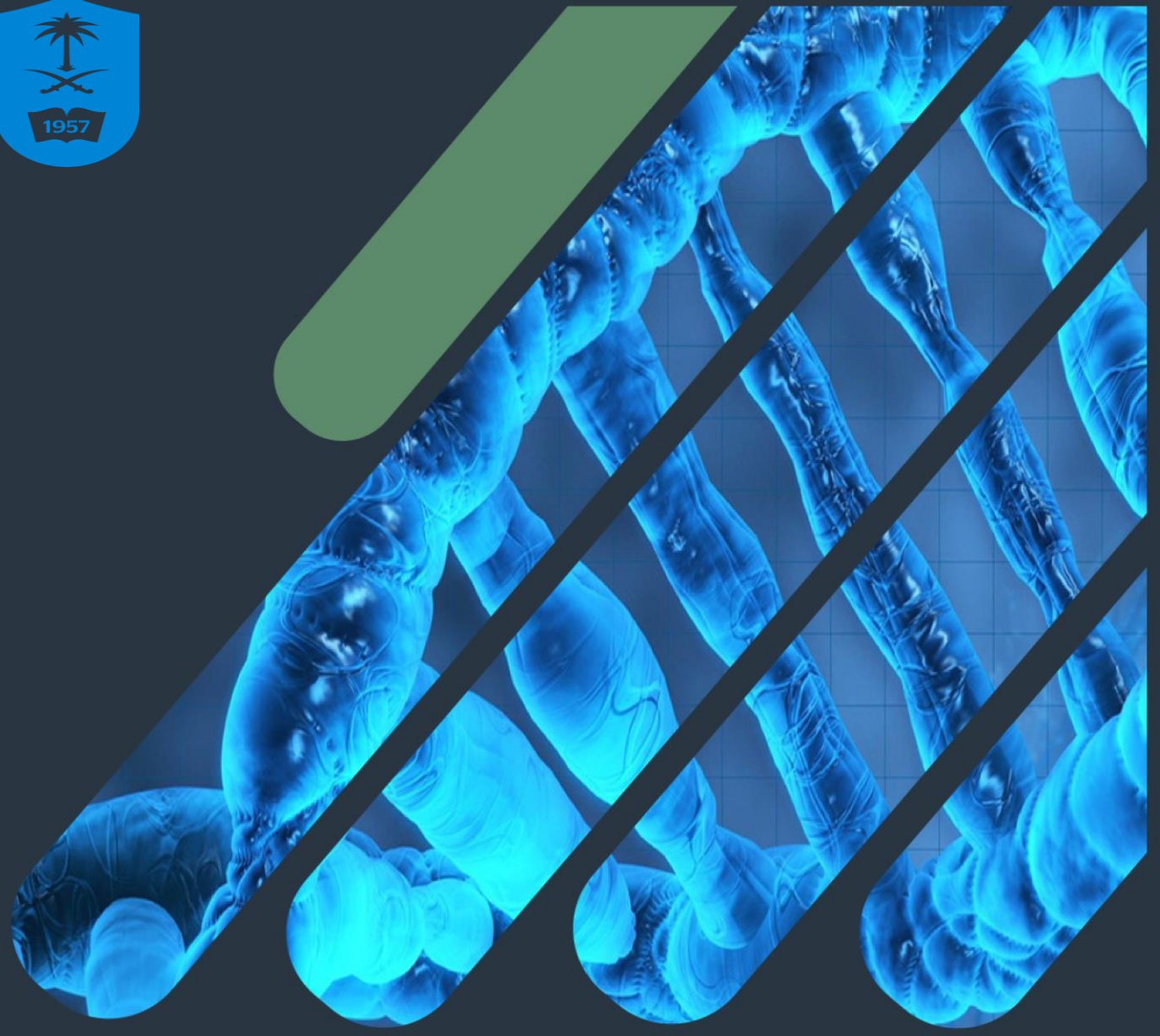
Biochemistry

Cholesterol Metabolism



A little progress each day adds up to big results ..

Revised by
شوق الأحمري & طراد الوكيل

Important.
Extra Information.
Doctors slides
Doctor's notes

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OBJECTIVES:

- By the end of this lecture the students will be able to:

  - Know the structure and function of cholesterol
  - Relate hypercholesterolemia and atherosclerosis.
  - Define cholesterol biosynthesis and its regulation.
  - List the factors that decrease blood cholesterol level.
  - Identify bile salt functions and cholesterol excretion.

Cholesterol

- Most important animal steroid because it is the structural component of all cell membranes.
- Maintains membrane fluidity and integrity which affects permeability and interaction with other cells.
- Insulating effect on nerve fibers such as myelin sheath.
- Cholesterol is the parent molecule for

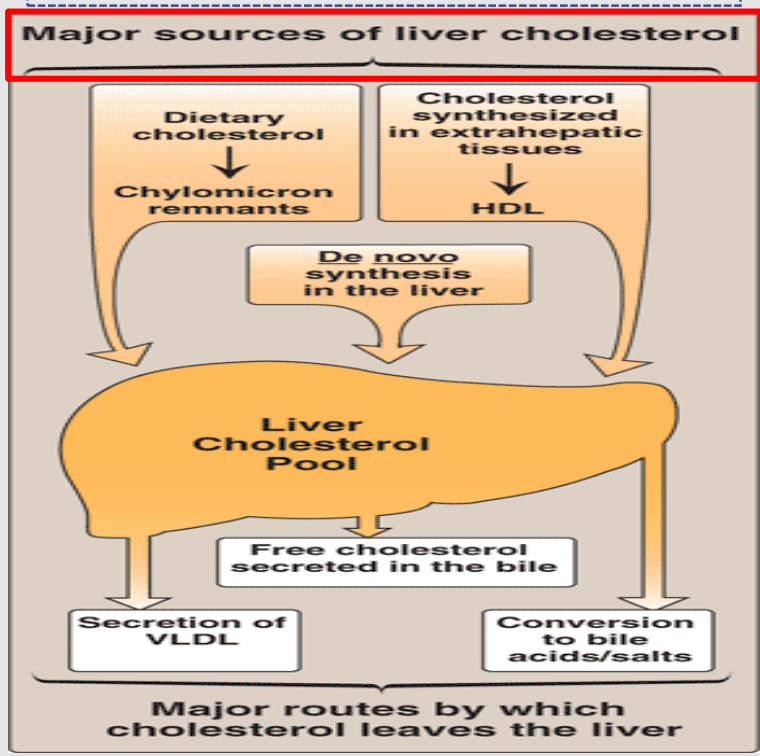
Vitamin D3

Bile acids and bile salts

Important for digestion of lipid and fat soluble vitamins such as vitamin A,D,E,K

Steroid hormones

Liver plays a central role in the regulation of cholesterol homeostasis



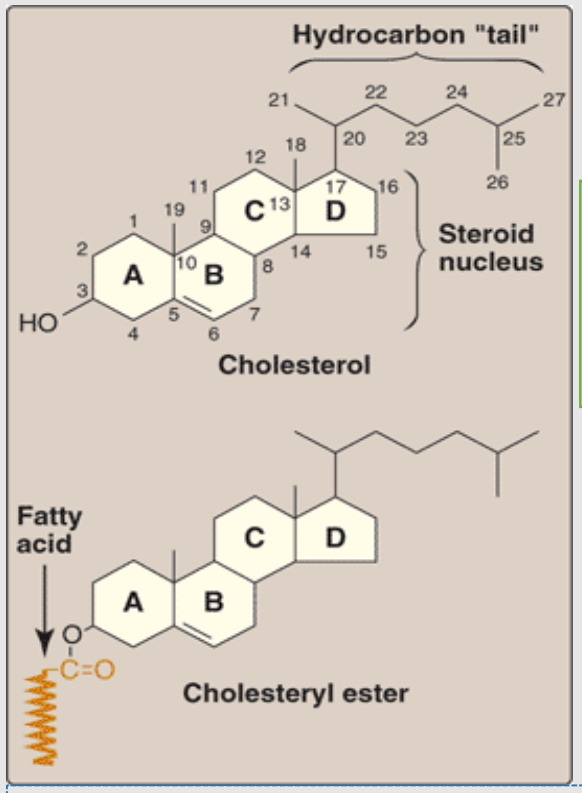
Cholesterol enters the liver's cholesterol pool from a number of sources including dietary cholesterol, as well as cholesterol synthesized **De novo** by extrahepatic tissues and by the liver itself. Cholesterol is eliminated from liver as unmodified cholesterol in the bile, or it can be converted to bile salts that are secreted into the intestinal lumen.

Cholesterol structure

- Four rings called (Steroid nucleus).
- At carbon atom no.17

(hydrocarbon tail) attaches .

- Hydrophobic because of the presence of fatty acid.



Sterols: a class of steroids that contain a hydrocarbon tail on C17 and a hydroxyl group on C3.

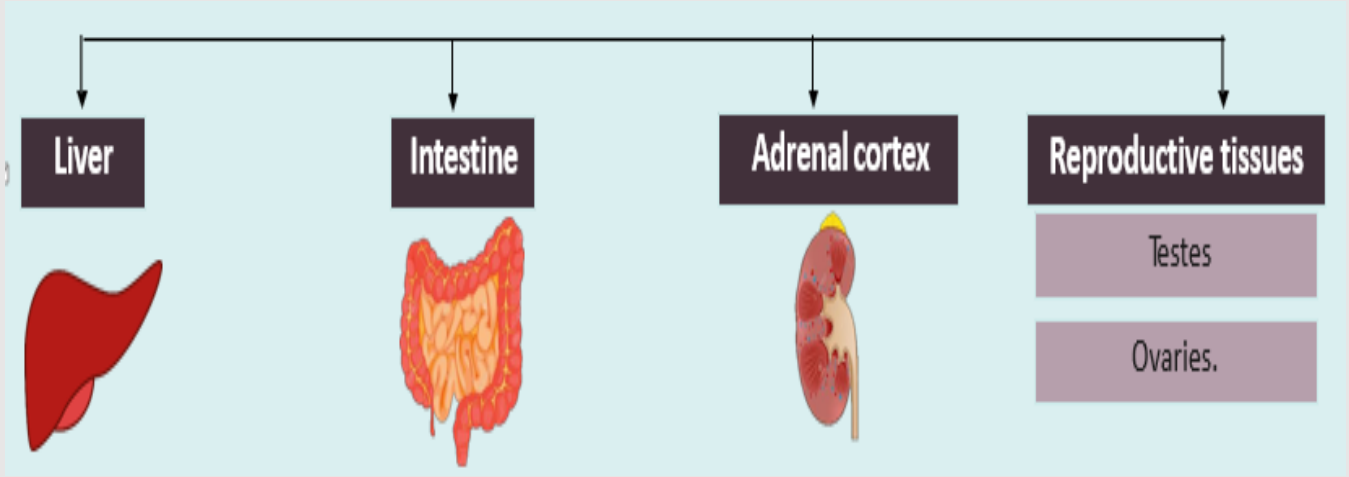
You don't have to memorize the structures

Cholesteryl esters

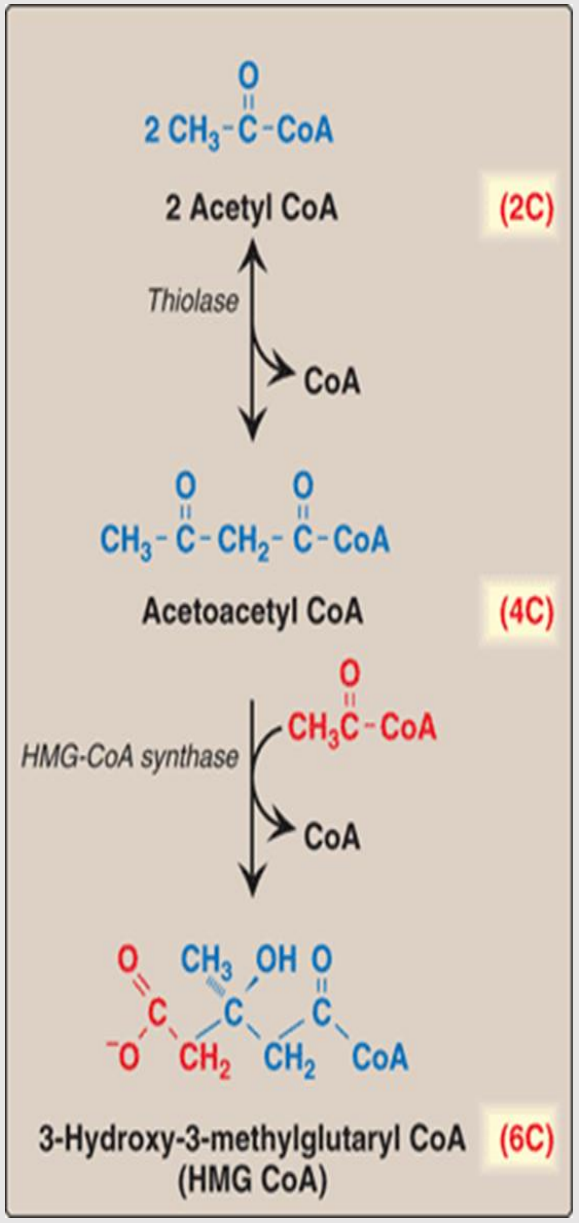
- Most plasma cholesterol is esterified with a fatty acid (the cholesterol found in the body and blood (plasma) is in the form of cholesteryl ester).
- CEs are not present in membranes (only free cholesterol).
- Present in small amounts in most cells .
- More hydrophobic than cholesterol (because of the fatty acid group, so it must be transported in association with proteins as a compound of lipoproteins or be solubilized by bile salts).

Cholesterol synthesis

- Synthesized in all tissues
- Major sites for synthesis: liver, adrenal cortex, testes, ovaries and intestine.
- All carbon atoms are derived from acetyl CoA (has 2 carbons) .
- Enzymes involved in biosynthesis are partly located in ER(smooth endoplasmic reticulum) and partly in cytoplasm or both.



HMG-CoA synthesis



HMG-CoA is a molecule that forms cholesterol after certain reactions.
We need 3 Acetyl CoA to get HMG CoA which has 6 carbon atoms.

In liver

- HMG-CoA synthase is present in both cytosol and mitochondria of liver.

In liver's mitochondria

- Its function is ketogenesis (ketone body synthesis).

In liver's cytosol (cytoplasm)

- Its function is cholesterol synthesis.

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Mevalonic acid Synthesis

- Why is it important ?

Rate limiting and key step of cholesterol synthesis.

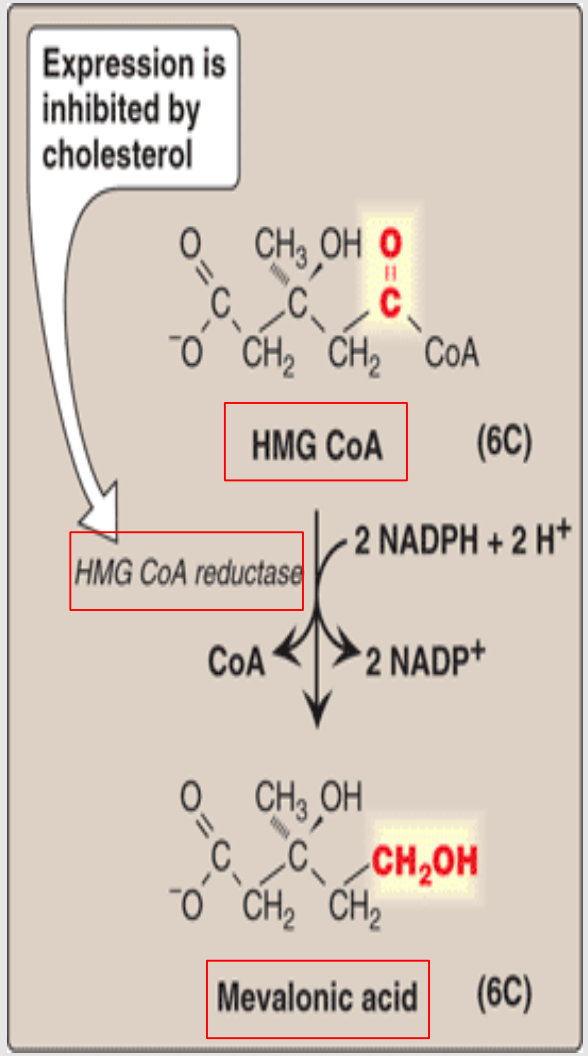
(step that regulates the whole pathway, which is an irreversible and slow step, and is the target for inhibitors)

- Where does it occur ?

It occurs in the Cytosol.

- Why does it occur in the cytosol even though HMG CoA reductase is an ER membrane enzyme?

Because it has active (catalytic) unit hanging in the cytosol .



Mevalonic acid Synthesis

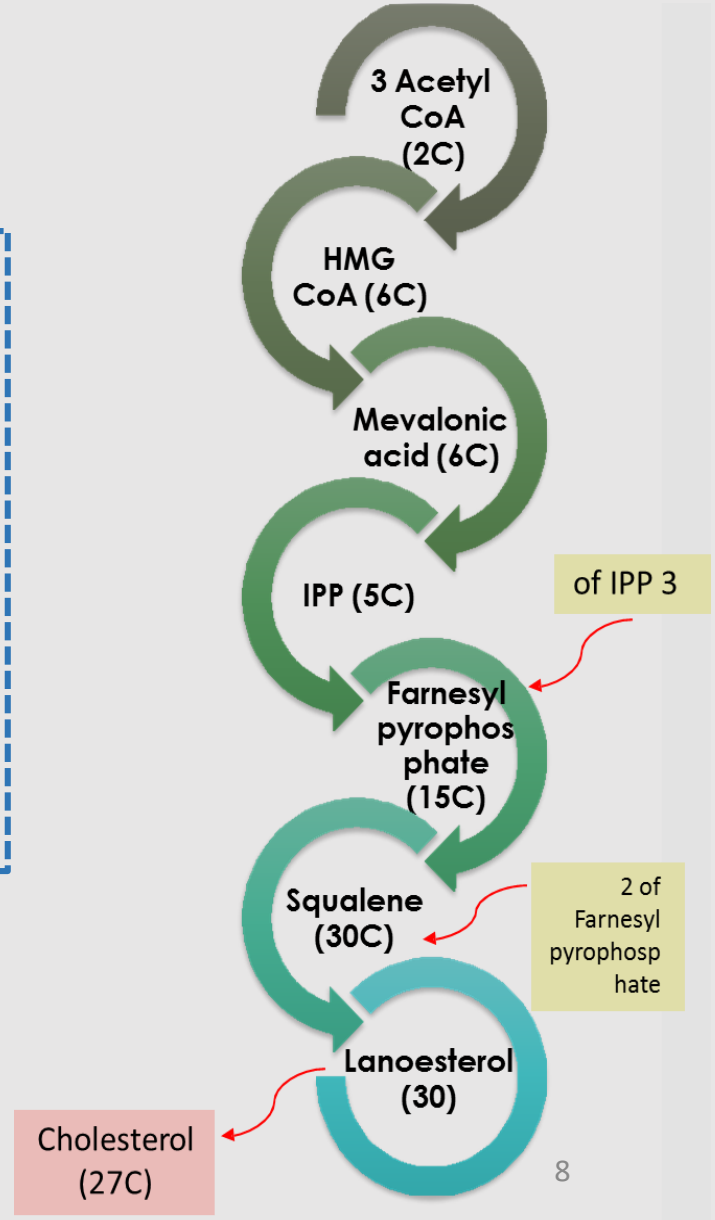
After being a Mevalonic acid, the complex undergoes some reactions to become a cholesterol, those steps are :

- Production of a 5-carbon unit:

- Isopentinyl pyrophosphate (IPP) (which is the patent sterol for all sterols, and the building block of cholesterol)

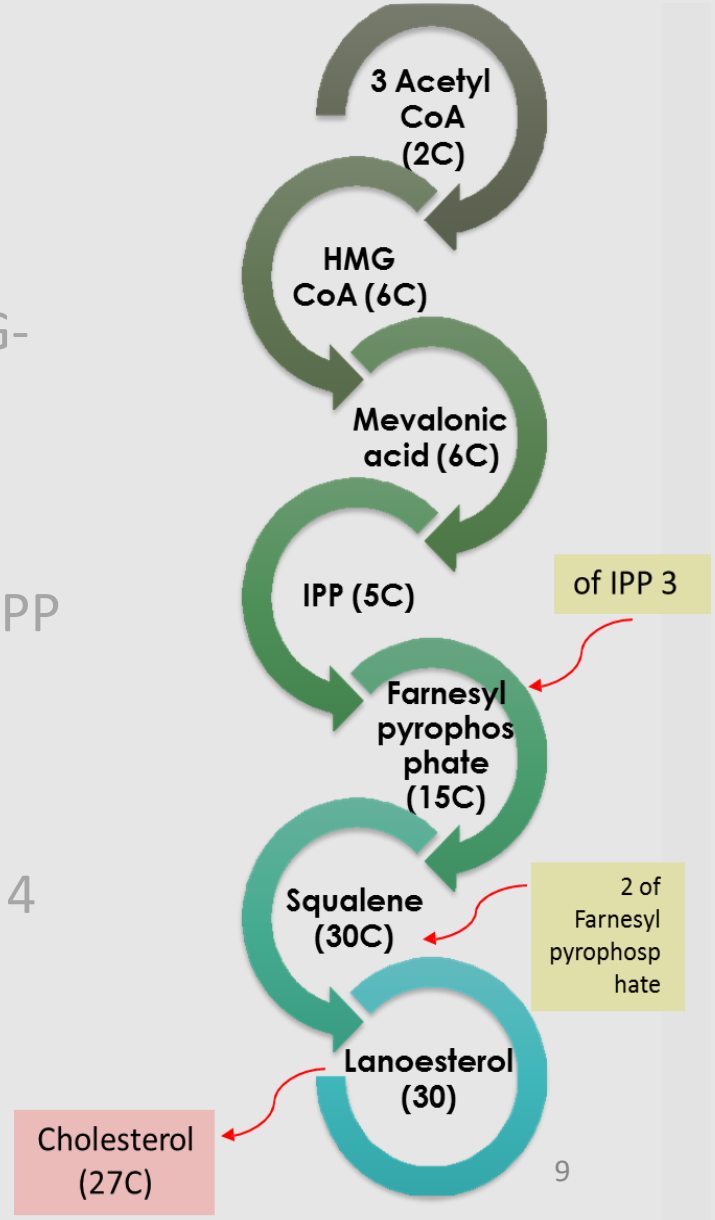
- Condensation to a 30C compound: squalene (which is an opened ring molecule)
- Cyclization of squalene to 30C Lanosterol
- Synthesis of 27-Carbon cholesterol (defect in this leads to Smith-Lemli-Opitz Syndrome (SLOS – An autosomal recessive disorder caused by a partial deficiency in 7-dehydrocholesterol-7-reducatse)

Important note: Lanosterol is the first Sterol made by the body .. Because it was a result for cyclization of other non cycled molecule . Check the chemical structure in next page for better understanding .

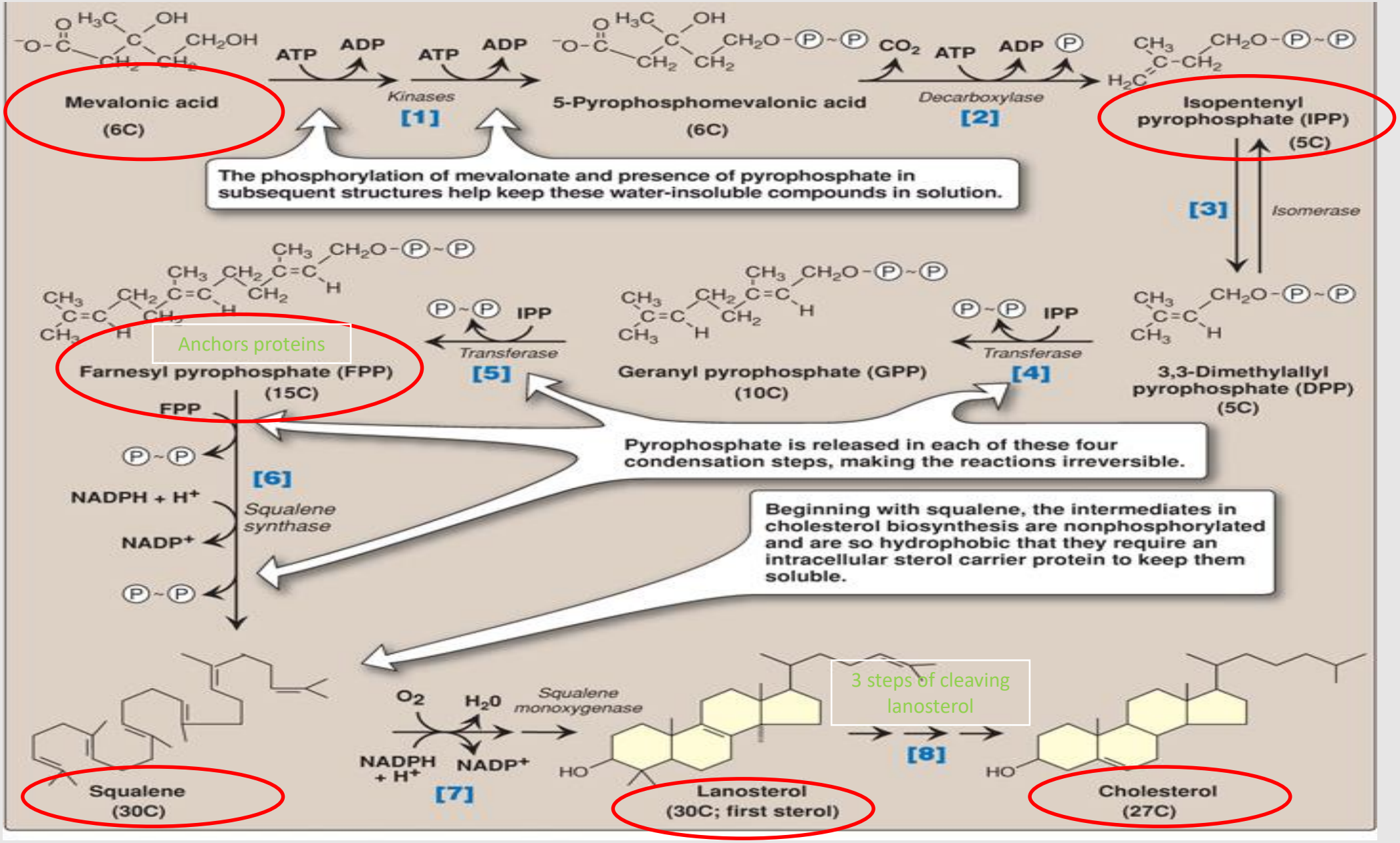


Mevalonic acid Synthesis – Summary

Step 1: Acetyl CoA + Acetyl CoA = Acetoacetyl CoA (enzyme : thiolase)
Acetoacetyl CoA + Acetyl CoA = HMG-CoA (enzyme : HMG-CoA synthase)
Step 2: HMG-CoA is reduced into mevalonic acid (enzyme : HMG-CoA reductase) – most important step, rate limiting.
Step 3: Mevalonic acid is converted into Isopentinyl pyrophosphate (IPP - 5 carbons)
Step 4: We put 3 IPPs together to get Farnesyl pyrophosphate (FPP - 15 carbons)
Step 5: We put 2 FPPs to get a 30 carbon unit compound : Squalene.
Squalene is then cyclized to give the first sterol in the body with 4 rings: Lanosterol.
Lanosterol is cleaved into a 27 carbon cholesterol.



The doctor said this is not required.. Just know the marked steps .



Regulation of Cholesterol Synthesis

- HMG CoA reductase is the rate-limiting enzyme of cholesterol synthesis

HMG-CoA Reductase Regulation

By four mechanisms

1. Sterol-dependent regulation of gene expression .
2. Sterol-accelerated enzyme degradation .
3. Sterol-independent phosphorylation/dephosphorylation .
4. Hormonal regulation .

(Next slides will explain them)
(Slide No. 17&18 from Lippincott)

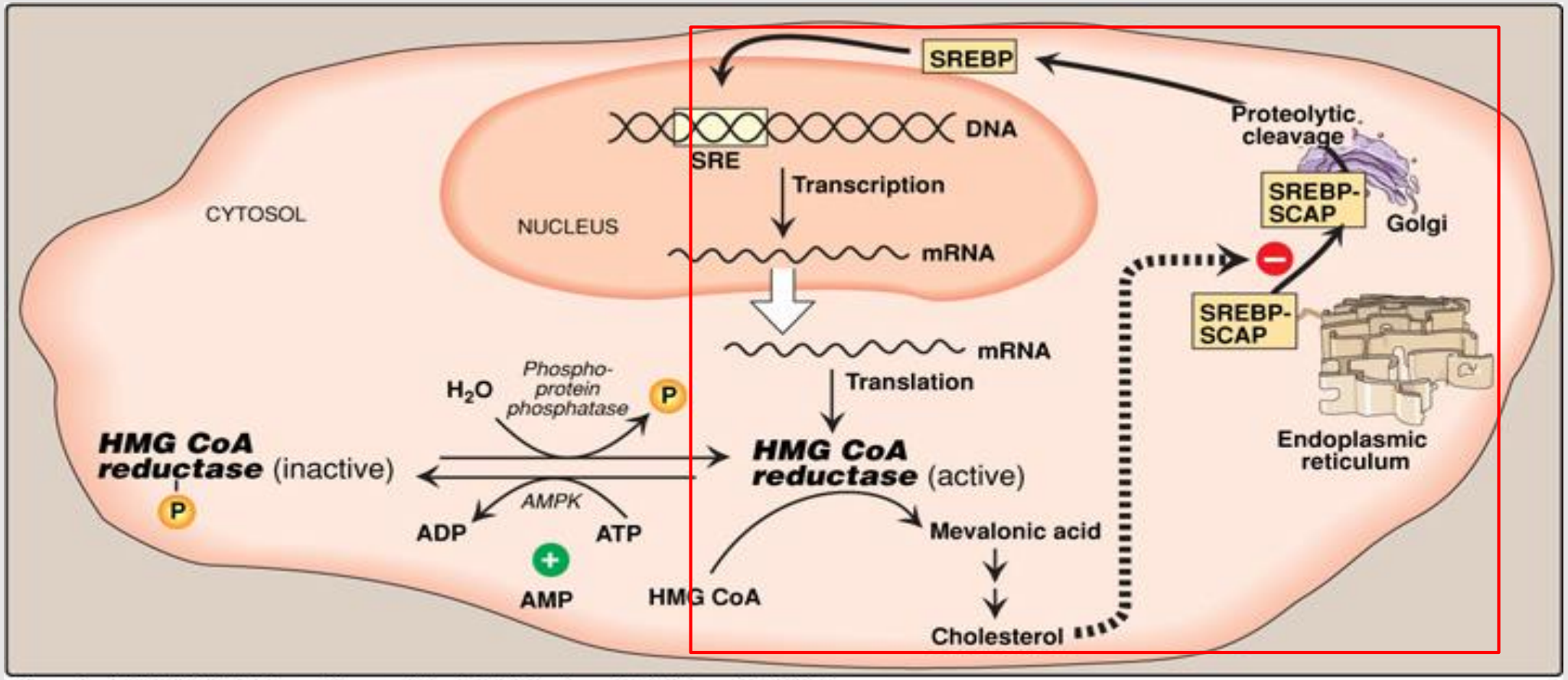
1-Sterol-dependent regulation of gene expression of HMG CoA

- ✓ When sufficient cholesterol is present, transcription is suppressed and vice versa (transcription factor is the portion that interacts with DNA either to increase or inhibit cholesterol synthesis).
- ✓ Sterol Regulatory Element (SRE) is a recognition sequence in the DNA (the area that binds with the transcription factor).
- ✓ SREBP type 2 (SRE binding protein) binding to SRE is essential for transcription of this gene .
- ✓ SREBP cleavage-activating protein (SCAP) is an intracellular cholesterol sensor, so when the levels of cholesterol decrease, SCAP will take SREBP to the ER and cleaves it to synthesize more cholesterol, and if cholesterol levels increase the cleavage will be stopped.

(يعني إذا صارت كمية الكوليسترول كافية .. الكوليسترول نفسه راح يثبط الجين المسؤول عن تكوين هذا الإنزيم وتوقف عملية تكوين الكوليسترول بالكامل)

1-Sterol-dependent regulation of gene expression of HMG CoA

Know the site where this mechanism of regulation takes a place and how



1-Sterol-dependent regulation of gene expression of HMG CoA

High Cholesterol	Low Cholesterol
• SCAP binds to insig protein (insulin-induced protein) in ER membrabe . • SCAP-SREBP is retained in the ER . • Down regulation of cholesterol synthesis .	• SCAP-SREBP moves to Golgi bodies • SCAP is removed from SREBP • SREBP binds to SRE in DNA • HMG CoA gene is activated

2-Sterol-accelarated enzyme degradation:

- ✓ When cholesterol is high, HMG-CoA reductase itself binds to insigs.
- ✓ Leading to degradation of enzyme.

3-Enzyme phosphorylation and dephosphorylation

- ✓ AMP- activated protein kinase (AMPK) for phosphorylation
- ✓ Phosphorylated form of enzyme is inactive
- ✓ Dephosphorylated form is active
- ✓ Low ATP or High AMP → Cholesterol synthesis <u>decreases</u> (So we will have more phosphorylation and inactivation in this case ☺) ..

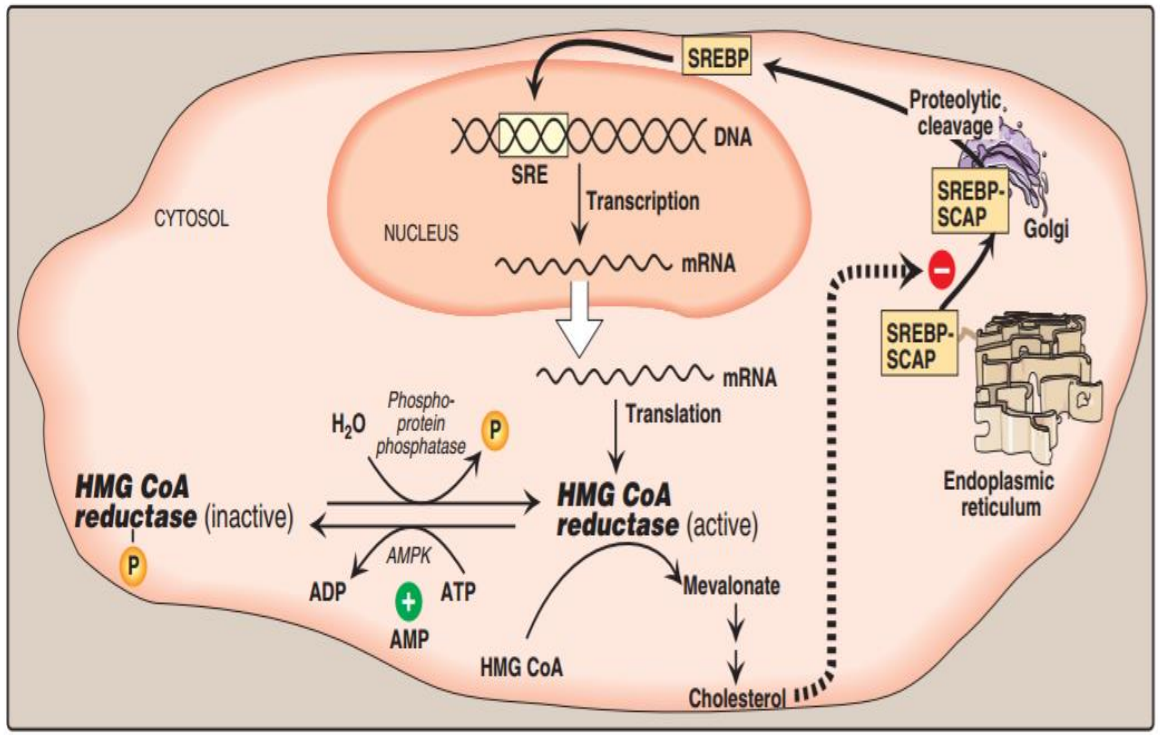
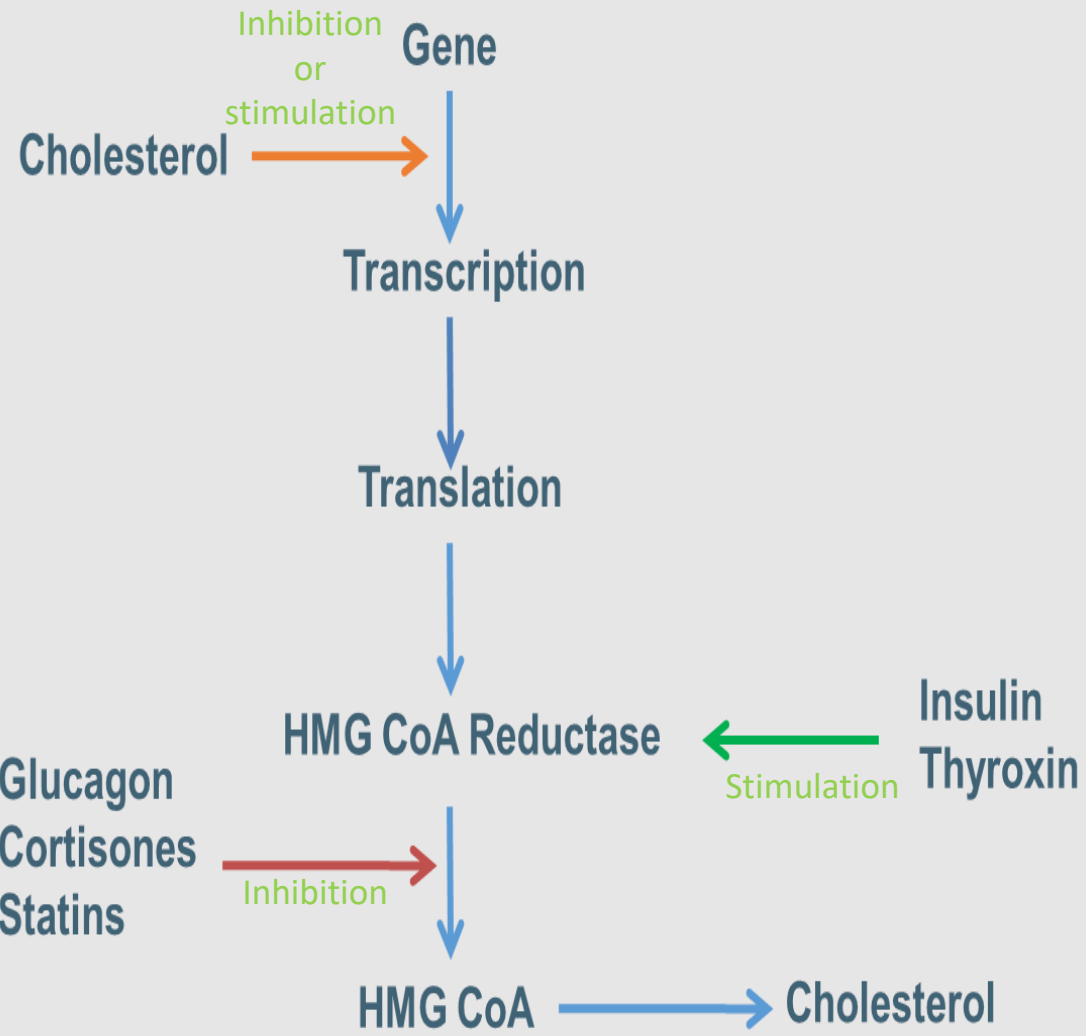


Figure 18.6
Regulation of *HMG CoA reductase*. SRE = sterol regulatory element; SREBP = sterol regulatory element-binding protein; SCAP = SREBP cleavage–activating protein.

4-Hormonal Regulation

- Insulin and thyroxine increase upregulation of enzyme expression . (They increase enzyme concentration, thus increase cholesterol synthesis, because insulin has a major role in lipogenesis) .
- Glucagon and cortisol have opposite effect .
  - (Cholesterol concentration itself controlling the gene, while hormones are controlling the enzyme) .

HMG CoA Reductase Regulation



Further explanation of statins in slide 20

HMG-CoA Reductase Regulation From Lippincott (More explanation for the previous slides)

D. Regulation of cholesterol synthesis

HMG CoA reductase, the rate-limiting enzyme, is the major control point for cholesterol biosynthesis, and is subject to different kinds of metabolic control.

1. **Sterol-dependent regulation of gene expression:** Expression of the gene for *HMG CoA reductase* is controlled by the transcription factor, SREBP-2 (sterol regulatory element–binding protein-2) that binds DNA at the cis-acting sterol regulatory element (SRE) of the *reductase* gene. SREBP is an integral protein of the ER membrane, and associates with a second ER membrane protein, SCAP (SREBP cleavage–activating protein). When sterol levels in the cell are low, the SREBP-SCAP complex is sent out of the ER to the Golgi. In the Golgi, SREBP is sequentially acted upon by two *proteases*, which generate a soluble fragment that enters the nucleus, binds the SRE, and functions as a transcription factor. This results in increased synthesis of *HMG CoA reductase* and, therefore, increased cholesterol synthesis (Figure 18.6). If sterols are abundant, however, they bind SCAP at its sterol-sensing domain and induce the binding of SCAP to yet other ER membrane proteins (insigs). This results in the retention of the SCAP-SREBP complex in the ER, thus preventing the activation of SREBP, and leading to down-regulation of cholesterol synthesis.

2. **Sterol-accelerated enzyme degradation:** The *reductase* itself is a sterol-sensing integral protein of the ER membrane. When sterol levels in the cell are high, the *reductase* binds to insig proteins. Binding leads to ubiquitination and proteasomal degradation of the *reductase* (see p. 247).

3. **Sterol-independent phosphorylation/dephosphorylation:** *HMG CoA reductase* activity is controlled covalently through the actions of *adenosine monophosphate (AMP)–activated protein kinase (AMPK,* see p. 183) and a *phosphoprotein phosphatase* (see Figure 18.6). The phosphorylated form of the enzyme is inactive, whereas the dephosphorylated form is active. [Note: *AMPK* is activated by AMP, so cholesterol synthesis, like fatty acid synthesis, is decreased when ATP availability is decreased.]

HMG-CoA Reductase Regulation From Lippincott (More explanation for the previous slides)

4. **Hormonal regulation:** The amount (and, therefore, the activity) of *HMG CoA reductase* is controlled hormonally. An increase in insulin and thyroxine favors up-regulation of the expression of the gene for *HMG CoA reductase*. Glucagon and the glucocorticoids have the opposite effect.

5. **Inhibition by drugs:** The statin drugs (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) are structural analogs of HMG CoA, and are (or are metabolized to) reversible, competitive inhibitors of *HMG CoA reductase* (Figure 18.7). They are used to decrease plasma cholesterol levels in patients with hypercholesterolemia.[1]

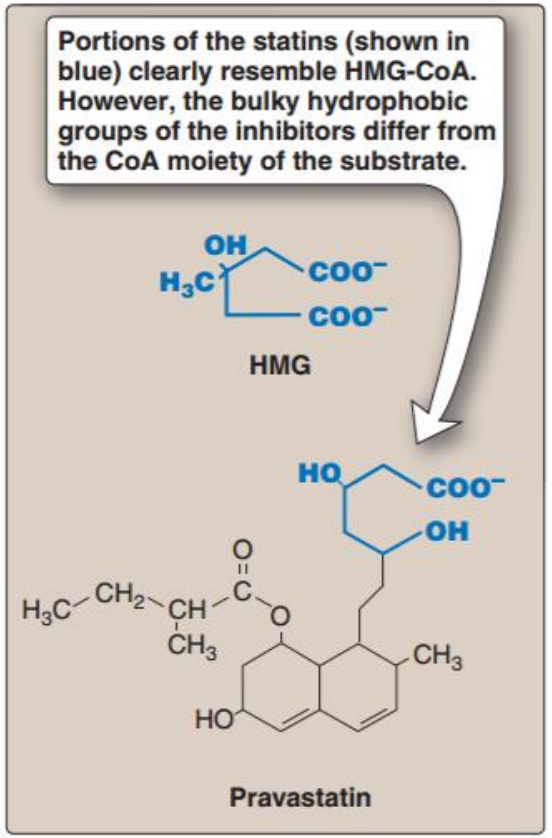
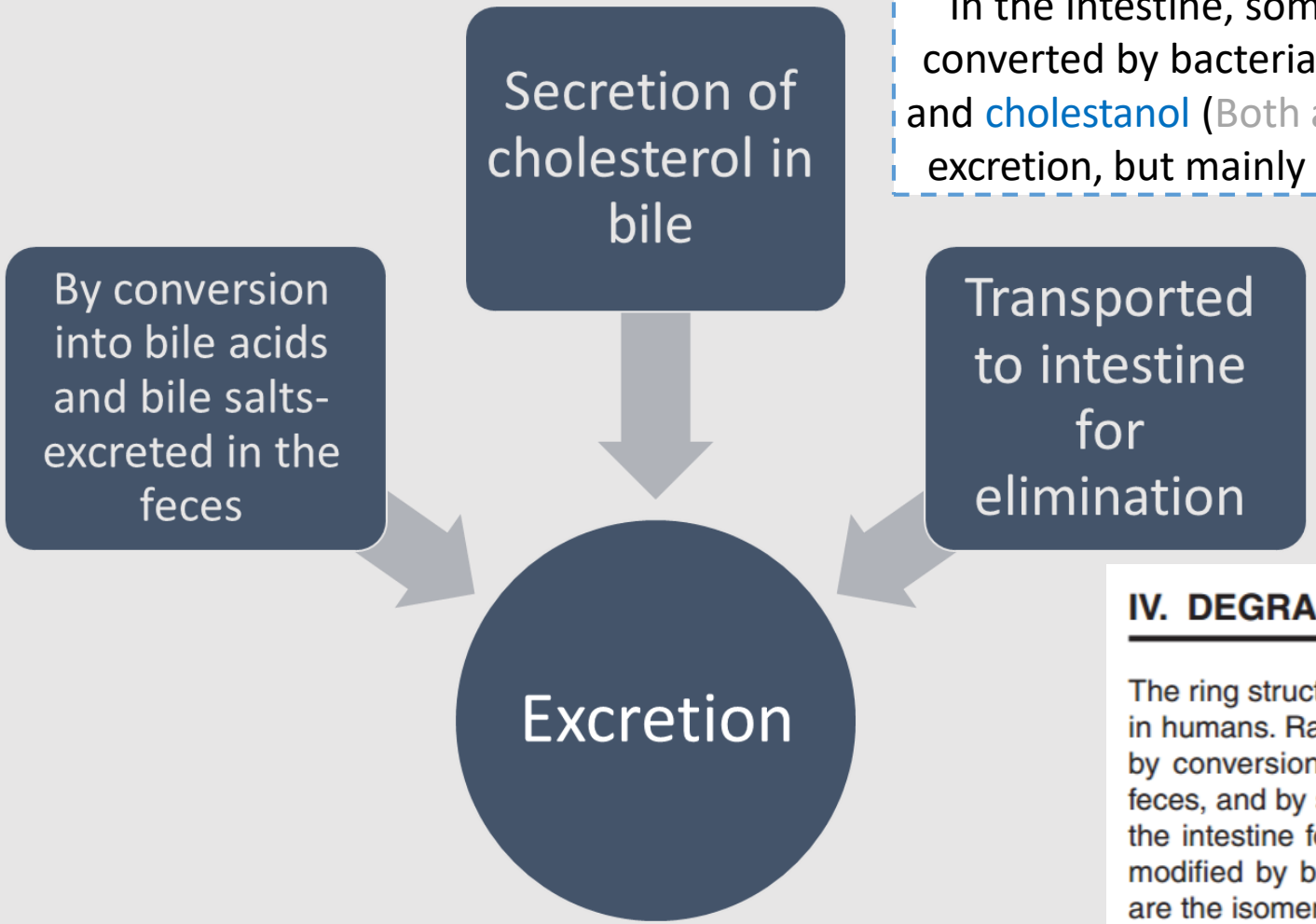


Figure 18.7
Structural similarity of HMG and pravastatin, a clinically useful cholesterol-lowering drug of the "statin" family.

Excretion of Cholesterol



In the intestine, some cholesterol is converted by bacteria into coprostanol and cholestanol (Both are sterols) before excretion, but mainly excreted in Bile .

Further explanation

IV. DEGRADATION OF CHOLESTEROL

The ring structure of cholesterol cannot be metabolized to CO_2 and H_2O in humans. Rather, the intact sterol nucleus is eliminated from the body by conversion to bile acids and bile salts, which are excreted in the feces, and by secretion of cholesterol into the bile, which transports it to the intestine for elimination. Some of the cholesterol in the intestine is modified by bacteria before excretion. The primary compounds made are the isomers coprostanol and cholestanol, which are reduced derivatives of cholesterol. Together with cholesterol, these compounds make up the bulk of neutral fecal sterols.

Hypercholesterolemia

- ✓ High concentration of cholesterol in blood that can lead to atherosclerosis or shock or hemorrhage. (due to the loss of regulation of cholesterol synthesis)

- ✓ Treatment:

Statin drugs

- They are drugs used to decrease **plasma cholesterol levels.**
- Structural analogs of **HMG-CoA** (have the same structure as the molecule) and are reversible, competitive inhibitors of HMG-CoA reductase.

β-Sitosterols / Phytosterols

- They are plant sterols and are poorly absorbed by human, clinically useful in: the **dietary treatment** of hypercholesterolemia by decreasing cholesterol levels.
- They block the absorption of dietary cholesterol.

Ezetimibe

- A drug that reduces the absorption of **dietary cholesterol**.
- It blocks **Neimann-Pick C1 like protein** (NPC1-L1) which is a protein that partly mediates intestinal uptake of cholesterol.

From lippincott 6th edition and Dr.Sumbul.

Quiz

SAQ

https://www.onlineexambuilder.com/cholesterol-metabolism-saq-s/exam-140473

MCQ's

https://www.onlineexambuilder.com/cholesterol-metabolism/exam-140410

Helpful video

Cholesterol excretion

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هيفاء بن طالب

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THANK YOU

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

- Review the notes

- Lippincott's Illustrated Reviews: Biochemistry, 6th E

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