Biochemistry

Lipoprotein and atherosclerosis

Revised by

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- Important.
- Extra Information.
- **Doctors slides**

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Objectives:

By the end of this lecture, the First Year students will be able to:

1-Correlate the imbalance in lipoprotein metabolism with the development of atherosclerosis

2-Understand the functions and metabolism of LDL and HDL cholesterol

3-Describe the receptor-mediated endocytosis of LDL and its regulation

4-Recognize how LDL is considered a bad cholesterol whereas HDL a good cholesterol

5-Understand the biochemistry of atherosclerosis and its laboratory investigations

6-Discuss the role of lipoprotein(a) in the development of heart disease

Recall what you studied in the previous lectures:

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.

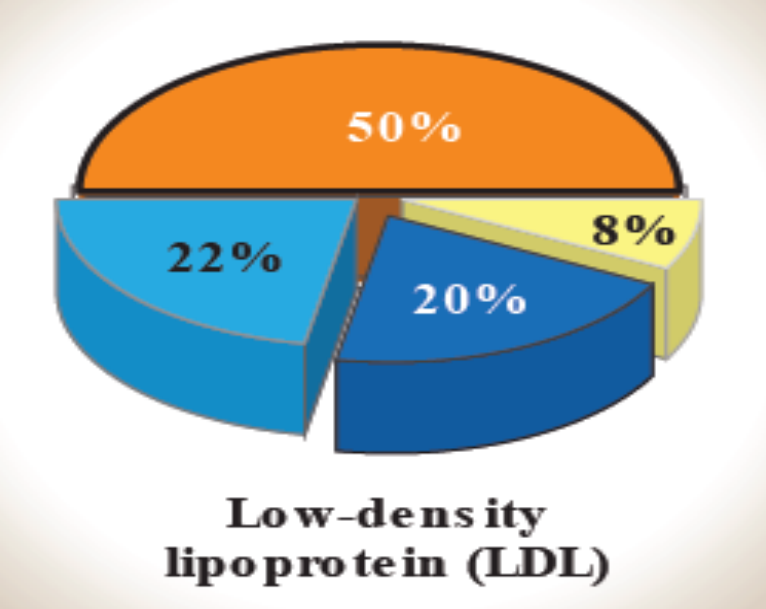
After the delivery of TAG the chylomicron becomes chylomicron remnant which has mainly cholesterol.

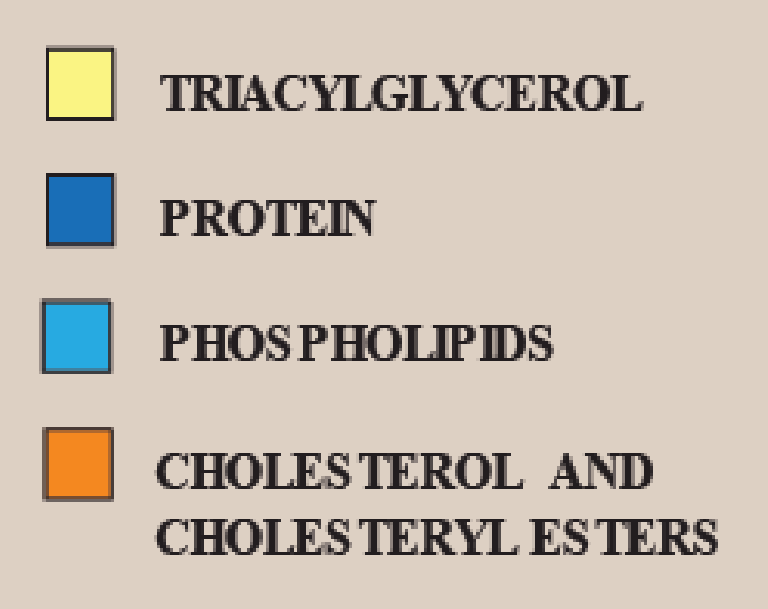
These molecules they are not clear from the circulation and they will increase the amount of cholesterol in the blood and the other molecule is HDL , all these 3 to be clear from the circulation they are recognized by ABO-e ABO-B100 BY the liver cells receptors .

Low density lipoprotein (LDL):

- LDL particles mainly **contain** cholesterol and cholesteryl esters
- **Produced from** VLDL particles
- **Contain** Apo B-100 lipoprotein
- **Provides** cholesterol to peripheral tissue
- LDL **binds** to cell surface receptors thru Apo B-100 Leading to receptor-mediated endocytosis.

cholesterol blood level indicates the level of these lipoprotein only; since no free floating cholesterol in the blood .





Receptor-mediated endocytosis of LDL particles:

Major steps

Binding of Apo B-100 to LDL receptor glycoprotein

- receptors are accumulated in the coated pits (coated with clathrin) (pits=small depression)

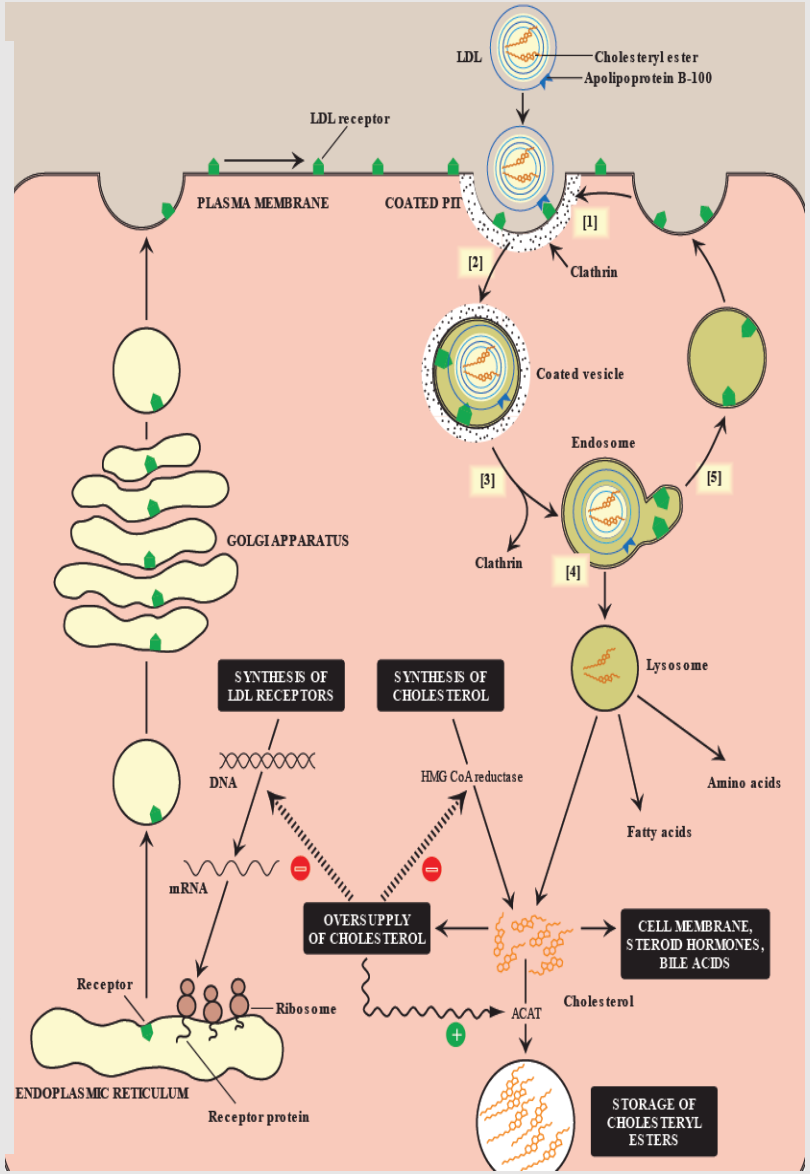
Endocytosis occur

- (and the vesicle is pinched off producing a coated vesicle (coated with clathrin) after endocytosis the clathrin coat is removed)

Endosome formation

- (LDL vesicle fuses with other vesicles) endosome has different enzymes one of these is; **endosomal ATPase** enzyme which is a proton transport pathway therefore increasing the amount of protons inside when the amount of protons increase -> PH decrease
- acidic PH leads to separation of receptor and LDL molecule

Separation of LDL from its receptor → **Receptor is recycled** → **LDL degraded by lysosomes releasing:** Free cholesterol, fatty acids, amino acids, phospholipids



Cellular up take & regulation of LDL particals:

This slide and the following one shows detailed explanation (Dr. Sumbul explained it in a similar way)

a) Receptor mediated endocytosis:

Binding of Apo B-100 to LDL receptor glycoprotein.

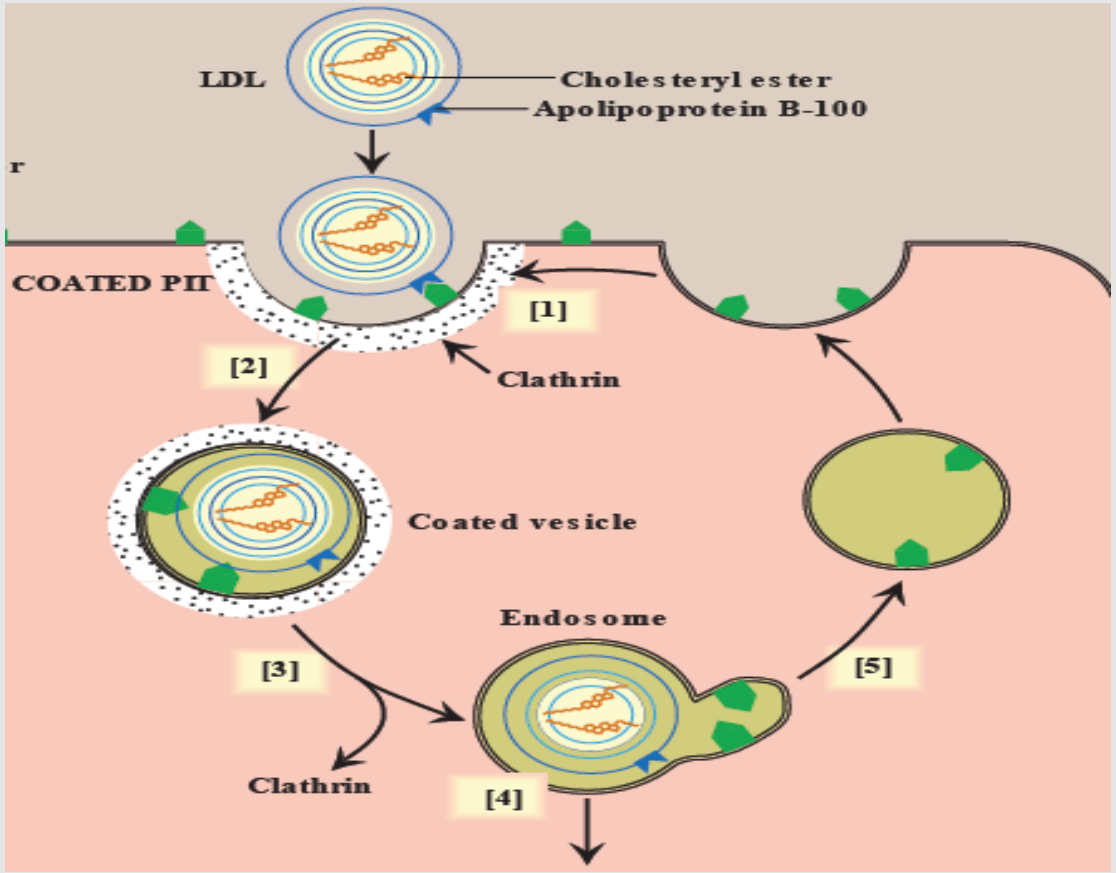
1 . LDL receptors are clustered in pits (depressions on the cell surface) which is coated with the protein Clathrin.

2 . After binding, LDL receptors is taken in by endocytosis.

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 . The PH of the endosome falls (due to the proton pumping activity of endosomal ATPase), which allows the separation of the LDL from its receptor.

5 . The receptors can be recycled.

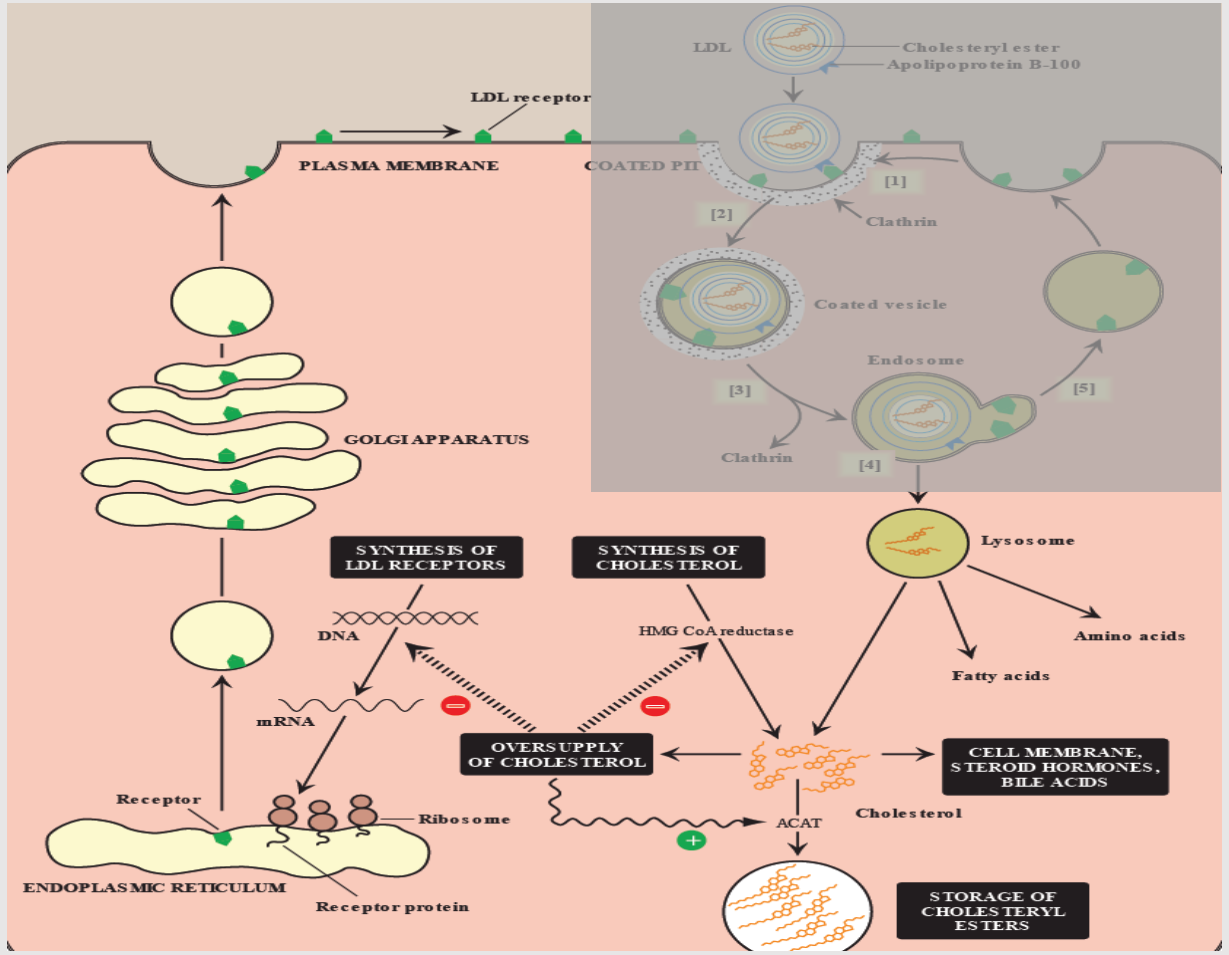


Cellular up take & regulation of LDL particals:

After the separation of LDL receptors and the vesicle, the remnants in the endosome are transferred to lysosomes and degraded by its enzymes into its primary components: The proteins into amino acids, the triacylglycrides into fatty acids and free cholesterol. Theses components can be reutilized (re-used) by the cell.

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. Use for cell requirements. If not or there is excess amount, it is esterified by (ACAT) producing a cholesterol ester that can be stored in the cell.



- ACAT= acyl CoA: cholesterol acyltransferase.
- HMG CoA= hydroxymethyl-glutaryl coenzyme A.

Regulation of LDL endocytosis:

	Down regulation:	Up regulation:
	High intracellular cholesterol level causes:	**Low intracellular cholesterol level causes:**
LDL receptors:	Degradation	Recycling
Receptor synthesis at gene level	**Inhibited**	**Increased**
cell surface receptors	Reduction	Synthesis
uptake of LDL by cells	**Decreased**	**Increased**
de novo synthesis of cholesterol	Decreased	Increased

LDL is bad cholesterol:

- Transports cholesterol to peripheral tissues. ⟶ (when cholesterol is transported to the liver, by HDL, it can be converted to bile acid or disposed via the bile but when in it transported to the tissues it only accumulates there).
- Elevated LDL levels → increased accumulation of cholesterol → increased risk for atherosclerosis / heart disease .
- **Deficiency or defects in LDL receptors results in:**
  - Decreased uptake of cholesterol by cells
  - Increased accumulation of cholesterol in blood vessels
- **This type of deficiency is called Familial Hypercholesterolemia**
  - Patients are unable to clear LDL from blood
  - Premature atherosclerosis and heart disease

High density lipoprotein (HDL):

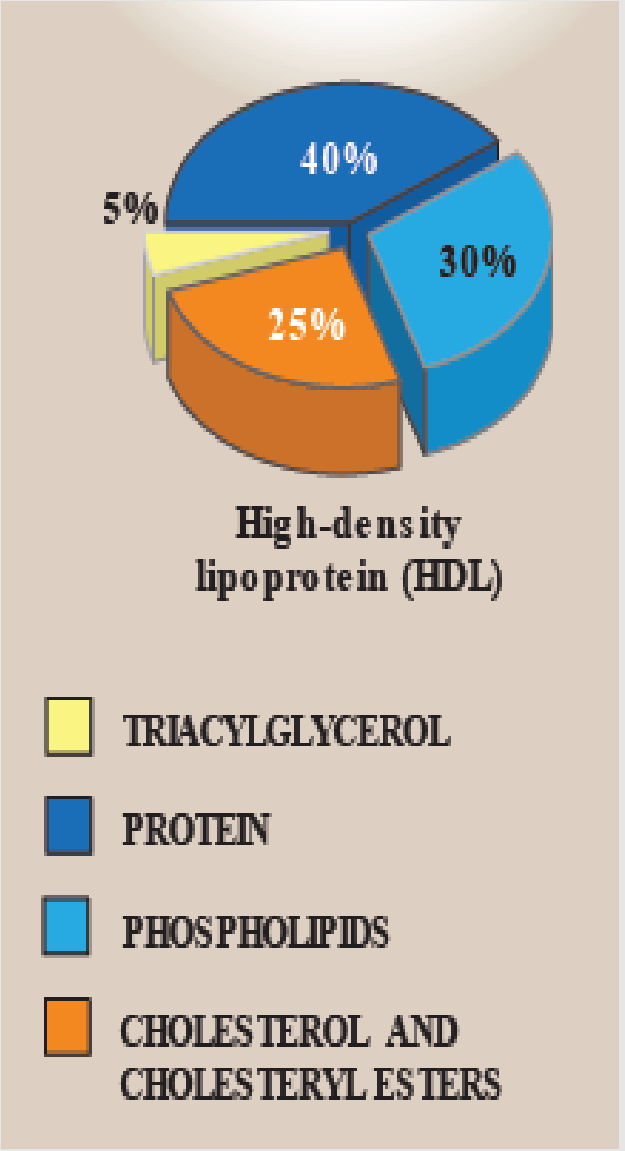
❖HDL particles mainly contain:

1) Protein, phospholipids, cholesterol, cholesteryl esters
2) **Produced in** the blood (mainly), liver and intestine

3) **Contains** Apo A-1 (70%), C-2 and E lipoproteins

4) Take up cholesterol **from** peripheral tissues to the liver.

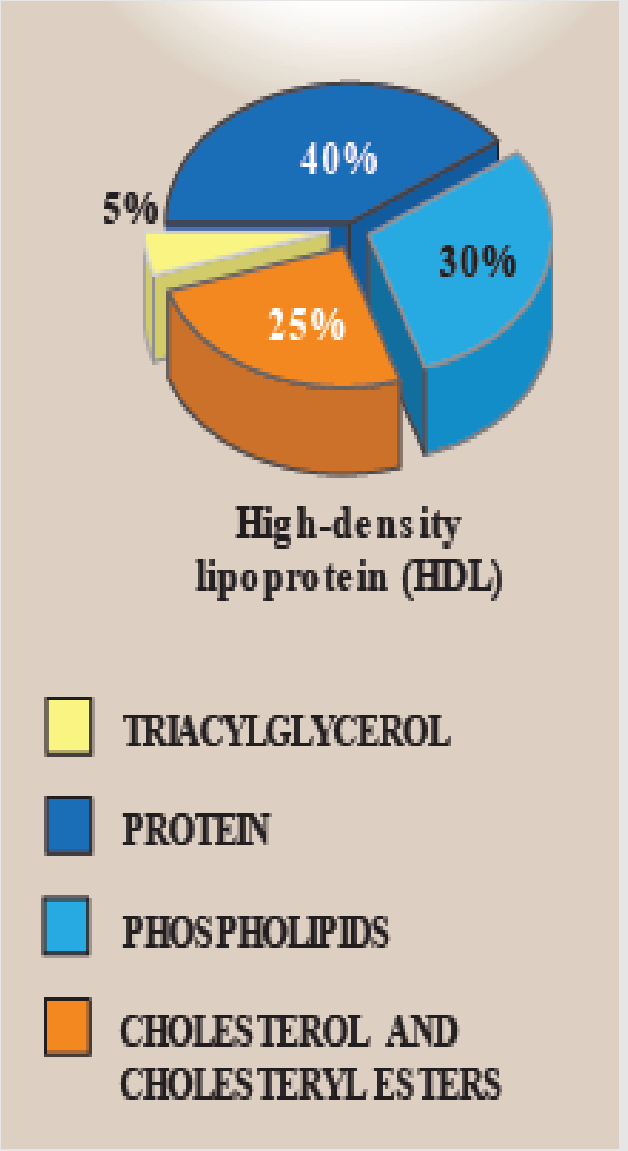
(therefore less cholesterol accumulates there. This decreases the risk of atherosclerosis; hence HDL is the "good cholesterol")



High density lipoprotein (HDL):

- When HDL is first produced it is in the form of Nascent HDL:
  - **Disk-shaped**
  - Contains apo **A-I**, **C-II** and **E** lipoproteins
  - Mainly contains phospholipids

- **How does it become Mature HDL?**
  1. Nascent HDL + cholesteryl esters (CE) → HDL_3 (CE poor)
  2. HDL_3 + more cholesteryl esters → **spherical** HDL_2 (CE rich)
  3. HDL_2 transfers cholesterol to the liver.



Functions of HDL:

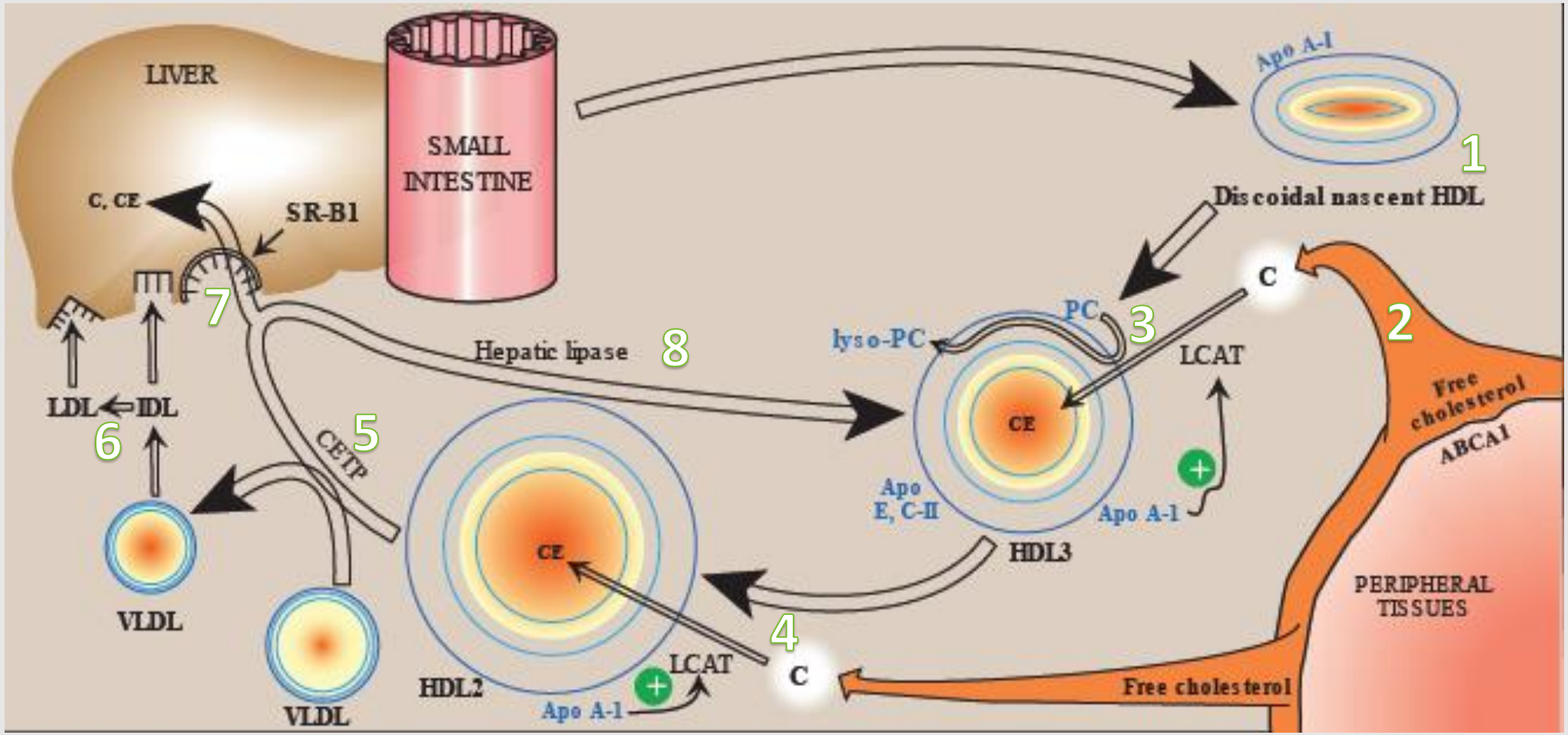
- Reservoir of apoproteins:
  - (1) Apo C-II
  - (2) Apo E
- Transports cholesterol to liver from:
  - Peripheral tissues
  - Other lipoproteins
  - Cell membranes
- Suitable for cholesterol uptake due to:
  - High content of phospholipids
  - Phospholipids solubilize cholesterol and provide fatty acids 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 ILDs and chylomicron remnants).

Note: HDL particles are excellent acceptors of unesterified cholesterol as a result of their high concentration of phospholipids, which are important solubilizers of cholesterol.

HDL metabolism:



ABCA1 = Transport protein, C = Cholesterol, CE= Cholesteryl Ester, LCAT = Lecithin Cholesterol Acetyl Transferase, CETP = Cholesteryl Ester Transfer Protein, SR-B1 = Scavenger Receptor B1

HDL metabolism:

1. Nascent HDL is present in the circulation.
2. Free cholesterol from the peripheral tissues is taken up by HDL with the help of ABCA1.
3. The free cholesterol is converted (inside HDL) into an ester through LCAT* (or PCAT) by adding a fatty acid. The source of the fatty acid is PC (phosphatidylcholine) which becomes lyso-PC after losing the fatty acid. HDL is now CE-poor HDL3.

   *note: LCAT is activated by Apo – A1
4. It takes up more cholesterol which is also esterfied by LCAT and becomes CE-rich HDL2.
5. CETP moves some of the cholesteryl esters from HDL to VLDL in exchange for TAG.
6. VLDL is then converted to IDL and LDL
7. When HDL reaches the liver, the scavenger receptors (SR-B1) will take up the CE and C from the HDL to the liver.
8. Hepatic lipase will then act on the TAG in the HDL (which it got from the VLDL). This converts HDL2 back to HDL3 and the cycle continues.

HDL is a good cholesterol:

- **HDL** transports cholesterol from **peripheral tissues** **to** **the liver** for degradation
- **High HDL levels** have **inverse correlation** with incidence of **atherosclerosis**

Why? HDL will transport cholesterol from the tissues to the liver, then the liver will excrete it as bile so, it is percentage will decrease and the risk of atherosclerosis as well .

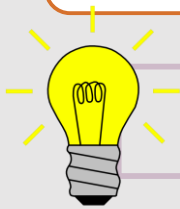
Reverse cholesterol transport

Reduces cholesterol level in tissues and circulation

Includes the following

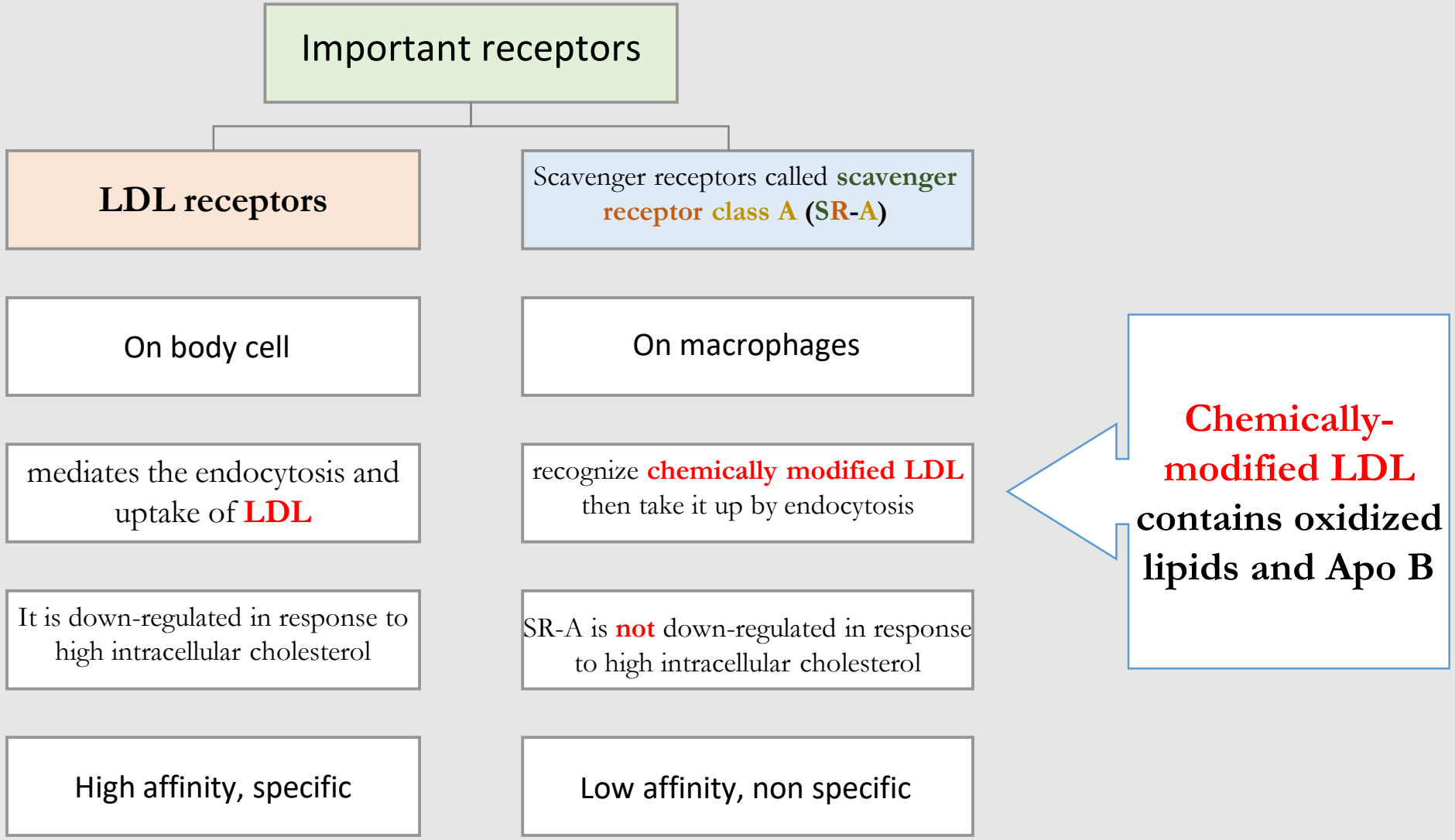
Cholesterol efflux from peripheral tissues to HDL → Cholesterol esterification → Binding and transfer of cholesteryl ester-rich HDL_2 to liver → Release of lipid-depleted HDL_3

esterification : transform into ester by the reaction between an acid and an alcohol with elimination of water



HDL2 LARGE
HDL3 SMALL

Atherosclerosis:



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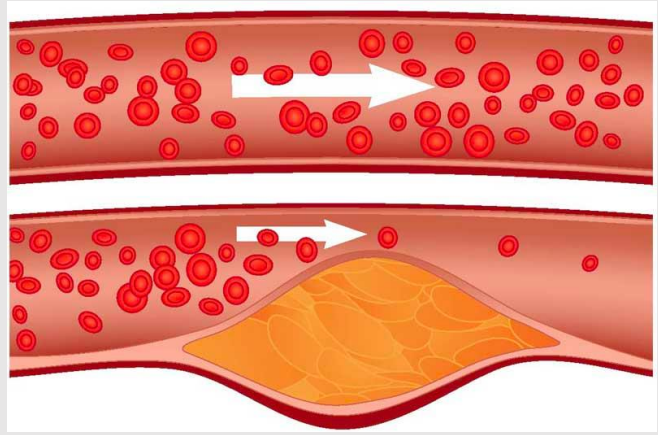
Atherosclerosis overview:

Imbalance between LDL and HDL → Cholesterol deposition in the walls → (LDL) particles in blood plasma become oxidized → invade the endothelium → Causes damage or injury to the endothelium → Inflammatory response: Monocytes converted into macrophages and consumes the oxLDL → Cholesteryl esters accumulate in macrophages converting to foam cells → Foam cells accumulate and release cytokines and growth factors → Migration of smooth muscle cells and formation of fibrous cap → Plaque formation → Atherosclerosis



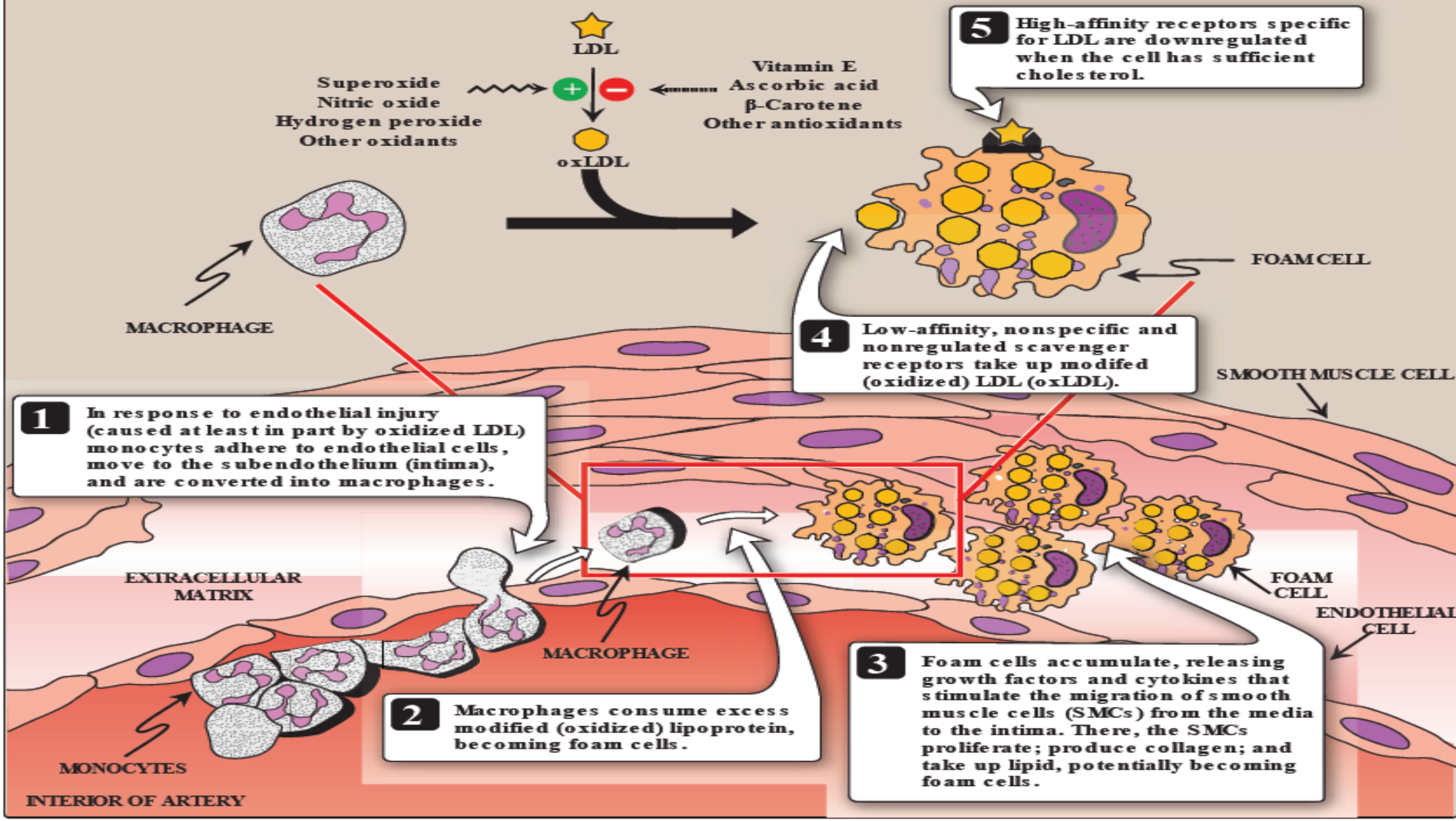


Figure 18.22
Role of oxidized lipoproteins in plaque formation in an arterial wall. LDL = low-density lipoprotein.

Lab investigations of atherosclerosis:

Fasting serum lipid profile:

1) TAG level (reflects chylomicron and VLDL levels)
2) LDL, HDL levels
3) Total cholesterol level (reflects LDL, HDL and cholesterol levels)

Other tests:

- ✓ Serum lipoprotein electrophoresis
- ✓ Serum apoprotein levels (e.g., apo-B)

Lipoprotein (a):

Lp (a) is identical in structure to LDL particle. Its distinguishing feature is > It contains apo (a) in addition to apo B-100

Circulating levels of Lp (a) are determined by:

- Genetics (mainly)
- Diet (trans fatty acids increase Lp (a) levels)
- Estrogen (decreases Lp (a) levels)

A risk factor for **CAD**

Why?

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

How?

It slows the break down of blood clots that trigger heart attacks

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

Plasminogen (pro-enzyme) > 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 .

Quiz

SAQ

https://www.onlineexambuilder.com/lipoproteins-saq/exam-145844

MCQ's

https://www.onlineexambuilder.com/lipoproteins/exam-145842

Good Luck ..

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THANK YOU

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

- Review the notes

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