جامعة الملك سعود
King Saud University

Biochemistry437

Lipoprotein & Atherosclerosis

Biochemistry Team 437

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Cardiovascular block

EDITING FILE

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Objectives:

- Correlate the imbalance in lipoprotein metabolism with the development of atherosclerosis
- Understand the functions and metabolism of LDL and HDL cholesterol
- Describe the receptor-mediated endocytosis of LDL and its regulation
- Recognize how LDL is considered a bad cholesterol whereas HDL a good cholesterol
- Understand the biochemistry of atherosclerosis and its laboratory investigations
- Discuss the role of lipoprotein(a) in the development of heart disease

Recall what you studied in the previous lectures:

from team 436

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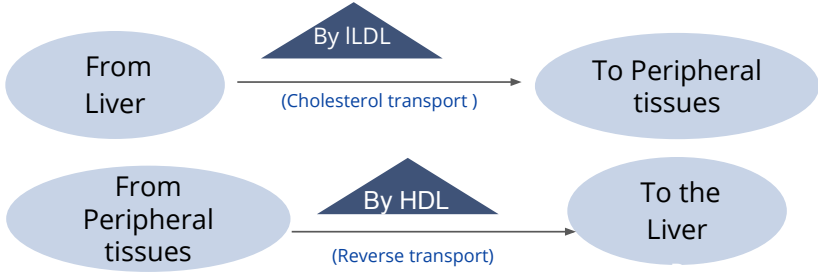
- Lipoproteins carry cholesterol and TAGs so if there's a problem there will be accumulation of these structures.
- Cholesterol deposition starts with the monocytes and get larger in the intima and then move to the media and then effect the cytokines that are released and other smooth muscle cells which leads to narrowing blood vessels and that's lead to Atherosclerosis.
- Chylomicron transports TAG to the liver.
- VLDL transports TAG from the liver to the adipose tissues.
- After the delivery of TAG the chylomicron becomes chylomicron remnant which has mainly cholesterol.
- These molecules they are not clear from the circulation and they will increase the amount of cholesterol in the blood and the other molecule is HDL , all these 3 to be clear from the circulation they are recognized by APO-e APO-B100 BY the liver cells receptors.

Overview:

- Receptor-mediated endocytosis of LDL and its regulation
- LDL is bad cholesterol
- High density lipoprotein (HDL) and its functions
- Metabolism of HDL
- HDL is good cholesterol
- Atherosclerosis
- Lipoprotein(a)

Cholesterol homeostasis is a balance between cholesterol transport:



- Imbalance in the above leads to:
  - Cholesterol deposition in blood vessels
  - Thickening and narrowing of the lumen of arteries
  - Atherosclerosis
  - Heart disease

• Normally there is a cholesterol homeostasis. When the Body is unable to maintain cholesterol homeostasis there will be an accumulation of cholesterol in the blood which will be deposited in the blood vessels which leads to atherosclerosis.

Low Density Lipoprotein (LDL) “last year slides”

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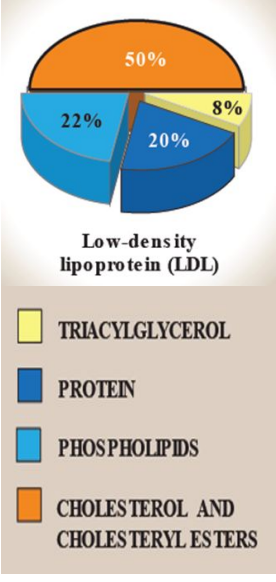
Lipid Composition	Origin	Apolipoprotein	Function	Comments
Consists of mainly : • Cholesterol • Cholesteryl esters	It is produced from VLDL particles Happens after the HDL takes TAG and gives cholesterol to VLDL	Contains : • Apo B-100 on its surface	It provides cholesterol to the peripheral tissues Considered as BAD CHOLESTEROL	It binds to the cell surface through special glycoprotein LDL receptor , leading to receptor-mediated endocytosis



Receptor mediated endocytosis of LDL particles

Major steps:

- Binding of Apo B-100 to LDL receptor glycoprotein
- Endocytosis[1]
- Endosome formation (LDL vesicle fuses with other vesicles)
- Separation of LDL from its receptor
- Receptor is recycled
- LDL degraded by lysosomes releasing:
  - Free cholesterol, fatty acids, amino acids, phospholipids

Explained in steps next slide

Remember!

- LDL is synthesized from VLDL in plasma
- It has Apo-B100 which acts as a surface recognition molecule for the receptors present on the surface of the liver and extrahepatic tissue

1- endocytosis is the process by which the LDL receptor recognizes the LDL molecule and takes it in

Cellular uptake & regulation of LDL particles

A)Receptor mediated endocytosis:

1. Binding of Apo B-100 to LDL receptor glycoprotein.
   a. LDL receptors are clustered in pits " depressions on the cell surface" , which are coated with the protein Clathrin.

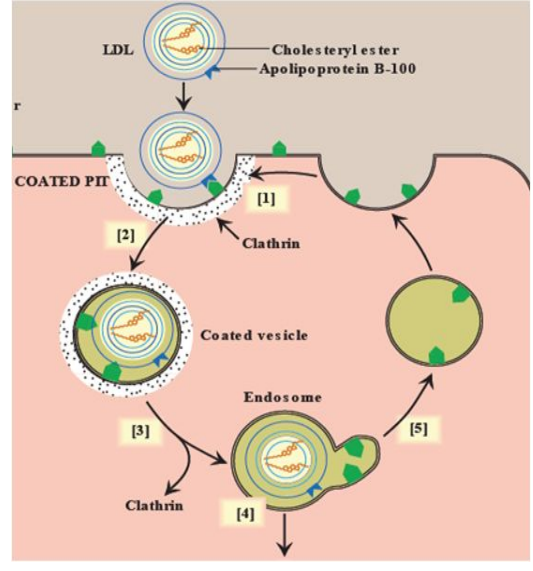
2. After binding, LDL receptors are taken in by endocytosis.
   a. The pits pinch on itself and creates a vesicle

3. The vesicle containing LDL loses its Clathrin coat, forming an endosome (Clathrin is responsible for maintaining and protecting the vesicle from being degraded or detached).

4. An enzyme in the endosome Then separates the LDL from its receptor. The LDL remains and the receptors are recycled back to the surface.

5. LDL will fuse with a lysosome and gets degraded forming amino acids , fatty acids and cholesterol

6. Cholesterol increases inside the cell, how will this affect the regulation? "Next slide"



Cellular uptake & regulation of LDL particles

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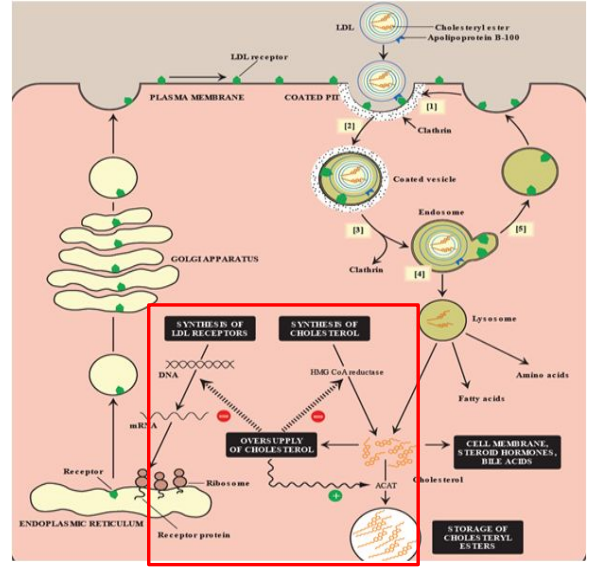
B) Effect of endocytosed cholesterol on cellular cholesterol homeostasis:

1. Inhibition of the gene expression for HMG CoA reductase.
2. Reduction of new LDL receptor synthesis.
3. Degeneration of old LDL receptors.
4. Use for cell requirements. If there is excess amount, it is esterified by (ACAT) producing a cholesterol ester that can be stored in the cell.



Regulation of LDL Endocytosis

Level of cholesterol present inside the cell (intracellular cholesterol level)
Not the level of cholesterol in the blood [1]

Down regulation:

High intracellular cholesterol level causes:

- Degradation of LDL receptor
- Inhibition of receptor synthesis at gene level
- Reduction in cell surface receptors
- Decreased uptake of LDL by cells
- Decreased de novo synthesis of cholesterol

Up regulation:

Low intracellular cholesterol level causes:

- Recycling of LDL receptors
- Increased receptor synthesis at gene level
- Increase in cell surface receptors
- Increased uptake of LDL by cells
- Increased de novo synthesis of cholesterol

Don't confuse it with HMG-COA regulation from the 2nd lecture, as it is activated by the level of cholesterol in the blood

LDL Is Bad Cholesterol

*Peripheral tissue has a capacity for cholesterol if it exceeds it, it will deposit cholesterol into the blood vessels

*Transports cholesterol to peripheral tissues

(Stores cholesterol)

Elevated LDL levels → increased risk for atherosclerosis and heart disease

Deficiency or defects in LDL receptors results in:

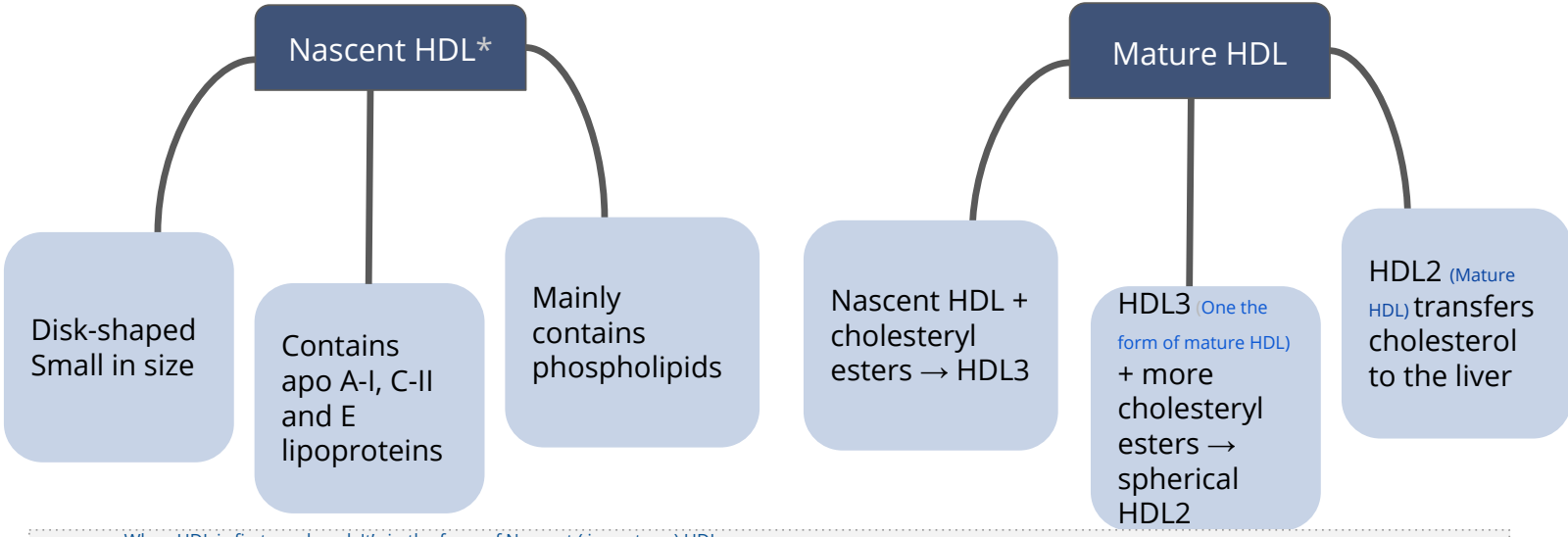
Decreased uptake of cholesterol by cells

Increased accumulation of cholesterol in blood vessels

Familial hypercholesterolemia (in chromosome 19) :
-Patients are unable to clear LDL from blood.
-Premature atherosclerosis and heart disease.

Another factors that Increases the level of cholesterol level in the blood : (hypercholesterolemia)
• Apo E deficiency

High Density Lipoprotein (HDL)



- When HDL is first produced, It's in the form of Nascent (immature) HDL.
- (*) • Immature
  • As it goes to the circulation and get in contact with the tissue it's starts taking cholesterol from it , HDL itself has the enzyme that converts cholesterol to cholesteryl ester
- Mature HDL are : HDL2, HDL3

Functions of HDL

Reservoir of apoproteins (Apo C-II and E)

Gives Apo c-|| and Apo E to chylomicron and VLDL

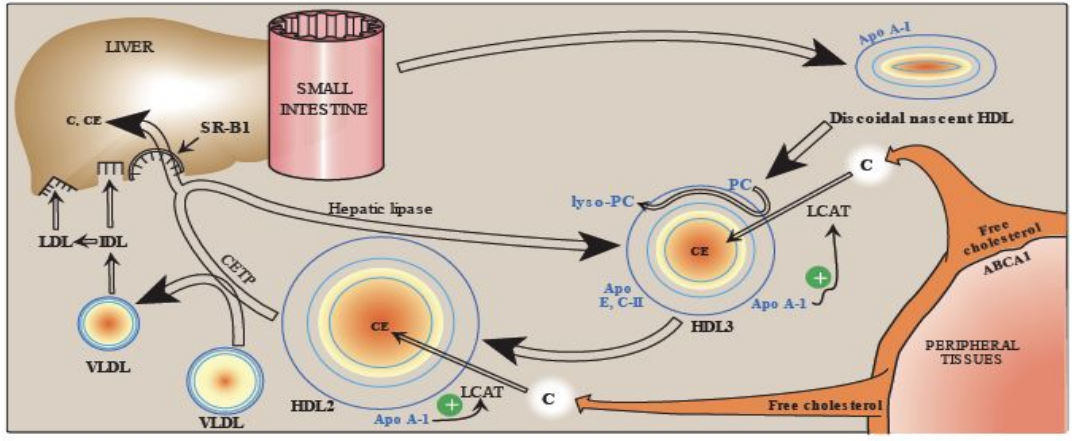
Suitable for cholesterol uptake due to:
- High content of phospholipids*
- Phospholipids solubilize cholesterol and provide fatty acids for cholesterol esterification

*Phospholipid are Good for solubilizing the hydrophobic cholesterol

Transports cholesterol to liver from:
- Peripheral tissues
- Other lipoproteins
- Cell membranes

HDL Metabolism

What is happening here ? :-



1. HDL is synthesized in the liver and intestines, then it goes through the circulation to the peripheral tissues.
2. the Cholesterol is released from the tissue via the ABCA1 enzyme
3. LCAT enzyme catalyzes the addition of fatty acid to the free cholesterol to transform it into → Cholesteryl ester , by this mechanism, the cholesterol inside the cell is still less than the cholesterol outside keeping a sufficient gradiente for more cholesterol intake.
4. The LCAT enzyme needs the Apo A-1 to be active
5. Cholesteryl ester will bind to the nascent HDL to become → HDL3
6. Further addition of cholesteryl ester will make the HDL3 → HDL2
7. HDL2 then goes to the liver and binds via the SR-B1 receptor to unload the cholesterol it collected
    - Bonus : HDL may unload its cholesterol content by exchanging it with the VLDL through the CETP enzyme
      It takes TAG and gives cholesterol.

*When it get off chlesterolester it become HDL3 again, So there's HDL3-HDL2 cycle that keeps bringing more and more cholesterol from peripheral tissue to the liver.
**with the help of lcat enzyme

Reverse cholesterol transport includes:
- Cholesterol efflux from peripheral tissues to HDL.
- Cholesterol esterification.**
- Binding and transfer of cholesteryl ester-rich HDL2 to the liver.
- Release of lipid-depleted HDL3.*

High HDL levels have inverse correlation with atherosclerosis

HDL is good cholesterol

HDL transports cholesterol from peripheral tissues to the liver for degradation (Into bile acids , bile salt and different types of steroids)

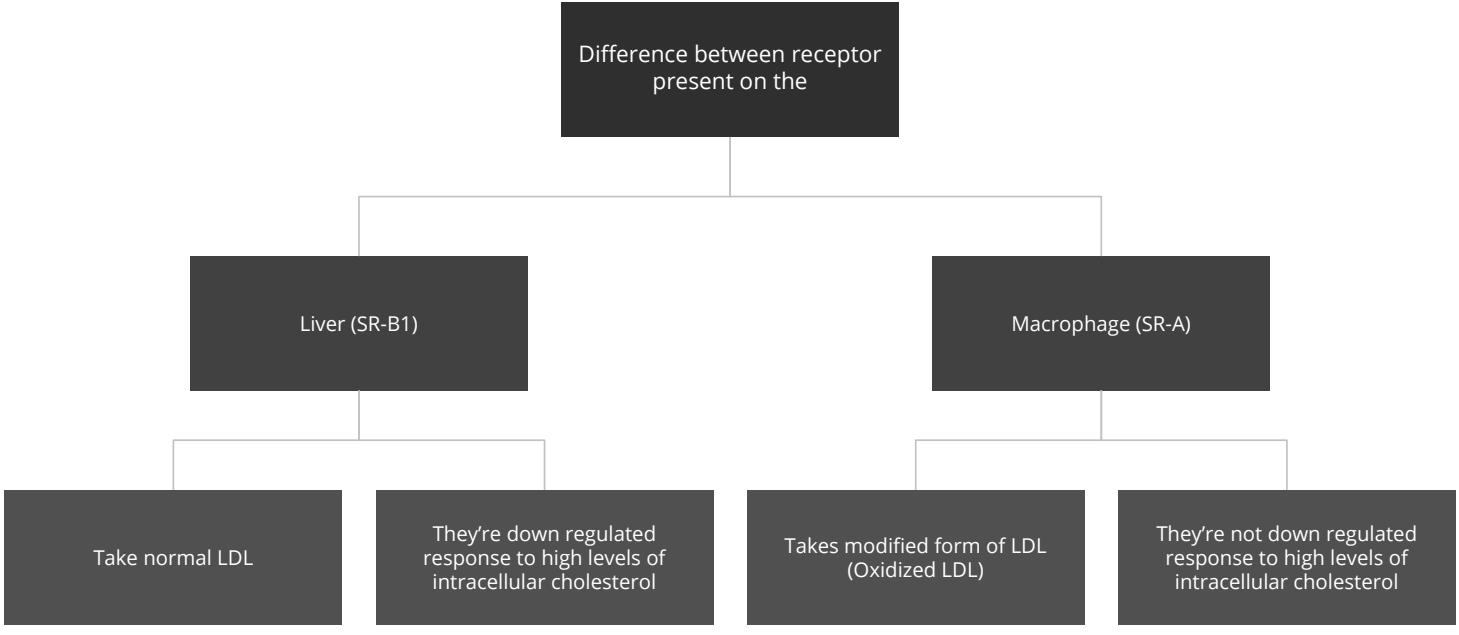
Reduces cholesterol level in tissues and circulation (reverse cholesterol transport)
(Because atherosclerosis increases the level of cholesterol in the blood while HDL lowers it ,, high levels of HDL —lower risk for atherosclerosis)

Atherosclerosis

- LDL uptake by cells is receptor mediated. (Resists upregulation)
- Additionally, macrophages possess scavenger receptors called scavenger receptor class A (SR-A).
- The macrophages take up chemically-modified LDL by endocytosis.
- Chemically-modified LDL contains oxidized lipids and Apo B.
- Unlike LDL receptors, the SR-A is not down-regulated in response to high intracellular cholesterol.
- Cholesteryl esters accumulate in macrophages converting to foam cells.
- Foam cells contribute to plaque formation and atherosclerosis.

Extra explanation :
Why are the SR-A receptors not helpful here? ... Well you remember in the previous slides when we talked about how increase in the amount of intracellular cholesterol can affect the cell behaviour by inhibiting cholesterol synthesis and down regulating the LDL receptors ? All of these good negative feedbacks don't happen here !! think of SR-A as a bad gym couch .. he will tell you to keep eating junk food because it's tasty (oxidized LDL) but in fact you don't want to eat too much because that will make you obese! (promote plaque formation) .. just like the poor macrophage (foam cell).

Extra Explanation



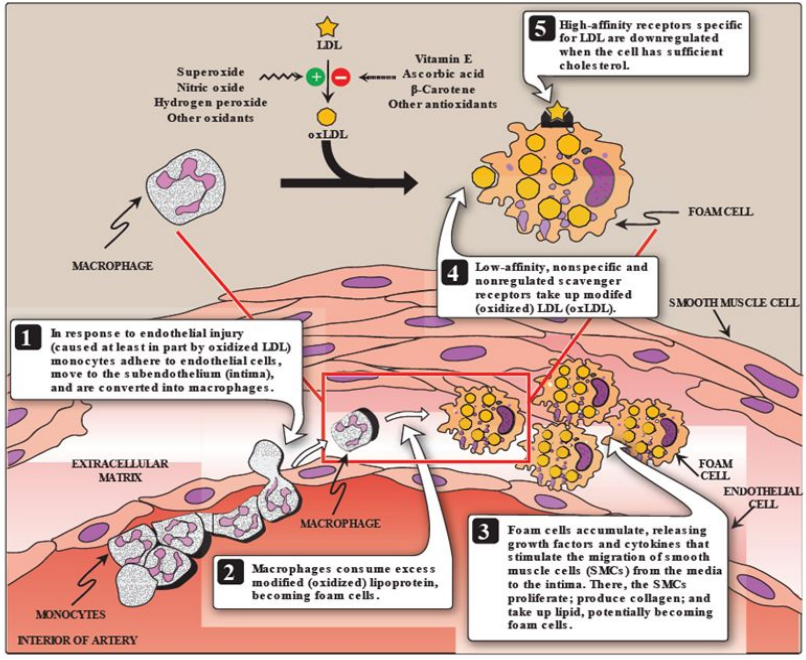


Figure 18.22
Role of oxidized lipoproteins in plaque formation in an arterial wall. LDL = low-density lipoprotein.

Picture Explanation :-

Uptake of chemically modified LDL (Oxidized) by macrophage scavenger receptors: In addition to the highly specific and regulated receptor-mediated pathway for LDL uptake, macrophages possess high levels of scavenger receptor activity. These receptors, known as scavenger receptor class A (SR-A), can bind a broad range of ligands, and mediate the endocytosis of chemically modified LDL in which the lipid components or apo B have been oxidized. Unlike the LDL receptor, the scavenger receptor is not down-regulated in response to increased intracellular cholesterol. Cholesteryl esters accumulate in macrophages and cause their transformation into “foam” cells, which participate in the formation of atherosclerotic plaque.

Lab Investigations of Atherosclerosis

- Fasting serum lipid profile:
  - TAG level (reflects chylomicron and VLDL levels)
  - LDL, HDL levels
  - Total cholesterol level (reflects LDL, HDL and cholesterol levels)
- Other tests:
  - Serum lipoprotein electrophoresis*
  - Serum apoprotein levels (e.g., apo-B)

*Separate the molecule on the bases of their:
1- Size
2- Density

HDL being the most dense would be slowest to move (will stay behind), the lightest will move faster.
Advantages of it: detects if there is a congenital defect that leads to hypercholesterolemia we check in there is any lipoprotein that is missing

Lipoprotein (a)

- Lp(a) is identical in structure to LDL particle
- It Contains apo(a) in addition to apo B-100
- High plasma Lp(a) level is associated with increased risk of coronary heart disease
- Circulating levels of Lp(a) are determined by:
  - Genetics (mainly)
  - Diet (trans fatty acids increase Lp(a) levels)[1]
  - Estrogen (decreases Lp(a) levels)[2]
- A risk factor for CAD

[1]Trans fatty acids:
- Not saturated fatty acids but behave like saturated fatty acids in the body.
- Used alot in the bakery products.
- Become solidified in room temp.

[2]Estrogen also helps in the increase of the HDL level

Lipoprotein (a)

High plasma Lp (a) level is associated with increased risk of coronary heart disease

↓ Why?

It slows the breakdown of blood clots that trigger heart attacks

↓ How ?

because the apo(a) protein is structurally similar to plasminogen, it competes with plasminogen for binding to fibrin

Plasminogen (proenzyme) > Plasmin (active enzyme)
Plasmin: is a nonspecific protease capable of breaking down fibrin and other circulating proteins including fibrinogen, clotting factor V & factor VIII.)

Take home message

- Imbalance in the LDL and HDL metabolism causes increased accumulation of lipids in the body
- LDL is bad cholesterol whereas HDL is good cholesterol
- The pathogenesis of atherosclerosis includes the uptake of oxidized LDL by macrophages through scavenger receptor class A (SR-A) producing foam cells and atherosclerotic plaque
- Individuals with high level of plasma Lp (a) are at higher risk for coronary heart disease

MCQs:

Q1 LDL binds to cell surface receptors through which of the following?

A- apo B-48 **B-** apo- E
C- apo B-100 **D-** apo- E2

Q2 Which of the following VLDL diseases will cause premature atherosclerosis?

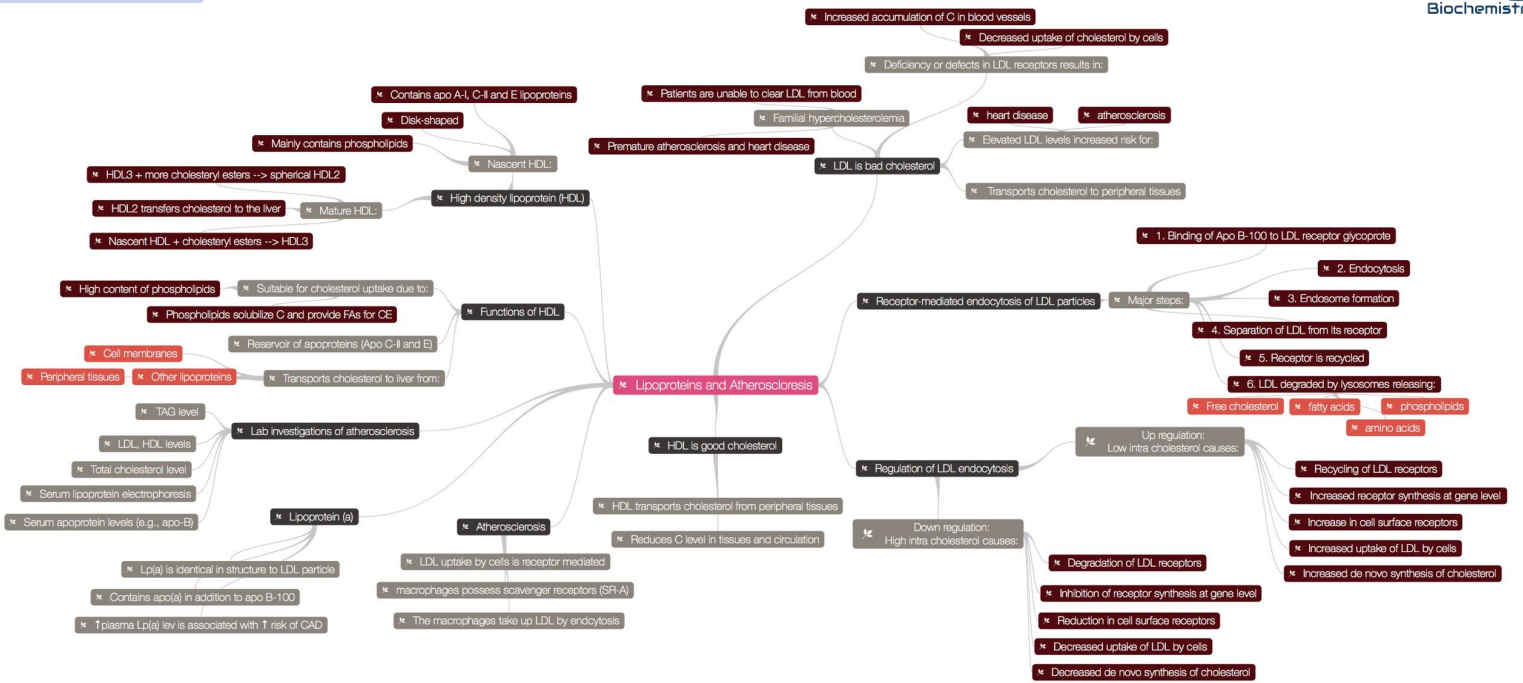
A- Familial dysbetalipoproteinemia **B-** Steatohepatitis
C- Hyperlipoproteinemia **D-** Both (A&C)

Q3 Which of the following statements is incorrect about HDL ?

A- Produced in the liver and intestine **B-** Contains Apo A-1
C- Take up cholesterol from the liver to peripheral tissue **D-** All are incorrect

Answers:
1:C
2:A
3:C

Summary


Lipoproteins and Atherosclerosis
Increased accumulation of C in blood vessels
Decreased uptake of cholesterol by cells
Deficiency or defects in LDL receptors results in:
Patients are unable to clear LDL from blood
Familial hypercholesterolemia
heart disease
atherosclerosis
Premature atherosclerosis and heart disease
Elevated LDL levels increased risk for:
LDL is bad cholesterol
Transports cholesterol to peripheral tissues
Contains apo A-I, C-II and E lipoproteins
Disk-shaped
Mainly contains phospholipids
Nascent HDL:
HDL3 + more cholesteryl esters --> spherical HDL2
HDL2 transfers cholesterol to the liver
Mature HDL:
High density lipoprotein (HDL)
Nascent HDL + cholesteryl esters --> HDL3
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Major steps:
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4. Separation of LDL from its receptor
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6. LDL degraded by lysosomes releasing:
Free cholesterol
fatty acids
phospholipids
amino acids
High content of phospholipids
Suitable for cholesterol uptake due to:
Phospholipids solubilize C and provide FAs for CE
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Regulation of LDL endocytosis
Up regulation:
Low intra cholesterol causes:
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Increased receptor synthesis at gene level
Increase in cell surface receptors
Increased uptake of LDL by cells
Increased de novo synthesis of cholesterol
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Atherosclerosis
LDL uptake by cells is receptor mediated
macrophages possess scavenger receptors (SR-A)
The macrophages take up LDL by endcytosis

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Team leaders

- رهام الحلبي
- معاذ الحمود

Boys team

- طارق العميم
- فيصل الطحان
- محمد الصويغ
- انس القحطاني
- صالح الوكيل
- عبد الملك الشرهان
- سعيد القحطاني
- نواف اللويمي
- عبدالرحمن التركي
- عبدالله الحربي
- محمد حكيم

Girls team

- رهف الشنيبر
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- لينا الرحمة
- منيرة المسعد
- ليلى الصّباغ
- العنود المنصور
- أرجوانة العقيل
- ريناد الغريبي
- رزان الزهراني
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