PASSION ACADEMIC TEAM

YU - MEDICINE

Cardiovascular System

Sheet# 3 - BIOCHEMISTRY

Lec. Date :

Lec. Title : Plasma Lipoprotein & Cholesterol Synthesis

Written By : Bayan Maqableh

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Plasma Lipoprotein and Cholesterol synthesis

CVS – Biochemistry 3

(RECORD)

- We will talk about cholesterol and cholesterol biosynthesis and regulation of cholesterol biosynthesis.
- Cholesterol is cyclic compound composes from four rings associate with hydrocarbon tail and it contains 27 carbons all derived from acetate.
- Cholesterol structure is characterized by present of branching on carbon 3 with OH and branching of hydrocarbon chain(8 carbon) on carbon 17.

- This is the major structure of cholesterol , and we know that cholesterol is intermediate for different sources of molecules inside human system such as bile salt and it precursor of vitamin D , aldosterone , cortisone and testosterone , all these depend on cholesterol so we will focus mainly on synthesis of cholesterol in human system.

Sources of cholesterol:

- Diet (300mg)
- Denovo synthesis (700 mg)

Biosynthesis of cholesterol

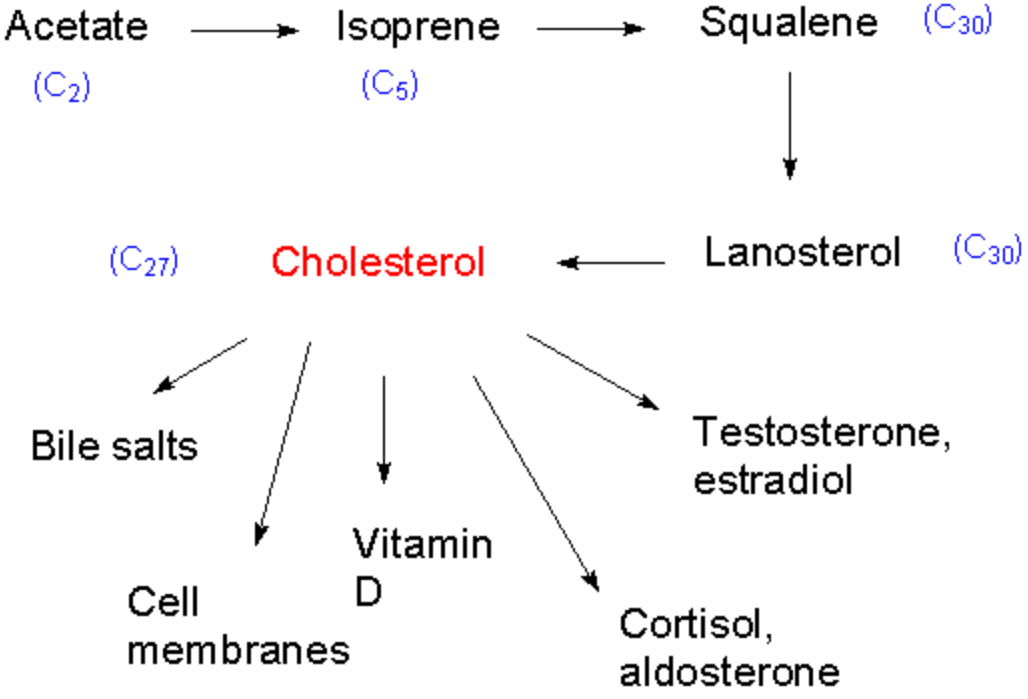
Major site of synthesis is liver (***Denovo synthesis***).

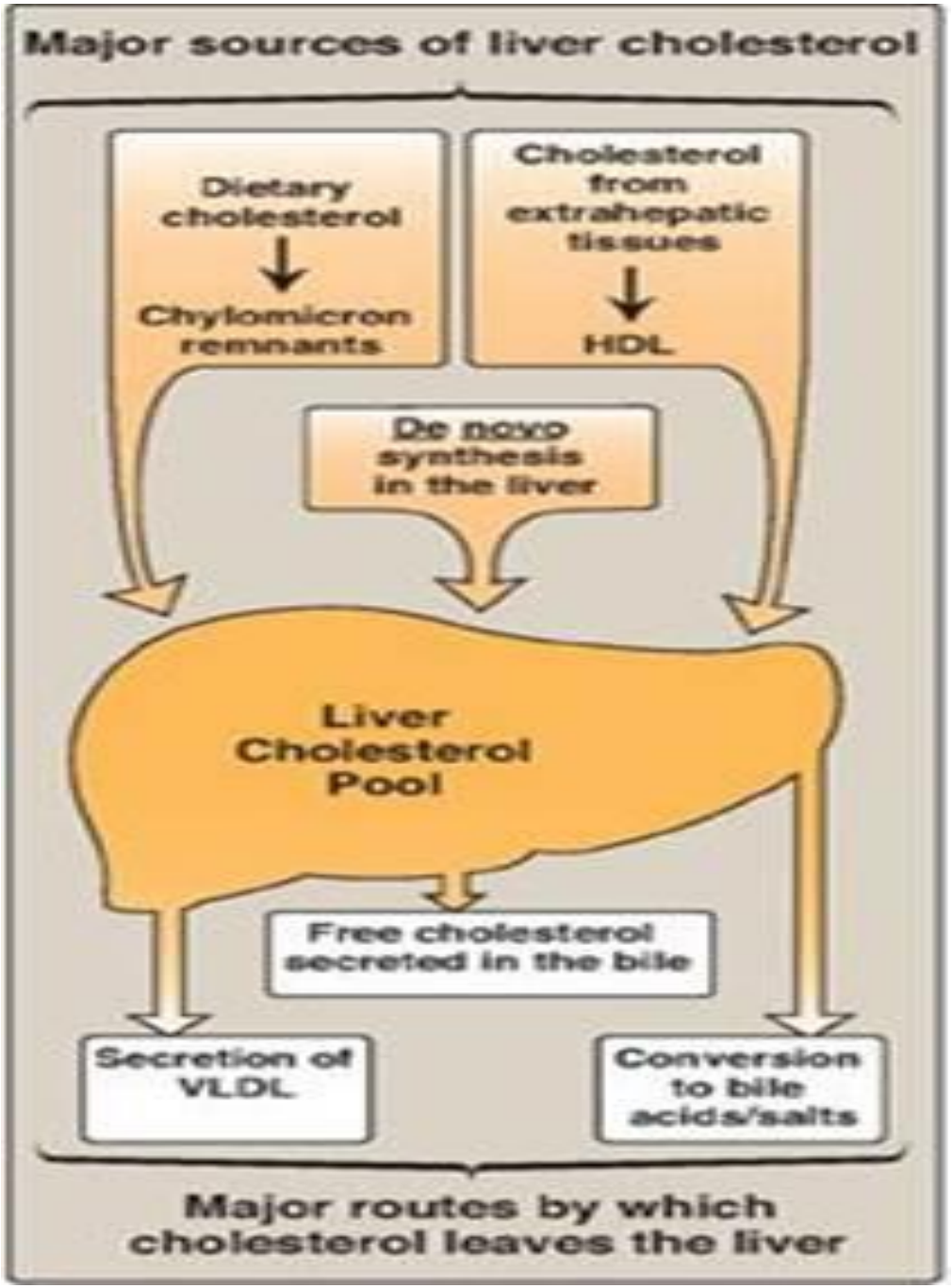
Other sites are adrenal cortex, testis, ovaries and intestine.

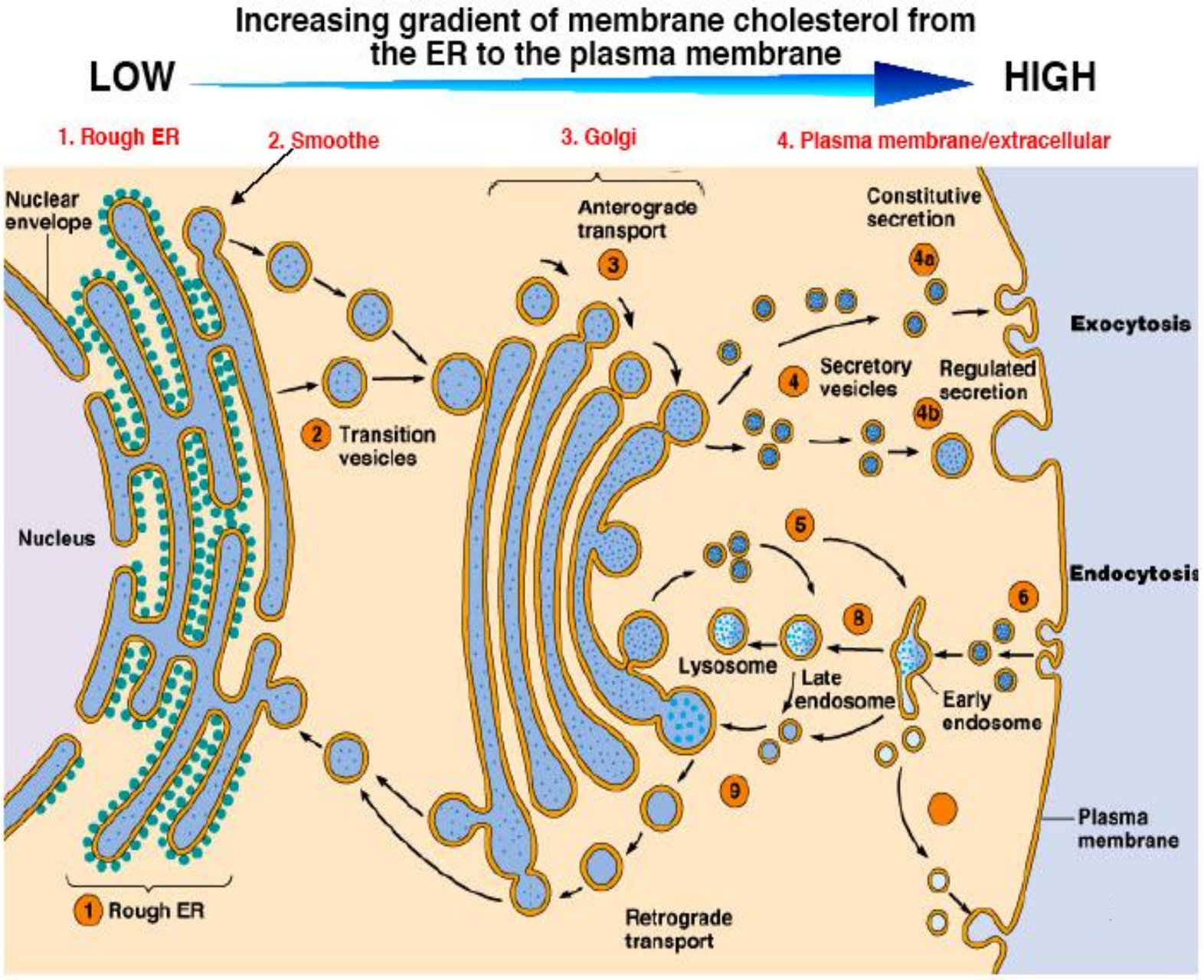
Liver is responsible for 80% of endogenous cholesterol synthesis.

Enzymes involved are partly located in **endoplasmic reticulum** and **partly in cytoplasm**

It represents cholesterol synthesis and fates of it and we will talk about them.




Major sources of liver cholesterol
Dietary cholesterol
Chylomicron remnants
Cholesterol from extrahepatic tissues
HDL
De novo synthesis in the liver
Liver Cholesterol Pool
Free cholesterol secreted in the bile
Secretion of VLDL
Conversion to bile acids/salts
Major routes by which cholesterol leaves the liver



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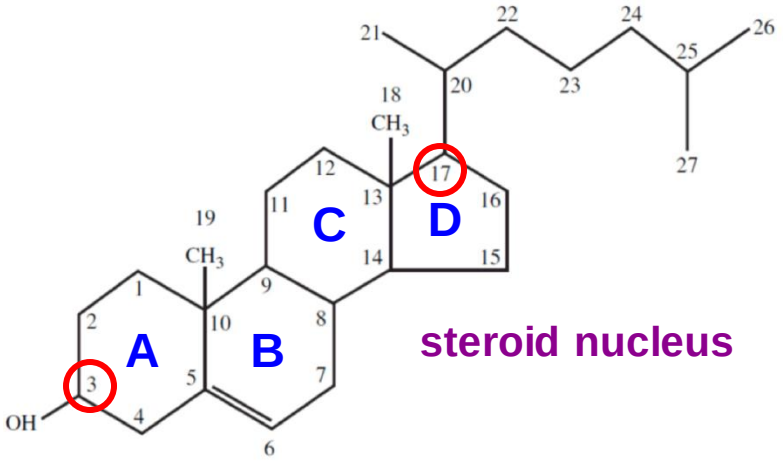
Cholesterol

- 27 carbons all derived from acetate
- C-3 hydroxyl group
- C-17 side chain with 8 carbons

cholesterol

hydrocarbon tail



steroid nucleus

Sources in the body

- synthesized primarily in liver and intestine
- not required in diet
- intestinal uptake from diet

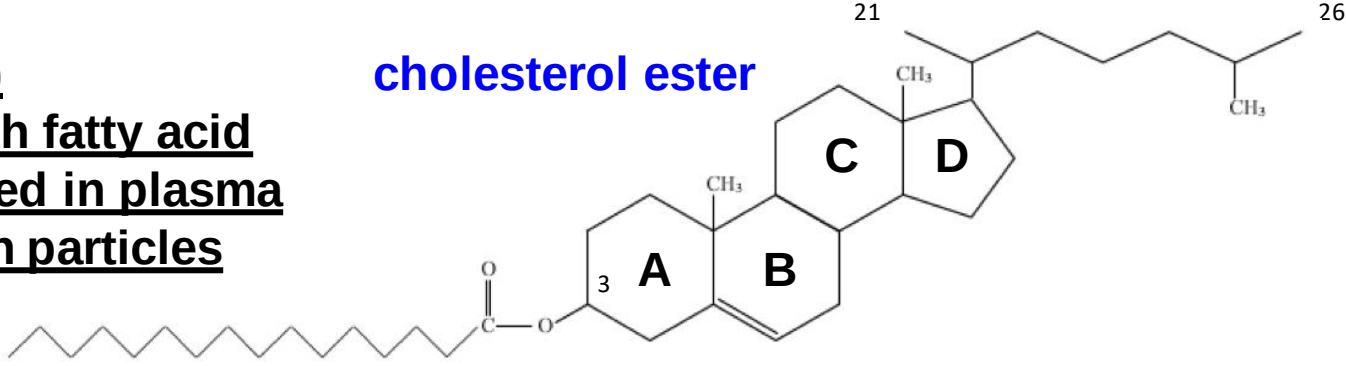
Elimination

- converted into bile acids and bile salts in liver
- stored in gall bladder, secreted into intestine
- small % excreted in feces

Cholesterol esters (CE)

- esterification at C-3 with fatty acid
- primary form transported in plasma
- packaged in lipoprotein particles (e.g. LDL, HDL)

cholesterol ester



fatty acid

Note :

- **Cholesterol esters (CE)**

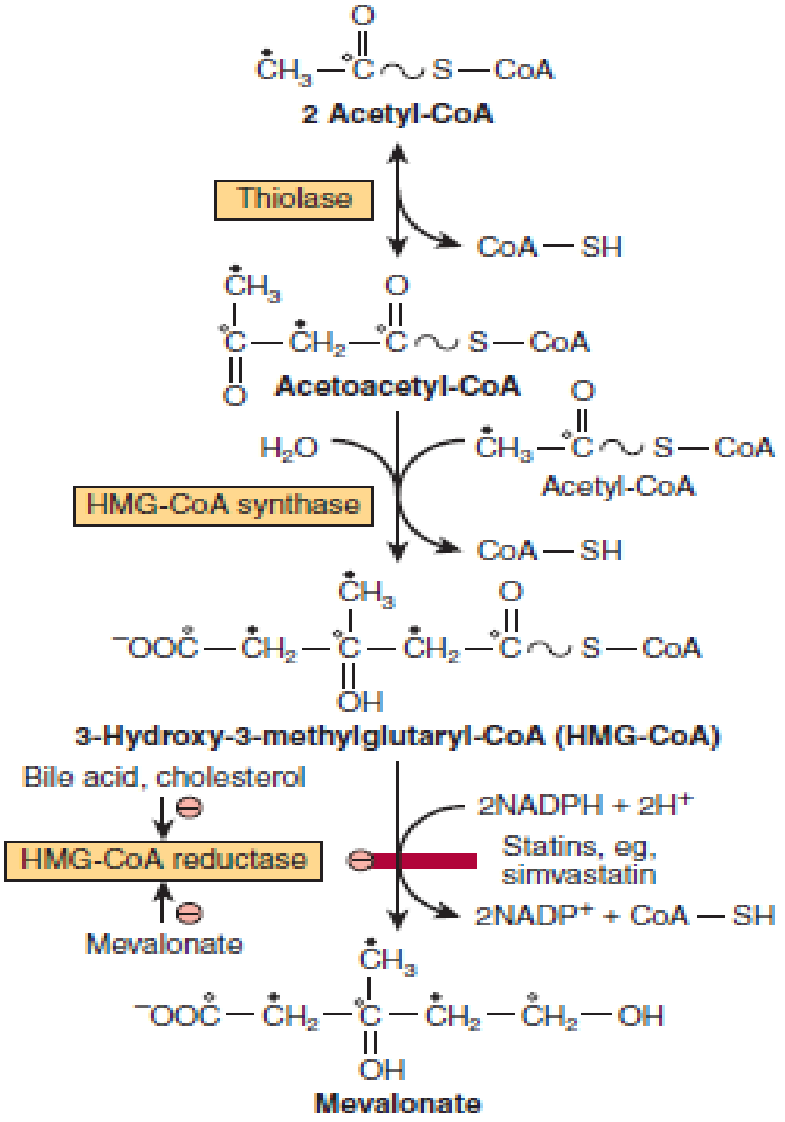
esterification at C-3 with fatty acid, primary form transported in plasma, packaged in lipoprotein particles (e.g. LDL, HDL)

that means cholesterol present as cholesterol ester which is the same structure of cholesterol ,but there is ester bond in C3 with fatty acid.

So, we have to know cholesterol ester is form transported in plasma and it has same structure of cholesterol ,but instead having OH there is having short fatty acid chain at C3.

Cholesterol biosynthesis

The most important topic in this lecture and we will talk about slides (6,7,8,9) together which talk about cholesterol biosynthesis.



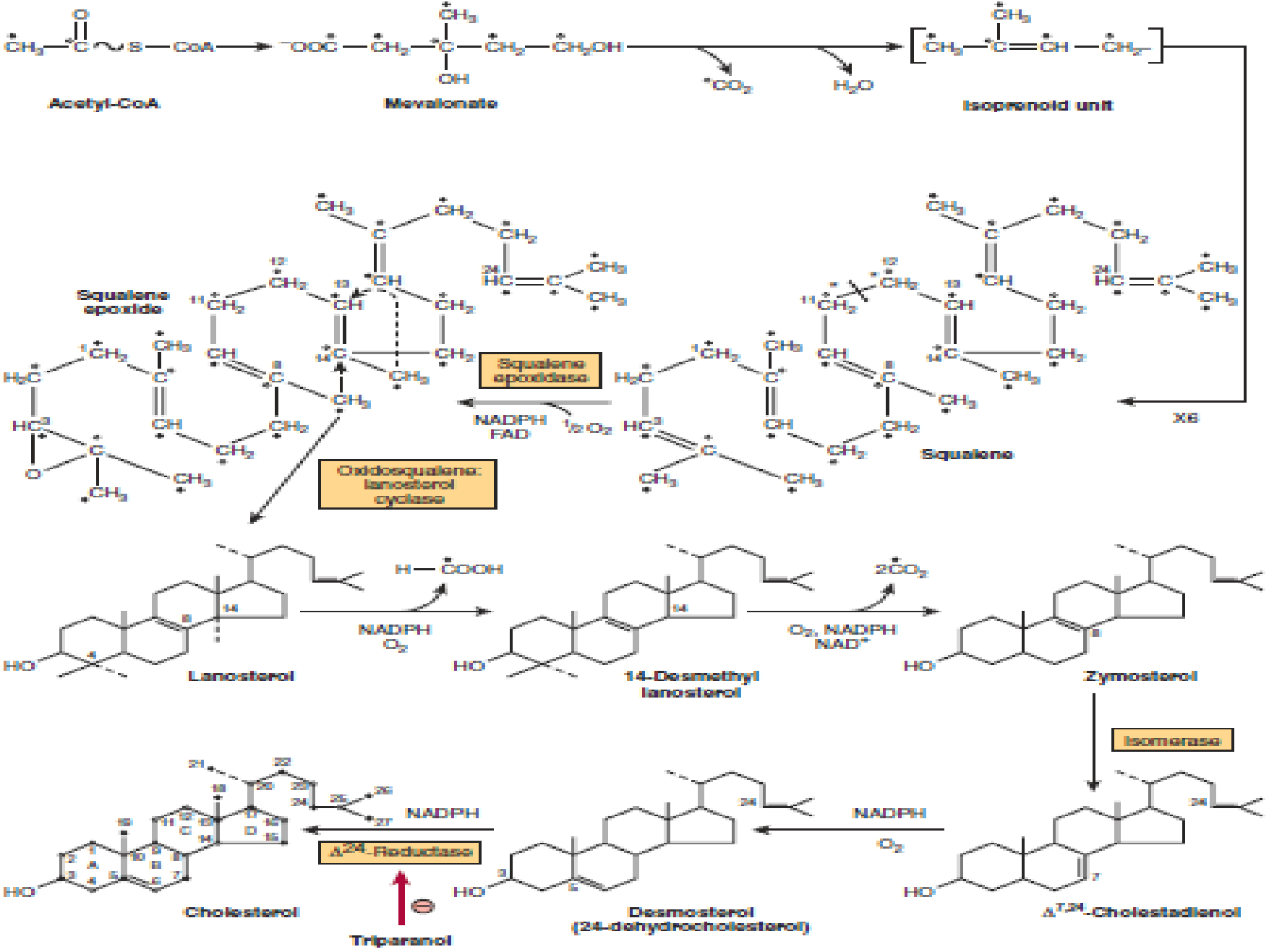
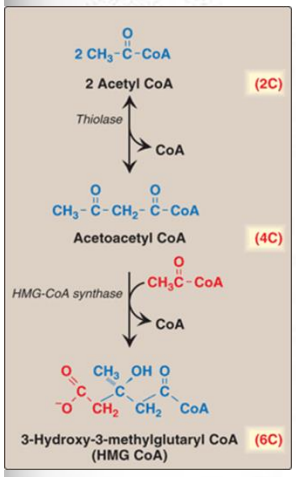


FIGURE 26–3 **Biosynthesis of cholesterol.** The numbered positions are those of the steroid nucleus and the open and solid circles indicate the fate of each of the carbons in the acetyl moiety of acetyl-CoA. (*Refer to labeling of squalene in Figure 26–2.)

Cholesterol biosynthesis

C5 + C5 = C10 (2x)
C10 + C5 = C15
(2x) C15 + C15 = C30



I

Acetyl CoA + Acetoacetyl CoA → HMG-CoA

2 NADPH; HMG-CoA reductase (− cholesterol) → Mevalonate

2 ATP; ATP; CO_2; P_i → Isopentenyl pyrophosphate (C_5 = isoprene unit)

2 isoprenes condense → Geranyl pyrophosphate (C_{10})

C_5 (isoprene unit) → Farnesyl pyrophosphate (C_{15})

2 farnesyl pyrophosphates combine → Squalene (C_{30})

cyclase → Lanosterol

19 steps → Cholesterol

Liver → Bile salts

Endocrine glands → Steroid hormones

II

III

(record “ about cholesterol biosynthesis)

- It is multistep and complicated reaction , there are three major steps we have to memorize them .
- Stage one : Formation of HMG-CoA from Acetyl CoA and acetoacetyl CoA then HMG CoA will convert to mevalonate by HMG CoA reductase enzyme .
- Stage 2 : Formation of isoprene unit which is carbon compound , each molecule of isoprene unit compose from five carbons. First, one isoprene unit (isopentenyl pyrophosphate) then, will be 2 units so C10 then will be addition of one unit and form farnesyl pyrophosphate C15 then there is combination of two farnesyl pyrophosphate C15 that will lead to form squalene C30 .

(cont ..)

Stage 3 :- formation of first cyclic compound in cholesterol synthesis which is lanosterol by convert squalene through cyclase enzyme to cyclic compound and form lanosterol , then there are multistep around 19 and we will not memorize all steps specifically , after 19 steps will be formation of cholesterol which is four rings structure with hydrocarbon at C17 and OH at C3.

(record " some notes about each stage ")

-so, these are 3 stages of cholesterol synthesis in

stage 1 : synthesis of HMG-CoA from Acetyl CoA and acetoacetyl CoA then HMG CoA will convert to mevalonate by HMG CoA reductase enzyme this reaction is completed with the aid of 2NADPH.

Note 1: if there is high cholesterol concentration in the blood stream that will give negative feedback that means if there is high cholesterol there will be inhibition of HMG –CoA reductase so inhibits conversion of HMG CoA to mevalonate .

Note 2 : statins (cholesterol lowering drugs) have similar structure to HMG-CoA so they are competitive inhibitors , so we use them to decrease cholesterol by inhibit conversion of HMG CoA to mevalonate.

- (cont..)

STAGE 2: then multistep occur to form isoprene unit (this multistep reaction need ATP) .

Isoprene unit = C5 , then then will form 2 isoprene then (C10) then, addition of one isoprene unit C15 “farnesyl pyrophosphate , after that combination of 2 farnesyl pyrophosphate lead to form squalene C30

C5 + C5 = C10 (2x)
C10 + C5 = C15
(2x) C15 + C15 = C30

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- **Stage 3 :**formation of first cyclic compound in cholesterol synthesis which is lanosterol by convert squalene through cyclase enzyme to cyclic compound and form lanosterol, after that there are 19 steps lead to formation of cholesterol.
- Cholesterol may go to the liver and convert to bile salt or to endocrine glands and use in steroid hormones steroid production , and part of it will be freely in the plasma as cholesterol ester as we said previously.

Cholesterol biosynthesis

1. The multiple rings of cholesterol are made 'from scratch' by linking carbons together. And all this starts by linking a 2-carbon Acetyl-CoA to a 4-carbon Acetoacetyl-CoA, making a 6-carbon HMG-CoA molecule (HMG = 3-hydroxy-3-methylglutaryl-CoA).

2. The enzyme HMG-CoA Reductase then catalyzes the conversion of HMG-CoA into Mevalonate.

3. Mevalonate is converted to isopentenyl pyrophosphate (IPP), with the concomitant loss of CO_2.

4. IPP is converted to squalene

5. Squalene is converted to Lanosterol.

6. Lanosterol is converted to cholesterol.

نفس الحكي ملخّص على شكل نقاط

Regulatory enzyme is HMG –CoA reductase (HMGR).

- Glucagon and epinephrine negatively affect cholesterol biosynthesis by increasing the activity of the inhibitor of phosphoprotein phosphatase inhibitor-1 (PPI-1).
- Insulin stimulates the removal of phosphates and, thereby, activates HMG-CoA reductase activity.

Very important topic we will talk about it in details.

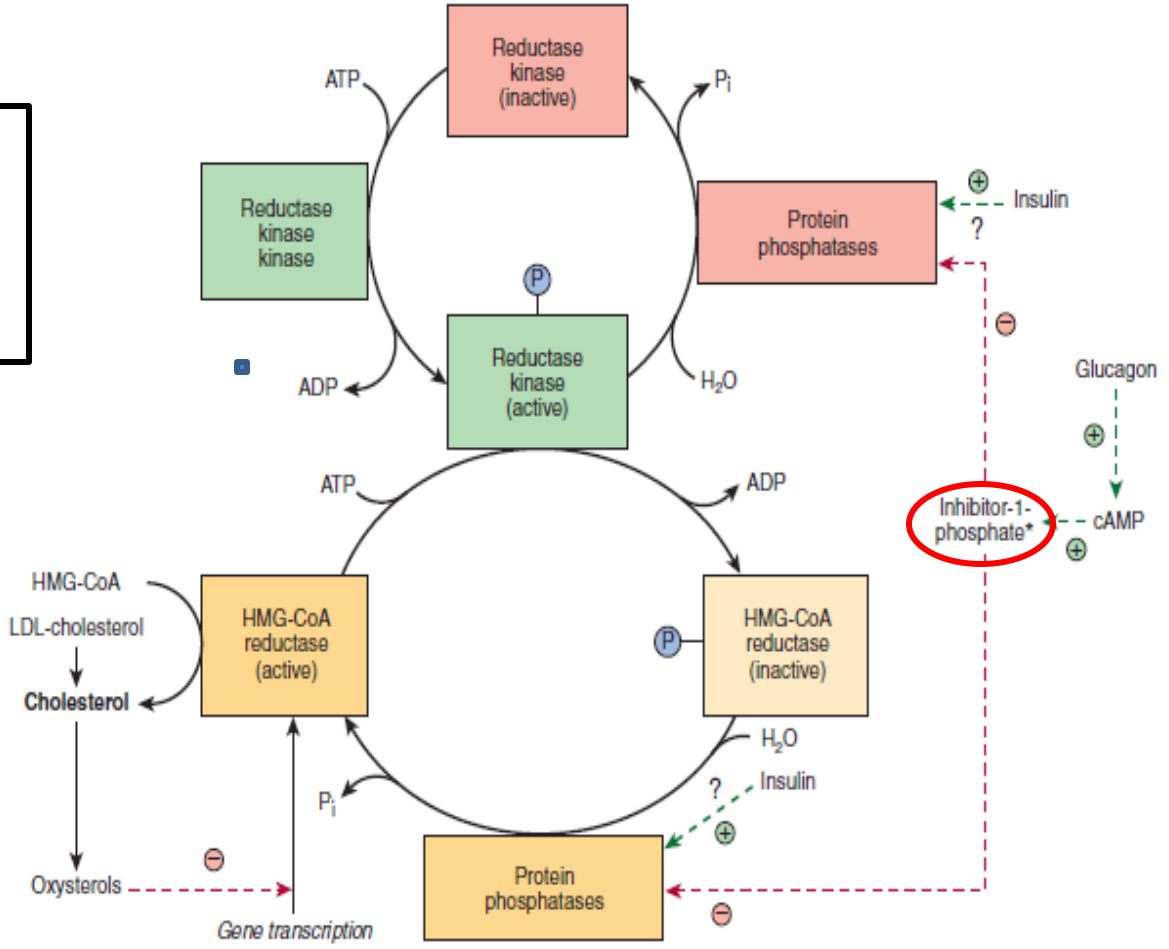


FIGURE 26–4 **Possible mechanisms in the regulation of cholesterol synthesis by HMG-CoA reductase.** Insulin has a dominant role compared with glucagon. (*See Figure 19–6.)

The rate of *synthesis of HMG –reductase* *mRNA* is controlled by the *sterol regulatory element binding protein (SREBP).*

The enzyme is controlled by three distinct mechanisms:

- Control of gene expression.
- Rate of enzyme degradation.
- Phosphorylation-dephosphorylation.

- **Active form** –dephosphorylated form.
- **Inactive form** –phosphorylated form.
- HMGR is phosphorylated by AMP-regulated protein kinase (**AMPRK**).
- AMPRK itself is activated *via* phosphorylation.
- The phosphorylation of AMPRK is catalyzed by kinase.

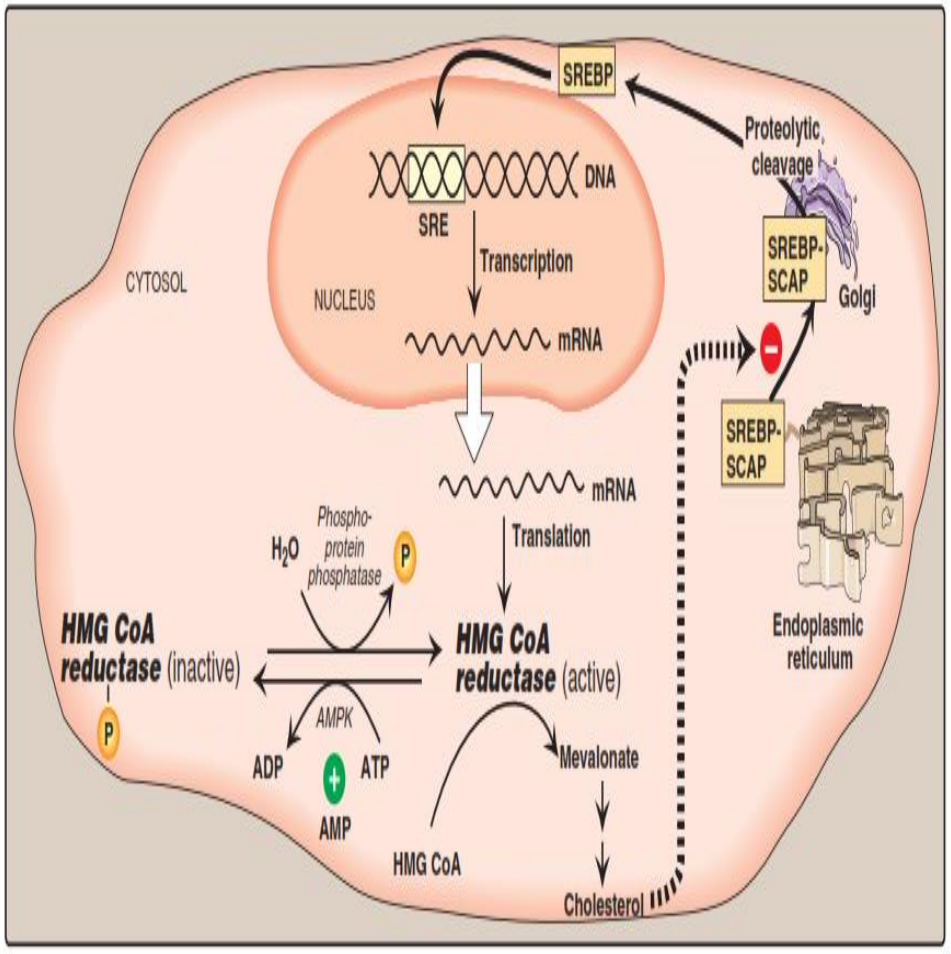


Figure 18.6

Regulation of *HMG CoA reductase*. SRE = sterol regulatory element; SREBP = sterol regulatory element-binding protein; SCAP = SREBP cleavage–activating protein.

- (record)

- We will focus in regulation , how body regulate cholesterol biosynthesis?
- There are three different machinery to regulate cholesterol synthesis by control HMGR enzyme :

1 control of gene expression.

2 rate of enzyme degradation.

3 phosphorylation-dephosphorylation

Important figure explains regulation of HMG CoA reductase and we will talk about it in details .

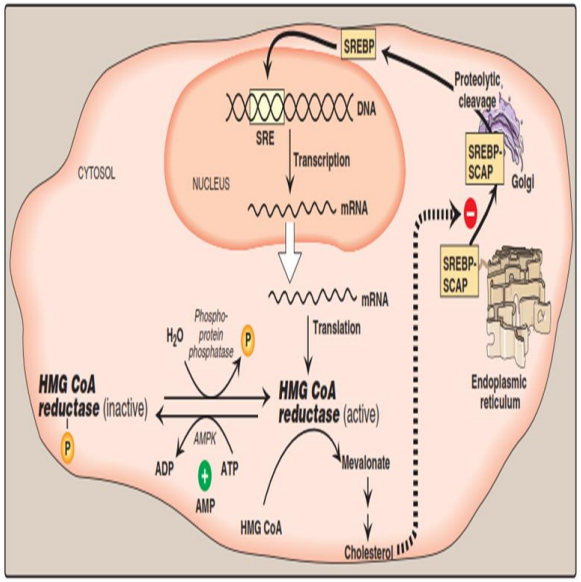


Figure 18.6
Regulation of *HMG CoA reductase*. SRE = sterol regulatory element; SREBP = sterol regulatory element-binding protein; SCAP = SREBP cleavage–activating protein.

(record " about figure")

- Cell has nucleus inside it there is DNA and there is SRE (sterol regulatory element) gene , sterol regulatory element binding protein SREBP "synthesize in ER " will bind with SRE and this lead to activate transcription , activation transcription lead to more production of mRNA "gene product" which give you more translation of protein , protein in this case is HMG CoA reductase , So gene that responsible for production HMGR is SRE, SREBP will bind with SRE lead to activation transcription, more transcription, more translation , more active protein which is HMGR, if there is more active form of HMG COA reductase lead to convert of HMG CoA to mevalonate …. Etc.
- This is the first mechanism of cholesterol synthesis.

- (cont..)
- Second process : rate of enzyme degradation
- There is SREBP- SCAP

SCAP “SREBP cleavage activation protein “is regulatory protein needed for proteolytic cleavage of SREBP , if there is low cholesterol SCAP bind with SREBP and mediates transport of it from ER to Golgi then SREP proteolytically cleaved then go to nucleus to bind with SRE … etc . But if there is high cholesterol that will inhibit (SREBP – SCAP) complex ,then proteolytic process will abolish that inhibit transport of SREBP from ER to Golgi for proteolytic cleavage after that will not be activation of transcription , no translation …etc , so down regulation of cholesterol.

(cont..)

3- phosphorylation- dephosphorylation

Active form of HMG CoA reductase is dephosphorylated form , if it is phosphorylated will be inactive so this mechanism is very important

- HMGR is phosphorylated by AMP-regulated protein kinase (**AMPRK**).

-Phosphatase produce active form of the HMG CoA (dephosphorylated)

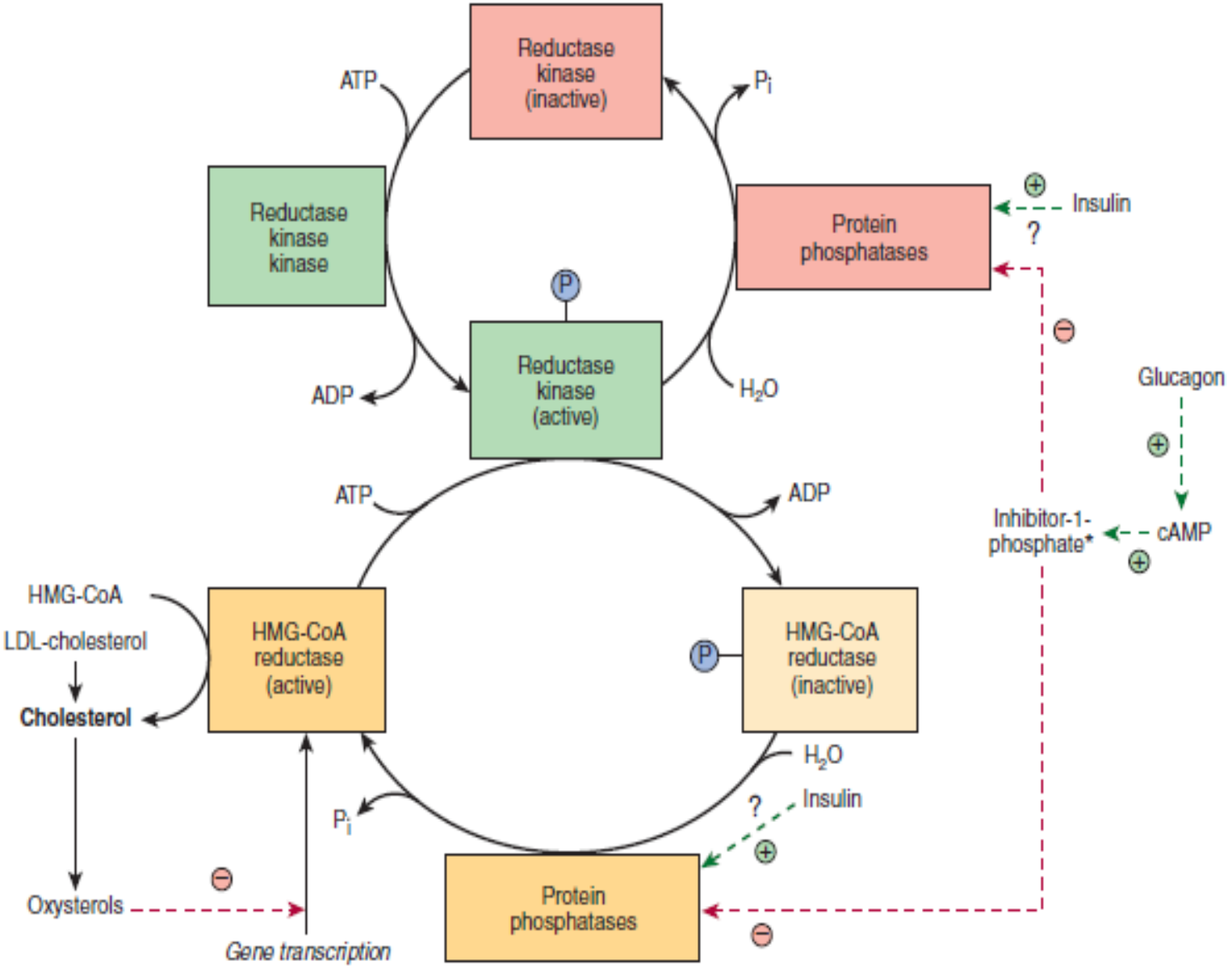


FIGURE 26–4 Possible mechanisms in the regulation of cholesterol synthesis by HMG-CoA reductase. Insulin has a dominant role compared with glucagon. (*See Figure 19–6.)

The last 8 slides are self reading and not mentioned in the record .

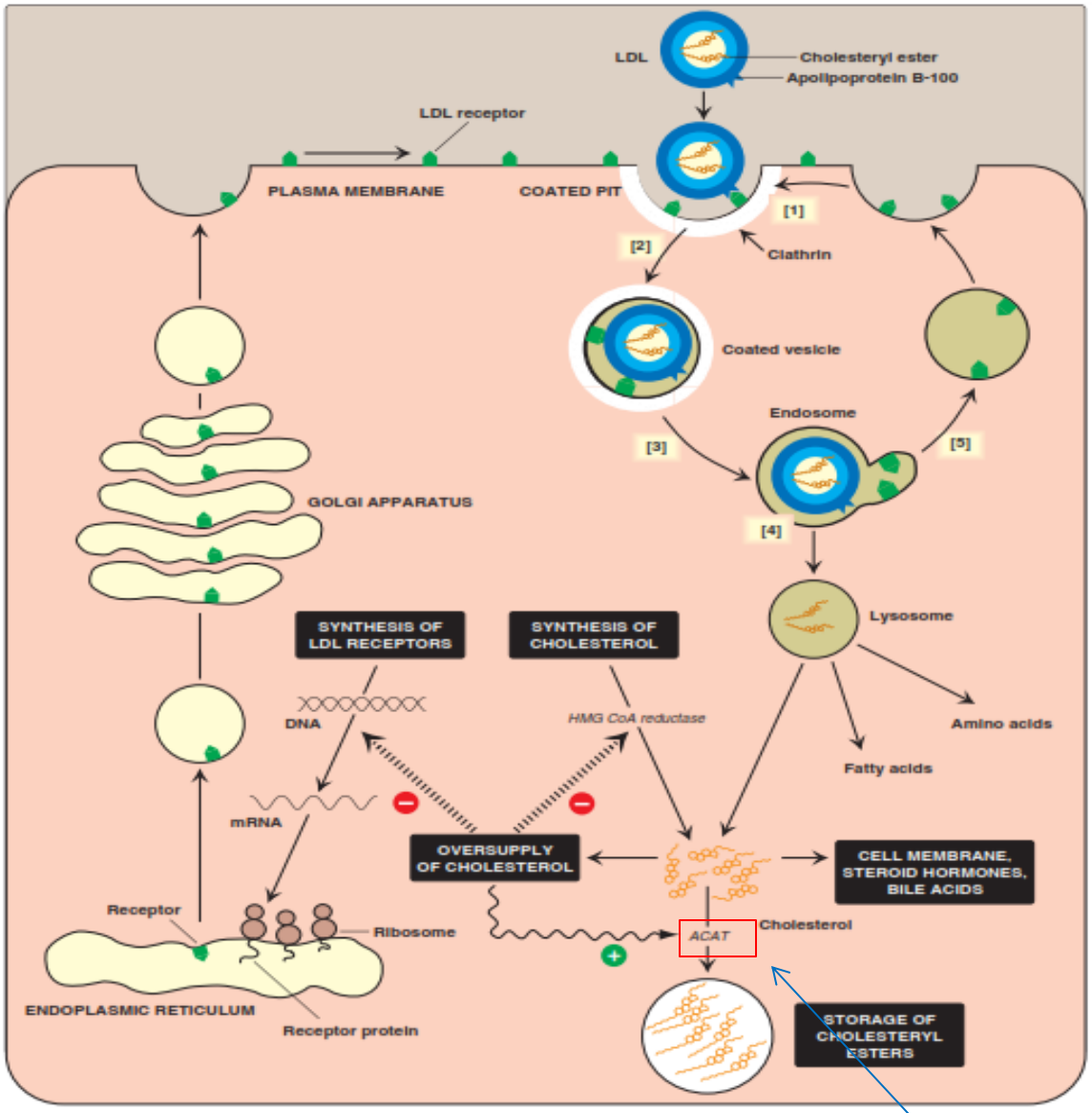
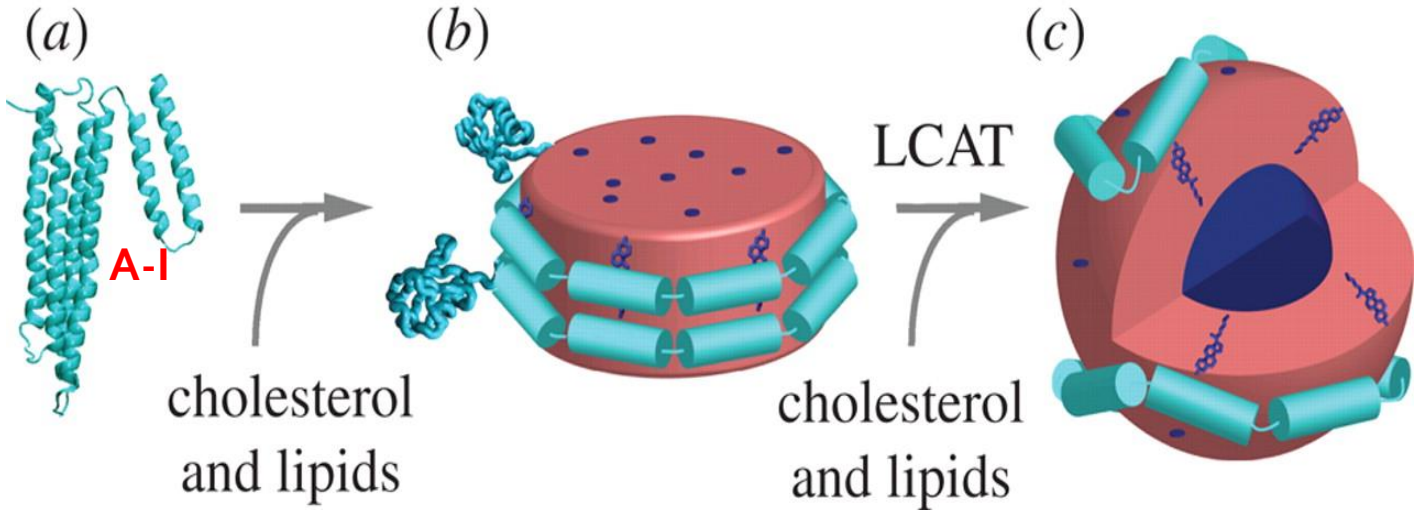


Figure 18.20
Cellular uptake and degradation of LDL. *ACAT = acyl CoA:cholesterol acyltransferase.*

Intercellular storage must undergo a reaction through an enzyme ACAT in the ER
65% of cholesterol are stored as cholesteyl ester.

Metabolism of HDL

- HDL particles are made in liver
- Nascent HDL are disc-shaped (bilayer of PL + proteins)
- HDL take free cholesterol (C) from cell membranes
- Once C is taken up, it is esterified by LCAT
- After this process HDL becomes spherical
- Spherical HDL are taken up by liver and CE are degraded



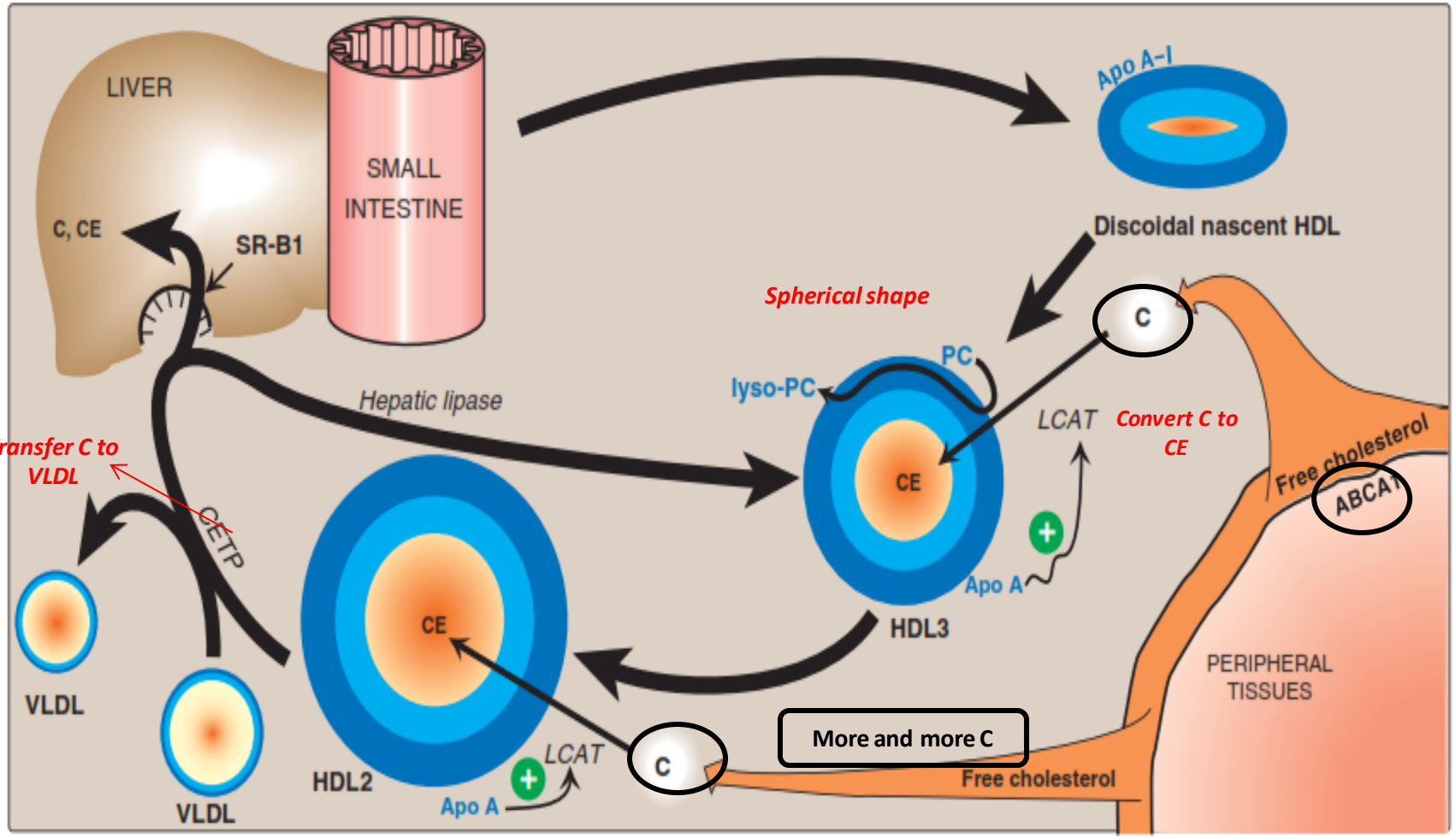


Figure 18.23

Metabolism of HDL. PC = phosphatidylcholine; lyso-PC = lysophosphatidylcholine. *LCAT = Lecithin cholesterol transferase.* CETP = cholesteryl ester transfer protein. ABCA1 = transport protein. [Note: For convenience the size of VLDLs are shown smaller than HDL, whereas VLDLs are larger than HDL.]

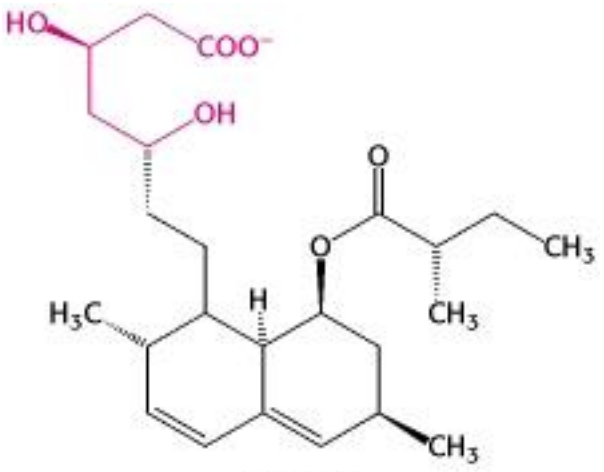
CLINICAL ASPECTS

- **The Serum Cholesterol Is Correlated with the Incidence of Atherosclerosis & Coronary Heart Disease..**
- Elevated plasma cholesterol levels **(>5.2 mmol/L**) are believed to be a major factor in promoting atherosclerosis.

Hypolipidemic drugs:

- Bile acid-binding resins decrease reabsorption of bile acids. E.g. Cholestyramine & Cholestipol
- HMG CoA reductase inhibitor (STATINS) are recently used. E.g. Lovastatin and Simvostatin.
- Nicotinic acid inhibits lipolysis and also lowers plasma cholesterol levels.
- **Ezetimibe** reduces blood cholesterol levels by inhibiting the absorption of cholesterol by the intestine by blocking uptake via the **Neimann Pick C-like 1 protein.**

- **Lovastatin, a Competitive Inhibitor of HMG-CoA Reductase**
- The part of the structure that resembles the 3-hydroxy-3-methylglutaryl moiety is shown in red.



Lovastatin

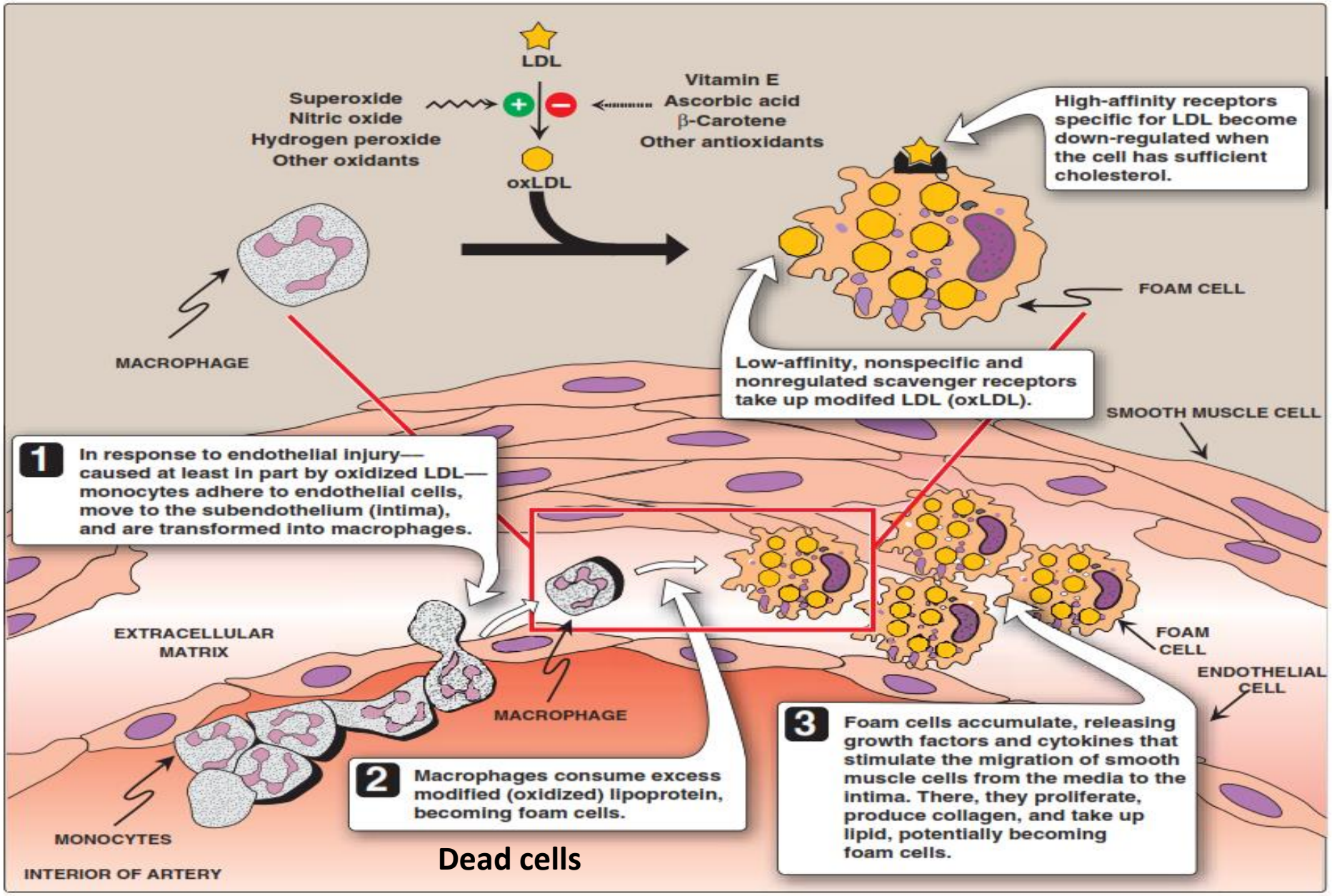


Figure 18.22
Role of oxidized lipoproteins in plaque formation in arterial wall.

Name	Defect	Remarks
Hypolipoproteinemias Abetalipoproteinemia	No chylomicrons, VLDL, or LDL are formed because of defect in the loading of apo B with lipid.	Rare; blood acylglycerols low; intestine and liver accumulate acylglycerols. Intestinal malabsorption. Early death avoidable by administration of large doses of fat-soluble vitamins, particularly vitamin E.
Familial alpha-lipoprotein deficiency Tangier disease Fish-eye disease Apo-A-I deficiencies	All have low or near absence of HDL.	Tendency toward hypertriacylglycerolemia as a result of absence of apo C-II, causing inactive LPL. Low LDL levels. Atherosclerosis in the elderly.
Hyperlipoproteinemias Familial lipoprotein lipase deficiency (type I)	Hypertriacylglycerolemia due to deficiency of LPL, abnormal LPL, or apo C-II deficiency causing inactive LPL.	Slow clearance of chylomicrons and VLDL. Low levels of LDL and HDL. No increased risk of coronary disease.
Familial hypercholesterolemia (type IIa)	Defective LDL receptors or mutation in ligand region of apo B-100.	Elevated LDL levels and hypercholesterolemia, resulting in atherosclerosis and coronary disease.
Familial type III hyperlipoproteinemia (broad beta disease, remnant removal disease, familial dysbetalipoproteinemia	Deficiency in remnant clearance by the liver is due to abnormality in apo E. Patients lack isoforms E3 and E4 and have only E2, which does not react with the E receptor.[1]	Increase in chylomicron and VLDL remnants of density < 1.019 (β-VLDL). Causes hypercholesterolemia, xanthomas, and atherosclerosis.

TABLE 26–1 Primary Disorders of Plasma Lipoproteins (Dyslipoproteinemias)

Name	Defect	Remarks
Hypolipoproteinemias Abetalipoproteinemia	No chylomicrons, VLDL, or LDL are formed because of defect in the loading of apo B with lipid.	Rare; blood acylglycerols low; intestine and liver accumulate acylglycerols. Intestinal malabsorption. Early death avoidable by administration of large doses of fat-soluble vitamins, particularly vitamin E.
Familial alpha-lipoprotein deficiency Tangier disease Fish-eye disease Apo-A-I deficiencies	All have low or near absence of HDL.	Tendency toward hypertriacylglycerolemia as a result of absence of apo C-II, causing inactive LPL. Low LDL levels. Atherosclerosis in the elderly.
Hyperlipoproteinemias Familial lipoprotein lipase deficiency (type I)	Hypertriacylglycerolemia due to deficiency of LPL, abnormal LPL, or apo C-II deficiency causing inactive LPL.	Slow clearance of chylomicrons and VLDL. Low levels of LDL and HDL. No increased risk of coronary disease.
Familial hypercholesterolemia (type IIa)	Defective LDL receptors or mutation in ligand region of apo B-100.	Elevated LDL levels and hypercholesterolemia, resulting in atherosclerosis and coronary disease.
Familial type III hyperlipoproteinemia (broad beta disease, remnant removal disease, familial dysbetalipoproteinemia	Deficiency in remnant clearance by the liver is due to abnormality in apo E. Patients lack isoforms E3 and E4 and have only E2, which does not react with the E receptor.[1]	Increase in chylomicron and VLDL remnants of density < 1.019 (β-VLDL). Causes hypercholesterolemia, xanthomas, and atherosclerosis.
Familial hypertriacylglycerolemia (type IV)	Overproduction of VLDL often associated with glucose intolerance and hyperinsulinemia.	Cholesterol levels rise with the VLDL concentration. LDL and HDL tend to be subnormal. This type of pattern is commonly associated with coronary heart disease, type II diabetes mellitus, obesity, alcoholism, and administration of progestational hormones.
Familial hyperalphalipoproteinemia	Increased concentrations of HDL.	A rare condition apparently beneficial to health and longevity.
Hepatic lipase deficiency	Deficiency of the enzyme leads to accumulation of large triacylglycerolrich HDL and VLDL remnants.	Patients have xanthomas and coronary heart disease.
Familial lecithin:cholesterol acyltransferase (LCAT) deficiency	Absence of LCAT leads to block in reverse cholesterol transport. HDL remains as nascent disks incapable of taking up and esterifying cholesterol.	Plasma concentrations of cholesteryl esters and lysolecithin are low. Present is an abnormal LDL fraction, lipoprotein X, found also in patients with cholestasis. VLDL is abnormal (β-VLDL).
Familial lipoprotein(a) excess	Lp(a) consists of 1 mol of LDL attached to 1 mol of apo(a). Apo(a) shows structural homologies to plasminogen.	Premature coronary heart disease due to atherosclerosis, plus thrombosis due to inhibition of fibrinolysis.

[1]There is an association between patients possessing the apo E4 allele and the incidence of Alzheimer's disease. Apparently, apo E4 binds more avidly to β-amyloid found in neuritic plaques.