بسم الله الرحمن الرحيم

Lipoproteins and Atherosclerosis

By

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Introduction

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"

مهم

LDL ::: ينقل الكولسترول من الكبد عبر الأوعية الدموية إلى البرفرال تشو

HDL ::: ينقل الكولسترول من البرفرال تشو عبر الأوعية الدموية إلى الكبد

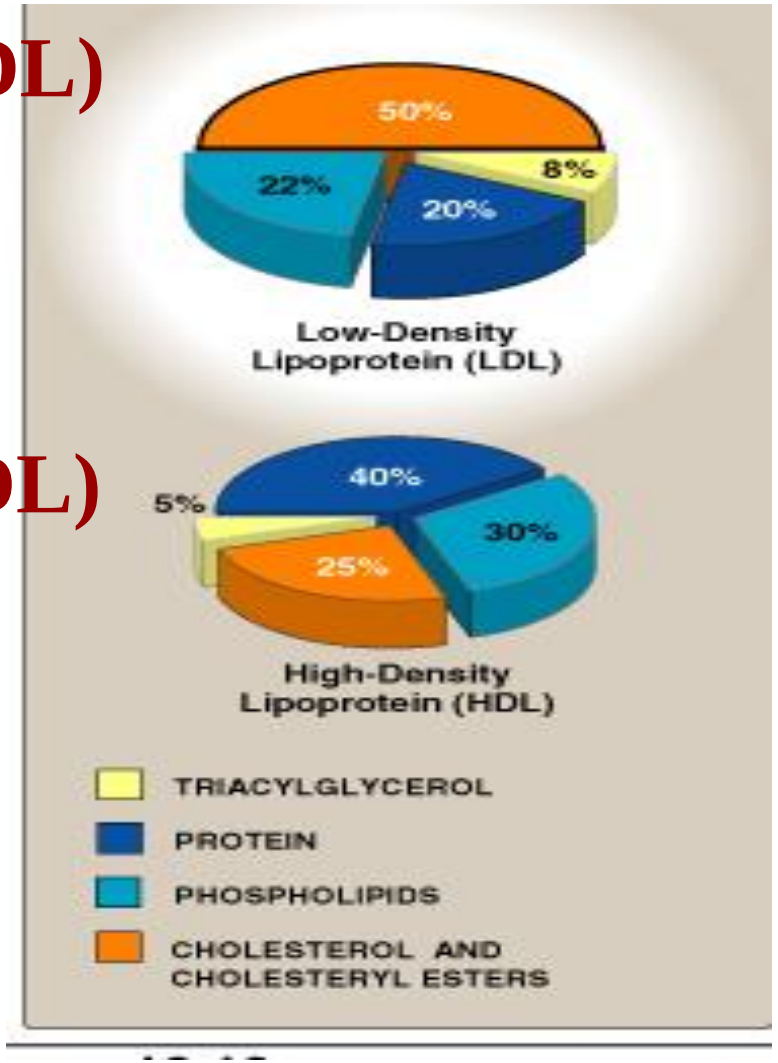
Composition of LDL and HDL

Low density lipoprotein (LDL)

- **Mostly free cholesterol**

High density lipoprotein (HDL)

- **Mostly cholesterol ester**
- **More % protein**
- **More % phospholipids**



Low Density Lipoproteins (LDL)

Produced in the circulation as the end product of VLDLs

- **LDL Features :**
  - **It contains ONLY apo B-100**
  - **Smaller size and more dense**
  - **Less TG**
  - **More cholesterol & cholesterol ester**

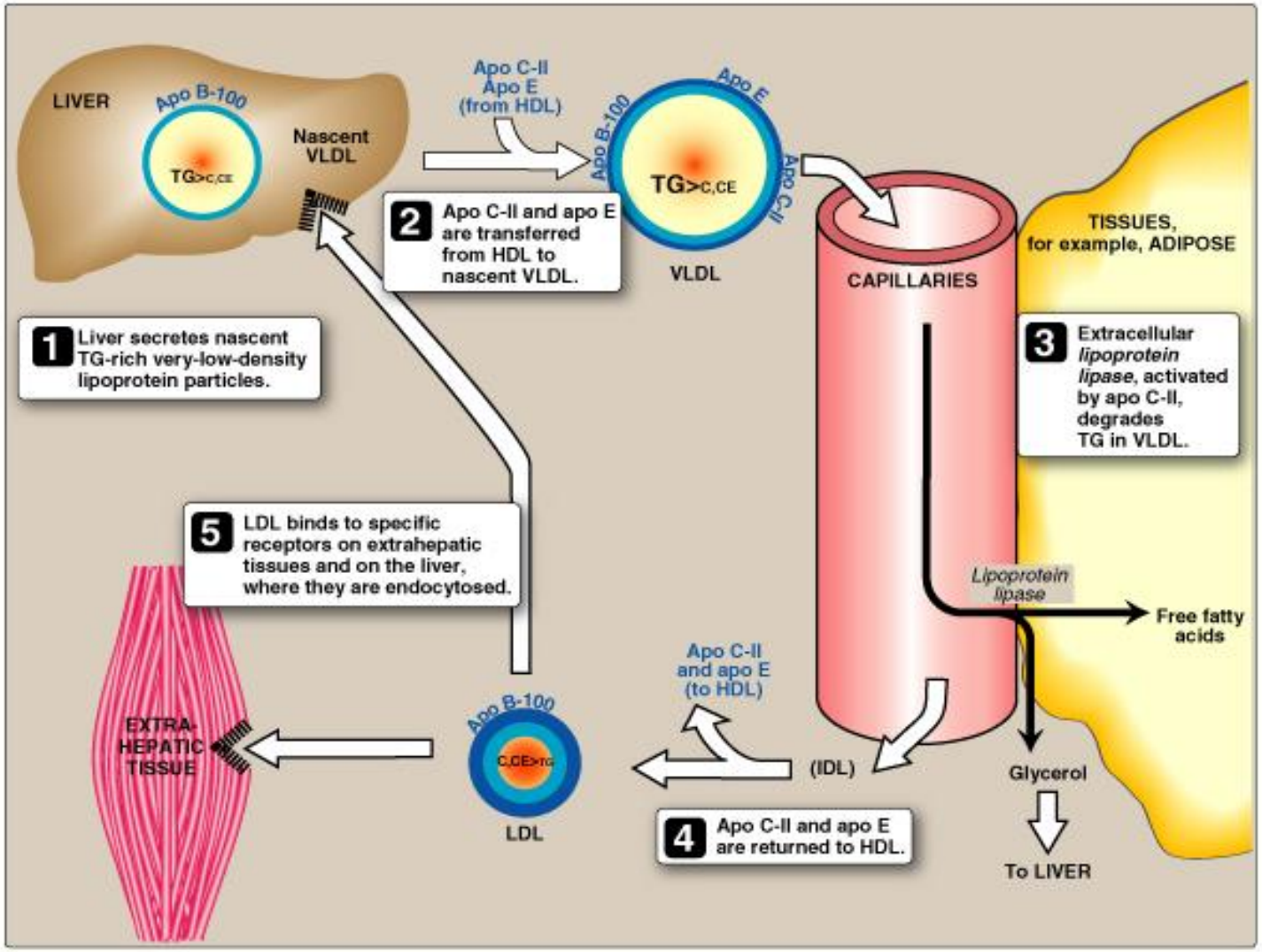
Transport cholesterol from liver to peripheral tissues

Uptake of LDL at tissue level by

LDL receptor-mediated endocytosis

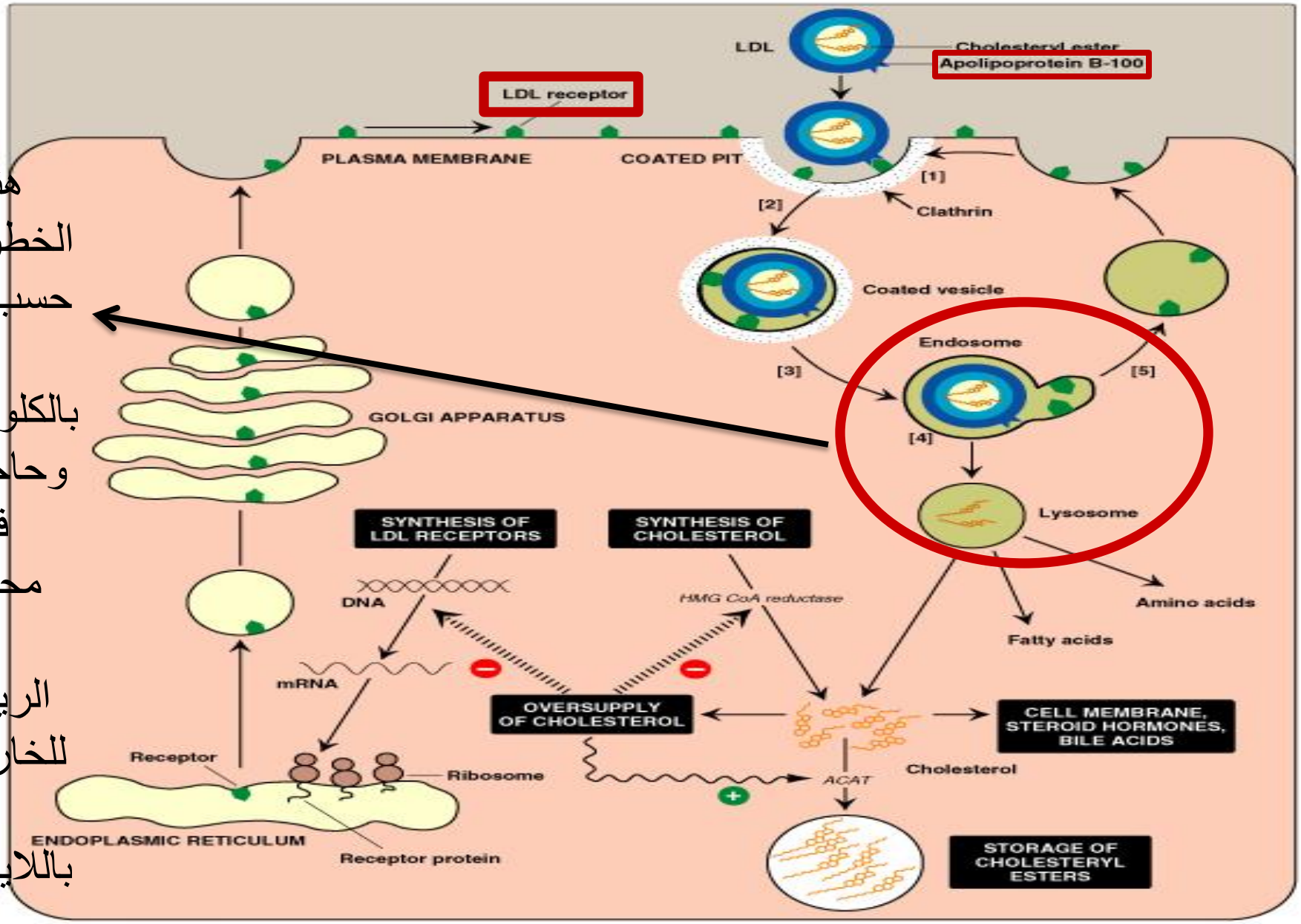
Recognized by apo B-100

عند ذهابه إلى البرفرال تشو تتعرف الخلايا عليه بواسطة apo B-100 الموجود على سطحه، بعد ارتباطه بالريسبتور يحصل لهما endocytosis



LDL Metabolism

هنا تكون الخطوة على حسب اكتفاء الخلية بالكلوسترول وحاجتها له. فإذا كان محتاجه له رجع الريسيبتور للخارج وإلا يحلل باللايسوسوم



LDL: Receptor-Mediated Endocytosis

Receptor-Mediated Endocytosis

- **LDL receptor:**
  Cell surface glycoprotein
  High-affinity, tightly regulated :: تذكر
- **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 Receptor-Mediated Endocytosis: Regulation

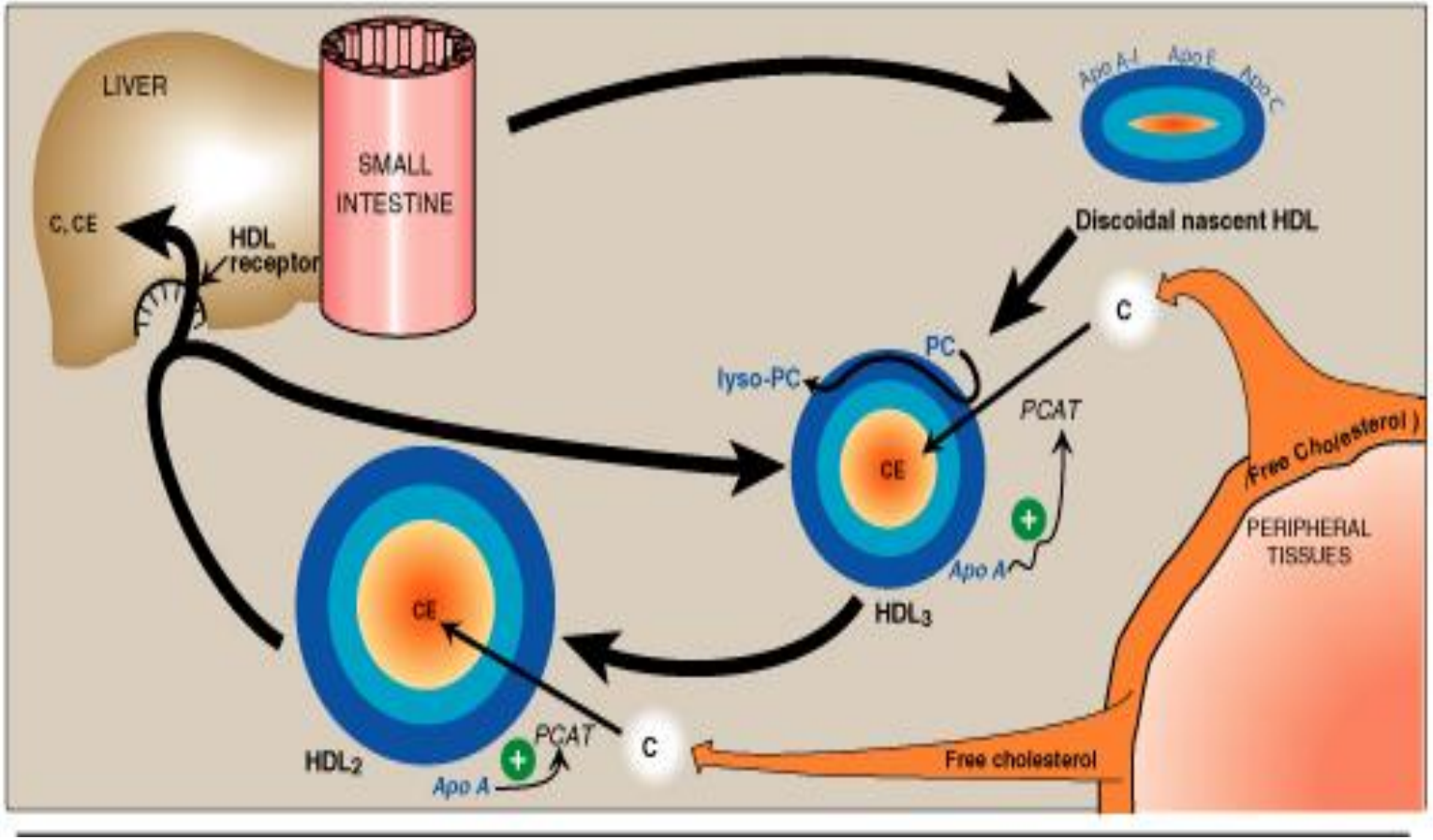
Down-regulation:

- 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

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 synthesis of cholesterol

HDL Metabolism



PC = Phosphatidylcholine/Lecithin

High Density Lipoproteins (HDL)

- **Produced by intestine and liver**
- **Nascent 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**

Functions of HDL

1. **Reservoir of apoproteins**
   e.g., Apo C-II and E to VLDL يعطيه اياه بعد ما يخرج للدم

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: Cholesterol ester (& Lyso-PC)

Why Is HDL a Good Cholesterol carrier?

- **Inverse relation between plasma HDL levels and atherosclerosis …. How?**
  - يعني يرجع الـكلوسترول للكبد
- **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 ::: HDL_3 has colesterol <u>less</u> than HDL_2

Atherosclerosis

Pathogenesis:

Modified (oxidized) LDL … Oxidative stress

Uptake of oxLDL by macrophage scavenger receptor:

Scavenger receptor class A (SR-A)

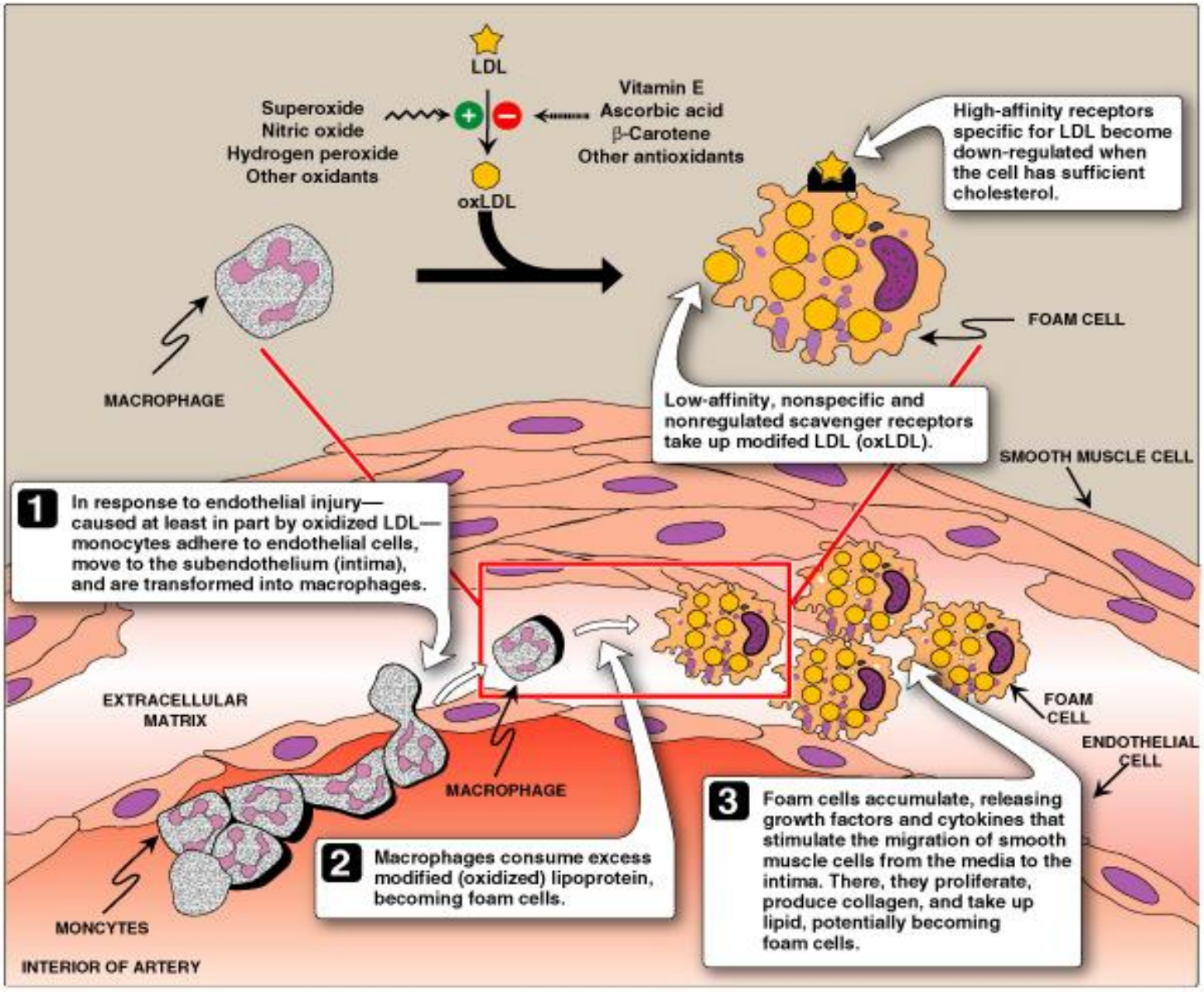
Low-affinity, non-specific receptor

Un-regulated receptor

Foam cell (macrophages when oxiLDL presented inside them) transformation

Atherosclerotic plaque formation

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



Atherosclerotic plaque Formation

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, Serum lipoprotein electrophoresis

Serum apoprotein levels e.g., apo-B

LDL-related Diseases

Hyperlipoproteinemia:
Type IIa Hyperlipoproteinemia
(Familial hypercholestrolemia)

- **Functional defect of LDL-receptor**
  يتغير شكل الريسيبتور مما يجعله لا يستقبل الـ LDL
- **Increase plasma LDL level & therefore, plasma cholesterol level** وبالتالي يكثر LDL في البلازما
- **Pre-mature atherosclerosis and increased risk for early-onset ischemic heart diseases**
- **Associated with the presence of tendon xanthomas on hands and ankles**