

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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)

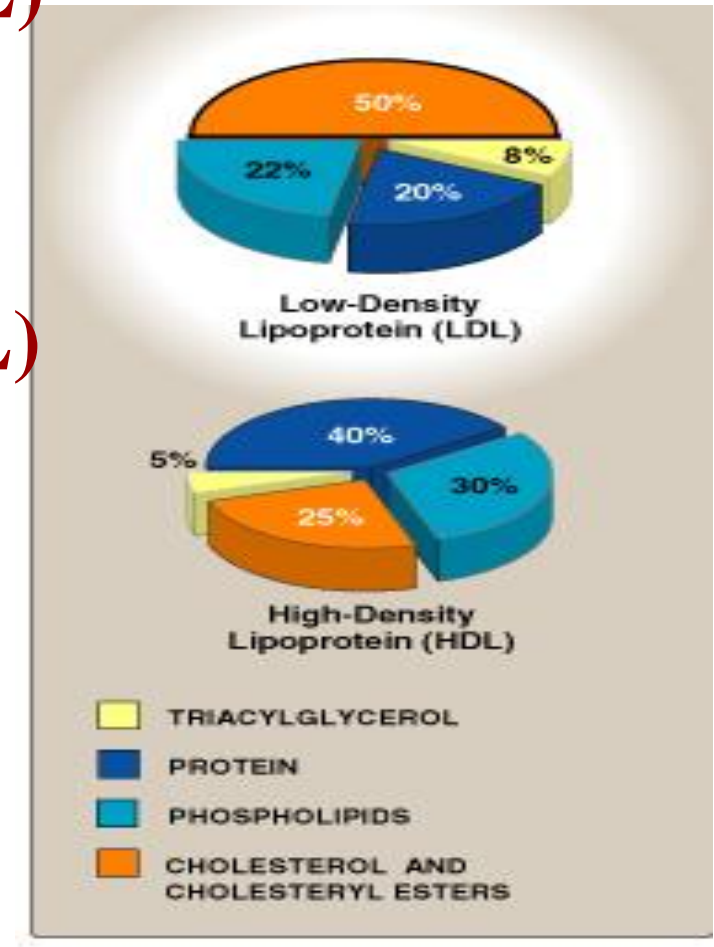
Mostly free cholesterol

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

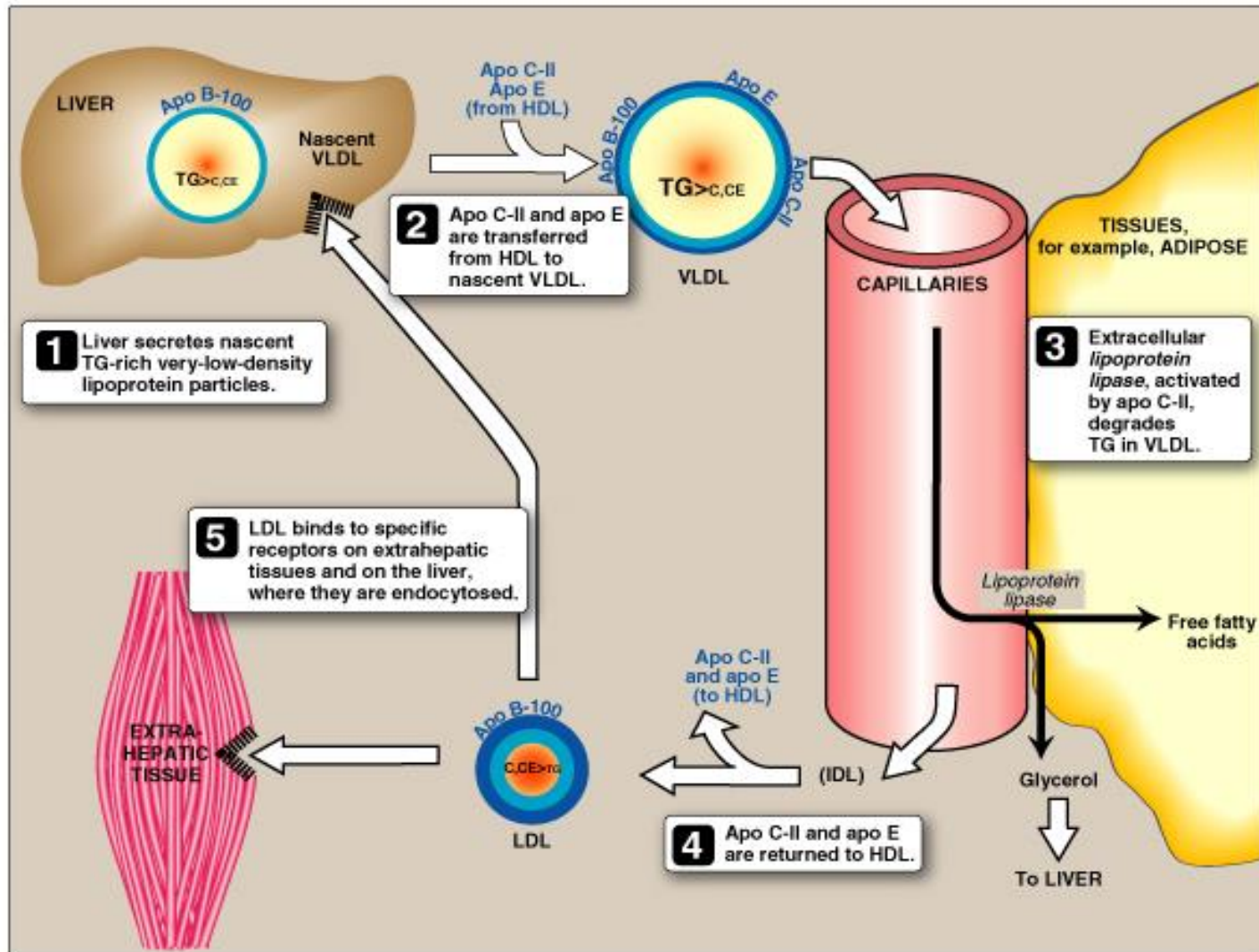
More cholesterol & cholesterol ester

Transport cholesterol from liver to peripheral tissues

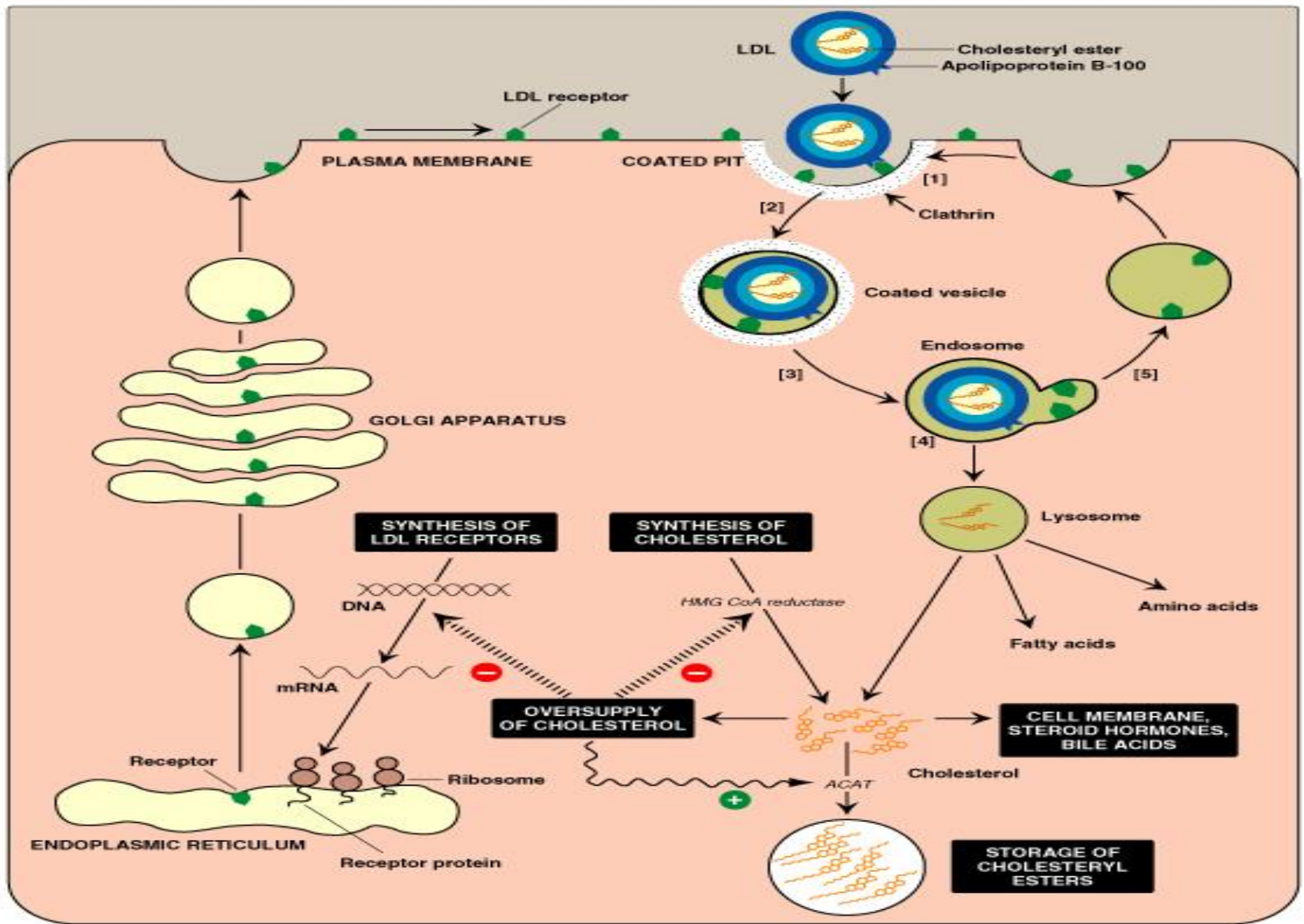
Uptake of LDL at tissue level by

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 receptor 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

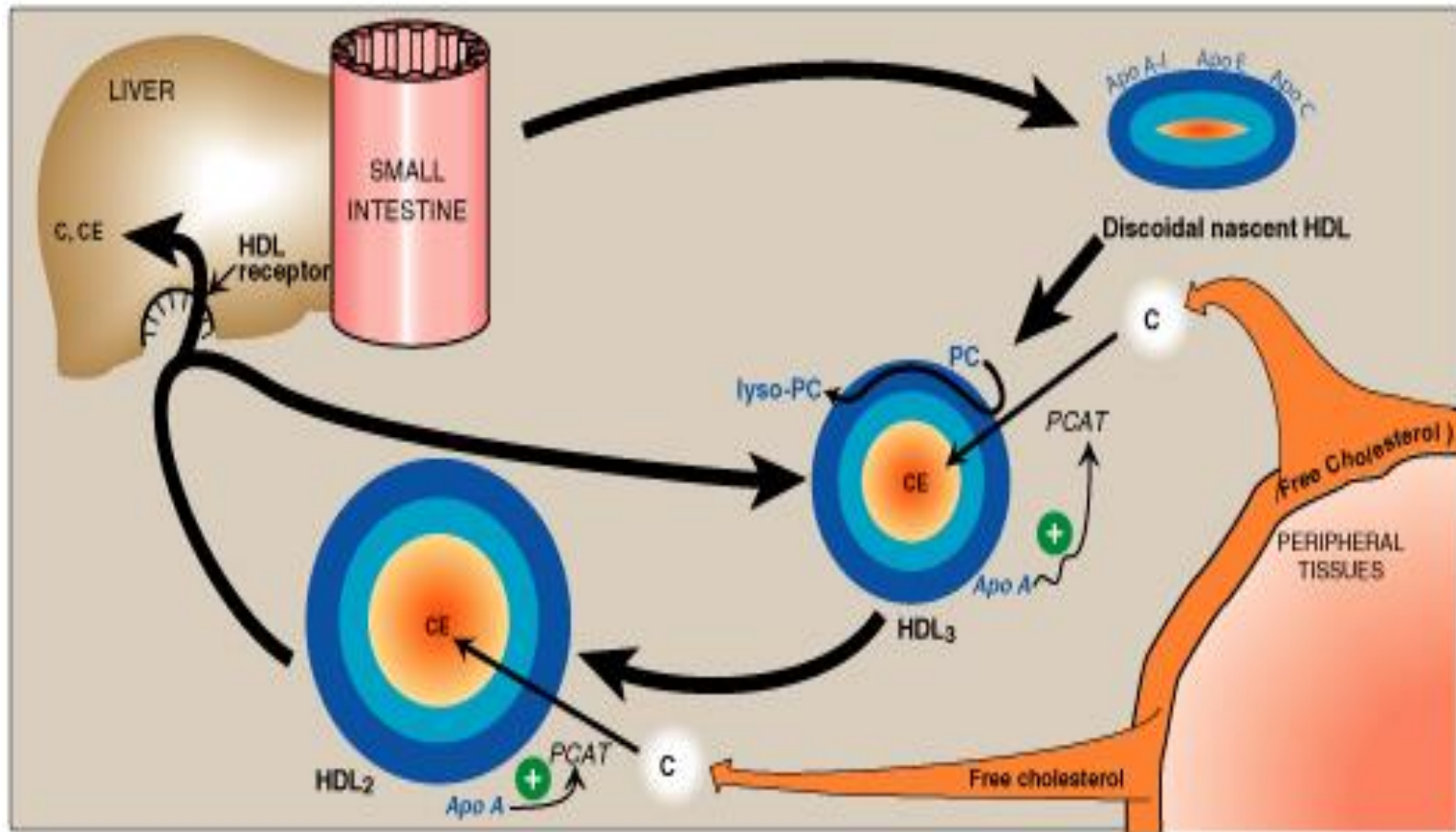
Stimulation of receptor synthesis at gene level

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 (HDL₂):
 - First, the HDL₃ collects cholesterol (C)**
 - Then, C is converted to CE (C- ester)**
 - The HDL₂ 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 solubilizes 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 HDL₃**

Esterification of cholesterol & binding of HDL₂ to liver and steroidogenic cells by scavenger receptor class B (SR-B1)

Selective transfer of cholesterol ester into these cells

Release of lipid-depleted HDL₃

Atherosclerosis

Pathogenesis:

Modified (oxidized) LDL ... Oxidative stress

Uptake of oxLDL by macrophage scavenger receptor:

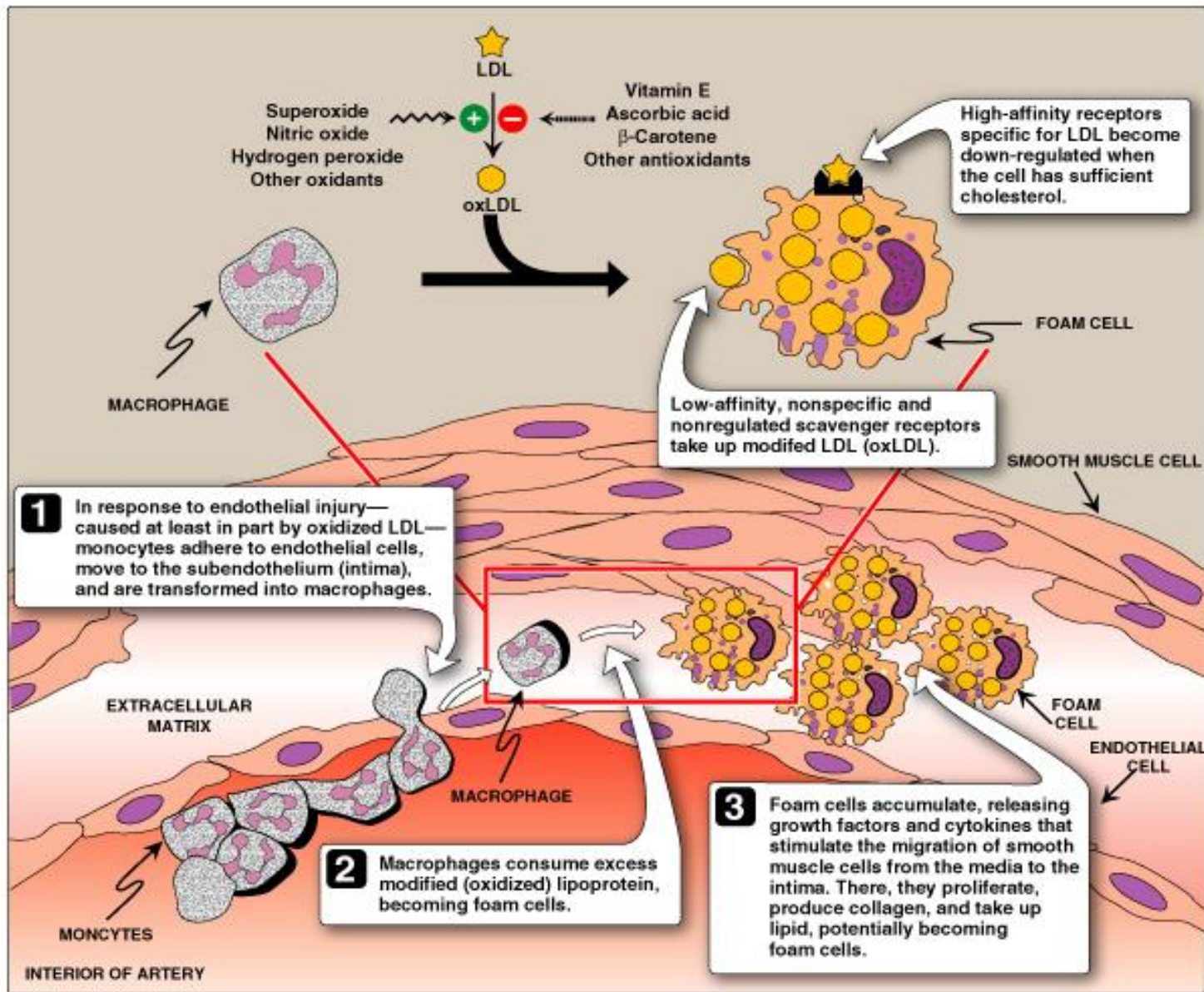
Scavenger receptor class A (SR-A)

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

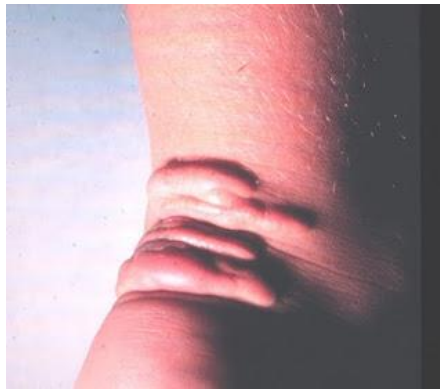
Serum apoprotein levels e.g., apo-B

LDL-related Diseases

Hyperlipoproteinemia:
Type IIa Hyperlipoproteinemia
(Familial hypercholesterolemia)

Type IIa Hyperlipoproteinemia (Familial hypercholesterolemia)

- **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 😊