Lipoproteins and Atherosclerosis

Cardiovascular Block

Objectives

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

- Correlate the imbalance in lipoprotein metabolism with the development of atherosclerosis
- Understand the functions and metabolism of LDL and HDL cholesterol
- Describe the receptor-mediated endocytosis of LDL and its regulation
- Recognize how LDL is considered a bad cholesterol whereas HDL a good cholesterol
- Understand the biochemistry of atherosclerosis and its laboratory investigations
- Discuss the role of lipoprotein(a) in the development of heart disease

Overview

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

Overview

Cholesterol homeostasis is a balance between cholesterol transport:

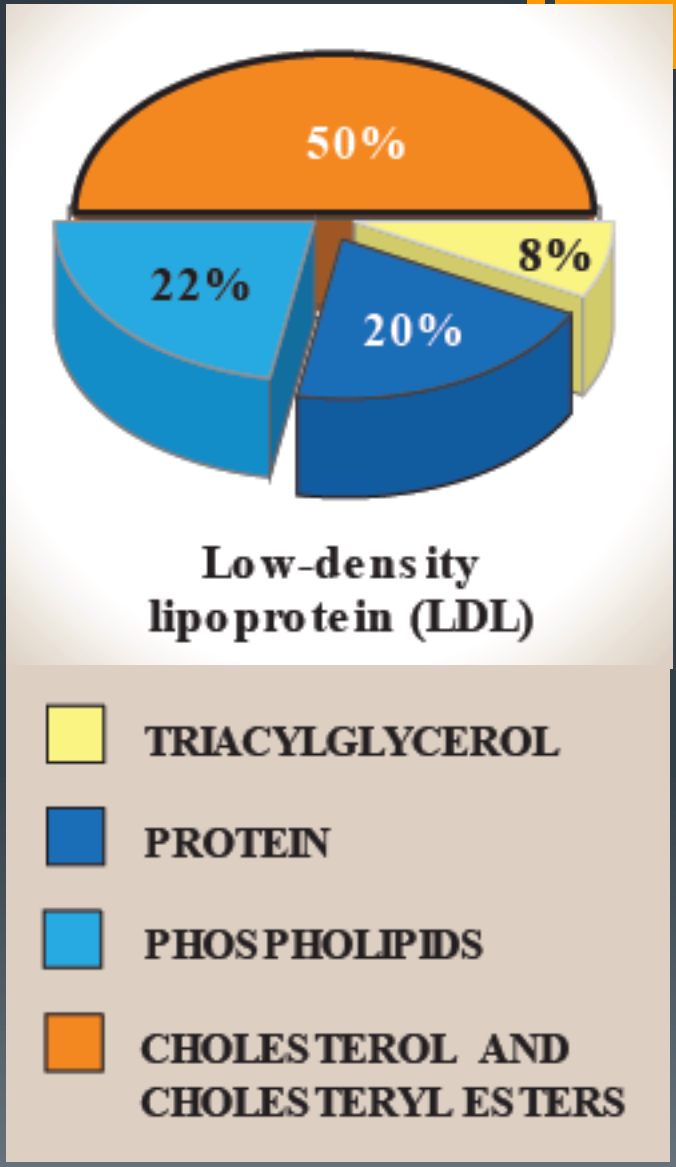
- From the liver to peripheral tissues by LDL
- From peripheral tissues to the liver by HDL

Imbalance in the above leads to:

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

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
- Called receptor-mediated endocytosis

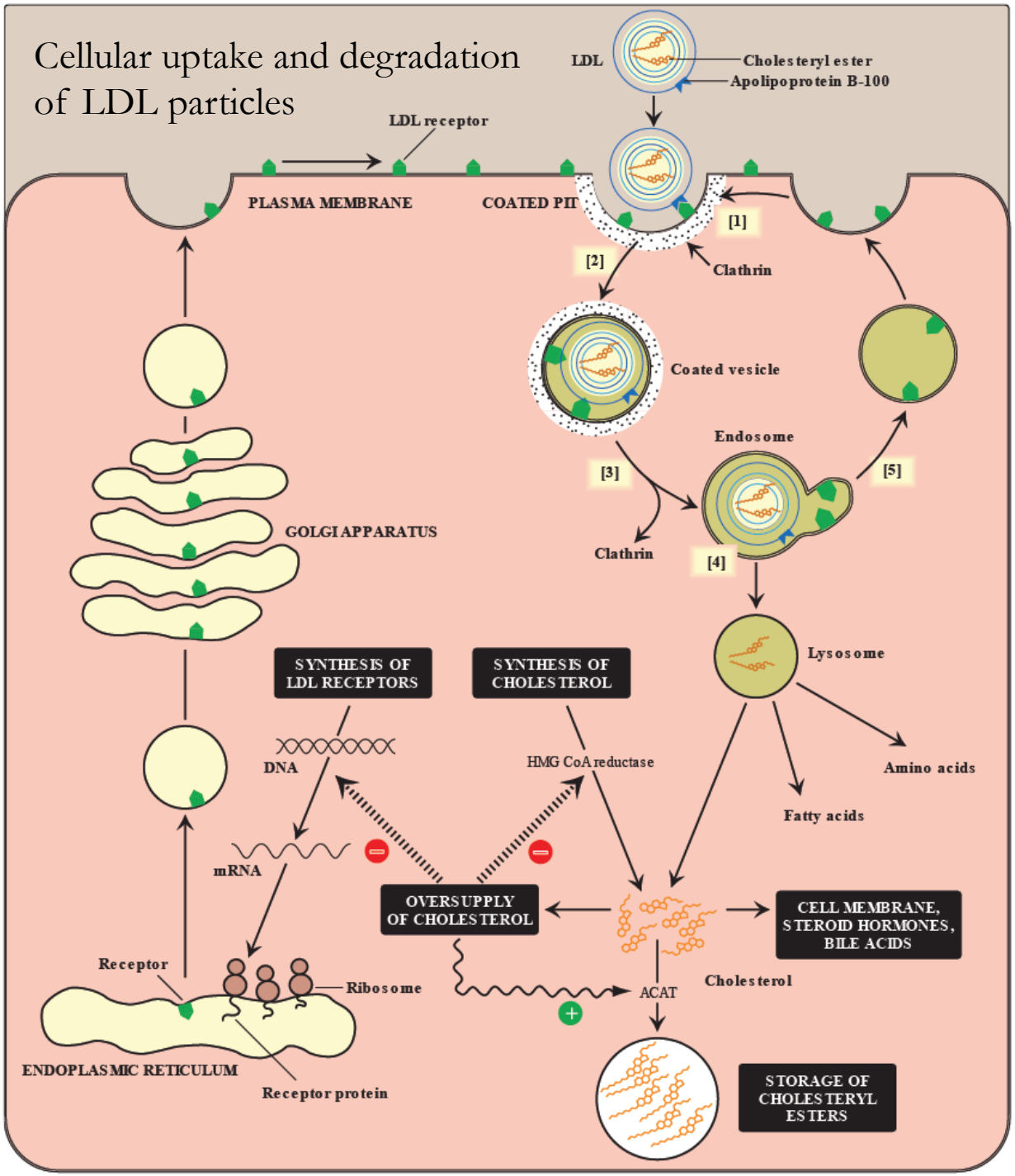


Receptor-mediated endocytosis of LDL particles

Major steps:

- Binding of Apo B-100 to LDL receptor glycoprotein
- Endocytosis
- Endosome formation (LDL vesicle fuses with other vesicles)
- Separation of LDL from its receptor
- Receptor is recycled
- LDL degraded by lysosomes releasing:
  - Free cholesterol, fatty acids, amino acids, phospholipids

Cellular uptake and degradation of LDL particles



Regulation of LDL endocytosis

Down regulation:

- High intracellular cholesterol level causes:
  - Degradation of LDL receptors
  - Inhibition of receptor synthesis at gene level
  - Reduction in cell surface receptors
  - Decreased uptake of LDL by cells
  - Decreased *de novo* synthesis of cholesterol

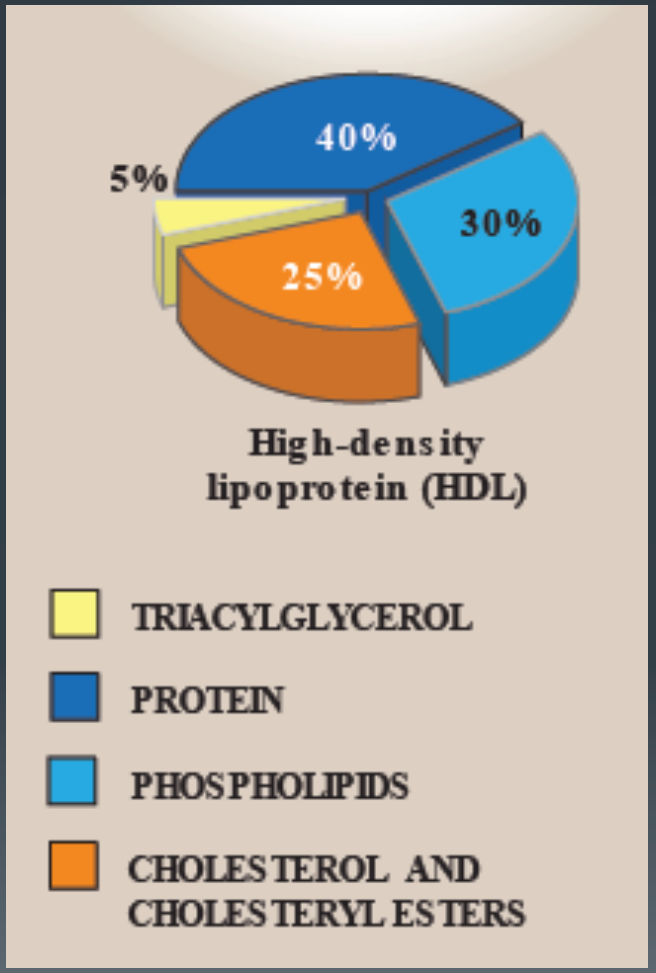
- Up regulation:
- Low intracellular cholesterol level causes:
  - Recycling of LDL receptors
  - Increased receptor synthesis at gene level
  - Increase in cell surface receptors
  - Increased uptake of LDL by cells
  - Increased *de novo* synthesis of cholesterol

LDL is bad cholesterol

- Transports cholesterol to peripheral tissues
- Elevated LDL levels → 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
- Familial hypercholesterolemia
  - Patients are unable to clear LDL from blood
  - Premature atherosclerosis and heart disease

High density lipoprotein (HDL)

- HDL particles mainly contain:
  - Protein, phospholipids, cholesterol, cholesteryl esters
- Produced in the liver and intestine
- Contains Apo A-1, C-2 and E lipoproteins
- Take up cholesterol from peripheral tissues to the liver



High density lipoprotein (HDL)

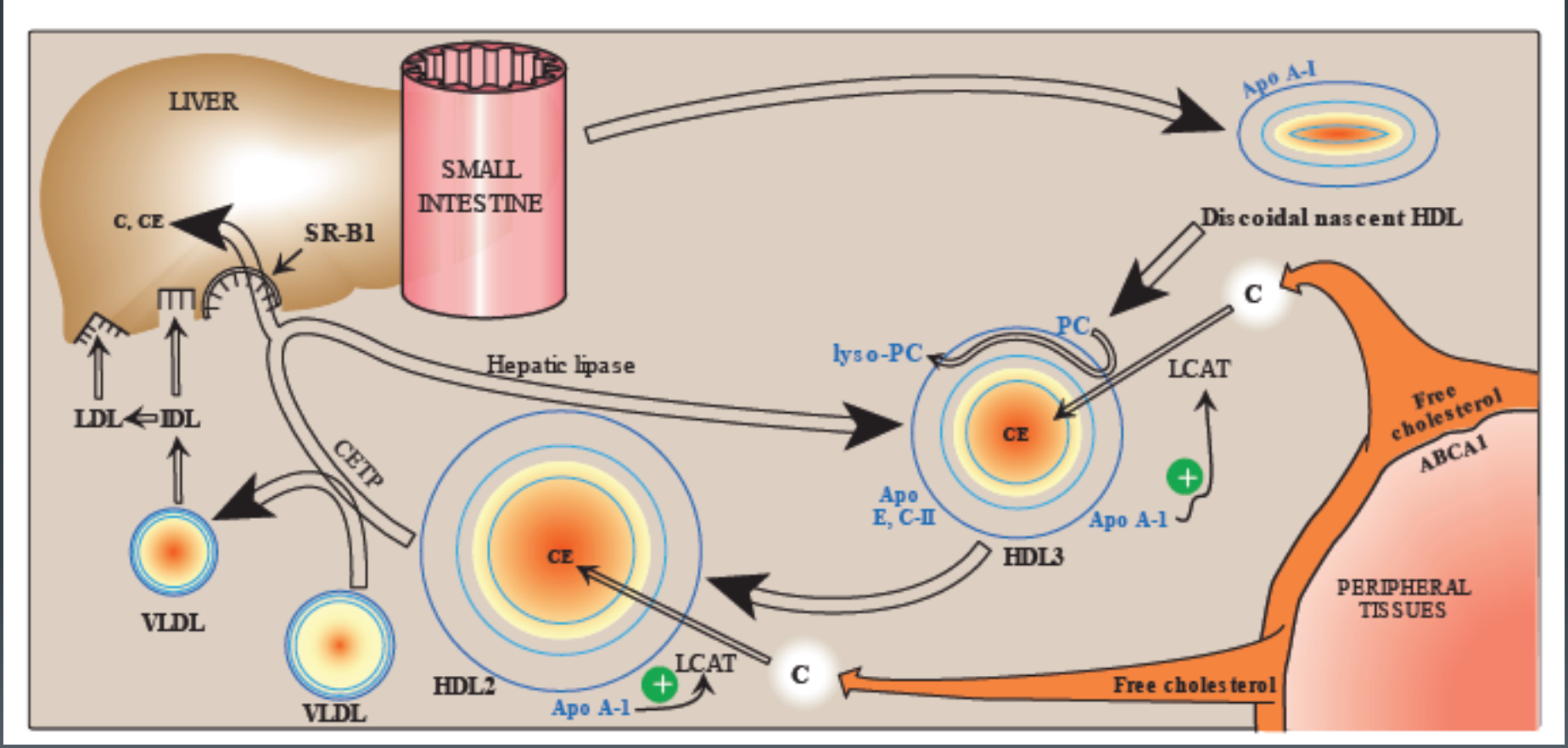
- Nascent HDL:
  - Disk-shaped
  - Contains apo A-I, C-II and E lipoproteins
  - Mainly contains phospholipids

- Mature HDL:
  - Nascent HDL + cholesteryl esters → HDL_3
  - HDL_3 + more cholesteryl esters → spherical HDL_2
  - HDL_2 transfers cholesterol to the liver

Functions of HDL

- Reservoir of apoproteins (Apo C-II and 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

HDL metabolism



HDL is a good cholesterol

- HDL transports cholesterol from peripheral tissues to the liver for degradation
- Reduces cholesterol level in tissues and circulation (reverse cholesterol transport)
- High HDL levels have inverse correlation with atherosclerosis
- Reverse cholesterol transport includes:
  - 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

Atherosclerosis

- LDL uptake by cells is receptor mediated
- Additionally macrophages possess scavenger receptors called scavenger receptor class A (SR-A)
- The macrophages take up chemically-modified LDL by endocytosis

Atherosclerosis

- Chemically-modified LDL contains oxidized lipids and Apo B
- Unlike LDL receptors, the SR-A is not down-regulated in response to high intracellular cholesterol
- Cholesteryl esters accumulate in macrophages converting to foam cells
- Foam cells contribute to plaque formation and atherosclerosis

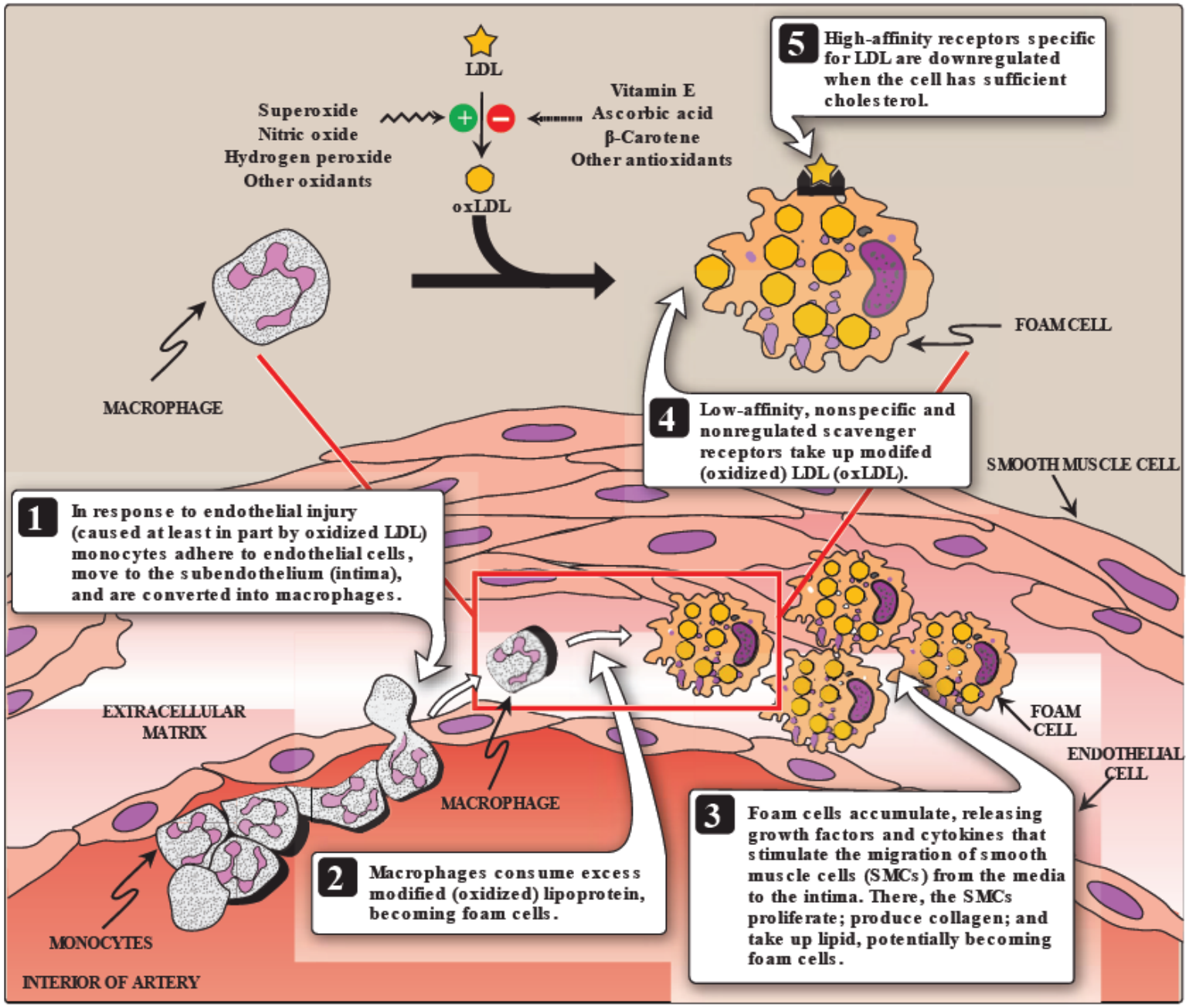


Figure 18.22
Role of oxidized lipoproteins in plaque formation in an arterial wall. LDL = low-density lipoprotein.

Lab investigations of atherosclerosis

- Fasting serum lipid profile:
  - TAG level (reflects chylomicron and VLDL levels)
  - LDL, HDL levels
  - 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
- Contains apo(a) in addition to apo B-100
- High plasma Lp(a) level is associated with increased risk of coronary heart disease

- Circulating levels of Lp(a) are determined by:
  - Genetics (mainly)
  - Diet (trans FAs increase Lp(a) levels)
  - Estrogen (decreases Lp(a) levels)

Lipoprotein (a)

- The apo(a) protein is structurally similar to plasminogen
  - Competes with plasminogen
  - Slows the breakdown of blood clots
  - Triggering heart attack
  - A risk factor for 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

References

- Lippincott's Biochemistry. 6th Edition, Chapter 18, pp. 231-237. Lippincott Williams & Wilkins, New York, USA.