بسم الله الرحمن الرحيم

Lipoproteins and Atherosclerosis

By

Reem M. Sallam, M.D.,MSc, Ph.D.

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"

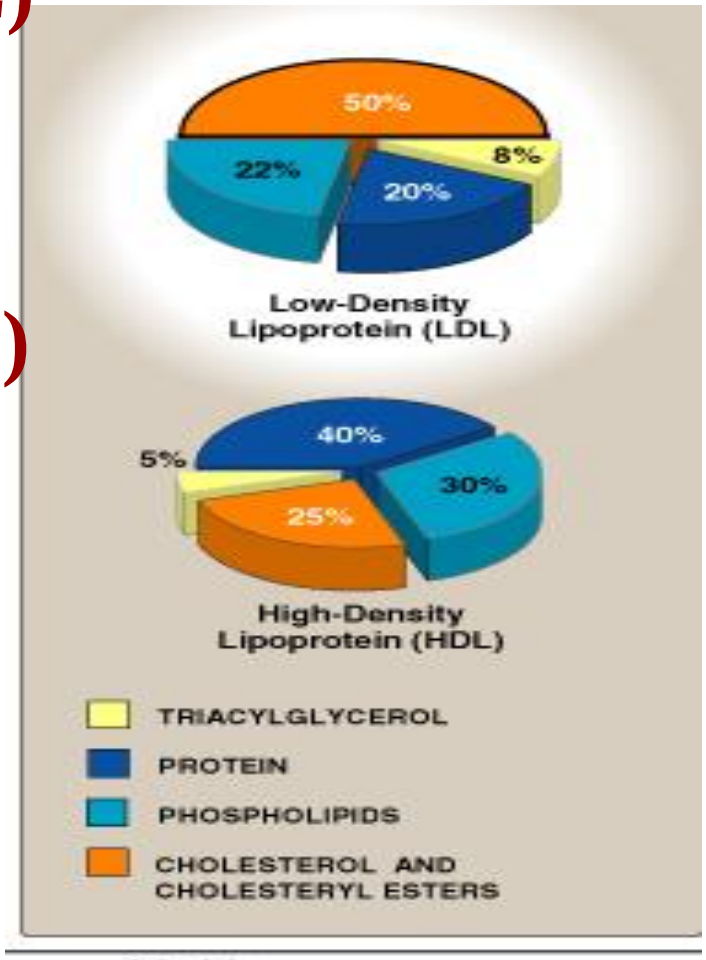
Composition of LDL and HDL

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

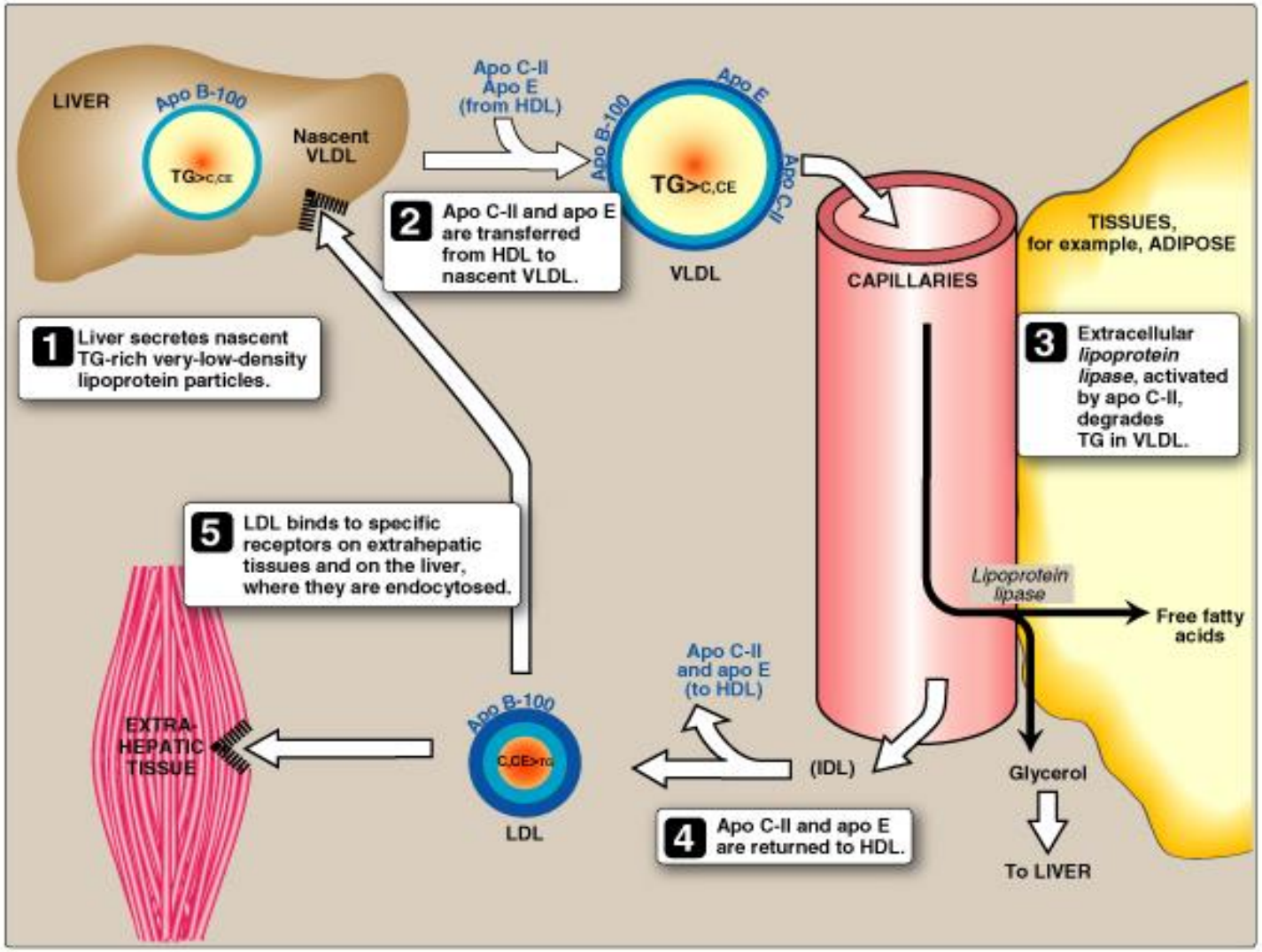
Compared to VLDLs:

- It contains only apo B-100
- Smaller size and more dense
- Less TG
- More cholesterol & cholesterol ester

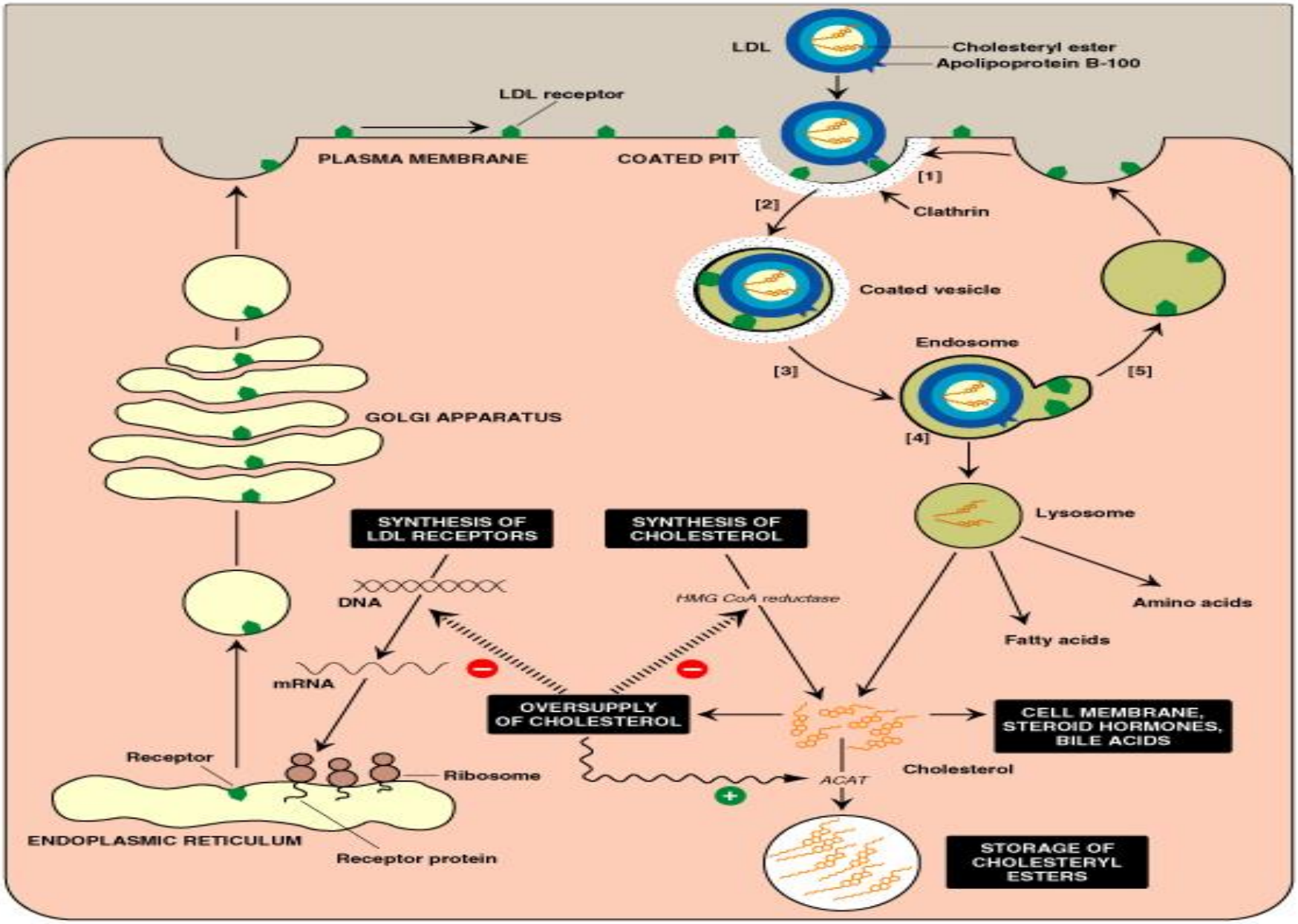
Transport cholesterol from liver to peripheral tissues

Uptake of LDL at tissue level by

- LDL receptor-mediated endocytosis
- Recognized by apo B-100



LDL Metabolism



LDL: Receptor-Mediated Endocytosis

Receptor-Mediated Endocytosis

- **LDL receptor:**
  - **Cell surface glycoprotein**
  - **High-affinity, tightly regulated**
- **LDL/Receptor binding and internalization of the complex by endocytosis**
- **Release of cholesterol inside the cells for:**
  - **Utilization**
  - **Storage as cholesterol ester**
  - **Excretion**
- **Degradation of LDL:**
  - **into amino acids, phospholipids and fatty acids**
- **Degradation or recycling of receptor**

LDL Receptor-Mediated Endocytosis: Regulation

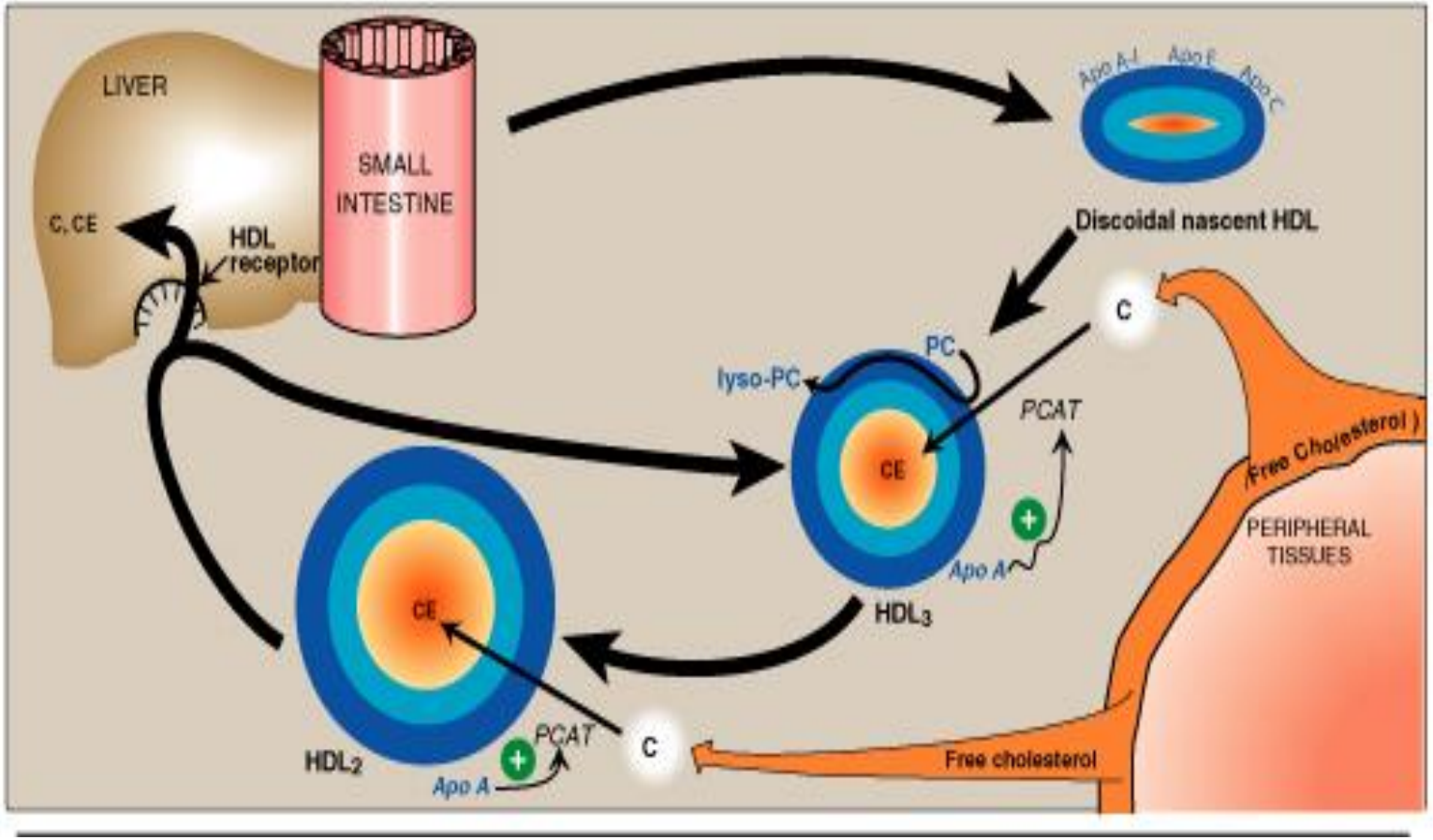
Down-regulation:

- 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 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, the HDL_3 collects cholesterol (C)**
  - **Then, C is converted to CE (C- ester)**
  - **The HDL_2 is the spherical mature particle**

Functions of HDL

- **Reservoir of apoproteins**
  e.g., Apo C-II and E to VLDL
- **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)
- **Esterification of cholesterol:**
  Enzyme:PCAT/LCAT
  Activator: Apo A-I
  Substrate: Cholesterol, Co-substrate: PC
  Product: Cholesterol ester (& Lyso-PC)
- **Reverse cholesterol transport**

Why Is HDL a Good Cholesterol carrier?

- **Inverse relation between plasma HDL levels and atherosclerosis …. How?**
- **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 steroidogenic cells by scavenger receptor class B (SR-B1)

  Selective transfer of cholesterol ester into these cells

  Release of lipid-depleted HDL_3

Atherosclerosis

Pathogenesis:

Modified (oxidized) LDL … Oxidative stress

Uptake of oxLDL by macrophage scavenger receptor:

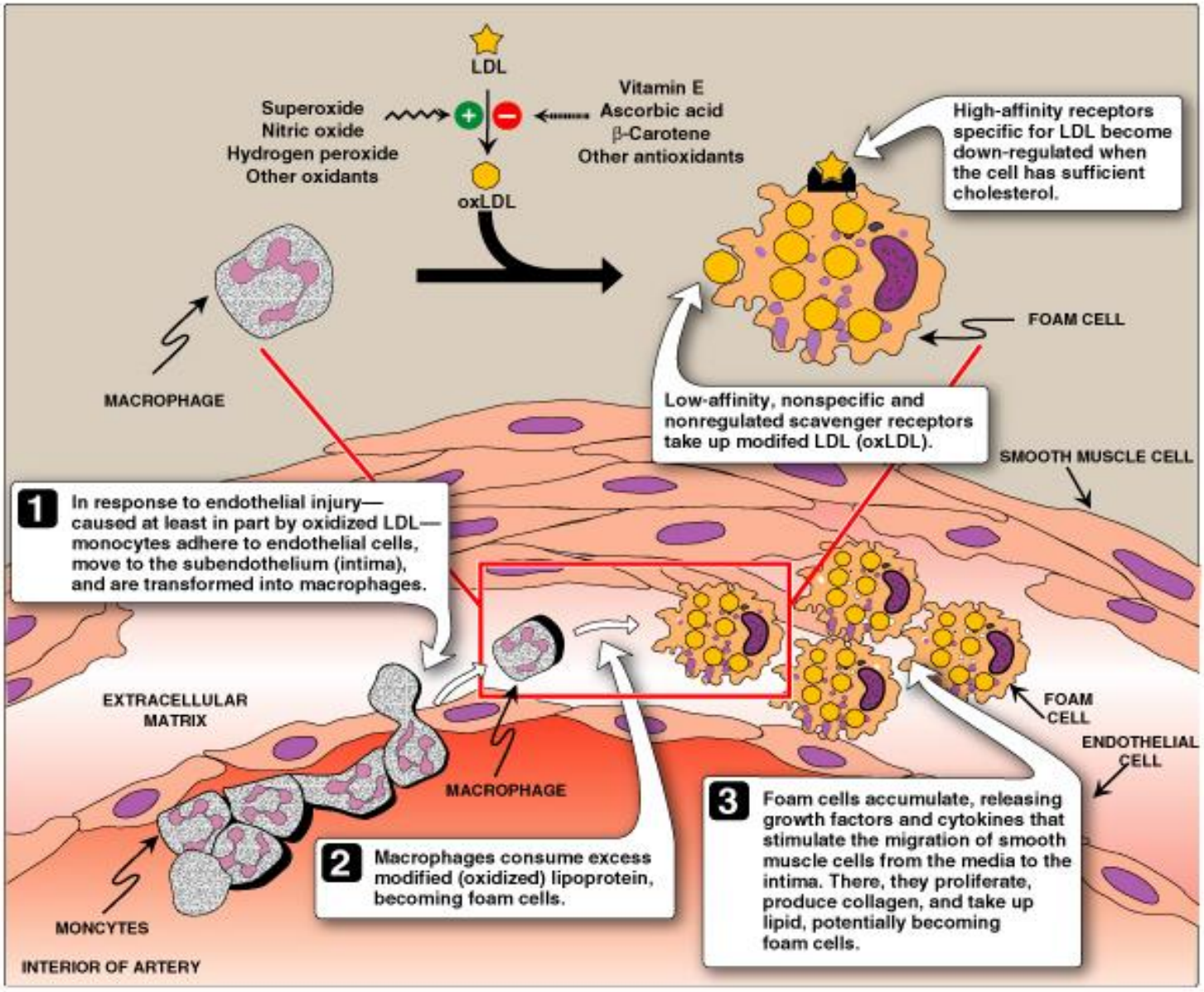
Scavenger receptor class A (SR-A)

Low-affinity, non-specific receptor

Un-regulated receptor

Foam cell transformation

Atherosclerotic plaque formation



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)

Type IIa Hyperlipoproteinemia (Familial hypercholestrolemia)

- Functional defect of LDL-receptor
- Increase plasma LDL level & therefore, plasma cholesterol level
- Pre-mature atherosclerosis and increased risk for early-onset ischemic heart diseases
- Associated with the presence of tendon xanthomas on hands and ankles

THANK YOU ☺