Biochemstry Team

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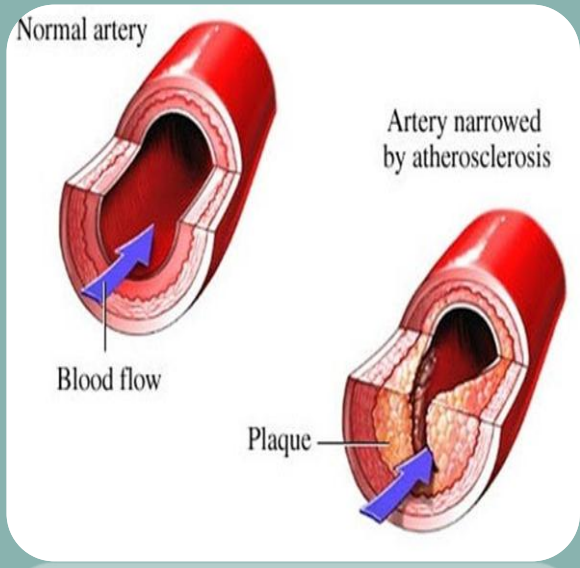
Objectives:

Upon completion of these two lectures, the students should be able to:

- know the composition of plasma lipoproteins (chylomicrons, VLDL, LDL and HDL).
- recognize the metabolism and functions of plasma lipoproteins
- identify the functions of apolipoproteins
- outline the clinical aspects of abnormal lipoprotein metabolism.



Done by : Abdullah Alatawi, Ibrahim Alfuraih , Haifa Aldabjan and Raghad almutlaq. (Special thanks to mohammed al-Jerbou)

Cholesterol balance

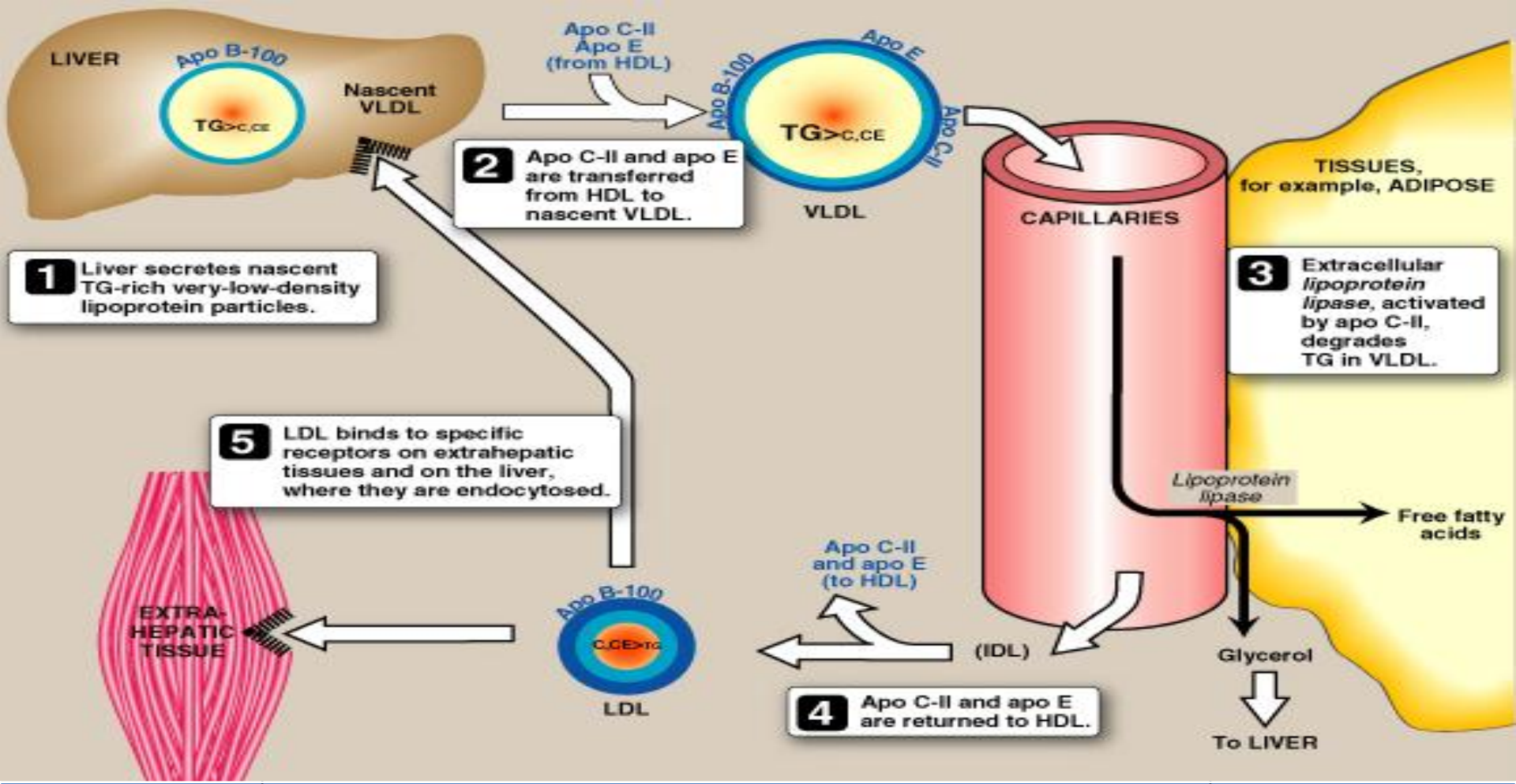
From Liver to Peripheral

LDL

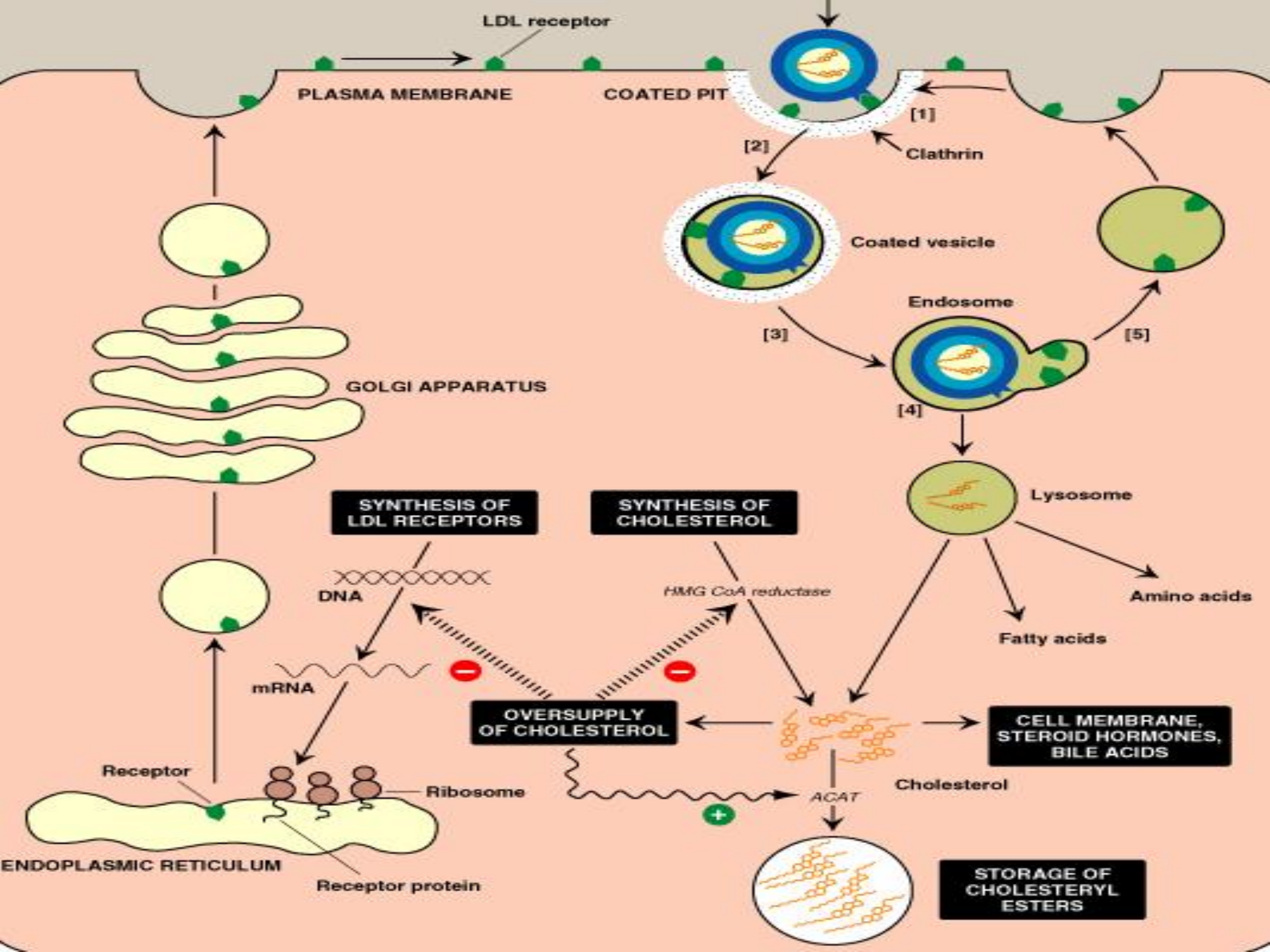
From Peripheral to Liver

HDL

IMBALANCE → Cholesterol deposition → Atherosclerosis



Lipoprotien	Production	Function
LDL	**in the circulation as the end product of VLDLs:** • **It contains only apo B-100** • **Smaller size and more dense** • **Less TG** • **More cholesterol & cholesterol ester**	Transport cholesterol from liver to peripheral tissue.


LDL receptor
PLASMA MEMBRANE
COATED PIT
[1]
Clathrin
[2]
Coated vesicle
Endosome
[3]
[4]
[5]
GOLGI APPARATUS
Lysosome
SYNTHESIS OF LDL RECEPTORS
SYNTHESIS OF CHOLESTEROL
DNA
HMG CoA reductase
Amino acids
Fatty acids
mRNA
OVERSUPPLY OF CHOLESTEROL
CELL MEMBRANE, STEROID HORMONES, BILE ACIDS
Cholesterol
Receptor
Ribosome
ACAT
ENDOPLASMIC RETICULUM
Receptor protein
STORAGE OF CHOLESTERYL ESTERS

Receptor-Mediated Endocytosis

- **LDL receptor (regulated either by recycling or digestion in cytosome)**

- Cell surface glycoprotein

- High-affinity, tightly regulated.

- **LDL Receptor binding and internalization of the complex by endocytosis where it degrades into : amino acids, phospholipids or fatty acids**
- **Release of cholesterol inside the cells for:**

Utilization , Storage as cholesterol ester or Excretion

LDL regulation

Down-regulation	Up-regulation
Down regulation (decreasing LDL when it's high) High intracellular cholesterol → inhibit receptors formation at gene level + degrades the existing bound receptors on the membrane→ lowering No. of receptors → dec. uptake of LDL → decrease de novo synthesis of cholesterol	Up regulation (increasing cholesterol) Exactly the opposite

HDL

- **Produced by intestine and liver**

Nascent HDL:

- Disk-shaped "like RBC"
- Contains apo A-I "unique for HDL", apoC-II and apoE
- Contains primarily phospholipid (PC)

Mature HDL (HDL2):

- First, the HDL3 collects cholesterol (C)
- Then, C is converted to CE (C- ester)
- Once it reaches specific size we call it HDL2
- The HDL2 is the spherical mature particle which have the receptors on liver cells

Functions of HDL:

1-Reservoir of apoproteins_ e.g., Apo C-II and E to VLDL

2-Uptake of cholesterol: _From other lipoproteins & cell membranes

(HDL is suitable for uptake of cholesterol because of high content of PC that can both solublize cholesterol and acts as a source of fatty acid for cholesterol esterification)

3-Esterification of cholesterol:

Enzymes : PCAT/LCAT

Activator: Apo A-1

Substrate: Cholestrol, Co-substrate : PC

Product: Cholesterol ester (& Lyso-PC)

4- Reverse cholesterol transport

Why Is HDL a Good Cholesterol carrier?

Inverse relation between plasma HDL levels and atherosclerosis How?

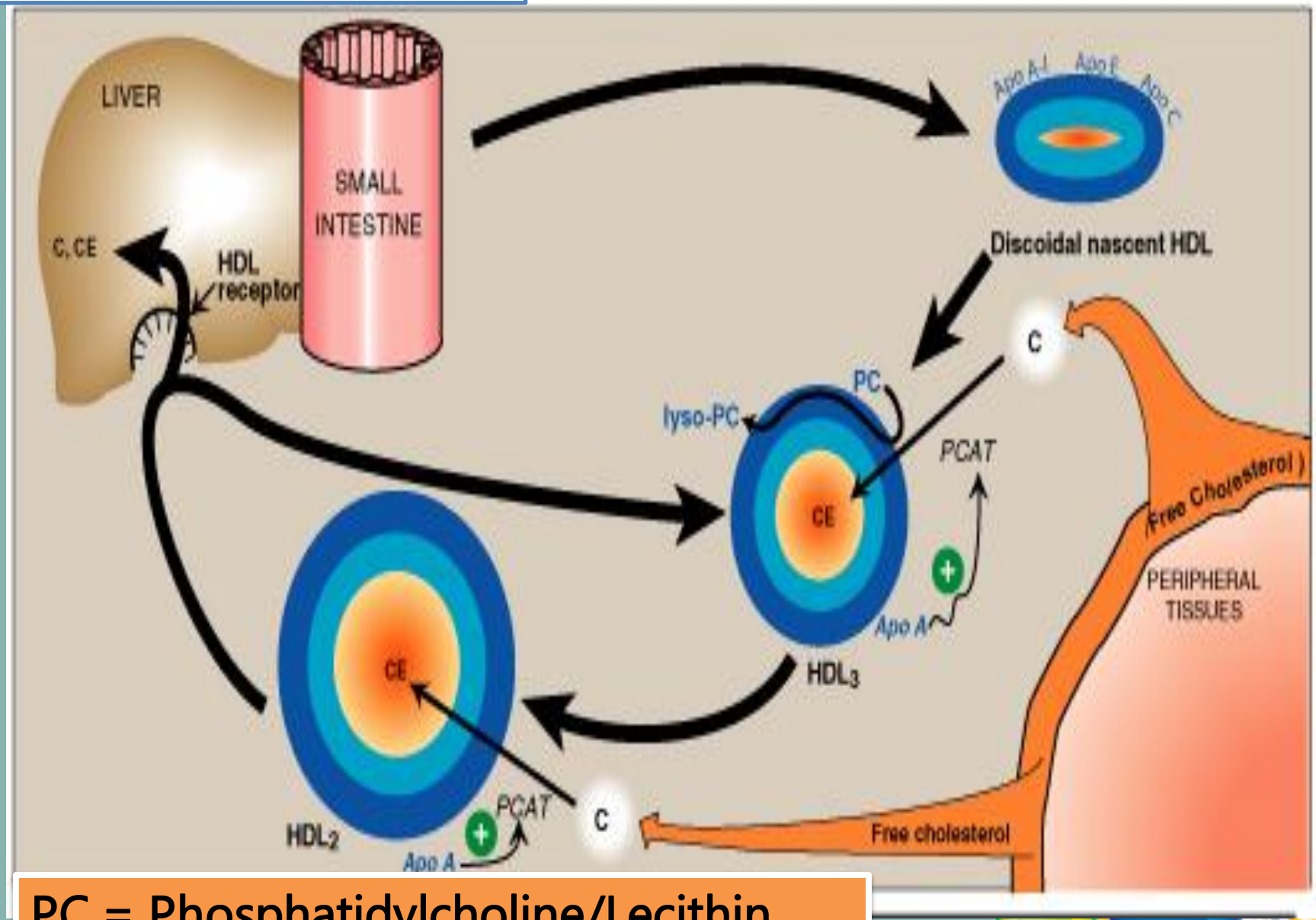
Reverse cholesterol transport involves: Efflux of cholesterol from peripheral tissues and other lipoproteins to HDL3

Esterification of cholesterol & binding of HDL2 to liver and stroidogenic cells "like ovary, testicle or adrenal cortex" by scavenger receptor class B (SR-B1) .

Selective transfer of cholesterol ester into these cells .

Release of lipid-depleted HDL3 .

HDL Metabolism



PC = Phosphatidylcholine/Lecithin

1-The HDL synthesis by the liver and intestine.
2-It leave as discoidal nascent HDL like the RBC because it has little amount of cholesterol and cholesterol ester and it has a lot of protein. On its wall has apo-A-1 (which is unique for HDL), apoC-II and apoE
3- It goes into the circulation and gain cholesterol from peripheral tissue ⟶ increase in size and decrease in density ⟶ become HDL3 more **spherical in shape**. it has a PC on the phospholipids component which serve as a donator of fatty acid.
4-**Esterification of cholesterol:**" conversion of cholesterol into cholesterol ester"
Apo A activate PCAT "**Lecithin-cholesterol acyltransferase** " enzyme
PCAT ⟶ PC ⟶ lyso-PC

cholesterol (c) + fatty acid = cholesterol ester (CE)

5- gain more cholesterol and cholesterol ester ⟶ increase in size and decrease in density ⟶ become HDL2 the mature form of HDL
6- HDL3 bind to the liver via **scavenger receptor class B (SR-B1) "HDL receptor"**

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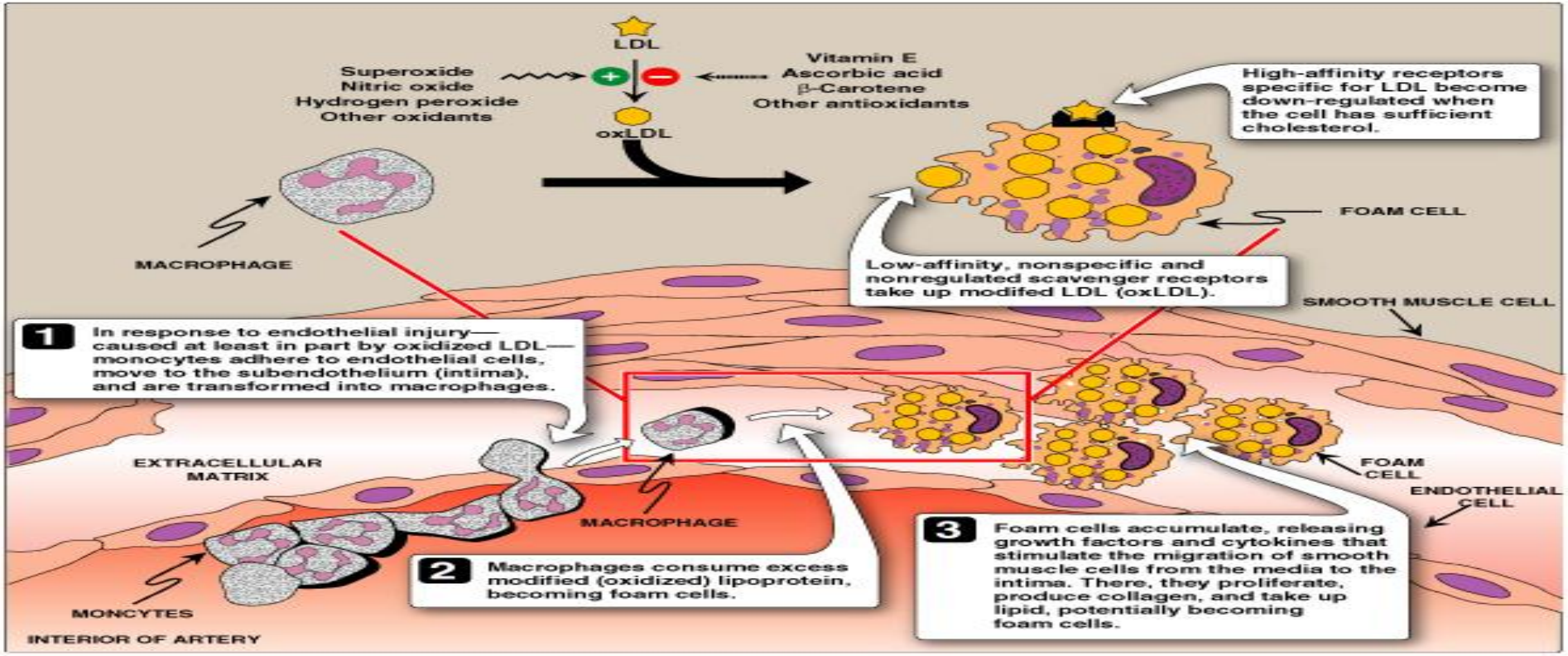
Note:
1-There is HDL1 which bigger but it found only in rats
2-As the size of lipid increases the density decrease.



Atherosclerosis

PATHOGENESIS:

*Modified (oxidized) LDL Oxidative stress.

* Uptake of oxLDL by macrophage scavenger receptor :

Scavenger receptor class A (SR-A)

Low-affinity, non-specific receptor

Un-regulated receptor

* Foam cell transformation

Macrophage transformed into foam cell which is very aggressive release cytokines, inflammatory mediators and hypertrophy of the muscle cell

* Atherosclerotic plaque formati

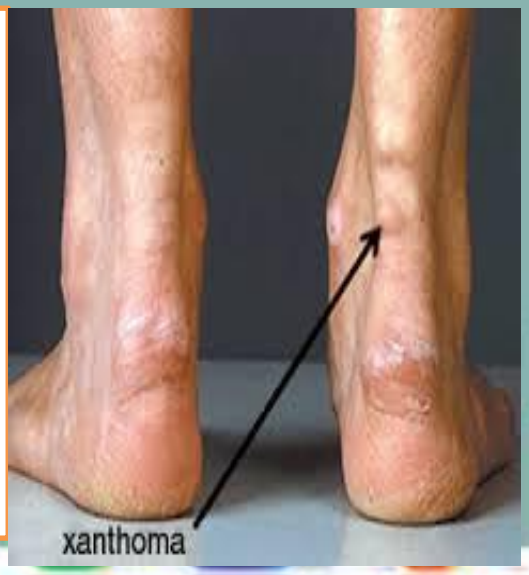
Laboratory Investigation of Atherosclerosis

Serum lipid profile: (10-12 hours (O/N) fasting)
Measurement of
Serum triglyceride level (reflect chylomicron and VLDL levels)
Serum total cholesterol level (reflect LDL and HDL levels)
Serum apoprotein levels e.g., apo-B
Serum HDL-cholesterol level Serum LDL-cholesterol level Others, Serum lipoprotein electrophoresis

LDL-related Diseases

Hyperlipoproteinemia:
Type IIa Hyperlipoproteinemia
(Familial hypercholestrolemia)

- **Functional defect of LDL-receptor**
- **Increase plasma LDL level & therefore, plasma cholesterol level**
- **Pre-mature atherosclerosis and increased risk for early-onset ischemic heart diseases**
- **Associated with the presence of tendon xanthomas(ترسب) on hands and ankles**



Questions

1- cholesterol amount affect:

A- LDL receptor no.

B- Cholesterol synthesis

C- both

2-The HDL leaves the liver as:

A- HDL1

B- Nascent HDL

C- HDL2

3- the name of HDL receptor in the liver is:

A- HDL3 receptor

B-scavenger receptor class A

C- scavenger receptor class B

4-All the following found in HDL except:

A- apo B-100

B- apo A-1

C- apo c-2

Additional videos :

http://www.youtube.com/watch?v=PifagmJRLZ0

http://www.youtube.com/watch?v=lh18qaShTZU

Answers	
1	C
2	B
3	C
4	A