Biochemistry Teamwork

Lipoprotein Metabolism

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Introduction :

Balance : LDL = HDL
(Normal condition)

Imbalance : LDL > HDL

(Abnormal condition)

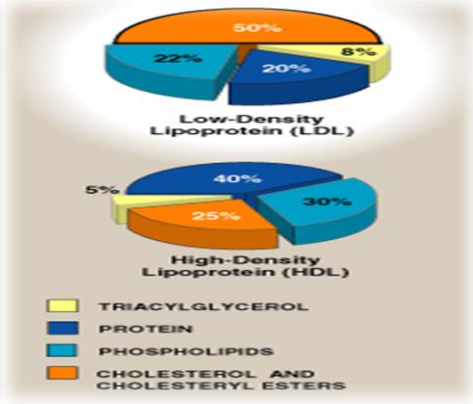
A key element for cholesterol homeostasis is the balance between:
- Cholesterol transport from liver to peripheral tissues by LDL (bad cholesterol carrier)
- Reverse cholesterol transport from peripheral tissues to liver by HDL (good cholesterol carrier)
- *Imbalance* results in cholesterol deposition in the wall of blood vessels, thickening of the wall and narrowing of the lumen "Atherosclerosis"

Composition of LDL and HDL :

- Low density lipoprotein (LDL)
  Mostly free cholesterol . (mainly free)

Apo- B 100 in LDL

Hint : LDL (β- Lipoprotein)



-High density lipoprotein (HDL)
Mostly cholesterol ester . (mainly esterify)
More % protein
More % phospholipids

Apo- A , C II and E in HDL

Hint : HDL (α - Lipoprotein)

Low Density Lipoproteins (LDL) :

Produced in the circulation as the end product of VLDLs compared to VLDLs:
- It contains *only* apo B-100
- Smaller size and more dense (because of increase in protein)
- Less TG
- More cholesterol & cholesterol ester

Transport cholesterol from liver to peripheral tissues (function of LDL) .

- Uptake of LDL at tissue level by:
LDL receptor-mediated endocytosis
Recognized by apo B-100 (apo B-100 which is the ligand and it is exist on the LDL's surface)

Endocytosis : A process of cellular ingestion by which the plasma membrane folds inward to bring substances into the cell. (It could be specific or non-specific)

When the LDL reaches to the peripheral tissues the cells recognize it by apo B-100 then Endocytosis will occur .

VLDL (catabolism) **LDL**

These are the steps :

Receptor-Mediated Endocytosis :

- LDL receptor :

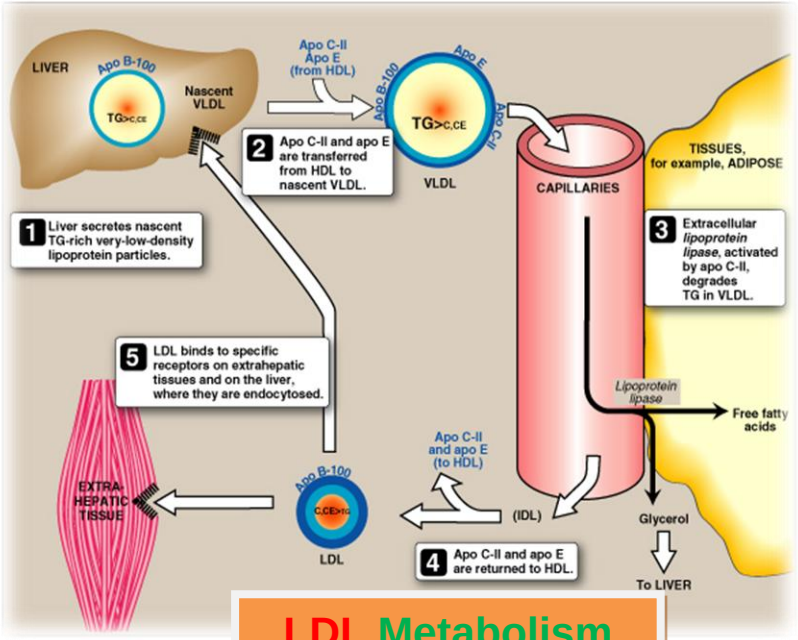
- Cell surface glycoprotein
High-affinity, tightly regulated

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

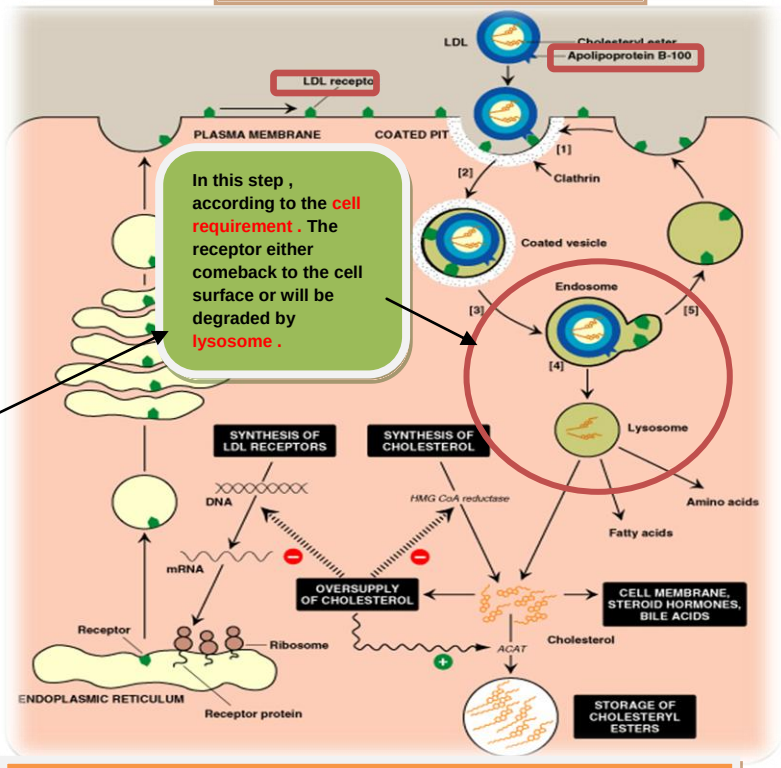
- Release of cholesterol inside the cells for:
1- Utilization
2- Storage as cholesterol ester
3- Excretion

- Degradation of LDL:
into amino acids, phospholipids and fatty acids .

- Degradation or recycling of receptor



LDL Metabolism



LDL : Receptor-Mediated Endocytosis

LDL Receptor-Mediated Endocytosis:Regulation

A-Down-regulation:

High intracellular cholesterol content
-Degradation of LDL receptors
- Inhibition of recepotor synthesis at gene level

Decrease No. of receptor at cell surface
-Decrease further uptake of LDL
-Decrease de novo (new) synthesis of cholesterol

B-Up-regulation:

Low intracellular cholesterol content
- Recycling of LDL receptors
-Stimulation of recepotor synthesis at gene level
Increase No. of receptor at cell surface
-Increase further uptake of LDL
-Increase de novo (new) synthesis of cholesterol

ACAT: stores excess cholesterol ester

If the cell needs more cholesterol , it will do Up-regulation .

If the cell does not need more cholesterol , it will do Down-regulation .

HMG-CoA reductase : a rate-controlling enzyme of cholesterol synthesis.

If the cell needs more cholesterol , the HMG-CoA reductase will be stimulated .

If the cell does not need more cholesterol , the HMG-CoA reductase will be inhibited .

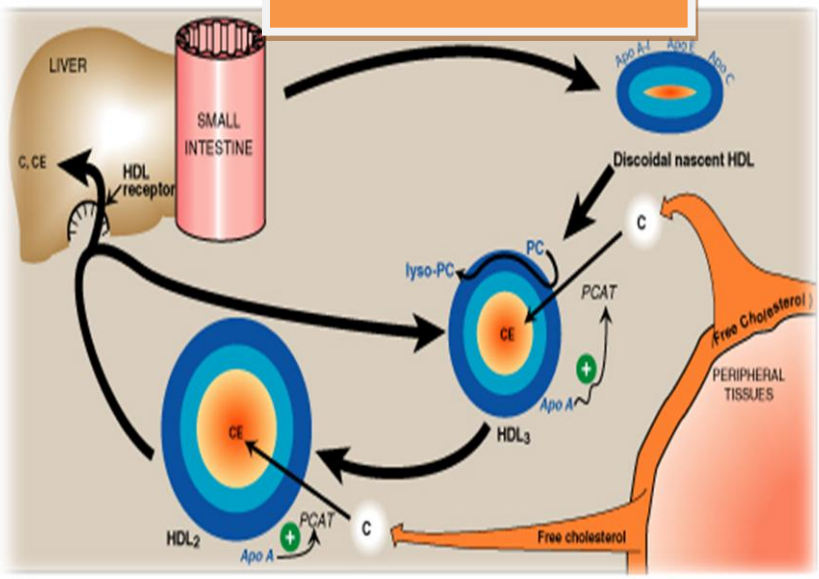
HDL Metabolism

High Density Lipoproteins (HDL) :

- Produced by intestine and liver

- Nascent (newly formed) HDL:
Disk-shaped
Contains apo A-I, C-II and E
Contains primarily phospholipid (PC)

- Mature HDL (HDL_2):
First, HDL_3 collect cholesterol
Converts cholesterol to cholesterol ester
Spherical mature particle HDL_2



PC = Phosphatidylcholine/Lecithin

PCAT or LCAT : It is the enzyme which converts the cholesterol to cholesterol ester to maintain the movement from tissues into HDL .

Q: What is the ligand in HDL ?

A: Apo A

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 *solublizes* cholesterol and acts as a source of fatty acid for cholesterol esterification)

3- Esterification of cholesterol:
Enzyme:PCAT/LCAT
Activator (coenzyme) : Apo A-I
Substrate: Cholesterol, Co-substrate: PC
Product: Primary : Cholesterol ester. Secondary : (& Lyso-PC)

Why is HDL a Good Cholesterol carrier?

Normal people : HDL level is normal .

Atherosclerosis patients : HDL level is low .

- Inverse relation between plasma HDL levels and Atherosclerosis …. How?

- Reverse cholesterol transport involves:
Efflux of cholesterol from peripheral tissues and other lipoproteins to HDL_3

Esterification of cholesterol & binding of HDL_2 to liver and stroidogenic cells by scavenger receptor class B (SR-B1)

Selective transfer of cholesterol ester into these cells

Release of lipid-depleted HDL_3

NOTE ::: HDL3 has colesterol less than HDL2

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

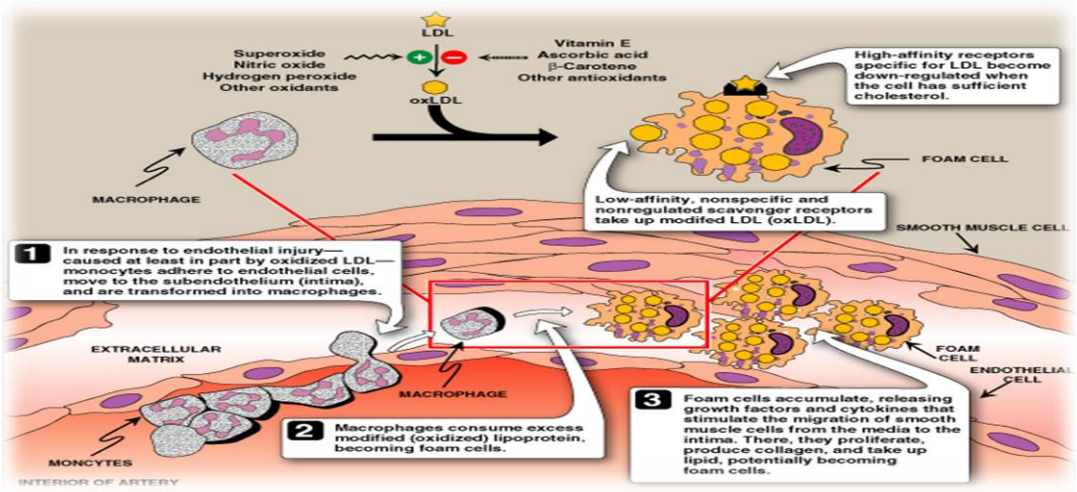
-Foam cell transformation

Atherosclerotic plaque formation

Foam cell : is the basic unit for Atherosclerotic plaque.

Oxidative LDL is more dangerous than LDL

Athersclerotic plaque Formation



Comparison between the receptors :

SR- B1 receptor	LDL receptor	SR-A receptor
In liver and stroidogenic cells	In peripheral tissue	In macrophages
For HDL	For LDL	For oxiLDL
Selective	Selective	Not selective
	High-affinity	Low-affinity
	regulated	Un-regulated

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 HDL-cholesterol level
-Serum LDL-cholesterol level
-Others:- (not usually done unless the doctor asks for it)
- Serum lipoprotein electrophoresis
-Serum apoprotein levels e.g., apo-B

LDL-related Diseases :
Hyperlipoproteinemia:

Type IIa Hyperlipoproteinemia
(Familial hypercholestrolemia)
Functional defect of LDL-receptor
(The receptor shape has changed then , it will not receive the LDL)
Increase plasma LDL level & therefore, plasma cholesterol level
(The LDL level will increase in the plasma then , the cholesterol level will increase in the circulation)
Pre-mature atherosclerosis and increased
risk for early-onset ischemic heart diseases
Associated with the presence of tendon xanthomas on hands and ankles

Xanthomas : A tumor composed of lipid-laden foam cells, which are histiocytes containing cytoplasmic lipid material.

Review Question

1-regarding Esterification of cholesterol in HDL , which of the following acts as activator ?

1- Apo A-I

2- : Apo B-100

3-: Apo C-11

4-: Apo D

2- why is HDL a good carrier ?

A-Esterification of cholesterol & binding of HDL2 to liver and stroidogenic cells by scavenger receptor class B (SR-A1)

b- Release of lipid-depleted HDL2

C-Efflux of cholesterol from peripheral tissues and other lipoproteins to HDL3

D- all above

3-patient comes to ER suffer from chest pain and dyspnea , clinical feture and lababtory diagnosis indicate that he suffer from Myocardial Infarcation ,, in addition his condition shows swelling in his ankle , he suffer from which of following,
A-fatty liver
B- Type Ia Hyperlipoproteinemia
C- Type IIa Hyperlipoproteinemia
D-non above

1-A
2-B
3-C