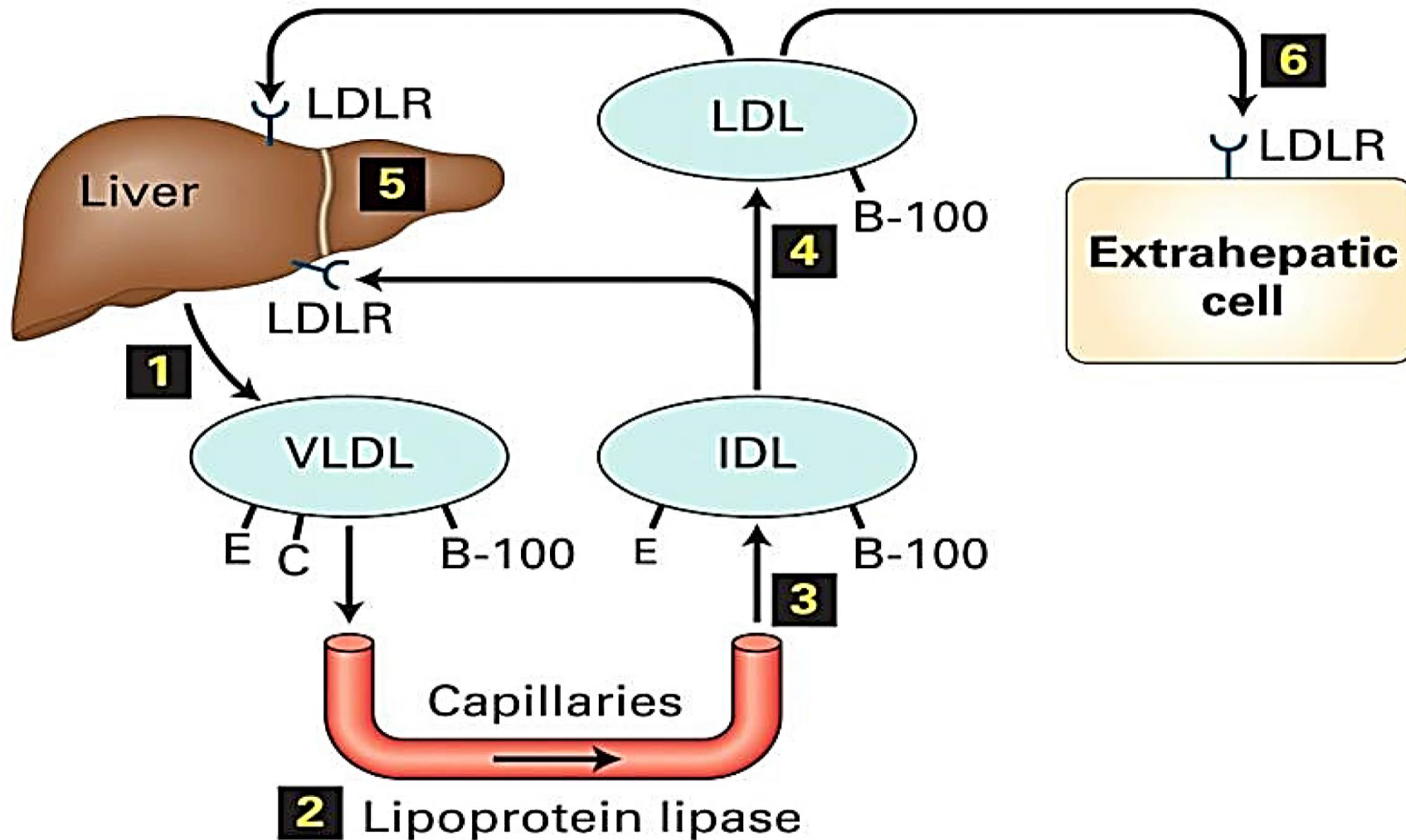
1. Deficiency of Lipoprotein Lipase (LPL), Deficiency or Mutation

in ApoC-II: → activates LPL

بالتالي معطاش
activation of LPL

co factor
نشط لـ LPL

Endogenous Lipid Transport

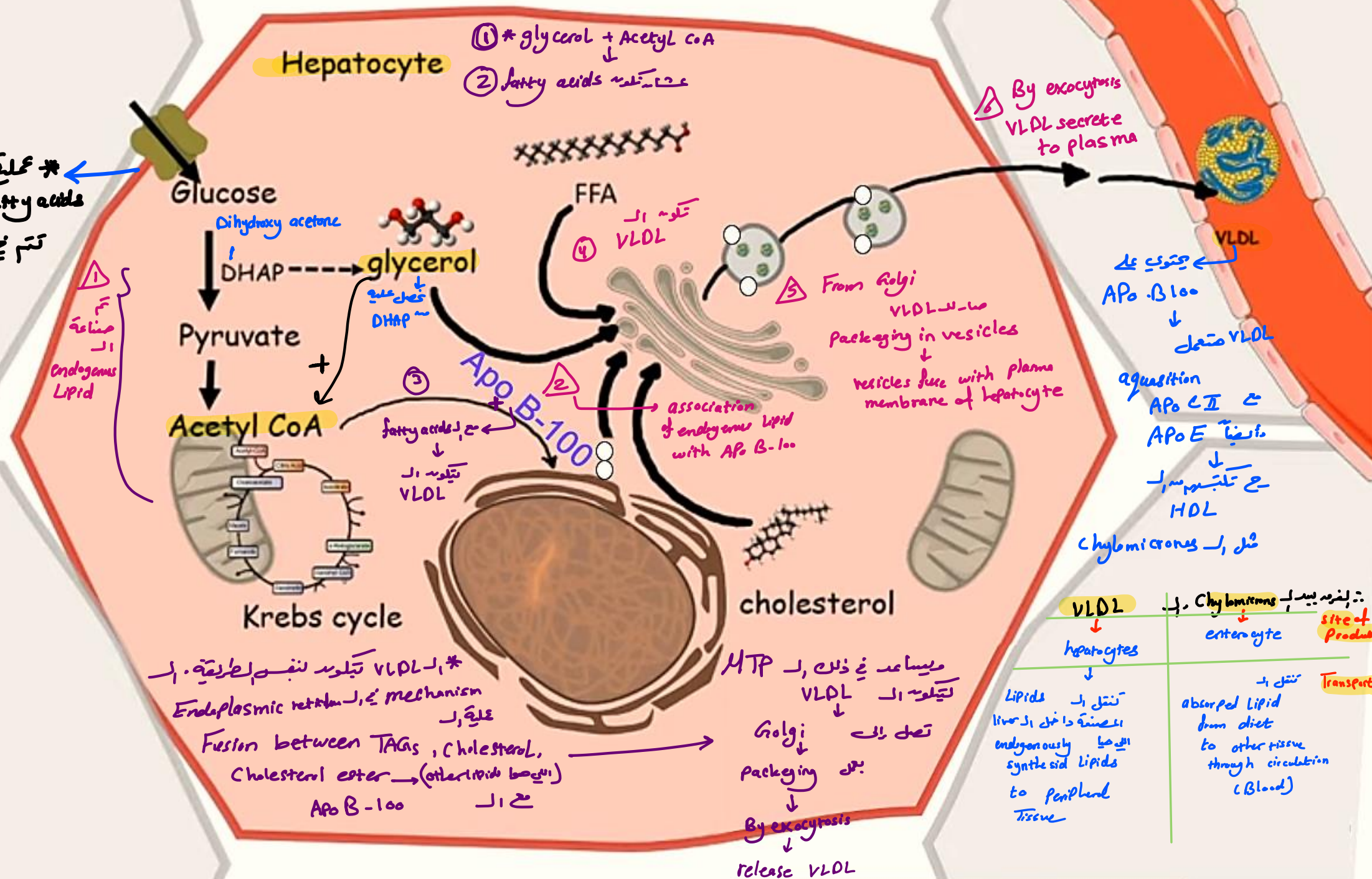


2) Very-low-density lipoprotein metabolism (VLDLs)

- VLDLs are produced in the liver.
- site of production
- synthesis
- Their function is to carry this lipid from the liver (site of synthesis) to the peripheral tissues.
Chylomicrons → small intestine
↑
endogenously synthesized Triglycerides
transport
↓
hydrolysis of TAGs
muscle → energy
adipose tissue → storage
- There, the TAG is degraded by LPL, as discussed for chylomicrons.
Lipoprotein Lipase

Synthesis & Release of VLDLs from the liver

Biosynthesis of fatty acids
liver (hepatocytes)
تتم في الكبد



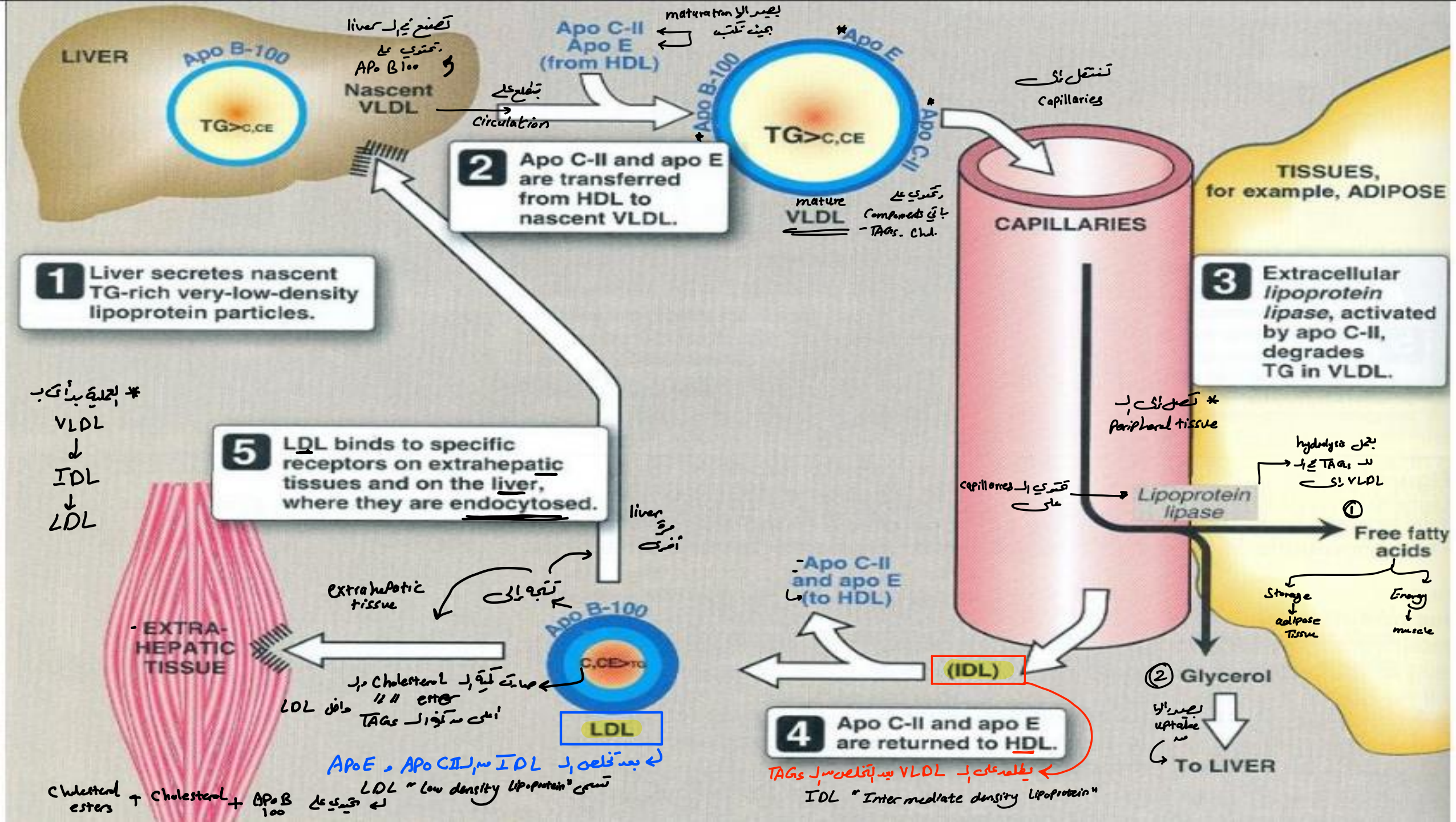
* VLDL تتركب من نفس الطريقة
Endoplasmic reticulum mechanism
عليه
Fusion between TAGs, cholesterol,
cholesterol ester → (other lipids)
Apo B-100

مساعد في ذوبان VLDL
تتركب من VLDL
تصل إلى
Golgi
↓
Packaging
↓
By exocytosis
↓
release VLDL

site of Production	Transport
VLDL ↓ hepatocytes	absorbed lipid from diet to other tissue through circulation (Blood)
Chylomicrons ↓ enterocyte	absorbed lipid from diet to other tissue through circulation (Blood)

Synthesis & Release of VLDLs from the liver

- ^{VLDL}
• They are composed predominantly of endogenous TAG (~60%).
- VLDLs are secreted directly into the blood by the liver containing apo B-100.
- They must obtain apo C-II and apo E from ^(acquisition) circulating HDL
- Apo C-II is required for activation of LPL.



Modifications on VLDLs through their circulation

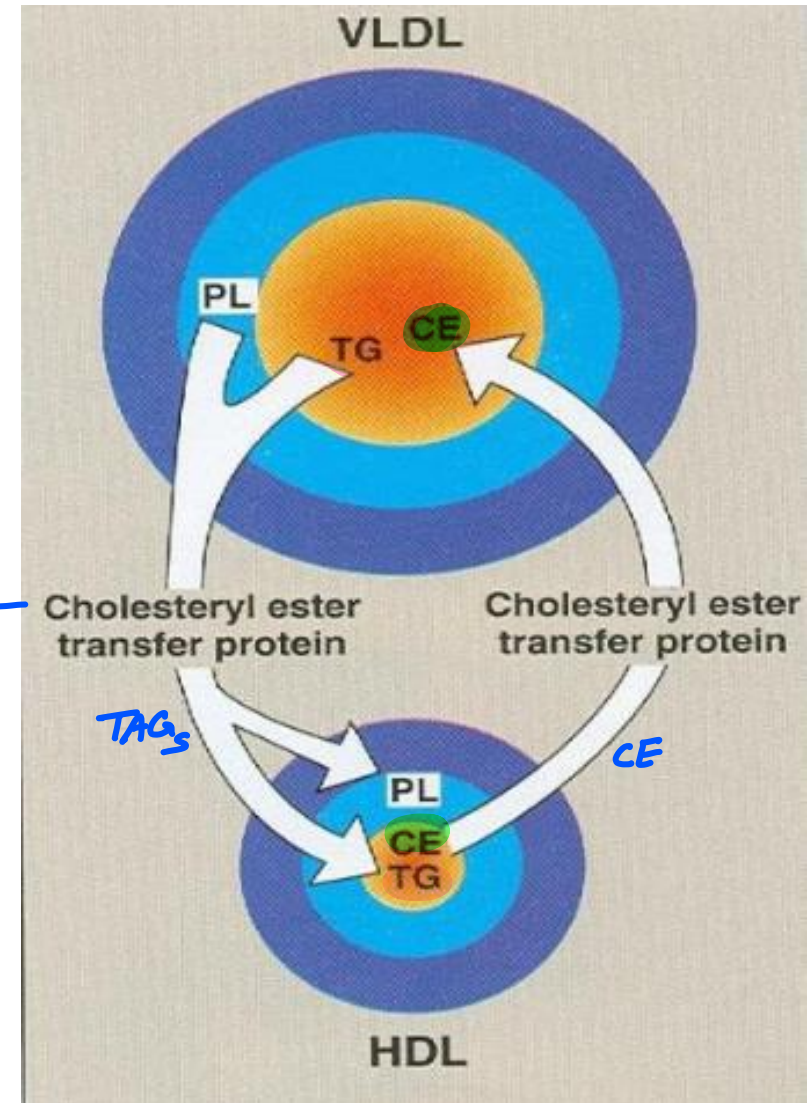
1. TAG is degraded by LPL. → *adipose tissue + muscles* → *در بافت چربی و عضله* → *رهایش و تبدیل به IDL*
2. The C and E apolipoproteins, are returned to HDL, but the particles retain apo B-100.
3. Additionally, some TAGs are transferred from VLDL to HDL in an exchange reaction that transfers cholesteryl esters from HDL to VLDL.
انتقال
در موجودات VLDL
VLDL TAG HDL
HDL Chole. Estrade VLDL
4. This exchange is accomplished by cholesteryl ester transfer protein (CETP) *الاسترول منقوله*
5. With these modifications, the VLDL is converted in the plasma to LDL. #

Transfer of cholesteryl ester (CE)
from HDL to VLDL in exchange
for triacylglycerol (TAG).

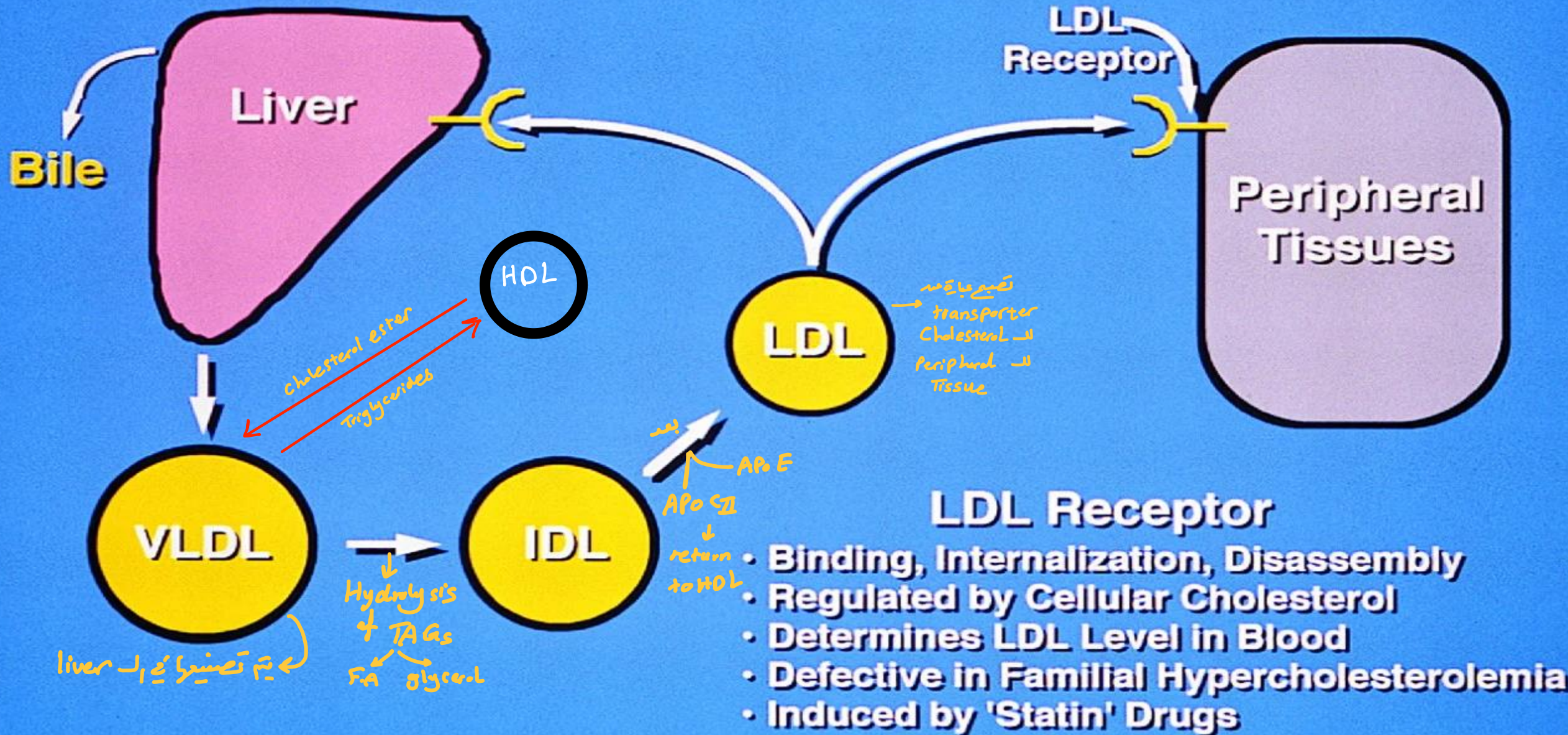
From VLDL to HDL

By CETP

← استبدال
exchange
reaction



LDL and Cholesterol Transport

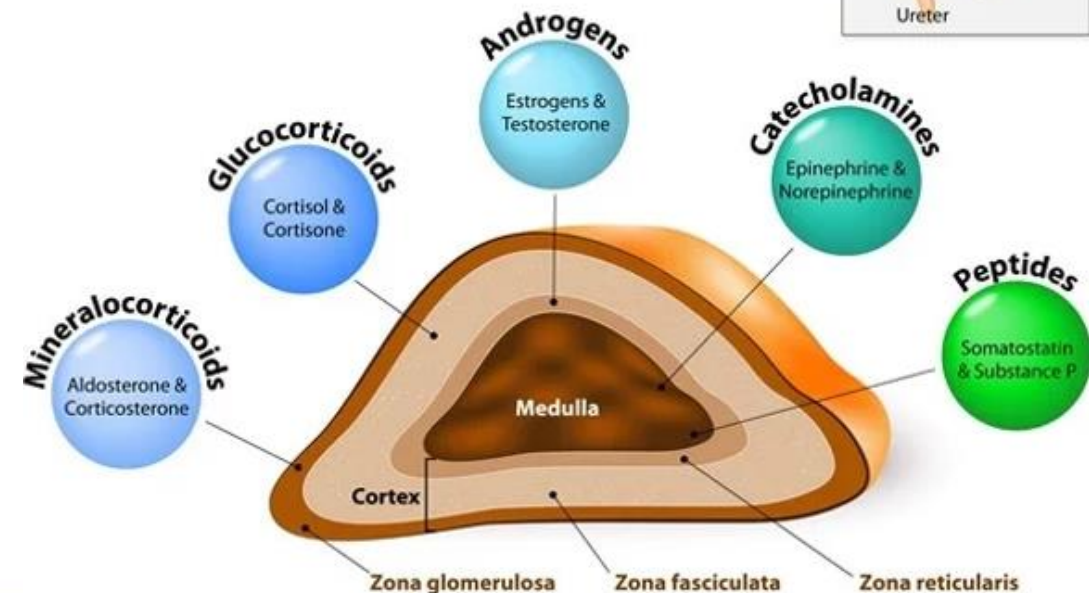
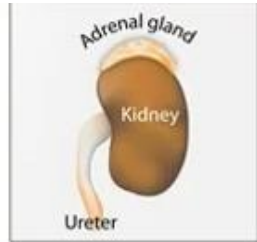


LDL and cholesterol transport

- The primary function of LDL particles is to provide cholesterol to the peripheral tissues (adrenal gland & testis) or to liver.
ex:
- They do so by binding to plasma membrane LDL receptors that recognize apo B-100 (but not apo

B-48).
↓
Chylomicrons

* عشاء صلیحہ LDL ریسیپٹر ہاں
LDL receptors
دوسری ریسیپٹر ہاں — Chylomicrons



* بعد ارتباط LDL مع LDL receptors على target tissue



بمساعدة internalisation LDL receptors



مصنعة mediated endocytosis



يتم عملية Transporting لـ LDL complex { LDL receptors + LDL }



ينتقل الـ complex إلى endosome (acidic environment)



الـ endosome يعمل على deassociation لـ LDL particles مع LDL receptors



الـ LDL receptor يرجع مرة ثانية إلى plasma membrane



الـ LDL يتم الـ degradation في الـ lysosome



يتم الـ release لـ cholesterol من الـ LDL

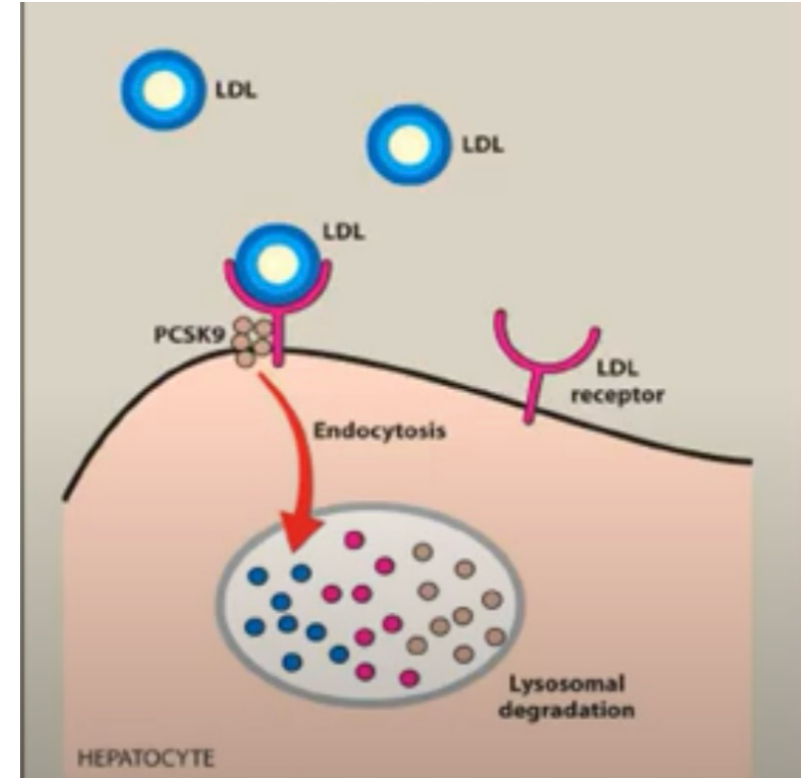
#

يتم الاستفادة

لـ membrane

لـ صنع steroid hormones

لـ صنع Bile إذا انتقل إلى liver



High-Density Lipoproteins (HDLs)

??

- HDLs are often referred to as "good cholesterol" because they play a critical role in reverse cholesterol transport—the process of transporting excess cholesterol from peripheral tissues back to the liver for excretion or recycling.

عملية لولة

RST

سیدہ Peripheral Tissue تمام کے RCT ؟

① Macrophages: تتواجد في arterial wall و blood vessels ← cholesterol accumulation في artery

تعمل macrophages على engulphment لـ cholesterol و تصبح foam cells

و بالتالي تعمل HDL على efflux هذا cholesterol بخلاف HDL

بما أنها تنقل cholesterol و تخرج مرة أخرى إلى liver بعملية RCT
recycling / excretion



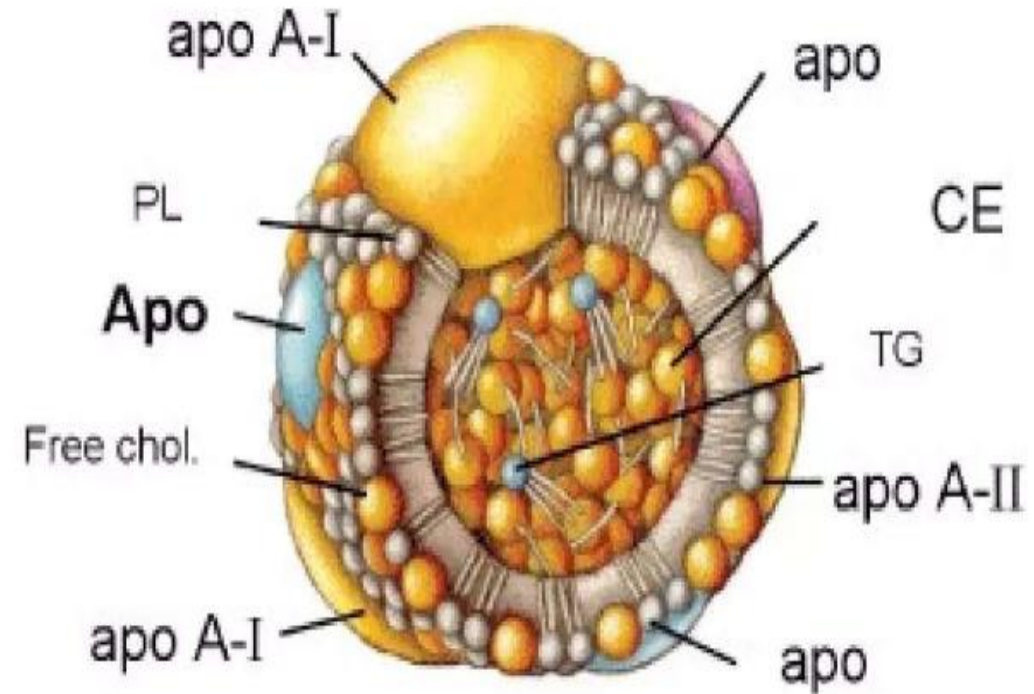
HDL

② Smooth muscle cells: تتواجد في blood vessels و يصير accumulation of cholesterol أثناء عملية Progression of atherosclerosis، بخلاف ما يحدث في RCT
تعمل cholesterol efflux

③ Extra hepatic tissue
: adipose tissue and skeletal muscles and Brain Lung Skin cells
تتراكم cholesterol في هذه الأنسجة

HDL contains several types of apolipoproteins

- apo-AI
- Apo-AII
- apo-CI
- apo-CII
- apo-D
- apo-E.
- Their most abundant apolipoproteins are apo A-I and apo A-II.

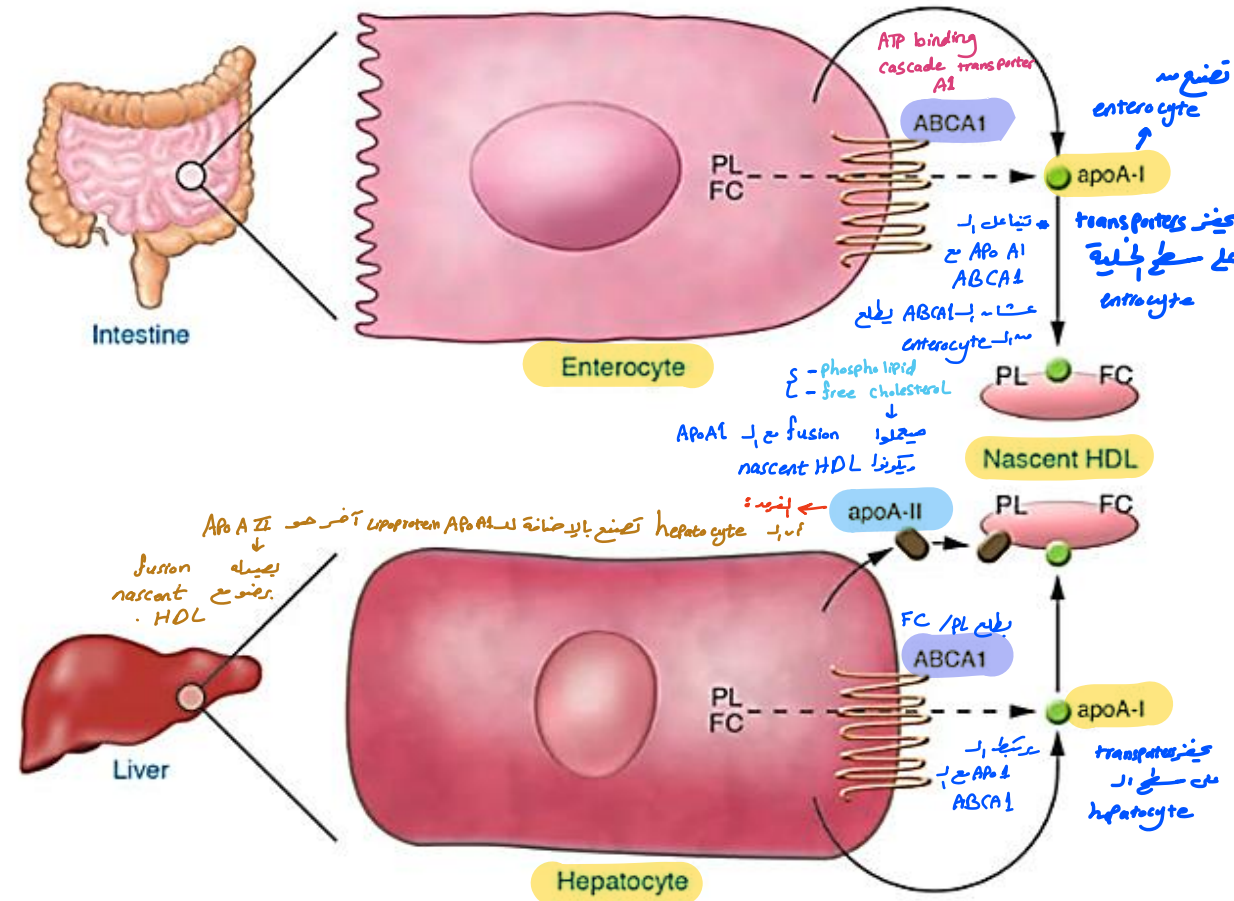


HDL Synthesis

① تصنيع الـ ApoA
 ② تلوين الـ nascent HDL
 . HDL

- **HDL** particles are synthesized in two main locations:
- **Liver:** Produces nascent HDL particles containing phospholipids, cholesterol, and apolipoproteins (mainly apo A-I and apo A-II).
- **Intestine:** Produces nascent HDL with apo A-I.

* الـ enterocyte ، الـ hepatocyte تصنيع الـ Apo A I
 Apo A I عبارة عن Lipid poor
 تازه Lipid
 newly synthesized.



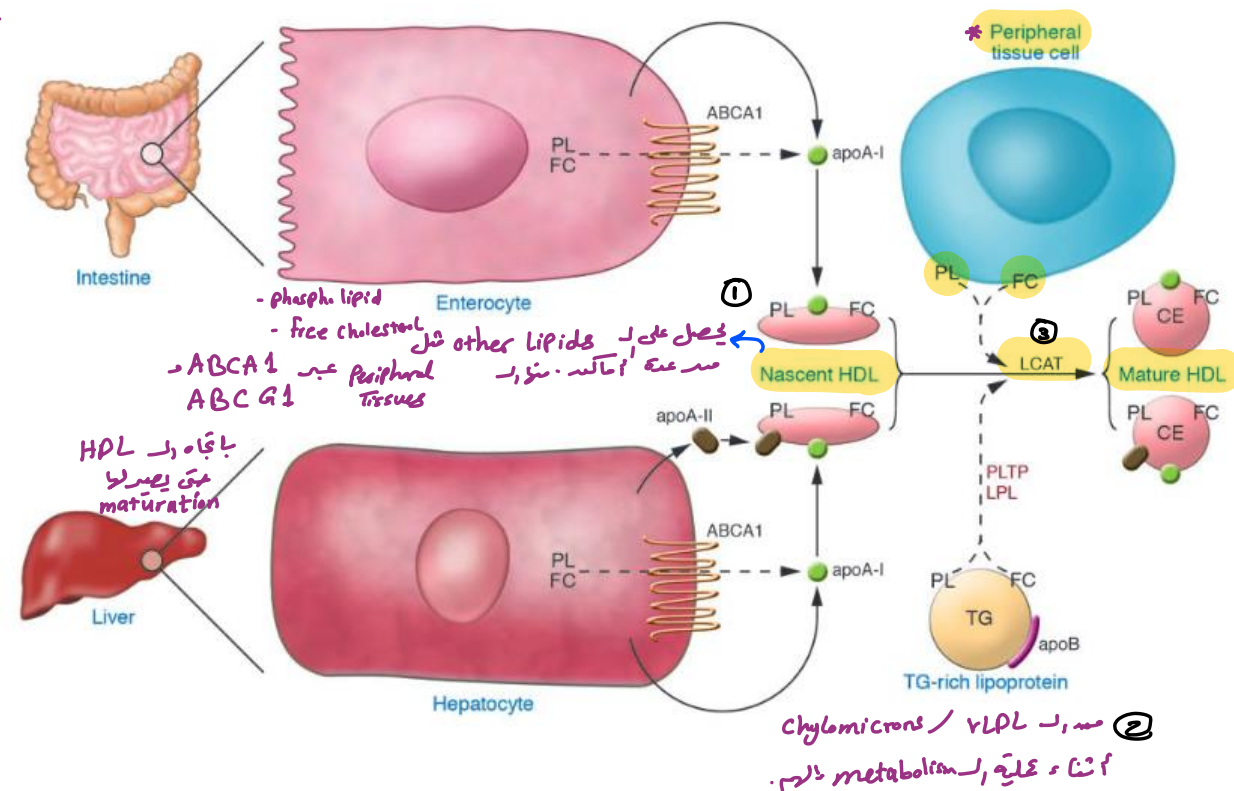
Maturation of HDL

- **Nascent HDL collects additional lipids from:**

1. Other peripheral tissues (via ABCA1 and ABCG1 transporters).
 ATP binding cassette transporter G1.
 efflux mechanism for free cholesterol and phospholipids.
 HDL formation.

2. Other lipoproteins, such as VLDL and chylomicrons, during their metabolism.

- ### 3. Lecithin-cholesterol acyltransferase (LCAT)



* ال HDL بيا غذاء excess cholesterol من peripheral tissue عن طريق كبد liver
 recycling excretion

Storage of Cholesterol (Next lecture)

ال Cholesterol عن طريق Storage لانهم يتحول من FC الى CE .
 cholesteryl ester
 Cholesterol ester is the storage form of cholesterol: It is formed in both tissues and plasma.

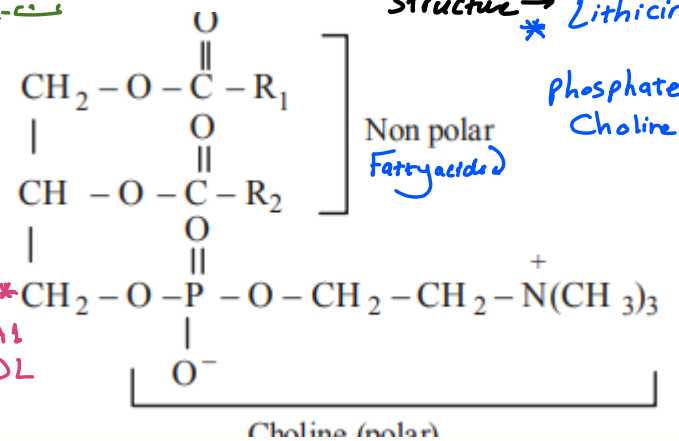
① In tissues (liver), cholesterol is esterified by ACAT enzyme (acyl CoA cholesterol acyl transferase):
 hydroxyl group fatty acids fatty acyl CoA liver
 Cholesterol + Acyl CoA → Cholesteryl ester + CoASH
 ACAT
 Less toxic and less reactive than FC.
 Cholesteryl ester
 يستخدم كخزن لل Cholesterol
 عندما تحتاجه الخلايا وتتحلل Cholesteryl ester الى Cholesterol و fatty acids
 عن طريق عملية hydrolysis

② In plasma, cholesterol is esterified by LCAT enzyme

(lecithin cholesterol acyl transferase). LCAT is associated with HDL.

Cholesterol + lecithin → Cholesteryl ester + lysolecithin
 LCAT
 activation by Apo A1 → HDL

يصنع في كبد liver
 ويصدر الى plasma
 يعمل في ال circulation



* لأنه هنا ال enzyme الموجود في plasma يتم تنقيطه بالـ
 Apo A, الموجود على ال HDL عشان يحول ال
 Cholesterol ← Cholesterol ester

ويتم incorporation على ال HDL وبالتالي
 يتم عليه ال RCT

* يتم تحويل free cholesterol من ال Peripheral tissue الى ال Cholesterol ester
 وينتج ال incorporation مع ال HDL على صورة
 • Cholesteryl ester

* مصنفه العملية أحد ال key steps في عملية RCT
 (Reverse Cholesterol Transport)

لأنه هي التي تتخلص من ال excess cholesterol من مجلد ال Liver
 بالتالي إما يصير ال excretion or recycling.

بالتالي هيلعزنا ليه قادم بعض ال lipids ونعرفها

ال Cholesterol ester في ال HDL عبارة عن ال LCAT enzyme

Thanks