



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

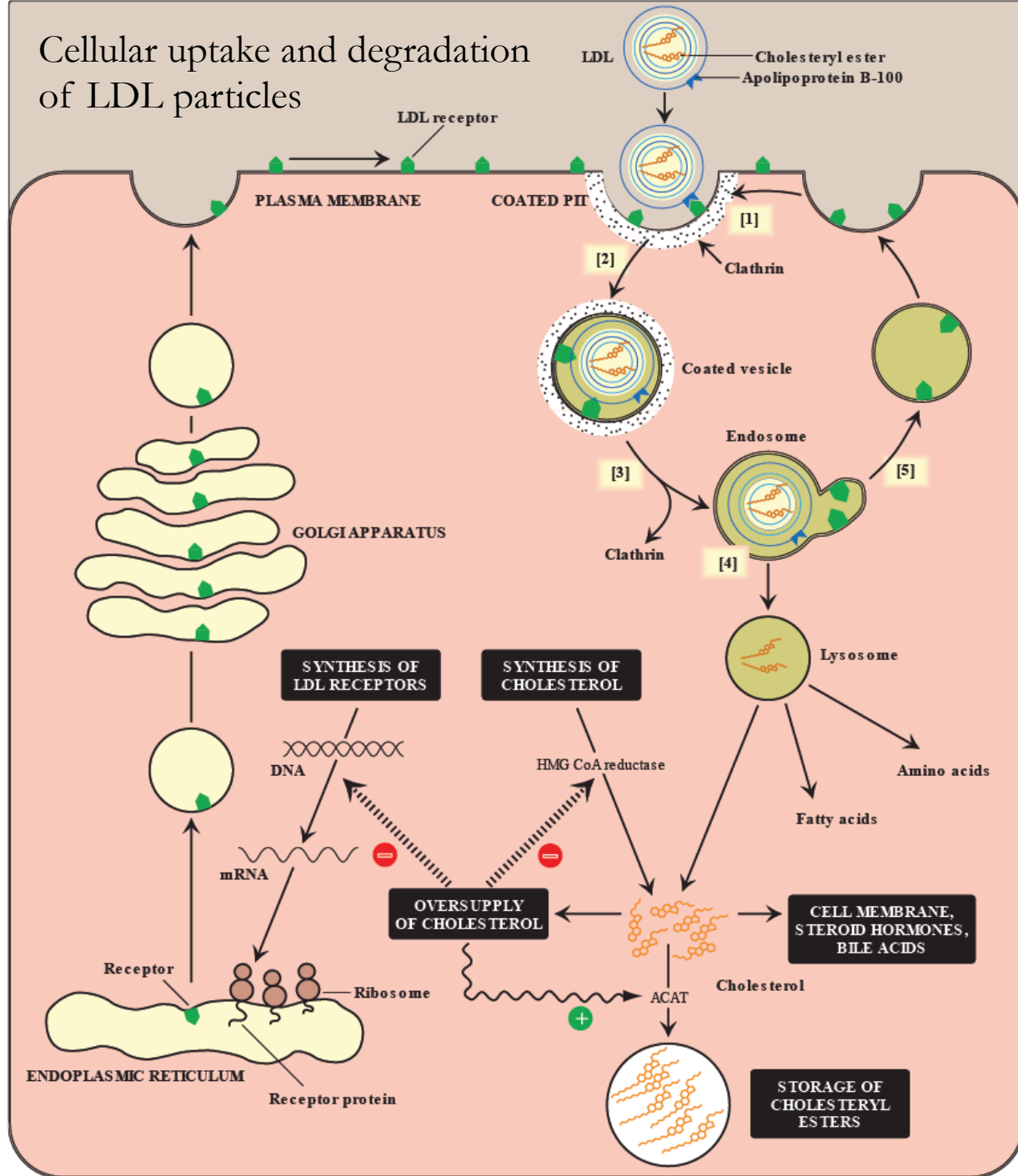
- Receptor-mediated endocytosis of LDL and its regulation
- LDL is bad cholesterol
- High density lipoprotein (HDL) and its functions
- Metabolism of HDL
- HDL is good cholesterol
- Atherosclerosis
- Lipoprotein(a)

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)

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

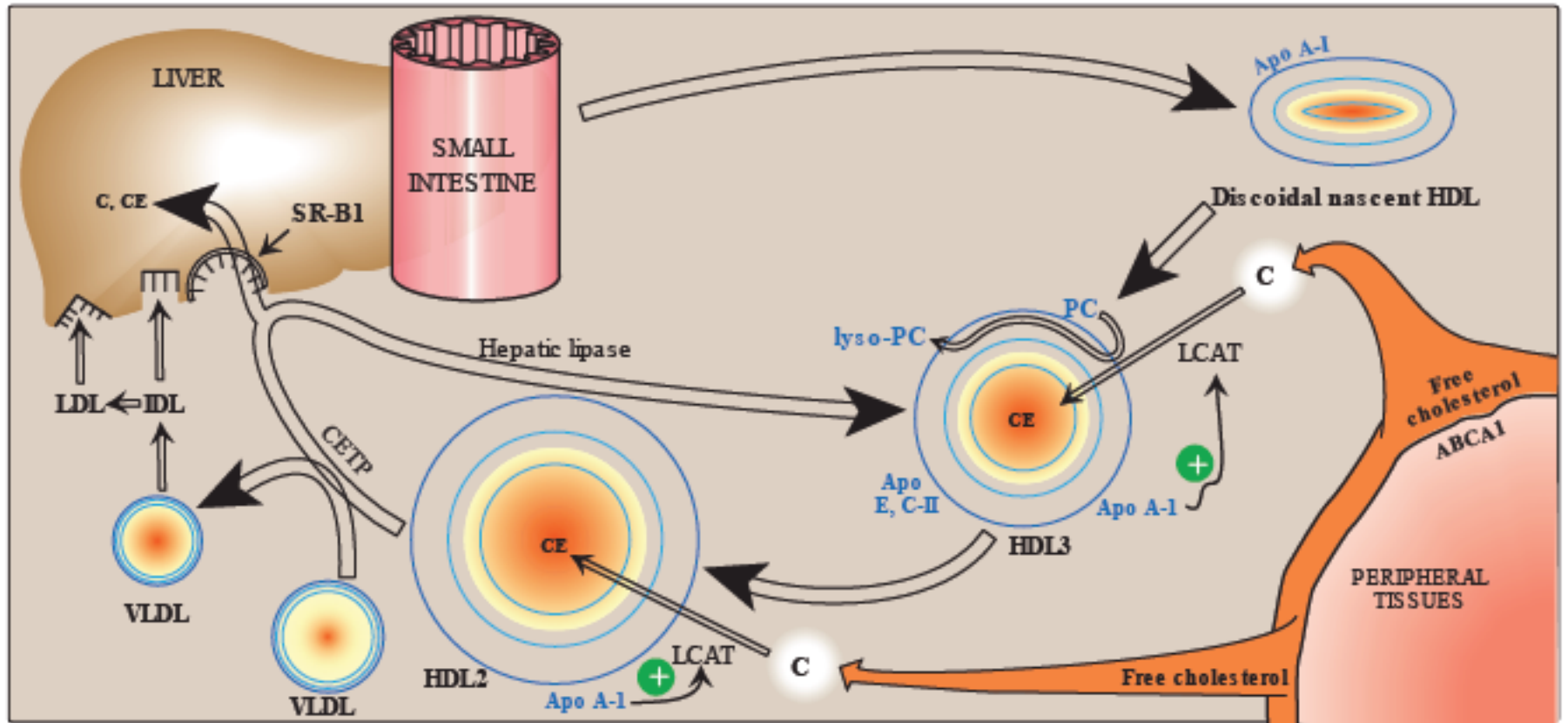
- Mature HDL:
 - Nascent HDL + cholesteryl esters \rightarrow HDL₃
 - HDL₃ + more cholesteryl esters \rightarrow spherical HDL₂
 - HDL₂ transfers cholesterol to the liver

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 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 HDL₂ to liver
 - Release of lipid-depleted HDL₃

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

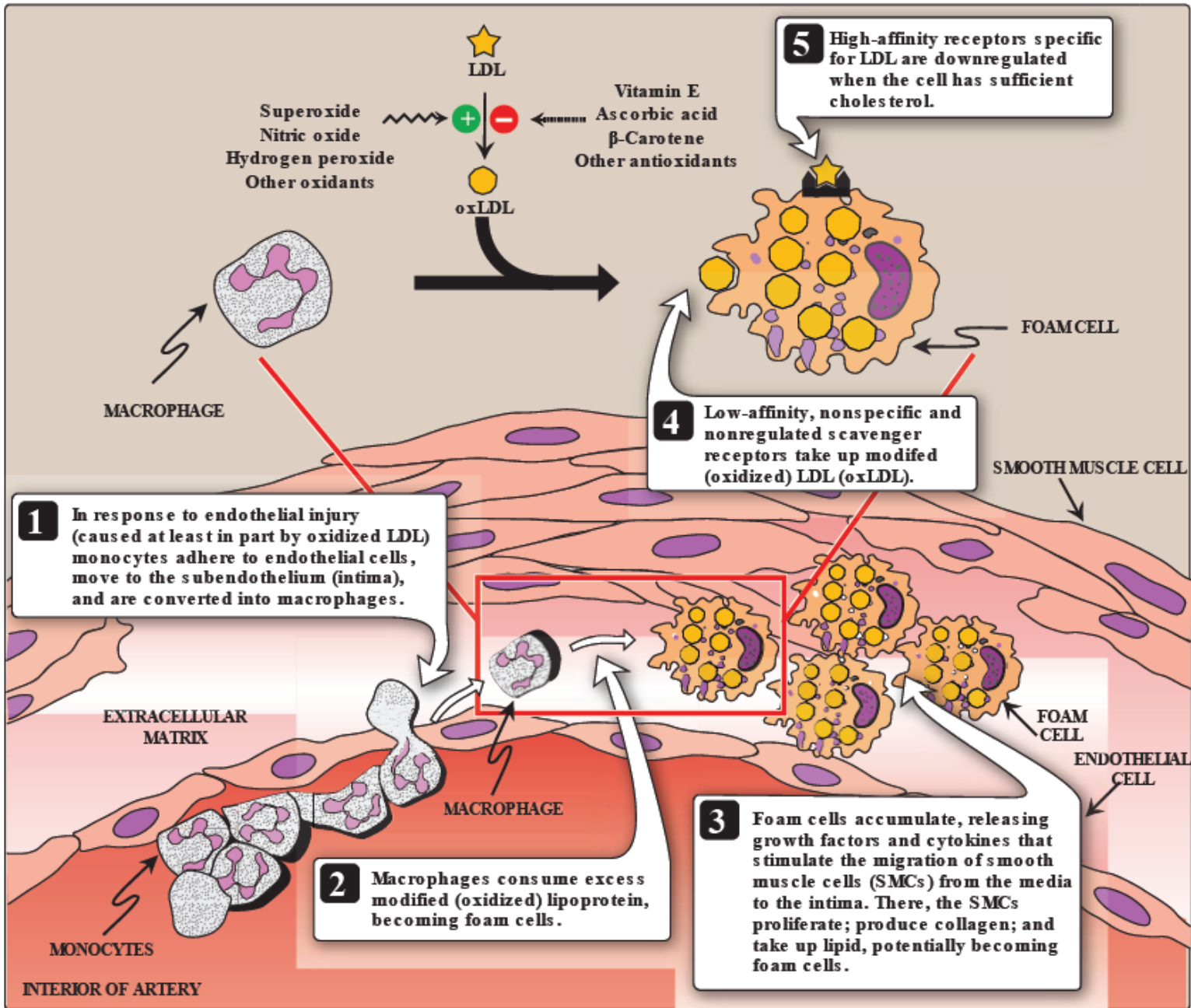


Figure 18.22

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.