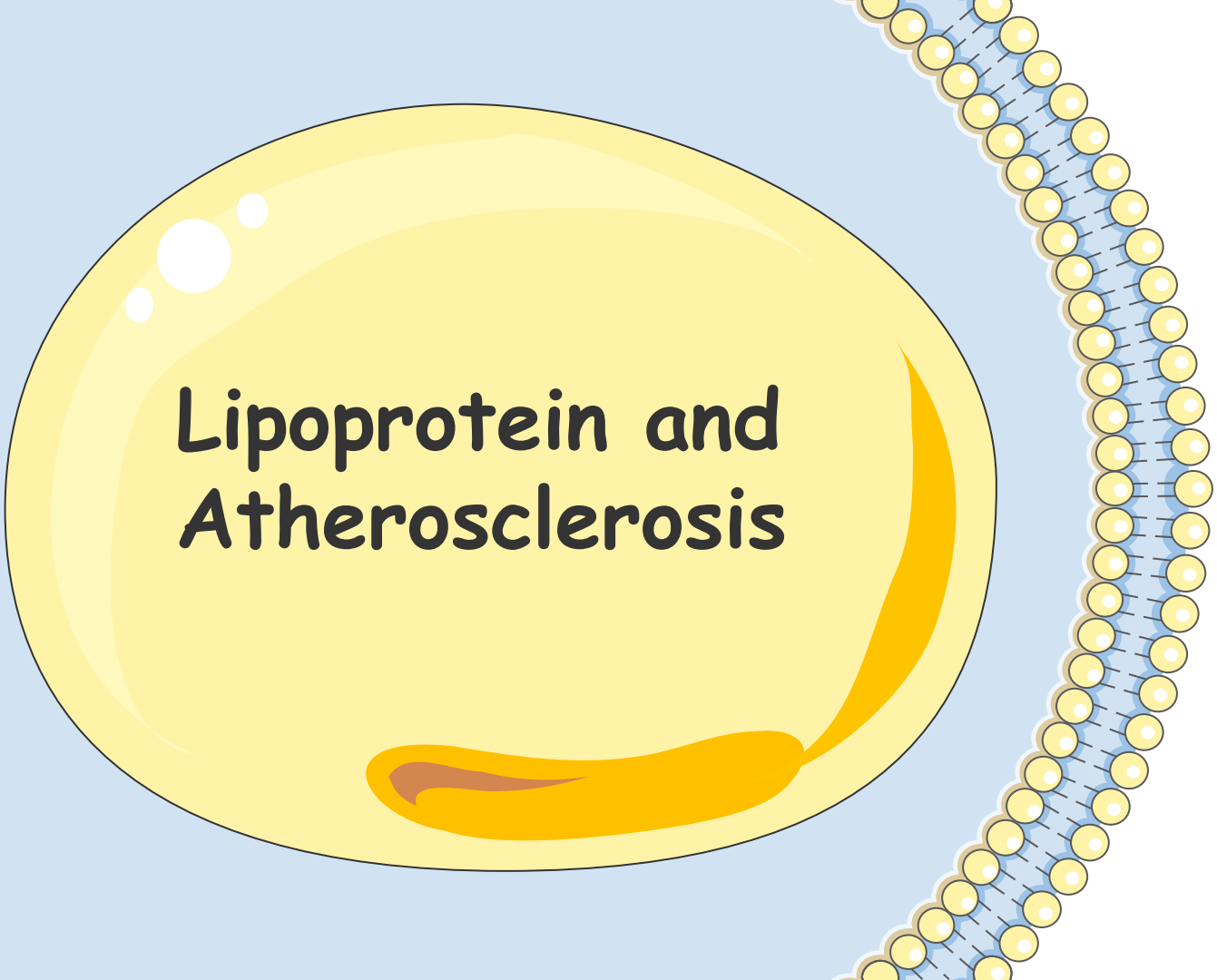


Lipoprotein and Atherosclerosis

Revised & Reviewed by Abdulaziz & Bahammam Faye Wael Sendi

MED441
KING SAUD UNIVERSITY

4

Cardiovascular Block - KSU

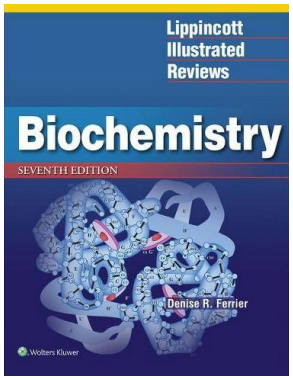
Main text
Important
Notes
Extra

Editing File

We recommend that to watch this video below to get general idea about this lecture & we suggest this book for you if you want more details

Lipoprotein • HDL metabolism || Biochemistry

By CallosumBD



Biochemistry Lippincott Illustrated Reviews 7th Edition

BY Denise R. Ferrier

Chapter 18
Pages 670-679

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

Receptor-mediated endocytosis of low density lipoprotein (LDL) particles

Video

01

Binding of Apo B-100 to LDL receptor glycoprotein

LDL receptors present on the cell surface, but they concentrated in the coated pit.

02

Endocytosis

The membrane close, and it comes inside as a coated vesicle. Then the clathrin coating will be removed.

03

Endosome formation (LDL vesicle fuses with other vesicles)

The endosome has an enzyme called “endosomal ATPase” which act as proton channel causes the accumulation of H+ inside the endosome which reduce its pH.

04

Separation of LDL from its receptor

The reduction in the pH will separate the LDL from its receptor and the receptor will start accumulating in one side of the endosome, and later they will separate as a vesicle.

05

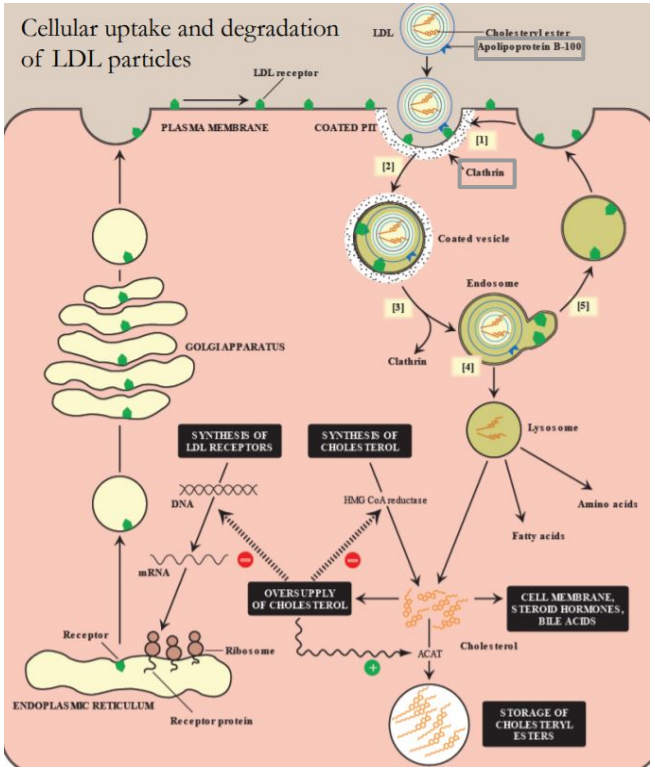
Receptor is recycled

Back to the surface

06

LDL degraded by lysosomes releasing:

Free cholesterol, fatty acids, amino acids, phospholipids

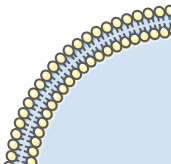


Apo B-100 is specific for LDL, it should be present in LDL for cell LDL receptor to recognize it

Clathrin is a large protein assist in the formation of coated pit on the inner surface of the plasma membrane of the cell, this pit then buds into the cell to form a coated vesicle in the cytoplasm of the cell.

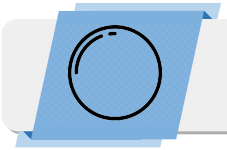
Regulation of LDL endocytosis

Up regulation Low intracellular cholesterol causes:	In this case	Down regulation High intracellular cholesterol causes:
Recycling of LDL receptors	What will we do ?	Degradation of LDL receptors
Increase receptor synthesis at gene level	How ?	Inhibition of receptor synthesis at gene level
Increase in cell surface receptors	What will happen ?	Reduction in cell surface receptors
Increase uptake of LDL by cells	The result ?	Decreased uptake of LDL by cells
Increase *de novo* synthesis of cholesterol	Anything else can help ?	Decreased *de novo* synthesis of cholesterol by HMG CoA reductase

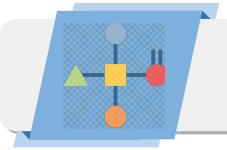


High density lipoprotein (HDL)

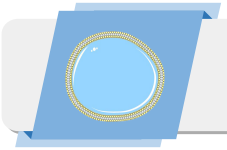
Nascent HDL



Disc shaped

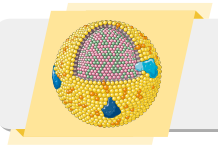


Contains apo A-I, C-II and E lipoproteins
(**Apo- A1 is specific for HDL**)

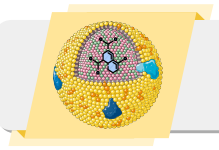


Mainly contains phospholipids

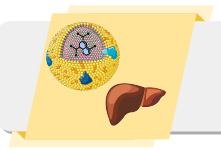
Mature HDL



Nascent HDL + cholesteryl esters = HDL_3



HDL_3 + more cholesteryl esters = spherical HDL_2



HDL_2 transfers cholesterol to the liver
It goes to liver so it can take care of it

High density lipoprotein (HDL)

Functions of HDL

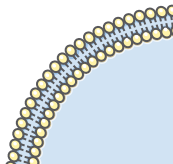
Transports cholesterol to liver from:

- Peripheral tissues
- Other lipoproteins
- Cell membranes

Reservoir of apoproteins (Apo C-II and E)
(Apo C2 is for attachment to peripheral tissues while Apo E is for attachment to liver)

Suitable for cholesterol uptake due to:

- High content of phospholipids
- Phospholipids solubilize cholesterol and provide fatty acids for cholesterol esterification.so it can be stored



Extra slide from doctor's explanation

HDL metabolism

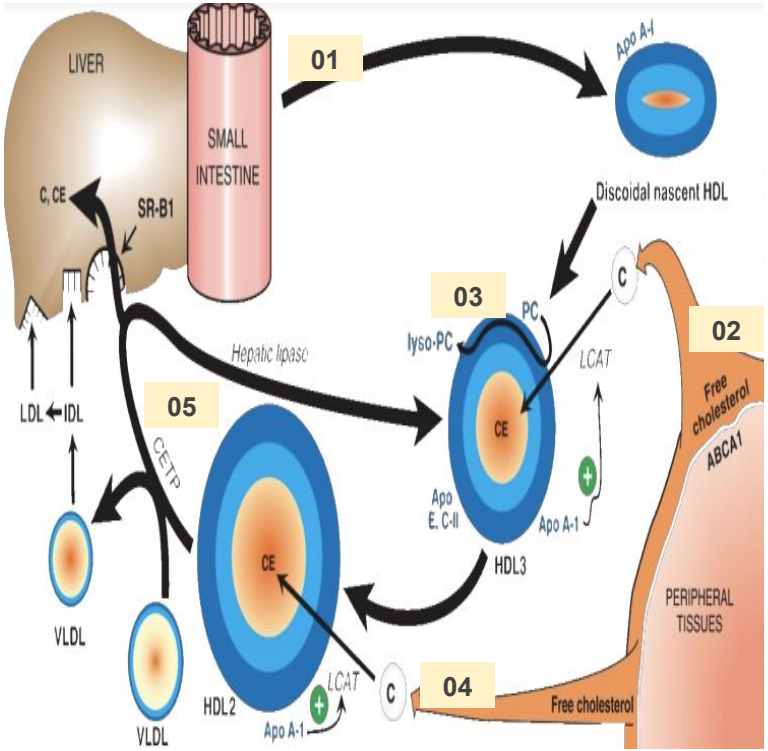
01 Small intestine releasing the discoidal nascent HDL (**immature HDL**)

02 Free cholesterol is removed from peripheral tissues by ABCA1

03 The free cholesterol then is **transformed** to cholesteryl esters before it fuses with HDL by LCAT which takes a fatty acid from phosphatidylcholine (PC) and gives it to the free cholesterol the **phosphatidylcholine** is then converted to **lysosomal phosphatidylcholine** as a byproduct this mechanism allows the binding of free cholesterol to **nascent HDL** producing HDL3

04 HDL3 collects more tissue cholesterol to form HDL2 (**mature HDL**)

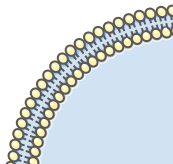
05 HDL2 gives some of its cholesteryl esters to VLDL using **Cholesteryl ester transferase protein** (CEPT) and the rest goes to the liver by binding to SR-B1 which converts HDL2 back to HDL3 using hepatic lipase



(PC =phosphatidylcholine) = (lecithin) so we can say LCAT or PCAT
LCAT = lecithin-cholesterol acyltransferase

Good cholesterol (HDL) & Bad cholesterol (LDL)

HDL "Good cholesterol"	LDL "Bad cholesterol"
Transports cholesterol from **peripheral tissues** to **liver** for degradation	**Transports** cholesterol **to peripheral tissues**
High HDL levels have **inverse correlation with atherosclerosis**	High LDL levels **increase** the risk of atherosclerosis / heart disease
Reduces cholesterol level in tissues and circulation (reverse cholesterol transport)	Deficiency or defects in **LDL receptors** results in: • Decreased uptake of cholesterol by cells • Increased **accumulation** of cholesterol in **blood** vessels
Reverse cholesterol transport includes: • Cholesterol efflux from peripheral tissues to HDL • Cholesterol esterification • Binding and transfer of cholesteryl ester-rich HDL2 to liver • Release of lipid-depleted HDL3	Deficiency of **LDL receptors** can lead to **Familial hypercholesterolemia:** type 2a (if it's LPL deficiency -> Type 1) • Patients are unable to clear LDL from blood • Premature atherosclerosis and heart disease



Atherosclerosis

1. LDL uptake by cells is **receptor mediated** (specific uptake)

2. Additionally, **macrophages possess** تمتلك **scavenger receptors called scavenger receptor class A (SR-A)** (not specific uptake, can react with other molecules)

3. The macrophages take up **chemically-modified LDL** by **endocytosis**

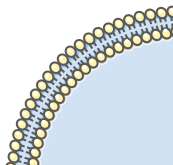
4. Chemically-modified LDL contains **oxidized lipids and Apo B** (some free radicals attack lipids and oxidize them)

5. Unlike LDL receptors, **the SR-A is not down-regulated in response to high intracellular cholesterol**

6. Cholesteryl esters accumulate in macrophages converting them to **foam cells**

7. **Foam cells** contribute to plaque formation and atherosclerosis

The specific LDL receptors (which has high affinity to LDL) get down-regulated (stop working) if the cell has enough cholesterol
The SR-A (which has low affinity to LDL) continue to take up the oxidized LDL



Atherosclerosis

Animation

01 In response to **endothelial injury** (caused at least in part by oxidized LDL) **monocytes** adhere to endothelial cells, move to the subendothelium (**intima**), and are converted into macrophages.

02 Macrophages **consume** excess modified (**oxidized**) lipoprotein, becoming **foam cells**.

03 Foam cells **accumulate**, releasing **growth factors** and **cytokines** that stimulate the **migration** of smooth muscle cells (**SMCs**) from the media to the intima. There, **the SMCs proliferate;** produce **collagen**; and **take up lipid**, **potentially becoming foam cells.**

04 Low-affinity, non-specific and non-regulated **scavenger receptors** take up modified (oxidized) LDL (oxLDL).

05 High-affinity receptors **specific** for LDL are downregulated when the cell has sufficient cholesterol

06 It will be either increase in the free radicals (left side) or deficiency in the antioxidants (right side). That lead to modify LDL into oxLDL, which can react with SR-A despite the cholesterol level.

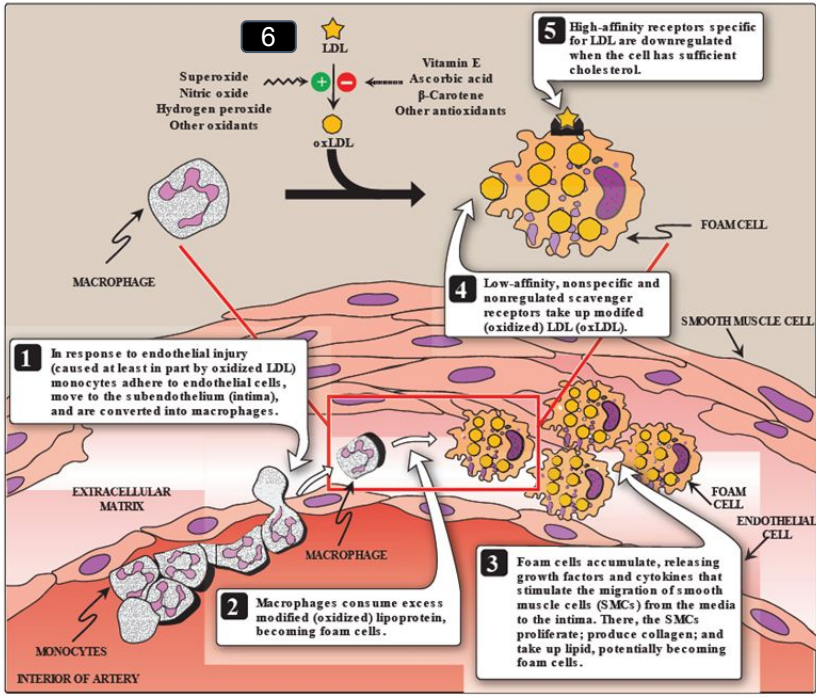


Figure 18.22
Role of oxidized lipoproteins in plaque formation in an arterial wall. LDL = low-density lipoprotein.

Lab investigations of atherosclerosis

Lab investigations

- Serum apoprotein levels (e.g., apo-B)
  - This test measures the amount of apo B in the blood. (the protein portion of apolipoprotein)
- Serum **lipoprotein electrophoresis** (gives the exact amount of different lipoprotein)
- Fasting serum lipid profile
  - TAG level (reflects **chylomicron** and **VLDL** levels)
  - Total cholesterol level (reflects LDL, HDL and cholesterol levels)
  - **LDL** level (will be high), **HDL** level(will be low)

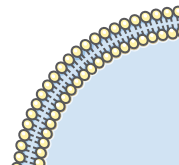
Lipoprotein (a)

LDL + apo a = Lp(a)

type of fatty acids that is unsaturated (has double bond) C=C and has H in different sides (If H are in same sides it called **cys fatty acids**)

Plasminogen is an enzyme that turns into plasmin which needed in **blood clot degradation** (keep the blood flow and breakdown thrombus)
Since apo(a) is similar to plasminogen it will mislead the **factor that activate plasminogen** (= it won't turn into plasmin). Which will stop the fibrinolytic pathway and the thrombus won't be broken down.

- **Lp(a)** is **identical in structure to LDL particle**
- Contains **apo(a)** in addition to **apo B-100**
- **High plasma Lp(a)** level is associated with **increased risk of coronary artery disease**
- **Circulating levels of Lp(a) are determined by:**
  - Genetics (mainly)
  - Estrogen (**decreases** Lp(a) levels)
  - Diet (trans FAs **increase** Lp(a) levels)
- **The apo(a) protein is structurally similar to plasminogen**
  - Competes with plasminogen
  - Slows the breakdown of blood clots
  - Triggering heart attack
  - A risk factor for CAD (coronary artery disease)



Take Home Messages

✦ 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

Summary

Click HERE

Or

Scan the code for the amazing summary

Quiz

Q1: LDL degraded by lysosomes releasing ?
A/ fatty acids
B/ free cholesterol
C/ amino acids
D/ all above

Q2: What is the specific type of Apoprotein is required for LDL receptors binding?
A/ Apo E
B/ Apo A1
C/ Apo B100
D/ Apo C

Q3:Nascent HDL contains which type of Apoprotein?
A/ Apo A1 & C2 & E
B/ Apo C2 & E & B48
C/ Apo E & B48 & B100
D/ Only Apo B100

Q4: HDL is formed in ?
A/ intestine
B/ liver
C/ plasma
D/ liver-intestine

Q5:Which one is not fasting serum lipids ?
A/ Total cholesterol level
B/ serum apoprotein level
C/ LDL, HDL level
D/ TAG level

Q6: Apoprotein (a) is structurally similar to ?
A/ C-II lipoprotein
B/ Plasminogen
C/ E lipoprotein
D/ Plasmin

Q:Why macrophages continue to uptake LDL?

Because SR-A doesn't get down-regulated

Q:Why HDL considered a good cholesterol?

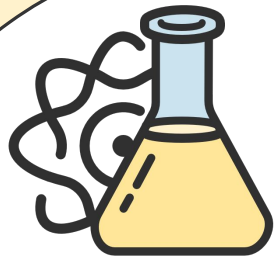
Because it Transports cholesterol from peripheral tissues to liver for degradation

Q:What are HDL functions?

Transport cholesterol to liver,Suitable for cholesterol uptake, Reservoir of Apoprotein (C2,E)

Click HERE for more questions Done by Qbank team!

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



Biochemistry 441

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Haya Alshaloob
Maram Alenazi
Futoon Almotairi

Organizer: Aisha Alhamed

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Leader: Abdulrahman Alroqi

Sub-leader: Hamad Aljubayr

Anas Alharbi
Rayan Alahmari
Mohammed Aloufi
Faisal Alazmi
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Special Thanks to Arwa Almobeirek for the Great Theme!

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