CHOLESTEROL METABOLISM

"IN ORDER TO SUCCEED WE MUST FIRST BELIEVE THAT WE CAN "- NIKOS KAZANTZAKIS

Color index:

- Important
- Extra explanation

*** Please check out this link to know if there are any changes.**

OBJECTIVES:

- 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 execution.

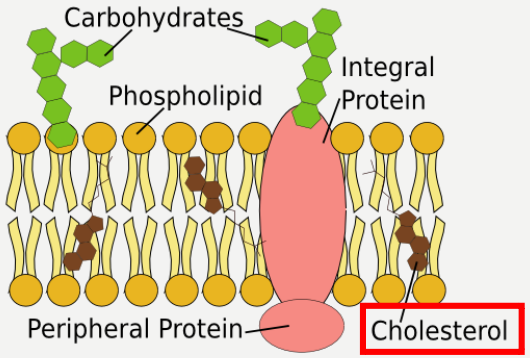
Cholesterol :

#IT is the **most important** animal steroid.

Importance of cholesterol

maintains membrane fluidity

(cholesterol enhances mechanical stability of lipid bilayers largely).



insulating effect on nerve fibers

cholesterol is required for the formation of the myelin sheath which insulates nerve cells and enhances the passing of electrical signals throughout your nervous system's circuitry) .

Parent molecule for

- Bile acids and bile salts
- Steroid hormones.
- Vitamin D_3.

cholesterol

Cholesterol :

Liver plays a central role in the regulation of cholesterol homeostasis. . .

- cholesterol enters the liver's cholesterol pool from number of sources, including:

1- Dietary cholesterol (chylomicrons bring them to the liver)

It hides cholesterol because it's hydrophilic and cholesterol is hydrophobic , so it transfers it.

2- cholesterol which are synthesized in extrahepatic tissues (HDL brings them to the liver).

3- Cholesterol synthesized de novo by the liver itself.

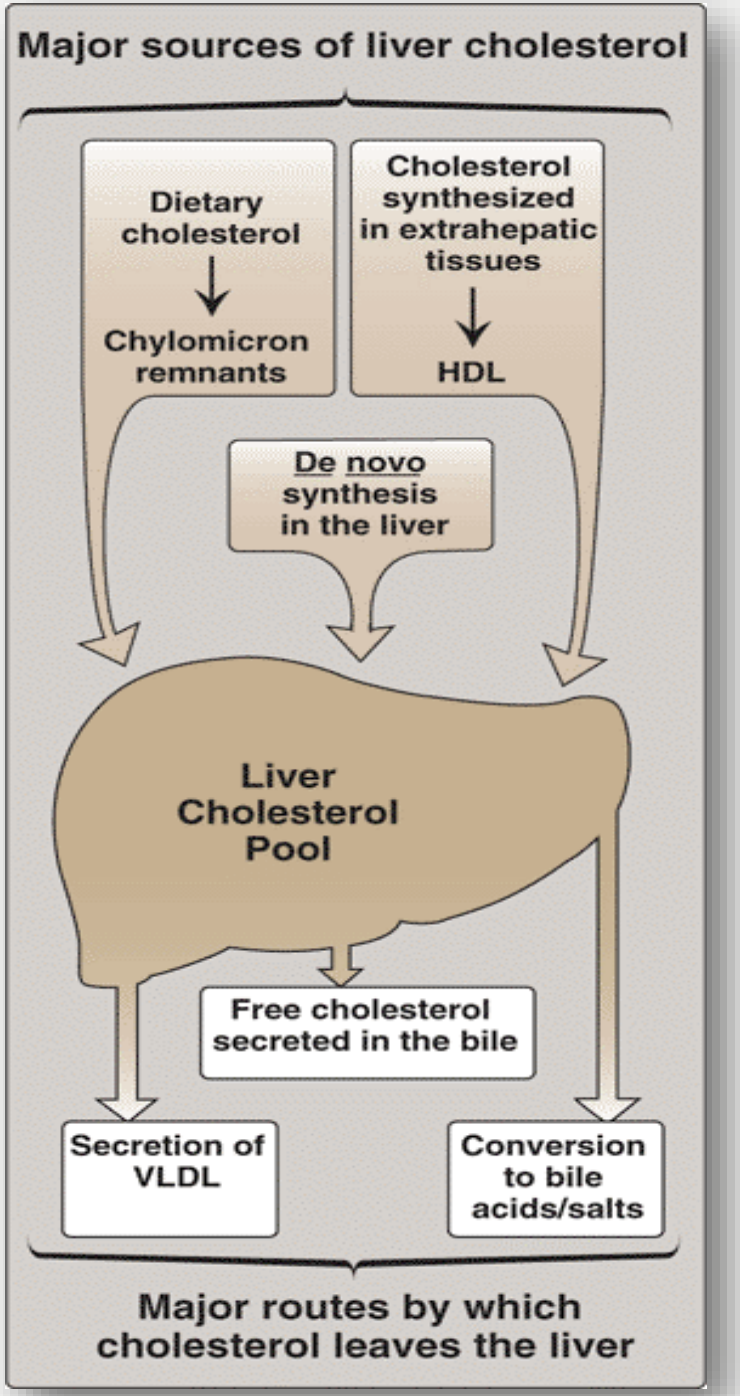
- Cholesterol is eliminated from the liver:

1- as a free cholesterol secreted in the bile.

2- by converting it to bile acids\salts.

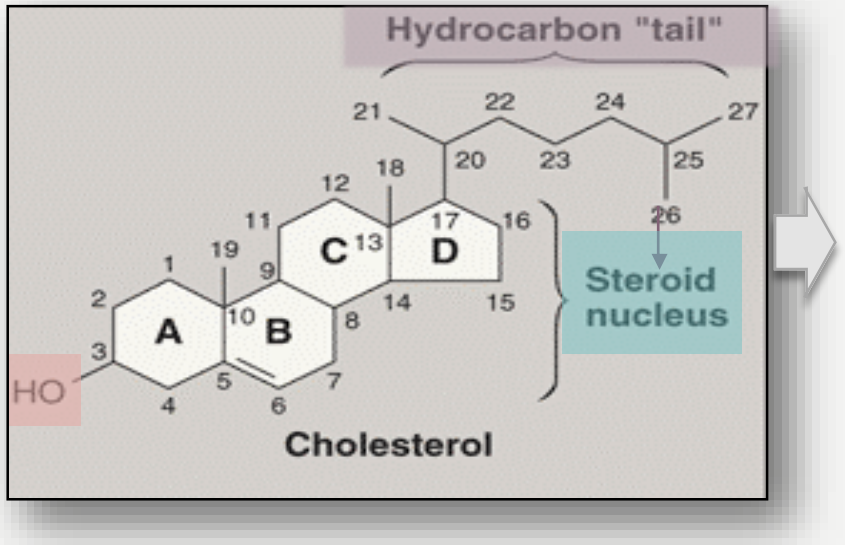
3- by secretion of VLDL.

Regulation of cholesterol



Cholesterol structure:

Cholesterol is the major steroid in animal tissues.



- Cholesterol is a very hydrophobic compound.
- It has a **27-carbon structure**, which contains:

Four fused hydrocarbon rings "Steroid nucleus"

Hydroxyl group "attached to C3"

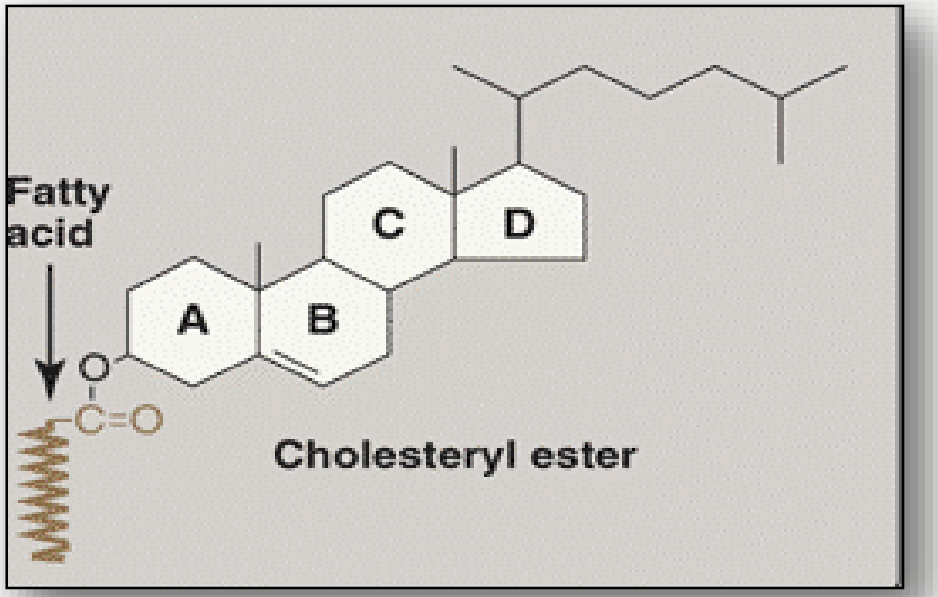
Hydrocarbon tail "attached to C17"

Extra: Steroid Vs Sterols

- Sterols are steroids but with hydrocarbon tail at C17 and hydroxyl group at C3 (that means Cholesterol is a kind of alcohol).
- all the sterols are steroids, but not all the steroids are sterols.
- Cholesterol is a sterol, thus it is a steroid.

Cholesteryl ester:

- Most plasma's cholesterols are esterified "with fatty acid attached at their C3".
- They're **more hydrophobic** than the un-esterified "free" cholesterol (because of the fatty acid, so it must be transported in association with proteins as a compound of lipoproteins or be solubilized by bile salts).
- Membranes → not present
- Most cells → present in small amounts.

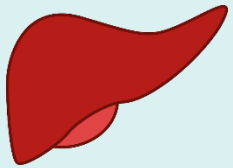


Cholesterol synthesis :

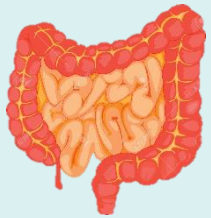
❖ **Location:**

It is located in all tissues, although the major sites are:

- **Liver**



- **Intestine**



- **Adrenal cortex**

- **Reproductive tissues**
  - Testes
  - Ovaries.

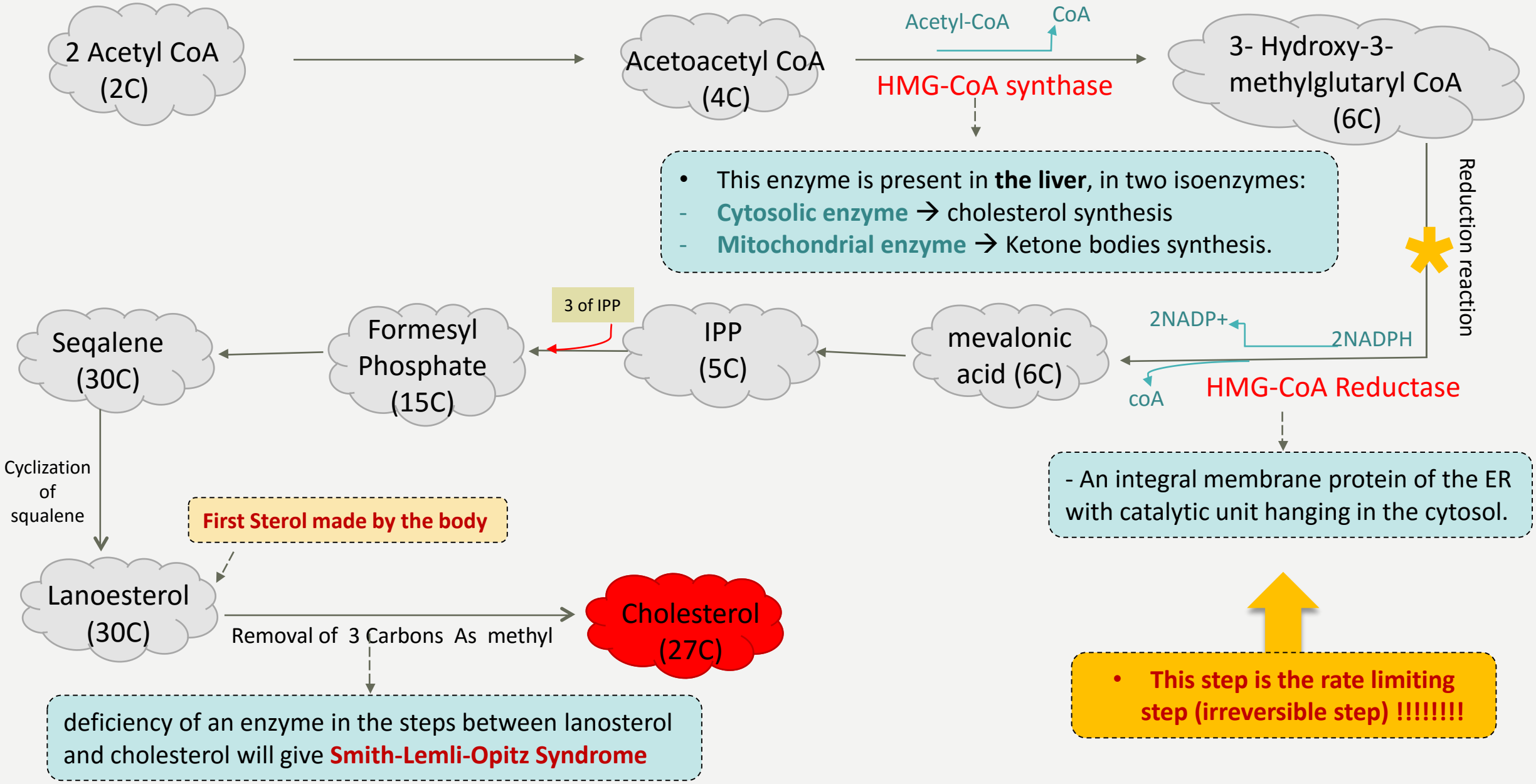
❖ **Source of carbon atoms:** Acetyl-CoA

❖ **Location of the enzymes involved in the biosynthesis:** cytosol + Endoplasmic reticulum.

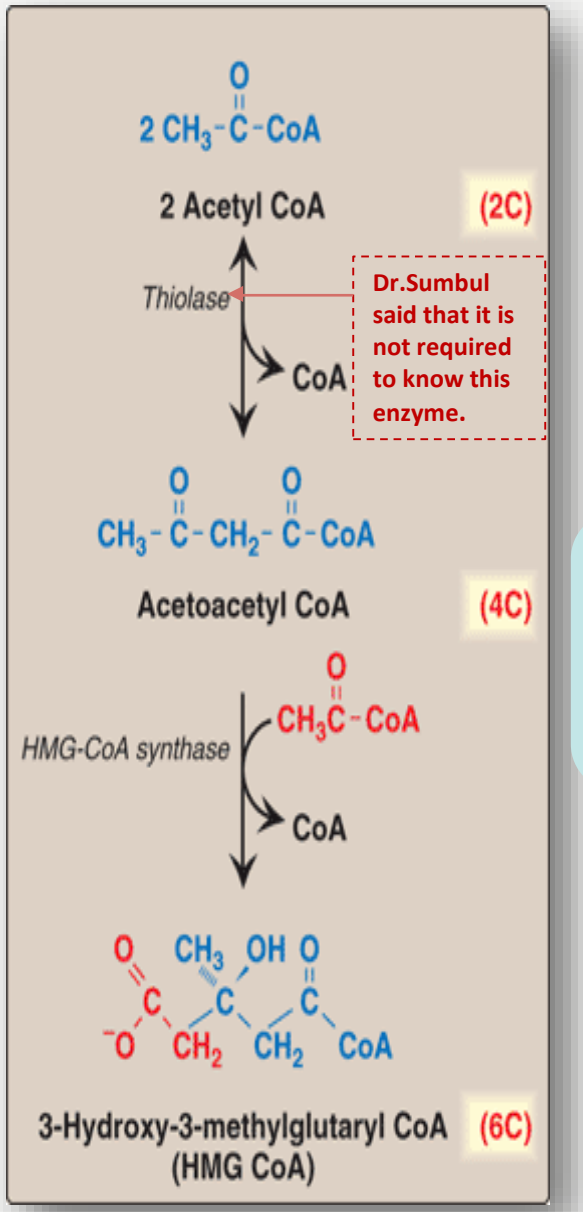
Note:

-cholesterol synthesis occurs in the cytoplasm while the involved enzymes are located in both ER + cytosol.

Cholesterol Synthesis (overview):



1-Synthesis of HMG CoA



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

HMG CoA synthase is present in:

Mitochondria	Cytosol
Involved in ketogenesis (Ketonbodies formation)	Involved in cholesterol synthesis

- 2 Acetyl CoA fuse to form → Acetoacetyl CoA by thiolase.
- Acetoacetyl CoA+ Acetyl CoA give → 3- Hydroxy-3-methylglutaryl CoA by HMG-CoA synthase.

Notes:

-the 2 initial steps are the same as ketonbodies formation

-2 Isoenzymes for HMG CoA synthase one is in the mitochondria and the other is in the cytosol (Isoenzymes are enzymes having the same function but slightly different structures)

Dr. Ghani said This picture (including the structures, names and information) is really important !!

Cholesterol biosynthesis

2-Synthesis of mevalonic acid

- **Why is it important?**

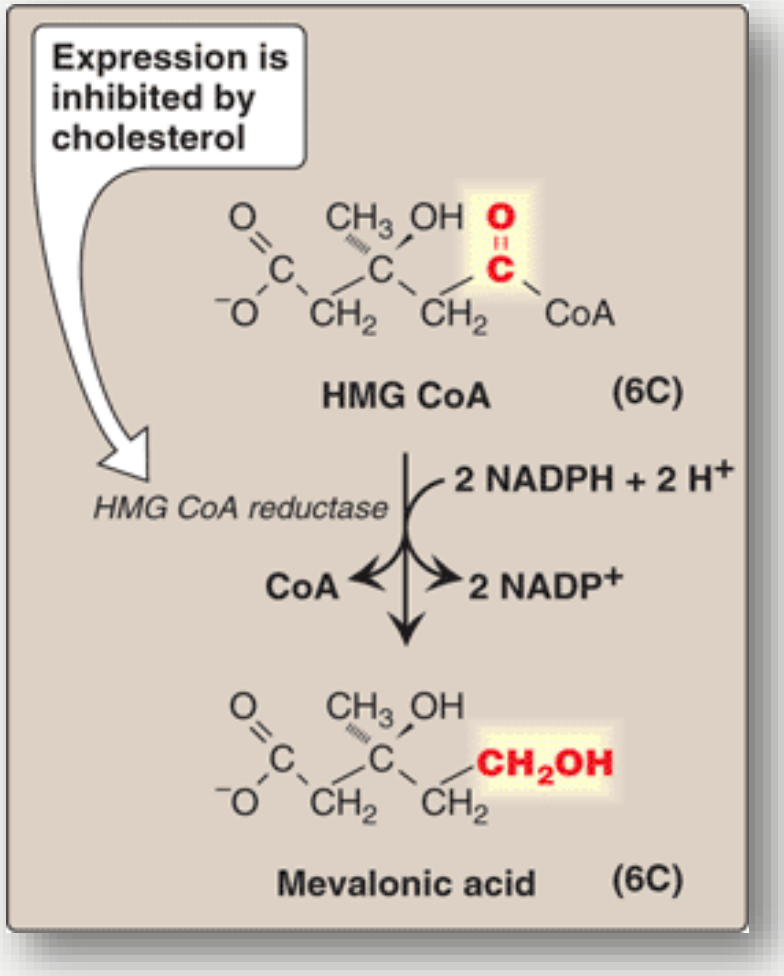
Rate limiting and key step

- **Where does it occur?**

Occurs in 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



Note:

- HMG CoA is reduced to → Mevalonic acid by HMG CoA reductase *in the presence of 2 NADPH + 2H+*

* Note the CoA is out*

- The co-enzyme in this reaction is NADPH.

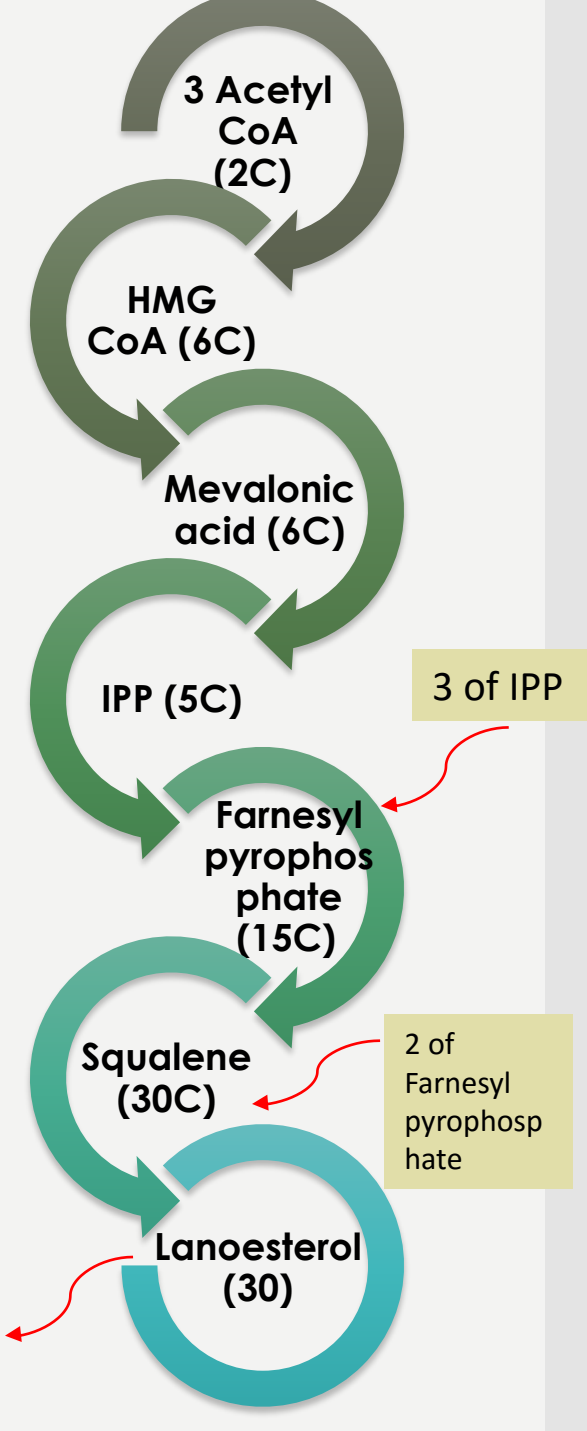
Dr.Sumbul said that this reaction is very important (since it's the rate limiting step), and the most important enzymes in this lecture are: (HMG CoA reductase + HMG CoA synthase)!!

3-Further steps in synthesis

- Production of a 5-carbon unit:
  Isopentinyl pyrophosphate (IPP)
- Condensation to a 30C compound: squalene
- Cyclization of squalene to 30C lanosterol
- Synthesis of 27-Carbon cholesterol (defect in this leads to **Smith-Lemli-Opitz Syndrome**).

Further explanation:

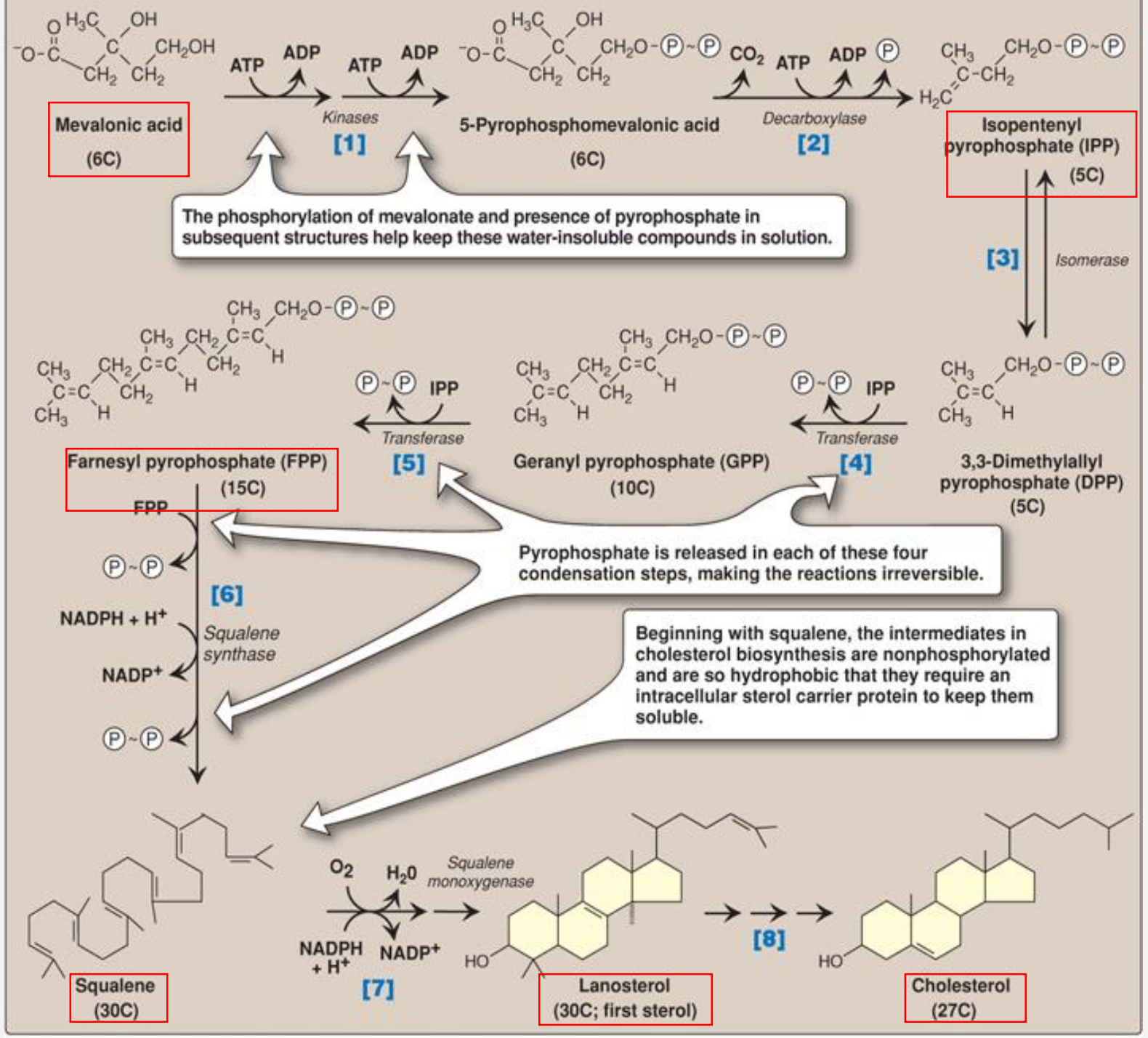
- 3 molecules of isopentenyl pyrophosphate will fuse to form → a 15-carbon unit Farnesyl pyrophosphate *1 isopentenyl pyrophosphate is formed of 5 carbons*.
- 2 molecules of Farnesyl pyrophosphate will give → a 30-carbon unit Squalene.
- Cyclization of squalene gives (Squalene is not yet a fused ring structure *we want to synthesize cholesterol which is a fused ring structure*)→ a 30-carbon unit lanosterol→ removal of 3 C as methyl groups to give→ a 27-Carbon unit cholesterol.
- *deficiency of an enzyme in the steps between lanosterol and cholesterol will give Smith-Lemli-Opitz Syndrome



Notes:

- Lanosterol is the first sterol to be made in the body.

- Farnesyl pyrophosphate is one of the anchoring molecule of protein (anchoring protein to itself in a process called prenylation.



Note:

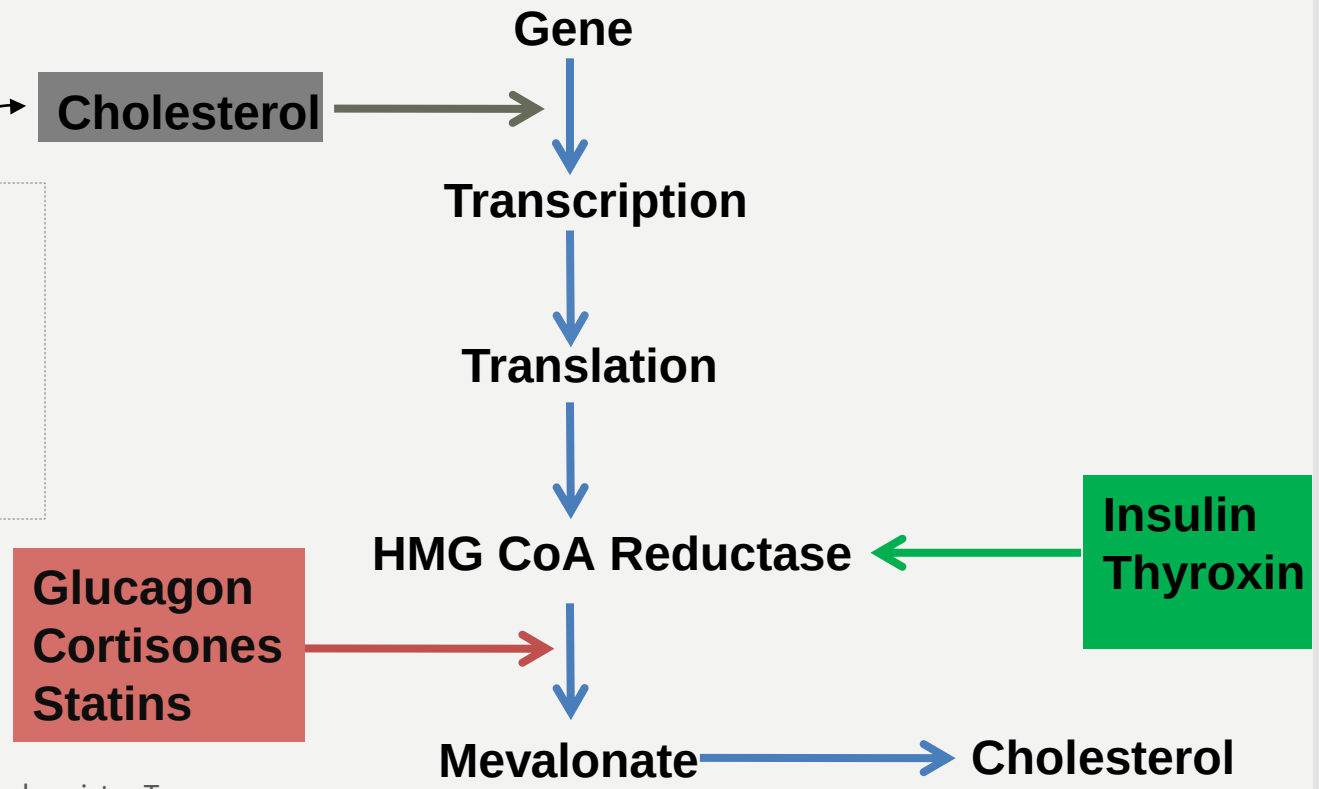
it is not required to know all the steps, just know the marked ones

HMG CoA Reductase Regulation

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

Rate-limiting: the point where you can regulate cholesterol synthesis.
This means if you speed up this process, the cholesterol synthesis will be faster, and if you stop it the synthesis will stop.

The cholesterol regulate (can activate or inhibit) the HMG CoA reductase's genes.
In case of high cholesterol levels, cholesterol will inhibit the transcription of the HMG CoA reductase's genes, and therefore cholesterol synthesis will stop. (feedback inhibition)



HMG CoA Reductase Regulation

Mechanism of regulation of HMG CoA reducatase

1-Sterol-dependent regulation of gene expression

2-Sterol-accelerated enzyme degradation

3-Sterol-independent phosphorylation/dephosphorylation

4-Hormonal regulation

-When sufficient cholesterol is present, transcription is suppressed (inhibited) and vice versa.

يعني إذا أصبحت كمية الكوليستيرول في الجسم كافية راح يثبط الكوليستيرول الترانسكربشن للجين المسؤول عن تكوين هذا الانزيم وبالتالي تتوقف عملية تكوين الكوليسترول بالكامل.

Sterol refers to cholesterol , which means this mechanism is depend on cholesterol.

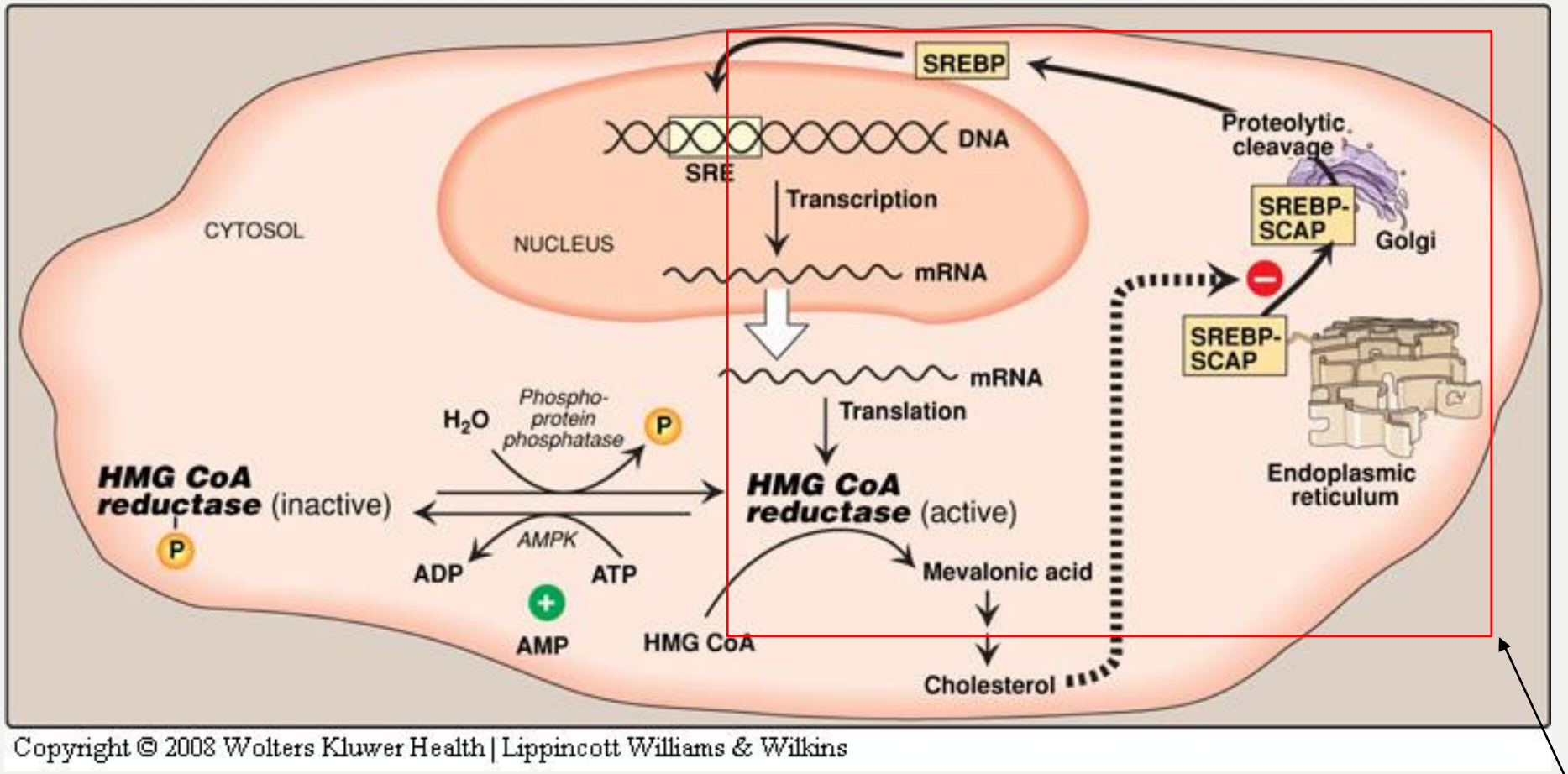
-Sterol Regulatory Element (SRE) is a recognition sequence in the DNA

-SREBP (SRE binding protein) binding to SRE is essential for transcription of this gene.

SREBP is the transcription factor for the gene that making HMG CoA. Every gene has a transcription factor, without it the transcription won't happen.

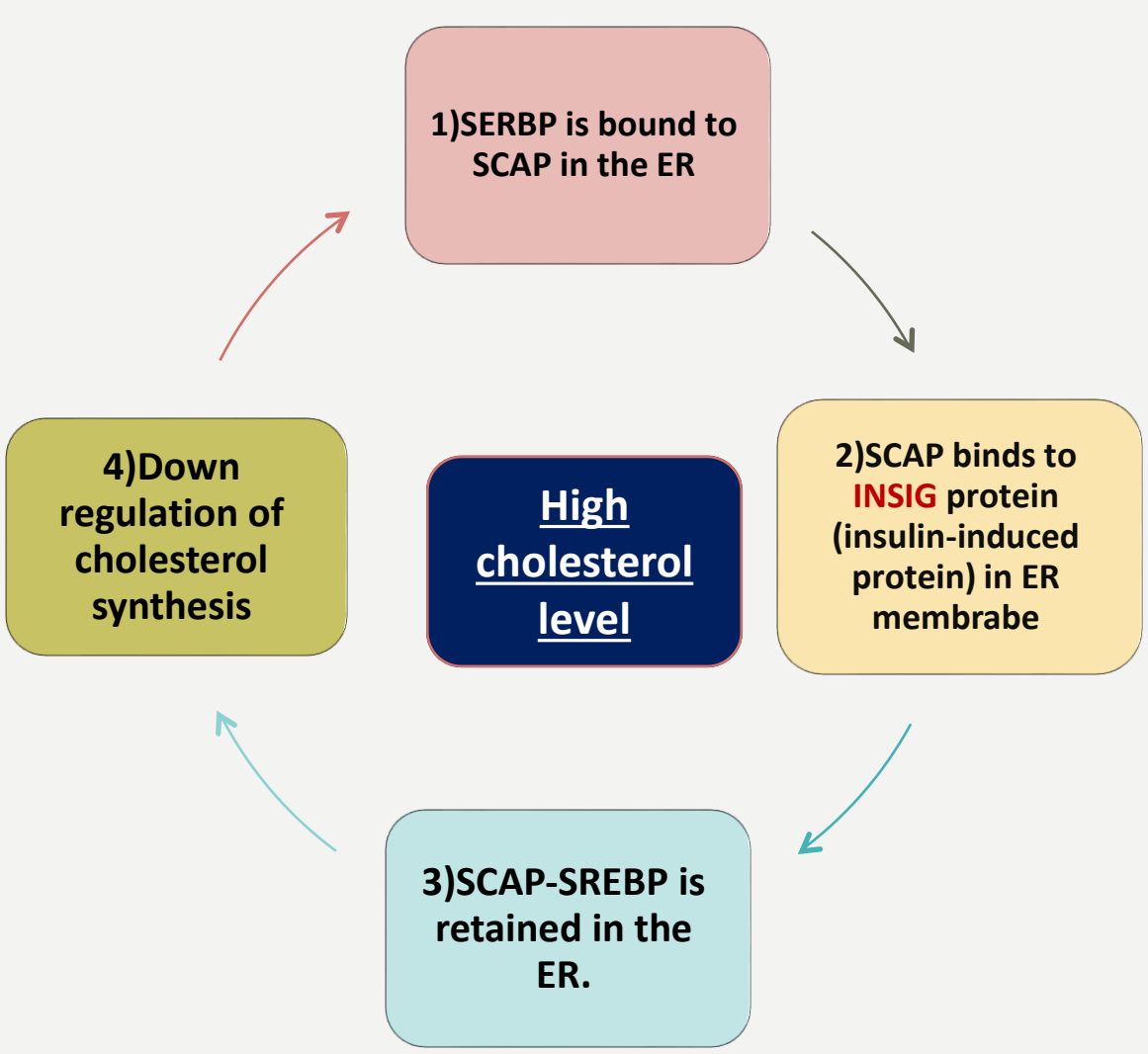
-SREBP cleavage-activating protein (SCAP) is an intracellular cholesterol sensor.

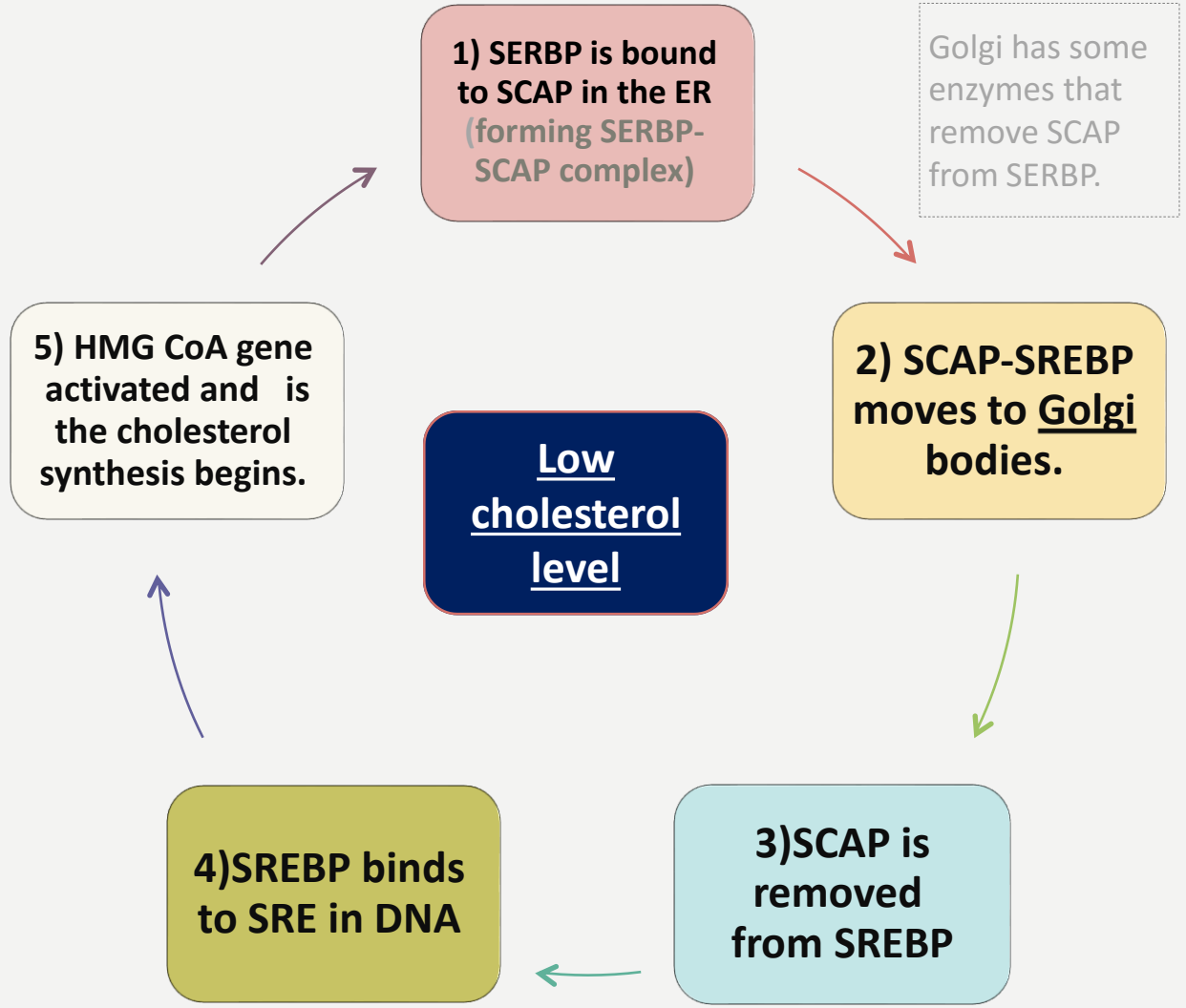
Sterol-dependent regulation



Sterol dependent regulation

Sterol-dependent regulation





Mechanism of regulation of HMG CoA reductase

1-Sterol-dependent regulation of gene expression

2-Sterol-accelerated enzyme degradation

- When cholesterol is high, HMG coA reductase itself binds to insigs, leading to degradation of HMG reductase.

When cholesterol levels in the cell are high, HMG coA reductase will bind with insig proteins, which ultimately will lead to the degradation of the reductase.
-in other words the INSIG will tag the enzyme, and the other enzymes will destroy it.

3-Sterol-independent phosphorylation/dephosphorylation

4-Hormonal regulation

- Insulin and thyroxine increase upregulation of enzyme expression. (cholesterol synthesis)

- Glucagon and cortisol have opposite effect (Decrease Cholesterol synthesis).

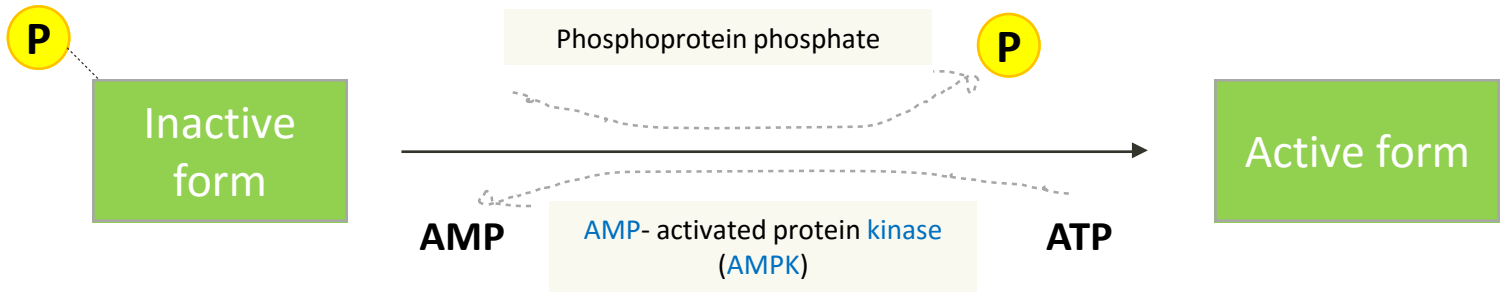
Mechanism of regulation of HMG CoA reductase

1-Sterol-dependent regulation of gene expression

2-Sterol-accelerated enzyme degradation

3-Sterol-independent phosphorylation & dephosphorylation

4-Hormonal regulation



❖ **Forms of HMG CoA reeducates:**

1- **Phosphorylated** form of enzyme is inactive

2- **Dephosphorylated** form is active

- **AMP- activated protein kinase (AMPK)** → adds phosphate group → inactivates the enzyme
- **Phosphoprotein phosphate** → Removes phosphate group → activates the enzyme

❖ Low ATP or High AMP → cholesterol synthesis decreases (so it phosphorylate it so it'll be inactive)

↑ **AMP** ↓ Decrease cholesterol synthesis

↑ **ATP** ↑ Increase cholesterol synthesis

Note: Low ATP means that ATP is converted to AMP.

STEROL-INDEPENDENT PHOSPHORYLATION&DEPHOSPHORYLATION

very detailed picture "you can skip this slide if you don't want to get confused":

We've mentioned in the previous slide that the enzyme HMG reductase has two forms:

- The active dephosphorylated from
- the inactive phosphorylated form.

So in the "Sterol-independent phosphorylation & dephosphorylation" type of regulation, we want to add or remove phosphate group, in order to activate or inactivate the enzyme!

The question is **"how do we get that phosphate group?"**

The answer is:

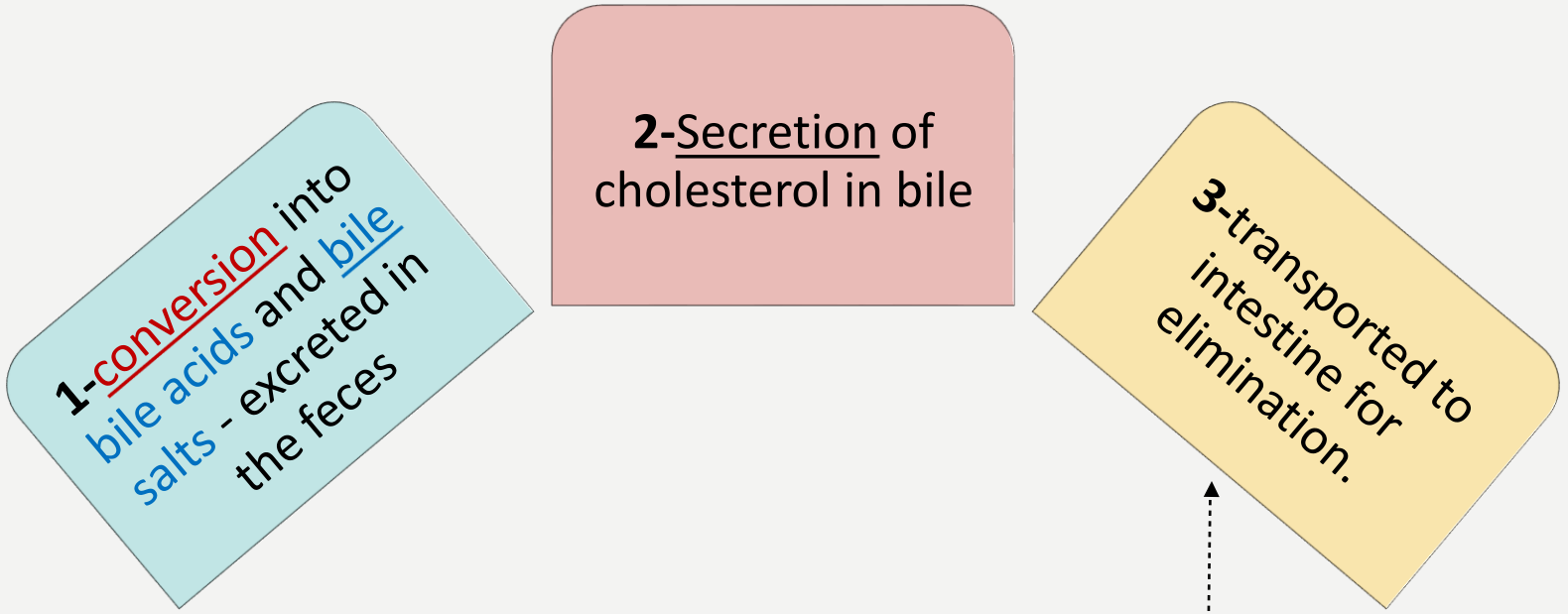
ATP will get converted into ADP by AMPK, and its phosphate group will bind to an adenosine to make an AMP, this AMP finally will give its phosphate group to the enzyme and phosphorylate it.

This explains why cholesterol synthesis decreases when AMP levels are high.

→ high ATP level means that it wasn't converted to AMP, therefore the enzyme won't get phosphorylated and it will still be active.

→ High AMP level means that the ATP level is low (ATP has given its phosphate group to adenosine).

EXCRETION OF CHOLESTEROL



Note: Cholesterol can't be destroyed or converted to CO_2 and water like glucose

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

Excretion of cholesterol

HYPERCHOLESTEROLEMIA

What is "Hypercholesteremia"?

- **High concentration of cholesterol in blood,** due to the loss of regulation of cholesterol synthesis.

Leads to: **Atherosclerosis**

Treatment:

	Statin drugs	beta-Sitosterols / Phytosterols
What are they?	**Drugs used to decrease plasma cholesterol levels.**	They are **plants cholesterols** that are clinically useful in : the **dietary treatment of hypercholesterolemia** by decreasing Cholesterol level
Mechanism:	- They're structural analogs of HMG CoA reductase (have the same structure as the enzyme) that inhibit its enzyme activity by **competitive inhibition**.	- They block the absorption of dietary cholesterol, therefore they decrease cholesterol level

Summary

Cholesterol Metabolism	
General information.	1- Most important animal steroid. 2- Maintains membrane fluidity. 3- Insulating effect on nerve fibres
Parent molecule for	**bile acid/salt, steroid hormones and vitamin D3**
Source of liver cholesterol	1- dietary cholesterol → chylomicron remnants. 2- cholesterol synthesized in extrahepatic tissue → HDL 3- de novo synthesis in liver . note: Liver plays a **central role** in cholesterol regulation
Cholesterol leaves the liver as	secreation of VLDL, free cholesterol secreted in bile, or conversion to bile acid/salt

Cholesterol & cholesteryl	
Cholesterol	(steroid nucleus with hydrocarbon + HO) - found in membrane, synthesized in all tissue. - major site : liver, adrenal cortex, testes/ovaries, and intestine.
cholesteryl	1- Plasma cholesterol esterified with fatty acid 2- more hydrophobic 3-not found in membrane 4- found in most cells in small amount.

Synthesis of HMG CoA & Mevalonic acid	
HMG CoA	Present in both cytosol and mitochondria of liver cells . Acetyl CoA → by thiolase enzyme → acetoacetyl CoA → by HMG CoA synhase → HMG CoA
Mevalonic	HMG CoA → by **HMG CoA reductase** (Rate limiting and key step) →**mevalonic acid** (occur in cytosol)

Summary

Cholesterol synthesis	
Further steps in synthesis	• Production of 5-carbon unit (Isopentinyl pyrophosphate (IPP) • Condensation to a 30C compound: squalene • Cyclization of squalene to 30C lanosterol • Synthesis of 27-Carbon cholesterol
Defect in 27-carbon synthesis leads to	Smith-Lemli-Opitz Syndrome
Regulation of Cholesterol Synthesis	By HMG reductase
HMG CoA Reductase Regulation	• Sterol-dependent regulation of gene expression (SCAP is the sensor) • Sterol-accelerated enzyme degradation • Sterol-independent phosphorylation/dephosphorylation (low ATP or high AMP) decrease cholesterol. • Hormonal regulation (insulin or thyroxine increase gene expression, glocagon & cortisol do the opposite.)
Excretion of cholesterol	• In bile then transport to intestine for elimination. • note : some cholesterol is converted by bacteria into coprostanol and cholestanol before excretion
Hypercholesterolemia	• High conc. of cholesterol in plasma
Treatment	• Statins drugs(inhibit HMG enzyme activity by competitive inhibition) • b-Sitosterols/ Phytosterols (Block the absorption of dietary cholesterol)

MCQs

1.When HMG CoA is present in mitochondria what will produce:

A. gloconeogensis
B. ketogenesis
C. cholesterol synthesis
D. glycolysis

2.Bile acids are derived from:

A.Cholesterol
B. Amino acids
C. Fatty acids
D. Bilirubin

3. what will happen in case of high cholesterol levels:

A. Transcription of HMG coA reductase's gene
B. HMG coA reductase is inhibited
C. hypercholesterolemia
D. both B and C

4.what is the function of insig protein :

A. moves SREBP-SCAP to golgi for cleavage
B. binds to SCAB and retains SCAP-SREBPin ER
C. it is an HMG CoA reductase
D. none of the above

5.which one of the following hormones increase cholesterol synthesis :

A. insulin
B. glucagon
C . Cortisol
D. estrogen

6. All carbon units of the cholestrol are derived from :

A. sualene
B. Acetyl CoA
C. mevalonic acid
D. IPP

1. B
2. A
3. D
4. B
5. A
6. B

MCQs

7. case of cholesterol metabolism, Increased AMP will lead to :

A. phosphorylation and increase in cholesterol synthesis.
B. dephosphorylation and increase in cholesterol synthesis.
C. phosphorylation and inhibition of cholesterol synthesis.
D. dephosphorylation and increase in cholesterol synthesis.

8. statin drugs inhibit the synthesis of the enzyme HMG CoA reductase by :

A. reversible inhibition.
B irreversible inhibition.
C. competitive inhibition.
D. uncompetitive inhibition.

9. First Sterol made by the body is:

A. IPP.
B. Squalene.
C. Lanoesterol.
D. cholesterol.

10. HMG CoA reductase is present in:

A. ER membrane.
B. cytosol.
C. Nucleus.
D. Golgi apparatus.

10.A
9.C
8. C
7. C

Team Members:

- نوره الرميح.
- بدور جليدان.
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- علا النهير.
- دلال الحزيمي.
- أفنان المالكي.
- خوله العريني.
- رهف بن عباد.
- غاده القصيمي.
- منيره العمري.
- نوف الرشيد.

- خالد النعيم .
- ثاني معافا .
- فارس المطيري.
- زياد العنزي .
- محمد الصهيل .
- إبراهيم الشايع .
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