LIPOPROTEINS AND ATHEROSCLEROSIS

"YOU DON'T HAVE TO BE GREAT TO START, BUT YOU HAVE TO START TO BE GREAT"

Color index:

- Important
- Extra explanation

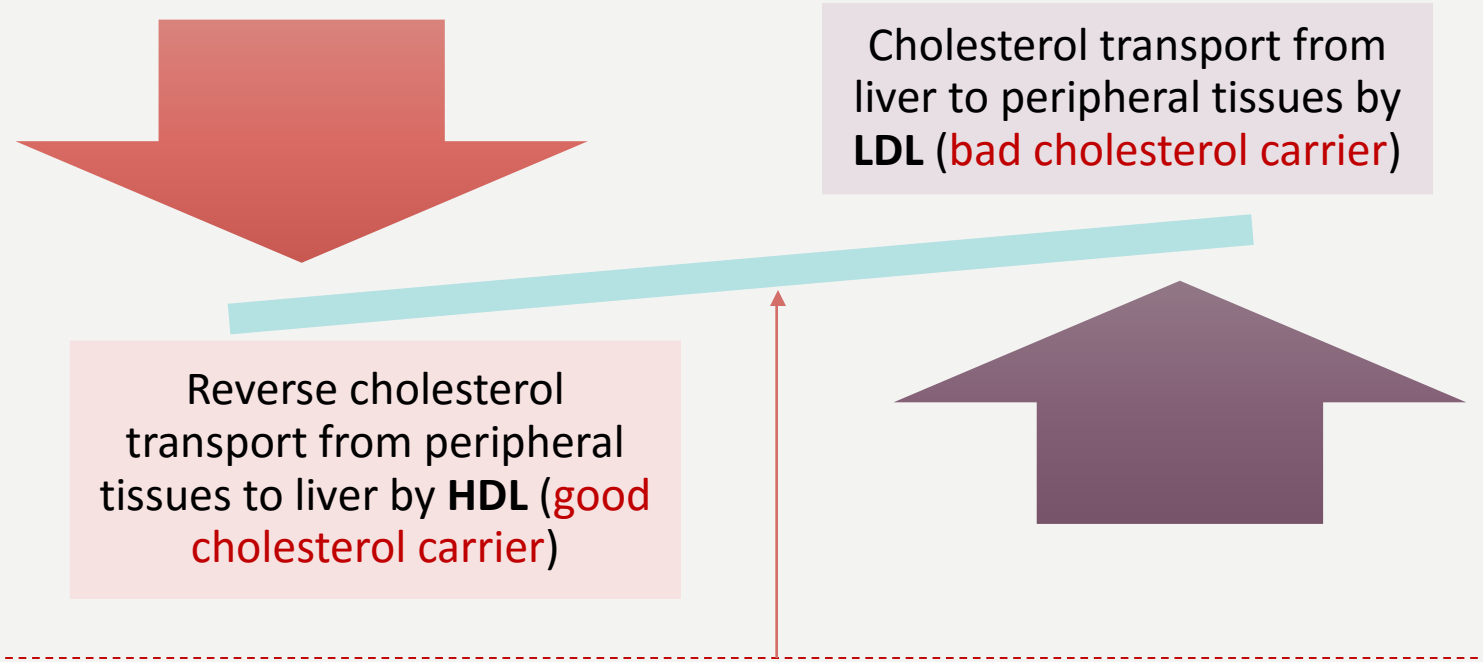
*** Please check out this link to know if there are any changes or additions.**

OBJECTIVES:

- Know the composition of plasma lipoproteins (chylomicrons, VLDL, LDL and HDL).
- Recognize the metabolism and function of plasma lipoproteins .
- Identify the functions of apolipoproteins.
- Outline the clinical aspects of abnormal lipoprotein metabolism.

Introduction

- A key element for cholesterol homeostasis is the balance between:



Note:

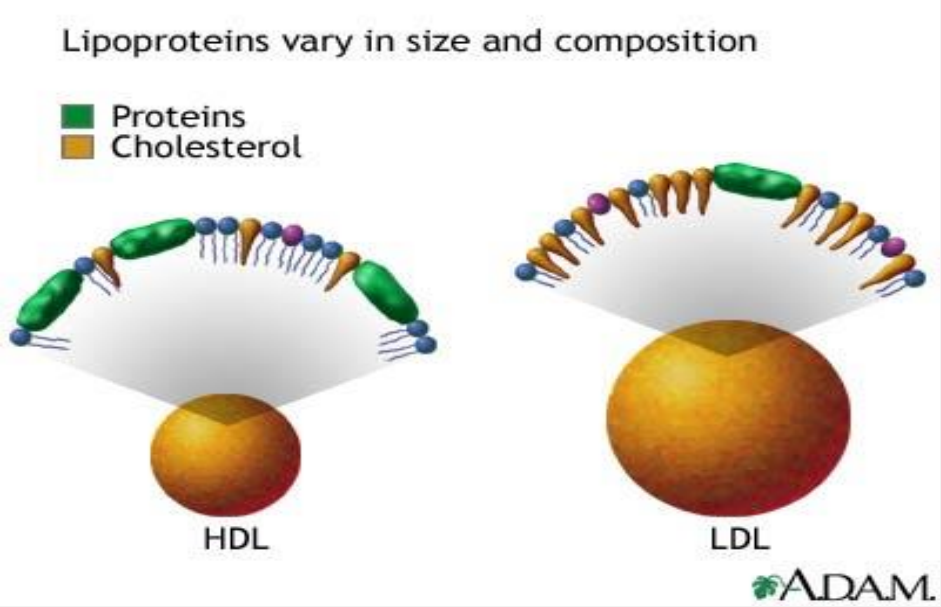
Imbalance results in cholesterol deposition in the wall of the blood vessels and this will **lead to**:

- Thickening of the wall.
- Narrowing of the lumen.

And this is known as "**Atherosclerosis**".

COMPOSITION OF LDL AND HDL

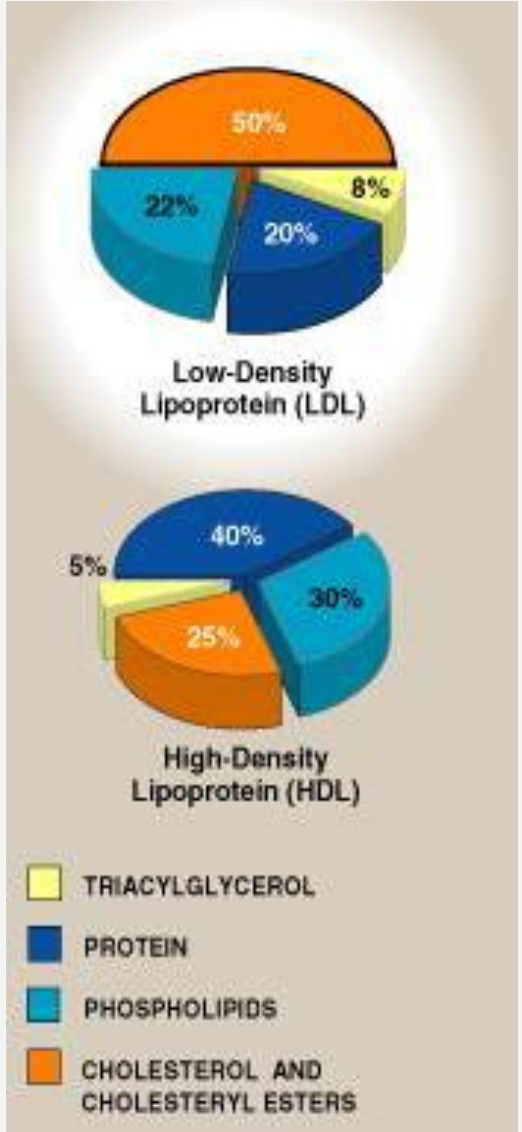
Different in	LDL	HDL
Mostly is	**Free cholesterol**	**Cholesterol ester**
Protein	Less	More
Phospholipids	Less	More



Note:

Esterification of cholesterol minimize the content ,so the HDL can accept more cholesterol from tissue.

HDL has more phospholipids because it needs it for the esterification

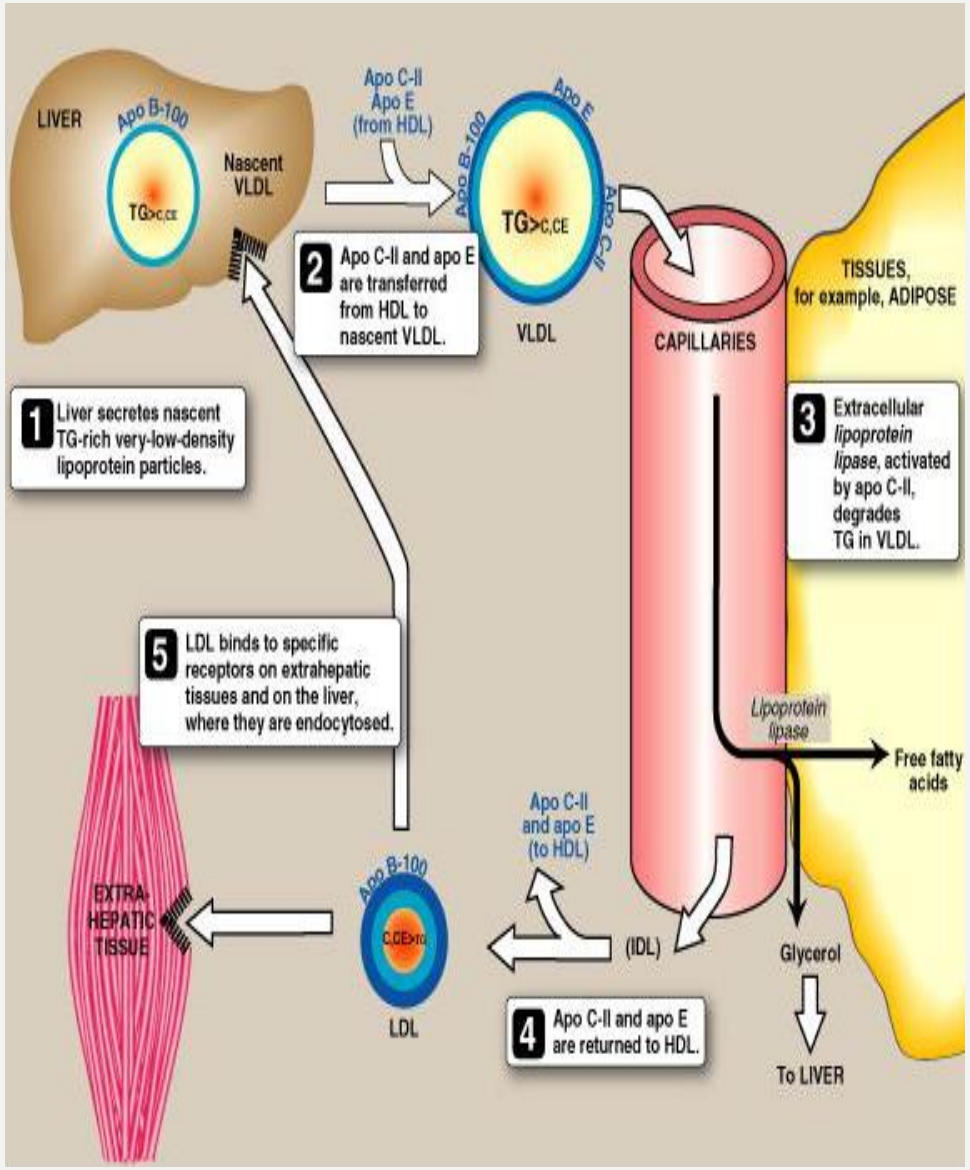


LDL METABOLISM – EXPLANATION FROM LIPPINCOTT

1.Release from liver: VLDLs are secreted directly into the blood by the liver as nascent particles containing apo B-100. They must obtain apo C-II and apo E from circulating HDL. (don't forget that apo C-II is required for activation of LPL).

2. Modification in the circulation: As VLDLs pass through the circulation, TAG is degraded by LPL, causing the VLDLs to decrease in size and become denser. Surface components, including the C and E apolipoproteins, are returned to HDL, but the particles retain apo B-100. Additionally, 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).

3. Conversion to low-density lipoproteins: With these modifications, the VLDL is converted in the plasma to LDL. Intermediate-sized particles, the intermediate density lipoproteins (IDLs), or VLDL remnants, are observed during this transition. IDLs can also be taken up by liver cells through receptor mediated endocytosis that uses Apo-E as the ligand.



LDL metabolism

LOW DENSITY LIPOPROTEINS (LDL)

- **Produced in:** the circulation as **the end product of VLDLs** "as mentioned in the previous lecture".

- **If we compared LDLs to VLDLs, the LDLs are:** من الجدول الموجود في المحاضرة السابقة نستطيع أن نستنتج أغلب الخصائص
  - They contain only **apo B-100.**
  - Smaller size and more dense.
  - Less TG "triacylglycerol".
  - More cholesterol & cholesterol ester.

- **Function of LDLs:** Transport cholesterol from **liver** to **peripheral tissues**.

- **How can tissue uptake LDL?**
  By: **LDL receptor-mediated endocytosis**.

- **How can the receptor recognized LDL?**
  By: **apo B-100.** «acts as a ligand»

*** In summary:** the tissue has a receptor called **LDL receptor,** this receptor can recognize LDL by **apo B-100** which is located on the surface of LDL.

Apolipoprotein B100 (apoB100) is a protein that plays a role in moving cholesterol around your body. It is a form of low density lipoprotein (LDL).

LDL METABOLISM – FURTHER EXPLANATION FROM LIPPINCOTT

1- synthesis of LDL receptor:
Transcription ⟶ translation ⟶ modification by Golgi apparatus ⟶ Vesicle fuse with the cell membrane

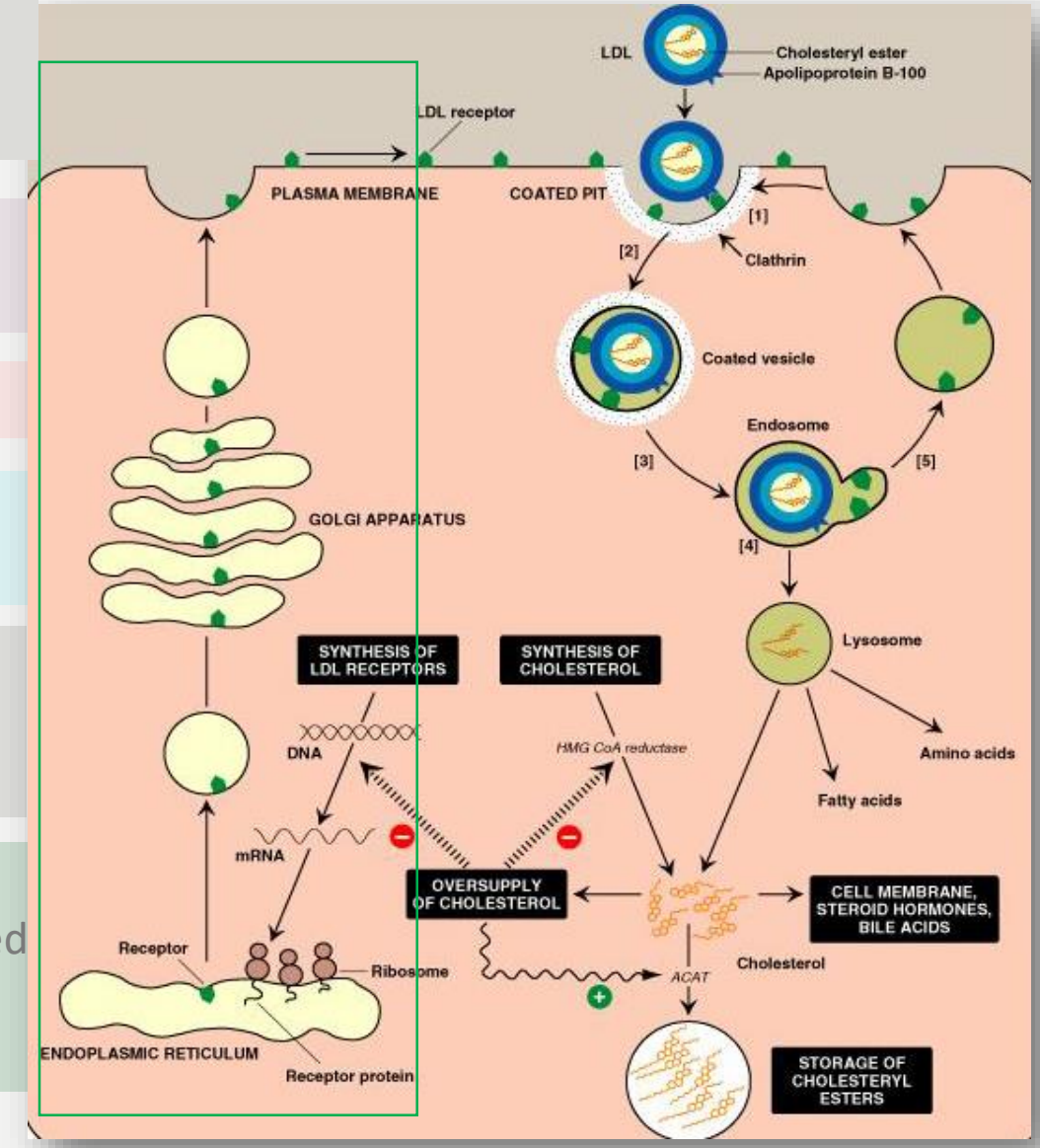
{1} LDL receptors are clustered in pits on cell membrane, their cytosolic side of the pit is coated with “clathrin” (stabilizes the pit)

{2} After binding, LDL-receptor complex is taken by endocytosis.

{3} Vesicle “that contains the complex” losses its clathrin coat and fuses with similar vesicle to form larger one.

{4} decreased of endosome’s PH which results in:
- Separation of LDL from its receptor → receptor migrate to one side of the endosome → LDL stays free in the lumen.

{5} A-Receptors can be recycled .
B- Lipoproteins in the vesicles are transferred to lysosome and degraded by lysosomal acid hydrolase, Releasing free cholesterol, amino acids, fatty acids, and phospholipids.



LDL METABOLISM – FURTHER EXPLANATION

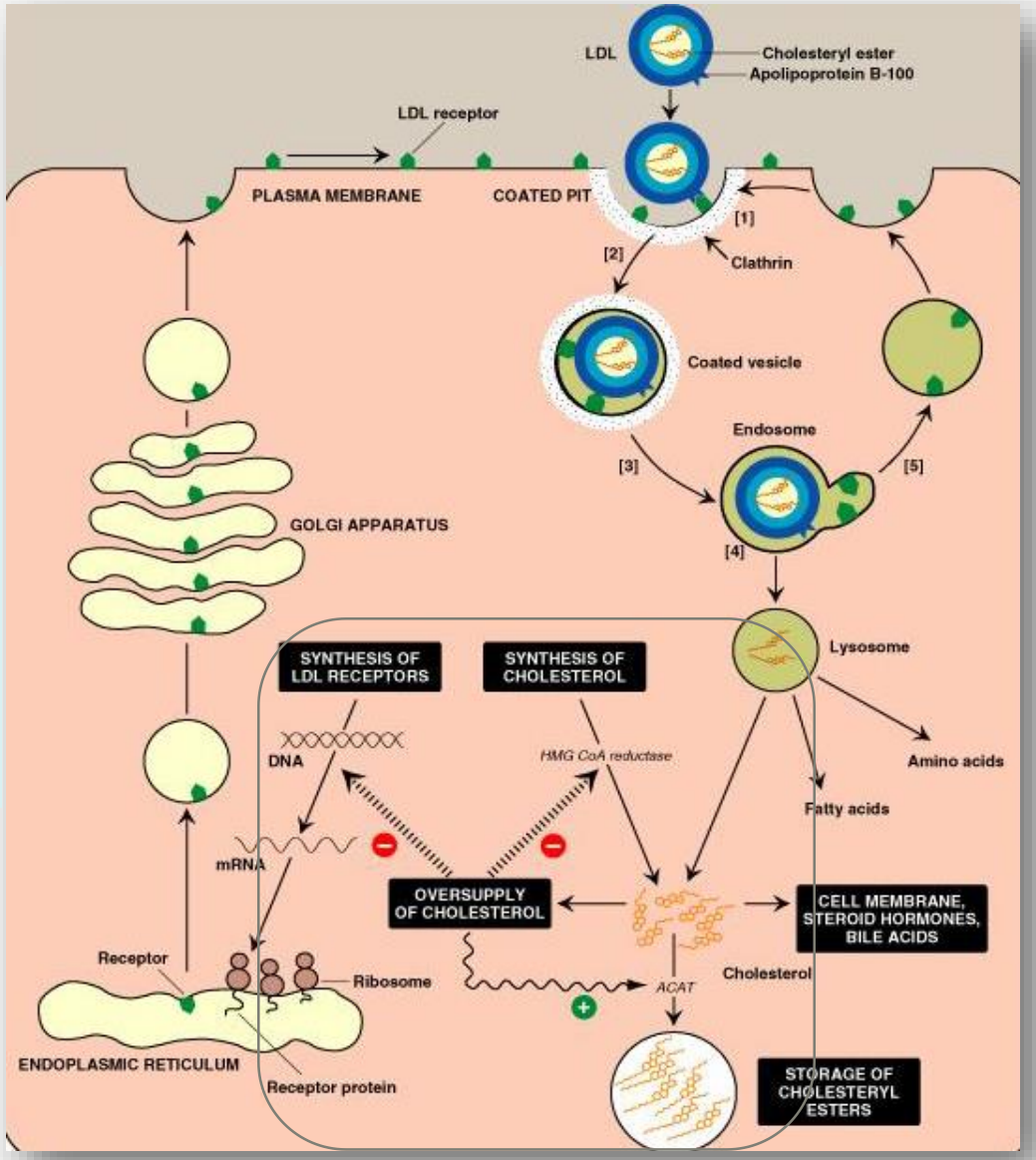
fate of cholesterol:

* converts to cell membrane, steroid hormone and bile acids.

* storage of cholesterol ester by ACAT " acyl-CoA cholesterol acyl transferase"

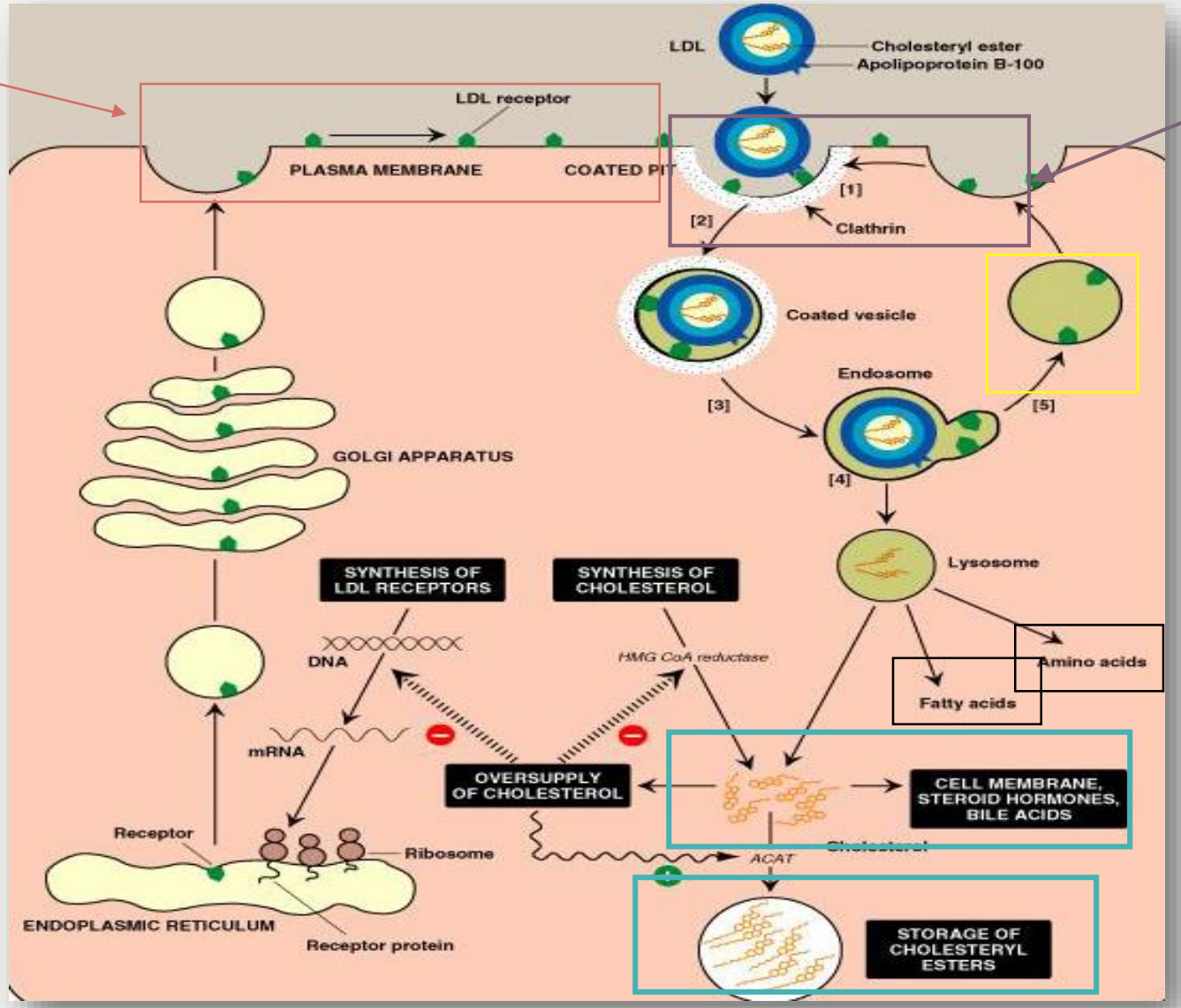
If cholesterol is increase in the cell ⟶ inhibition of cholesterol and LDL receptor synthesis .

- Inhibit HMG CoA reductase " rate limiting step in cholesterol synthesis.
- Inhibit the LDL receptor gene transcription



RECEPTOR-MEDIATED ENDOCYTOSIS

1- LDL receptor are characterized by:
- Cell surface glycoprotein.
- High-affinity "can recognize small amounts"
- **tightly regulated**.



2-LDL/Receptor binding and internalization of the complex by endocytosis.

3- Release of cholesterol inside the cells for (A):
- Utilization.
- Storage as cholesterol ester.
- Excretion.

4- Degradation of LDL into (B):
- Amino Acids.
- Phospholipids.
- Fatty acids.

5-Degradation or recycling of receptor.

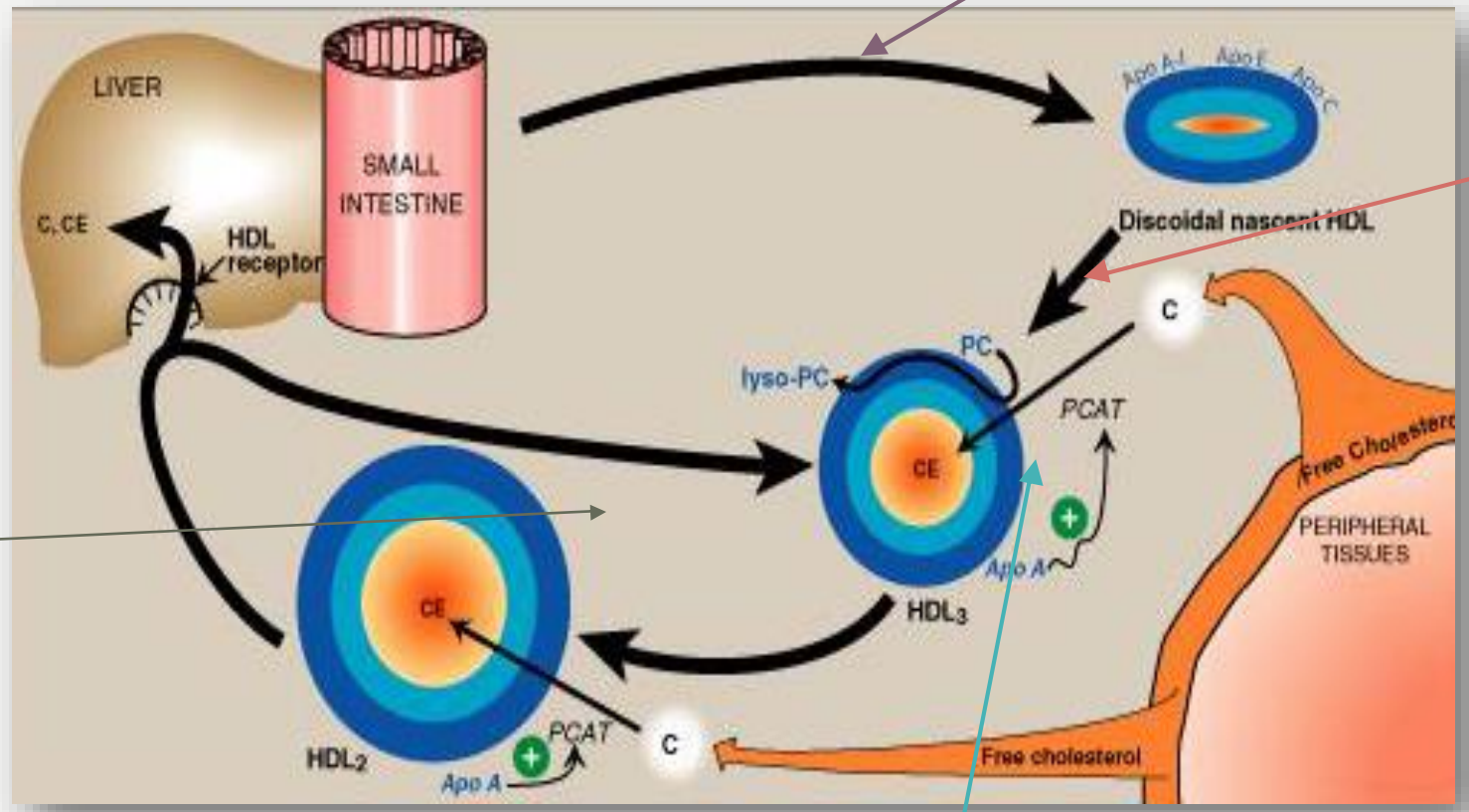
Receptor-mediated endocytosis

REGULATION OF LDL RECEPTOR-MEDIATED ENDOCYTOSIS

		Down Regulation (High intracellular cholesterol content)	Up Regulation (Low intracellular cholesterol content)
Intracellular Cholesterol Content:	LDL Receptor:	Degradation	Recycling
	Receptor synthesis at gene level	Inhibition	Stimulation
Number of Receptors at cell surface:	Further Uptake of LDL	Decrease	Increase
De novo synthesis	-	Decrease	Increase

HDL METABOLISM –EXPLANATION

{1} HDL is produced by intestine and the liver.



HDL metabolism

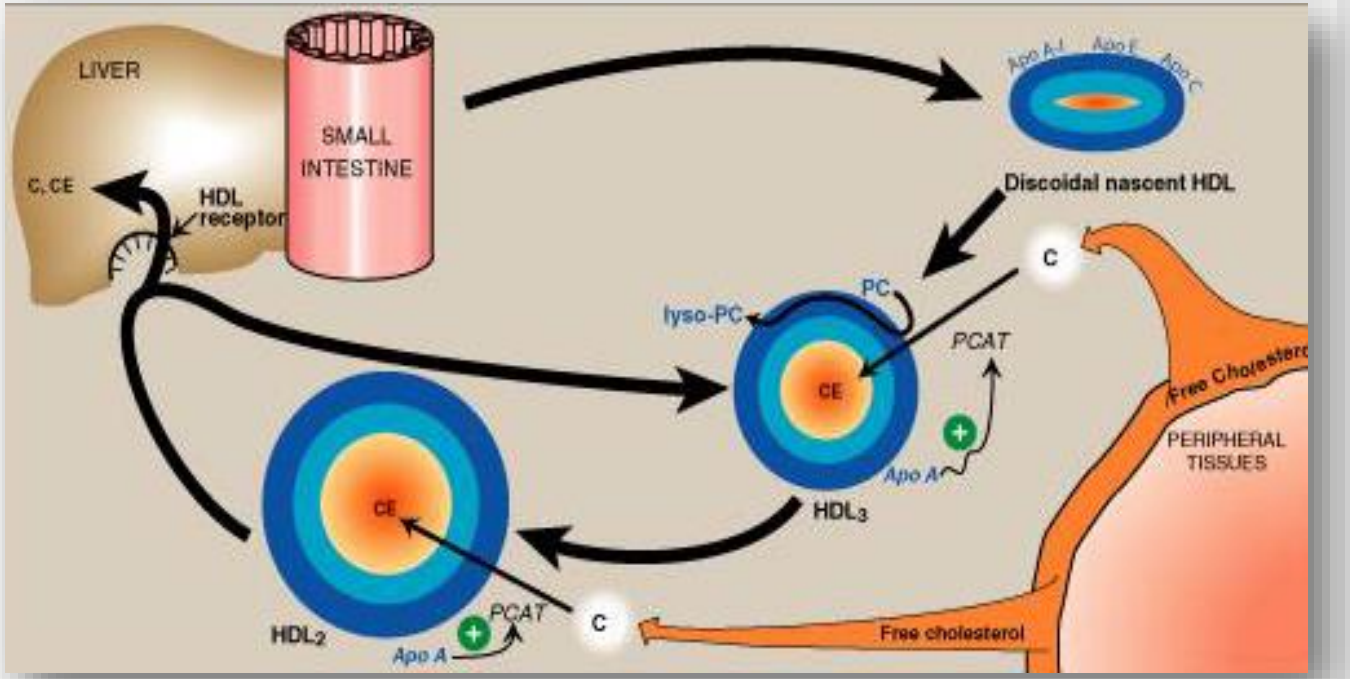
{2} Nascent HDLs (disc shaped particles **containing: Apo A-I , C-II and** E) take up free cholesterol from non-hepatic (peripheral) tissues and return it to the liver as cholesteryl esters. (they're excellent acceptors of free cholesterol as a result of their high conc. Of phospholipids, which are cholesterol stabilizers)

{3} once cholesterol is taken by HDL, it is immediately esterified by LCAT\PCAT (by transferring the fatty acid from lecithin to cholesterol) and it is activated by Apo-A.

{4} As the discoidal nascent HDL accumulates cholesteryl ester, it first becomes a cholesteryl-poor HDL3 and eventually a cholesteryl-rich HDL2 particle that carries the esters to the liver ☺

HIGH DENSITY LIPOPROTEINS (HDL)

❖ **Produced By:** **Intestine + Liver**



Forms ❖	
Nascent HDL:	**Mature HDL (HDL2)**
- **Shape:** Disk-shaped (donut-shaped :P). - **Contained Apoproteins**: Apo-AI, C-II and E. - **Contains** primarily phospholipids.	1- HDL3 collects cholesterol (C). 2- cholesterol is converted to cholesteryl ester. 3- HDL2 is formed which is spherical mature particle.

#Functions of HDL

Reservoir of apoproteins

Example: Apo C-II and E to VLDL

Esterification of cholesterol

Cholesterol + Phosphatidylcholine (PC) $\xrightarrow{\text{PCAT\LCAT}}$ **cholesterol ester + Lyso-PC**

(+) → Apo A-I

- **Enzyme:** *PCAT\LCAT.
- **Substrate:** cholesterol.
- **Product:** Cholesterol ester (& Lyso-PC)
- **Activator:** Apo A-I
- **Co-Substrate:** Phosphatidylcholine (PC)

Reserve cholesterol transport

Uptake of cholesterol

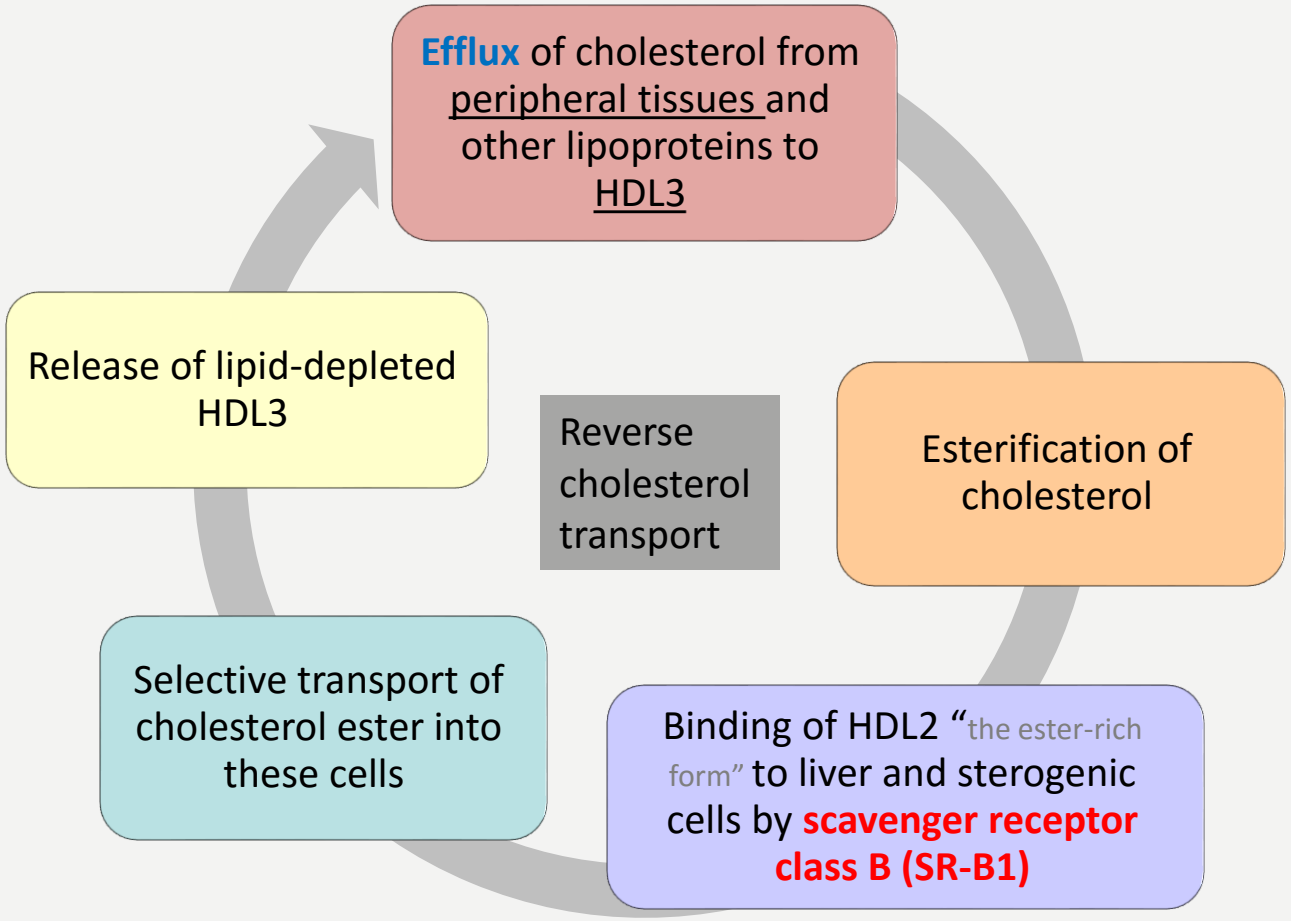
From other lipoproteins and cell membrane.

HDL is suitable for the cholesterol uptake because of high content of PC that can both solubilizes cholesterol and acts as a source of fatty acid for cholesterol esterification.

*LCAT= Lecithin cholesterol acyltransferase.

WHY IS HDL A GOOD CHOLESTEROL CARRIER?

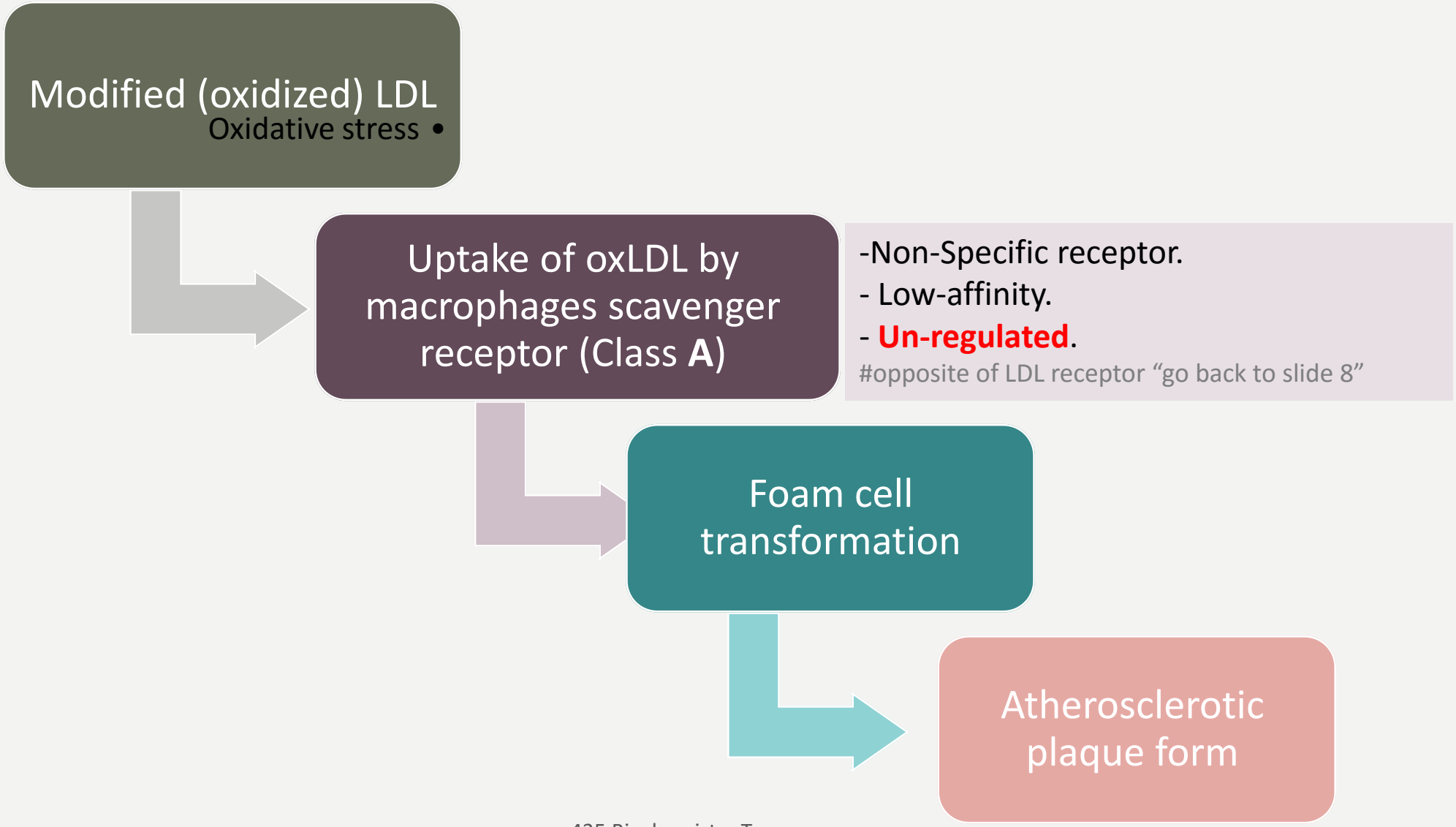
Inverse Relation between plasma HDL levels and atherosclerosis.



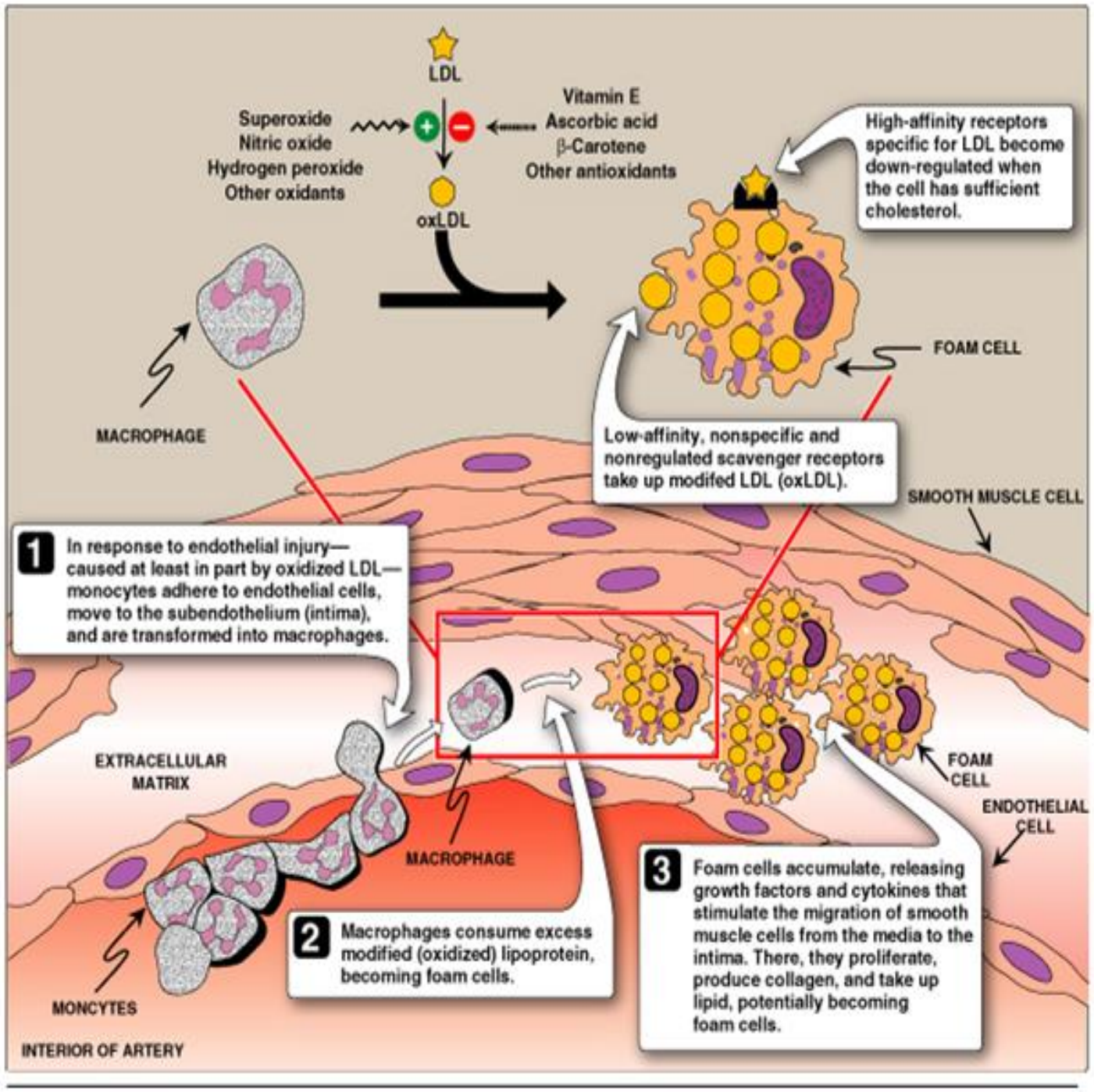
العلاقة بين HDL و Atherosclerosis علاقة عكسية ، فكلما زاد HDL كلما قلت فرصة حدوث Atherosclerosis. ياترى ماهو السبب؟
وظيفة الـ «إتش دي إل» هي: نقل الكوليسترول من التيشوز إلى الكبد ، عندما تذهب للكبد سيتم إخراجه على شكل Bile وستقل نسبته

Note:
Estrogen and exercise increase HDL.

ATHEROSCLEROSIS



Biochemistry Team 435



Plaque formation

LABORATORY INVESTIGATION OF ATHEROSCLEROSIS

- **Measuring Serum Lipid profile**

- **Requires** 10-12 hours overnight fasting

- **Measurement of:**

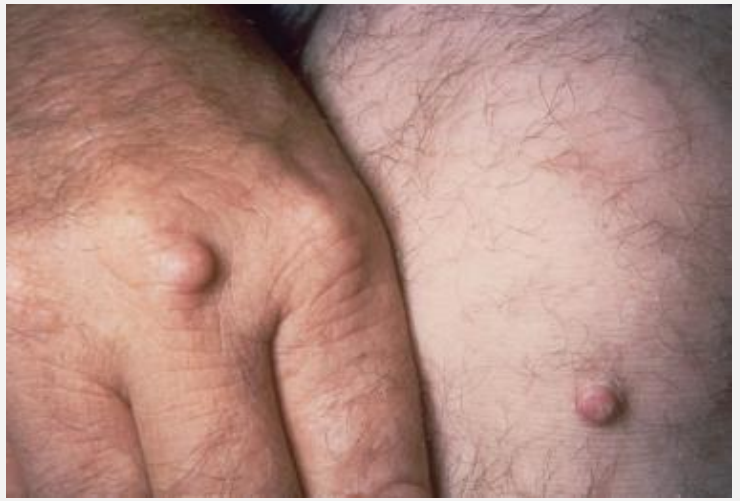
- Serum triacylglycerol (reflects chylomicrons and VLDL levels)
- Serum total cholesterol (reflects LDL and HDL)
- Serum HDL-cholesterol level
- Serum LDL-cholesterol level

Or

- Serum lipoprotein electrophoresis
- Serum apoprotein levels e.g., apo-B

LDL-RELATED DISEASES

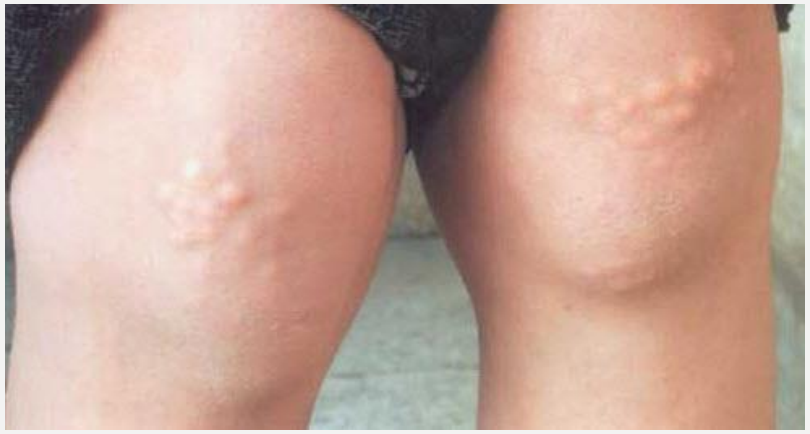
Type IIa hyperlipoproteinemia
"Familial hypercholesterolemia"

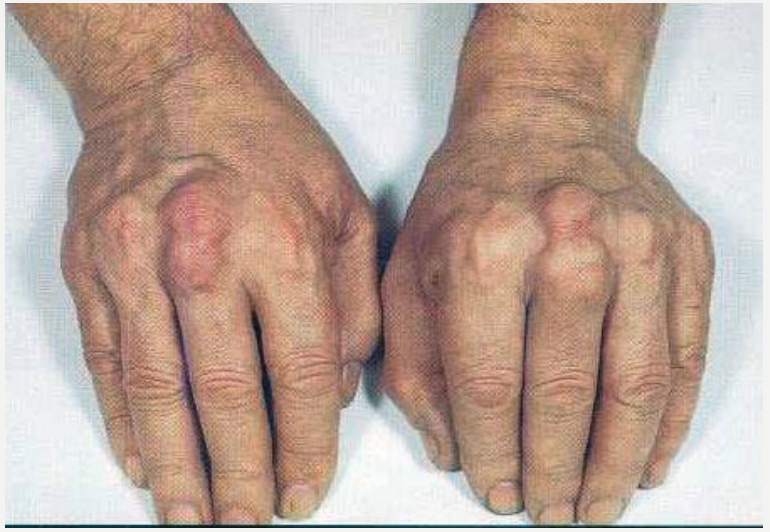


- **Caused by:** functional defect of LDL-receptor
- **Leads to:**

Increase plasma LDL level and therefore, plasma cholesterol level

- **Associated with:** the presence of tendon xanthoma on hands and ankles.
- Premature (means it happens to young people) atherosclerosis and increased risk for early-onset ischemic heart disease





MCQs

1.Which is correct for HDL:

A- it is the biggest lipoprotein

B- its lipid content is higher than its protein content

C- removes cholesterol from the periphery and delivers to liver for metabolism

D- has an insignificant role in cholesterol transportation

2. In terms of size, which lipoprotein is the smallest:

A- LDL

B- VLDL

C- Chylomicron

D- HDL

3. Atherosclerosis is a pathological condition that can lead to thrombus formation. Which one of these is essential in the process:

A- LDL

B- RBCs

C- B12

D- vitamin D

4. Familial hypercholesterolemia is caused by a defect in:

A- HDL receptor.

B- LDL receptor.

C- apo B-100.

D- apo E.

5. HDL act as a reservoir of :

A- cholesterol

B- lipids

C- apoproteins

D- phospholipids

6. the origins of the HDL is:

A- liver & intestine

B- lymph nodes & in the ciruclation

C- intestine & circulation

D- bile & liver

1. C
2. D
3. A
4. B
5. C
6. A

MCQs

7. What is the major apoprotein in LDL:

A- apo B-100
B- apo A
C- apo D
D- apo C

8. Type IIa hyperlipoproteinemia leads to:

A- decrease plasma cholesterol level.
B- Increase plasma cholesterol level.
C- hepatic steaosis.
D- increase plasma HDL level.

7. A
8. b

Team Members:

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- منيره العمري.
- رهف بن عباد.
- دلال الحزيمي.
- بدور جليدان.
- أثير النشوان.
- علا النهير.
- أفنان المالكي.
- خوله العريني.
- غاده القصيمي.
- نوف الرشيد.

- خالد النعيم .
- ثاني معافا .
- فارس المطيري.
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