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Lipoprotein & Atherosclerosis

Color Index:

- Original content
- Important
- Extra info, Dr's notes

Objectives:

Slide No. 10	Correlate the imbalance in lipoprotein metabolism with the development of atherosclerosis.
Slides (4,7,8)	Understand the functions and metabolism of LDL and HDL cholesterol.
Slides (4, 5)	Describe the receptor-mediated endocytosis of LDL and its regulation.
Slide No. 9	Recognize how LDL is considered a bad cholesterol whereas HDL a good cholesterol.
Slides (10,11)	Understand the biochemistry of atherosclerosis and its laboratory investigations.
Slide No. 11	Discuss the role of lipoprotein(a) in the development of heart disease.

Overview:

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

Cholesterol homeostasis is a balance between cholesterol transport:

- From the liver to peripheral tissues by LDL
- From peripheral tissues to the liver by HDL

Imbalance leads to:

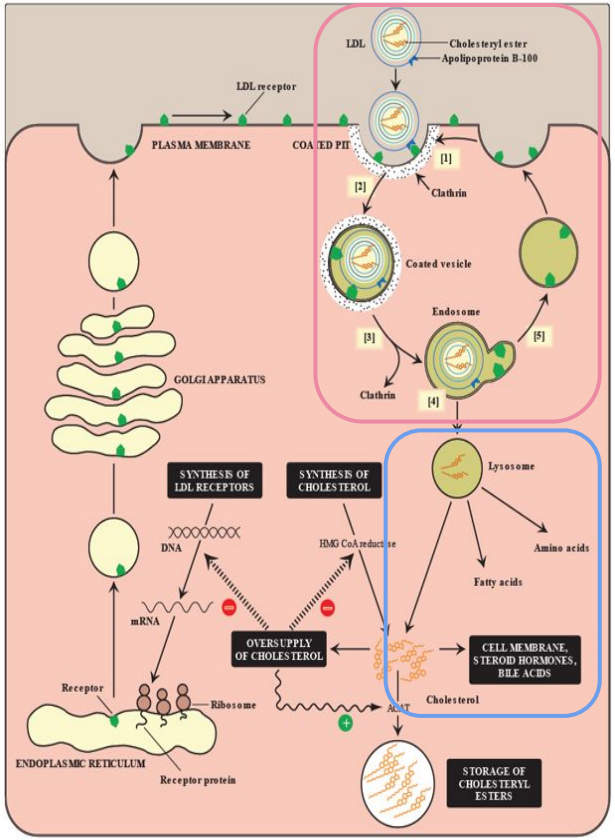
- Cholesterol deposition in blood vessels
- Thickening and narrowing of the lumen of arteries
- Atherosclerosis
- Heart disease

Receptor-Mediated Endocytosis Of LDL Particles

Major steps:

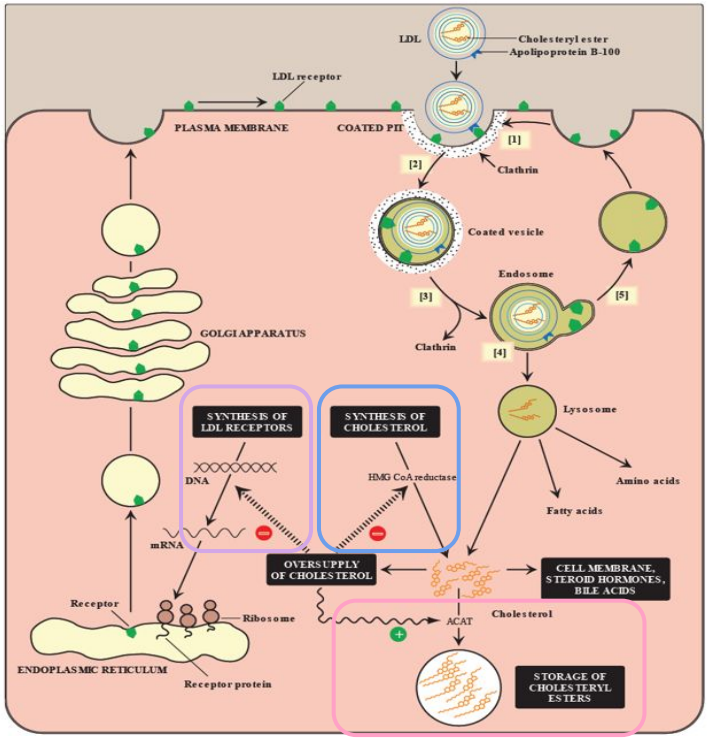
1. **Binding of Apo B-100 to LDL receptor glycoprotein**
   Apo B-100 on the LDL surface will bind to LDL receptor that exists on the cell surface which linked to Clathrin protein
2. **Endocytosis**
   as endocytosis begins clathrin will pinch on itself to creates a coated vesicle
3. **Endosome formation (LDL vesicle fuses with other vesicles)**
   The vesicle containing LDL loses its clathrin coat and fuses with other similar vesicles, forming larger vesicles called endosomes.
4. **Separation of LDL from its receptor**
   The pH of the endosome falls (due to the proton-pumping activity of endosomal ATPase), which allows separation of the LDL from its receptor.
5. **Receptor is recycled**
   The receptors migrate to one side of the endosome, whereas the LDL stay free within the lumen of the vesicle.

LDL degraded by lysosomes releasing:
Free cholesterol, fatty acids, amino acids, phospholipids



Similar mechanism is used for the uptake and degradation of chylomicron remnants and IDL by the liver.

Effects of endocytosed cholesterol on cellular cholesterol homeostasis

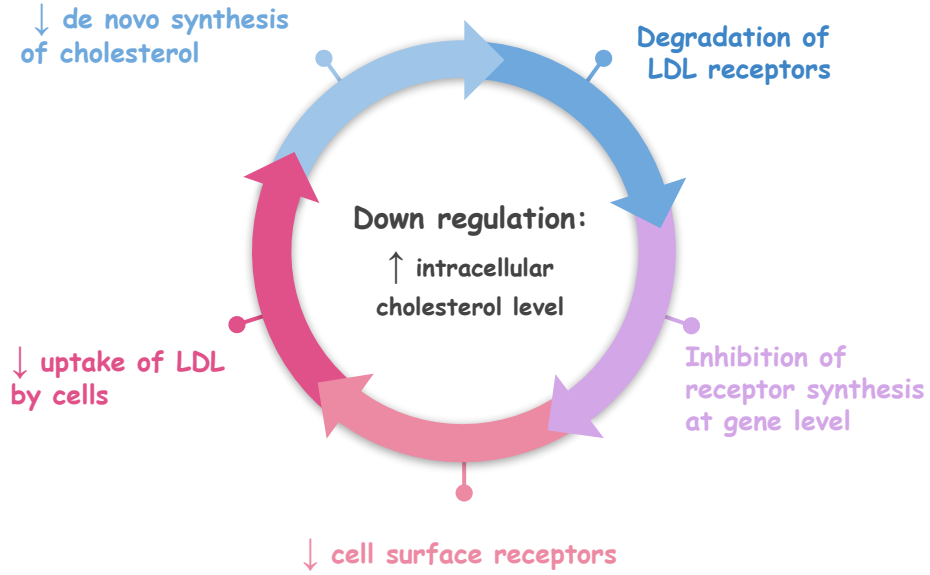


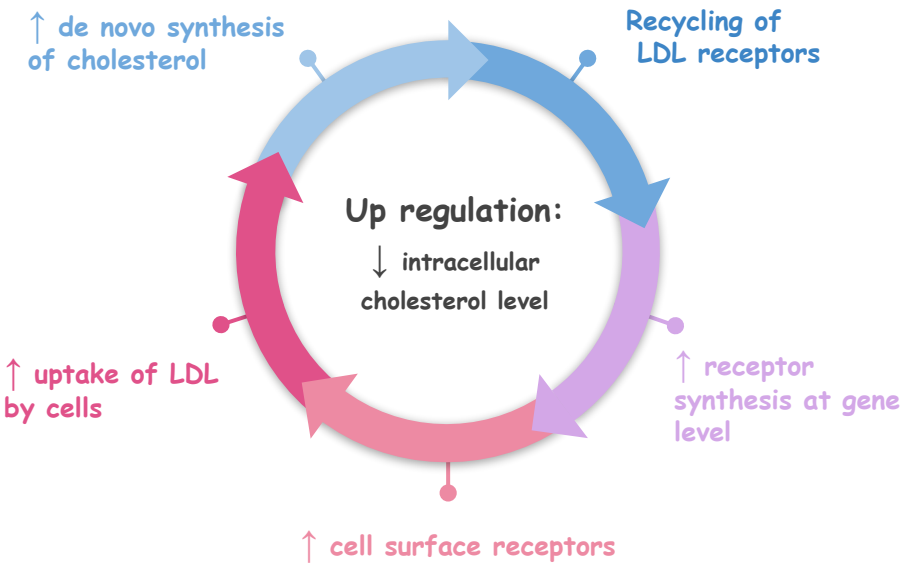
1. Expression of the gene for HMG CoA reductase is inhibited
2. de novo cholesterol synthesis decreases as a result
3. degradation of the reductase is accelerated

LDL receptor synthesis reduced.
thus limiting further entry of LDL-C into cells

Use for cell requirements.
if the cholesterol is not required immediately for some structural or synthetic purpose, it is esterified by acyl CoA:cholesterol acyltransferase (ACAT). ACAT transfers a FA from a fatty acyl CoA to cholesterol, producing a cholesteryl ester that can be stored in the cell

Regulation Of LDL Endocytosis





De novo = Endogenous, Self-growth

High Density Lipoprotein (HDL)

- Disk-shaped
- Contains apo A-I, C-II and E lipoproteins
- Mainly contains phospholipids

Nascent HDL + cholesteryl esters

HDL3 + more cholesteryl esters

- spherical
- transfers cholesterol to the liver

Functions Of HDL

Reservoir of apoproteins

- Apo C-II
- Apo E

Transports cholesterol To liver from:

- Peripheral tissues
- Other lipoproteins
- Cell membranes

Suitable for Cholesterol uptake due to

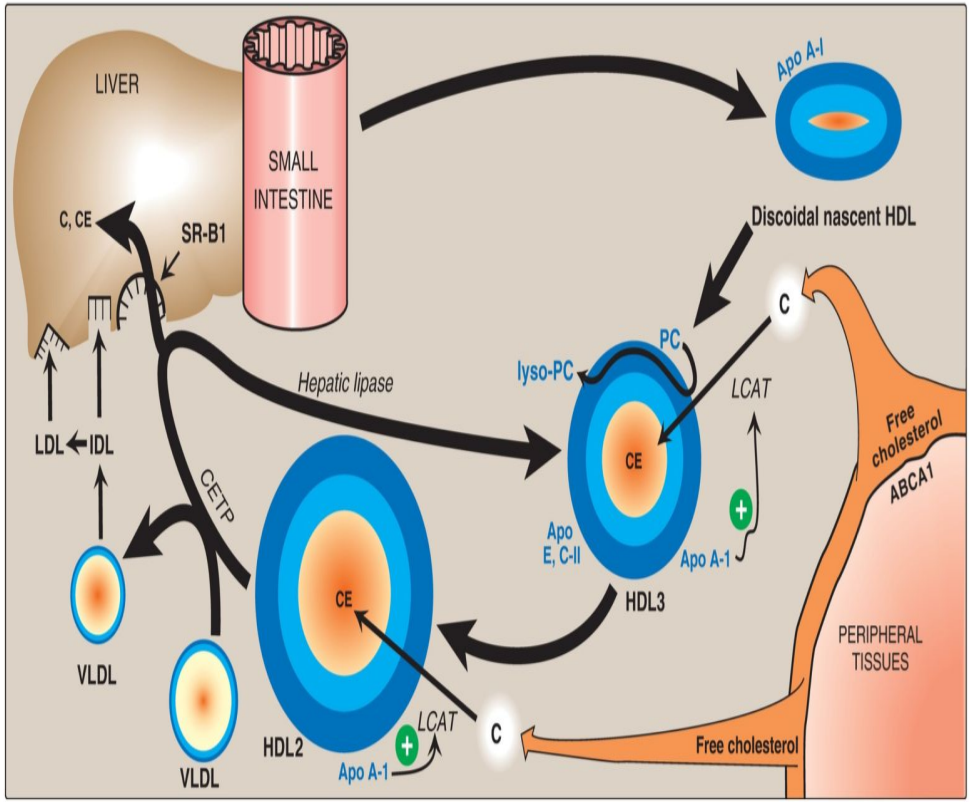
- High content of phospholipids
  - → Phospholipids solubilize cholesterol and provide fatty acids for cholesterol esterification.

☆ apo C-II: the apolipoprotein that is transferred to VLDL and chylomicrons and is an activator of LPL
☆ apo E: the apolipoprotein required for the receptor-mediated endocytosis of IDL and chylomicron remnants

HDL Metabolism

Explanation:

- Nascent HDL synthesized in the liver and intestines, then it's transported to the circulation then
- ABCA1 enzyme will release the cholesterol from the tissue to the circulation
- Nascent HDL will take up cholesterol from nonhepatic (peripheral) tissues
- Apo A-1 activate LACT enzymes that esterficate the cholesterol, turning it into a Cholesteryl ester and therefor transforming nascent HDL to HDL3
- Esterification maintains the cholesterol concentration gradient, allowing continued efflux of cholesterol to HDL3 so it will convert it to HDL2
- Unloading of the cholesterol to the liver from HDL2



Direct
via SR-B1 receptor

InDirect
Mediated by **CETP**

transfers some of the cholesteryl esters from HDL to VLDL in exchange for TAG

Because VLDL are catabolized to LDL, the cholesteryl esters transferred by CETP are ultimately taken up by the liver

☆ Hepatic lipase: degrades TAG and phospholipids, participates in the conversion of HDL2 to HDL3
☆ LCAT: Lecithin cholesterol acyltransferase
☆ Lecithin: phosphatidylcholine

LDL Is A Bad Cholesterol

(Why?)

1. ★ Transports cholesterol
   Liver → peripheral tissues.
2. ↑ LDL levels
   ↑ risk for atherosclerosis / heart disease
3. Deficiency or defects in LDL receptors:
   - ↓ uptake of cholesterol by cells
   - ↑ accumulation of cholesterol in blood vessels
4. Familial Hypercholesterolemia (LDL Receptor deficiency) :
   - Patients are unable to clear LDL from blood
   - Premature atherosclerosis and heart disease

HDL Is A Good Cholesterol

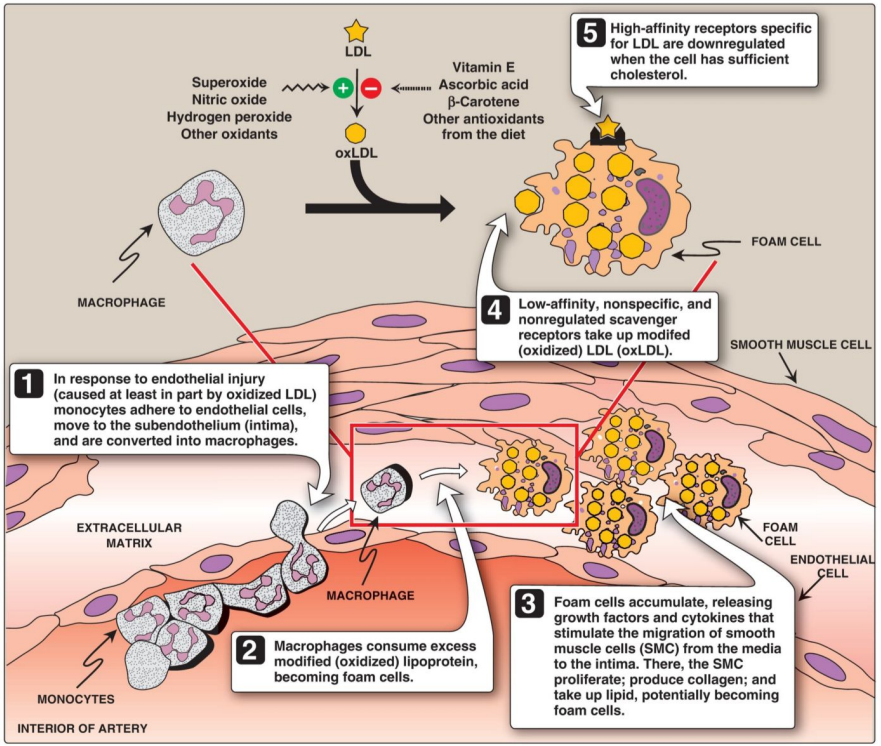
(Why?)

1. Transports cholesterol
   Peripheral tissues → liver (for degradation)
2. ↑ HDL levels
   ↓ risk for atherosclerosis
3. ↓ cholesterol level in tissues and circulation
   (reverse cholesterol transport)
4. Reverse cholesterol transport includes:
   - Cholesterol efflux from peripheral tissues to HDL.
   - Cholesterol esterification.
   - Binding & transfer of cholesteryl ester-rich HDL2 to the liver.
   - Release of lipid-depleted HDL3.

☆Normal cholesterol transport: liver → peripheral Tissues
☆Reverse cholesterol transport: peripheral tissues → liver

Atherosclerosis

- **LDL** uptake by cells is receptor mediated.
- Chemically-modified LDL contains **oxidized lipid** and **Apo-B**.
- Macrophages take up chemically-modified LDL by **Endocytosis** "through scavenger receptors (SR-A)".
- Unlike LDL-receptors, the **SR-A** is **not** down-regulating in response to high intracellular cholesterol.
- Cholesteryl esters accumulate in macrophages converting them to **foam cells**.
- Foam cells contribute to plaque formation and **atherosclerosis**.



Lab Investigations

☆Fasting serum level profile:

Level of	TAG ↑	• LDL • HDL	Total cholesterol
reflects	• chylomicron • VLDL Level		• LDL • HDL • cholesterol

☆Other tests:

★ Serum lipoprotein electrophoresis

measures lipoprotein fractions to determine abnormal distribution and concentration of lipoproteins in the serum
(helpful in measuring IDL)

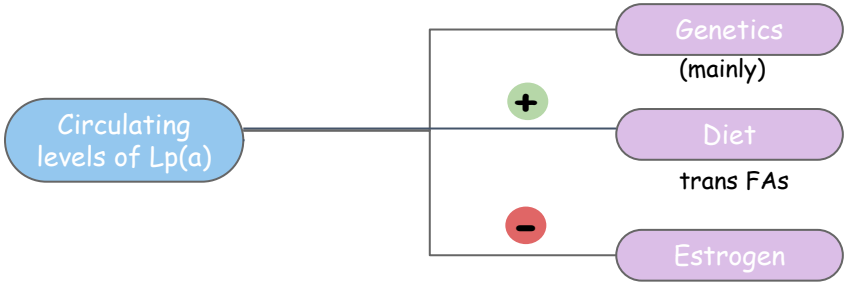
★ Serum apoprotein levels (eg. apo-B)

Lipoprotein (a)

☆ Lp(a) is identical in structure to LDL particle.

→ contains apo(a) "small not capital a" + apo B-100.

☆High plasma level associated with increase risk of coronary heart disease.



☆ The apo(a) protein is similar structure to plasminogen.

★ Compete with plasminogen
★ Slow the breakdown of blood clot
★ Triggering heart attack
→ A risk factor of CAD

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.

Quiz

MCQs

Q1: LDL binds to cell surface receptors through which of the following?
a) Apo B-48 b) Apo C-II c) Apo E d) Apo B-100

Q2: 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

Q3: In terms of size, which lipoprotein is the smallest?
a) HDL b) Chylomicron c) LDL d) VLDL

Q4: Familial hypercholesterolemia is caused by a defect in which of the following?
a) HDL receptor b) LDL receptor c) Apo B-100 d) Apo E

Q5: HDL act as a reservoir of which of the following?
a) Cholesterol b) Lipids c) Apoproteins d) Phospholipids

Q6: Lipoprotein (a) differs from LDL in which of the following?
a) Apo B-48 b) Apo B-100 c) Apo A d) Apo C-II

SAQs

Q1: What do LDL particles mainly contain?

Q2: Where nascent HDL is present?

Q3: Deficiency or defects in LDL receptors results in what?

Q4: A patient presented to the ER with atherosclerosis symptoms, how can you investigate that he has Atherosclerosis?

★ **MCQs Answer key:**

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

★ **SAQs Answer key:**

1) Cholesterol and cholesteryl esters.
2) In the circulation.
3) * Decreased uptake of cholesterol by cells,
   * Increased accumulation of cholesterol in blood vessels.
4) Fasting serum lipid profile: TAG level (reflects chylomicron and VLDL levels), LDL, HDL levels and Total cholesterol level (reflects LDL, HDL and cholesterol levels).

Team members

Girls team :

- Ajeed Al-rashoud
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- Reem Algarni
- Shahd Alsalamh
- Taif Alotaibi

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- Alkaseem binobaid
- ★ Fares Aldokhayel
- Naif Alsolais
- Sultan Alhammad

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Deema Almaziad **Mohannad Alqarni**

★ This lecture was done by

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