Biochemistry
Team 434

Cholesterol metabolism

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overview

- Introduction
- Cholesterol structure
- Cholesteryl esters
- Cholesterol synthesis
- Regulation of cholesterol synthesis
- Excretion of cholesterol
- Hypercholesterolemia and treatment

color index:

Red: important
Grey: explanation

Cholesterol:

Most important animal steroid.

Maintains membrane fluidity.

cholesterol is a part of the body system (cell membrane) gives fluidity (flexibility) to the membranes

Insulating effect on nerve fibres.

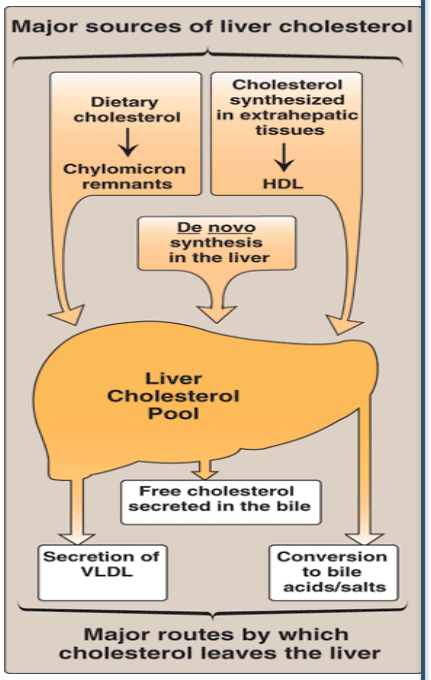
Cholesterol is the parent molecule for:

1-Bile acids and bile salts: **IMPORTANT in digestion of other lipids.**

2-Steroid hormones

3-Vitamin D_3

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



- **Liver processes all of your cholesterol**
- **Major sources of cholesterol (cholesterol is water insoluble):**
  1. Diet (food), blood cannot dissolve it, absorbed from intestine to blood and transported in blood by chylomicrons to the liver
  2. Synthesized by tissues, transported by HDL hormone to the liver
  3. The liver itself makes cholesterol
- **How does it go out of the body? major routes:**
  1. Free cholesterol secreted in bile
  2. Secretion of VLDL (Very Low Density Lipoprotein
  3. Conversion to bile acids/salts

Cholesteryl esters

Most plasma cholesterol is esterified with a fatty acid.

CEs are not present in membranes.

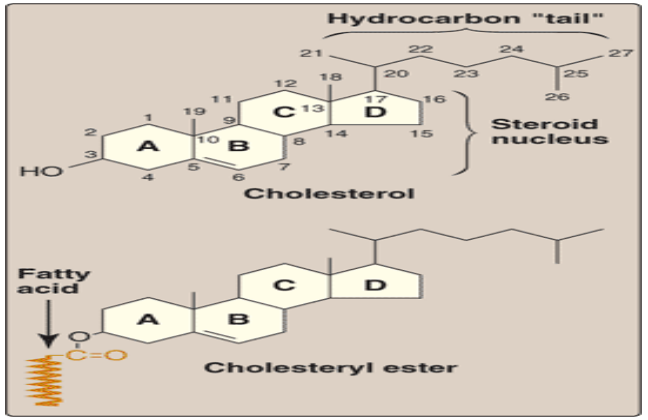
Present in small amounts in most cells.

More hydrophobic than cholesterol.

Cholesterol structure:

Cholesterol is a 27 carbon compound.

- A steroid has 4 rings
- In cholesterol:
  - Carbon 3 has hydroxyl group
  - Carbon 17 has hydrocarbon tail attached to it
- cholesterol in the blood is in the form of cholesteryl ester (hydrophobic)



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.

Enzymes involved in biosynthesis are partly located in ER* and partly in cytoplasm.

Synthesis of HMG CoA:

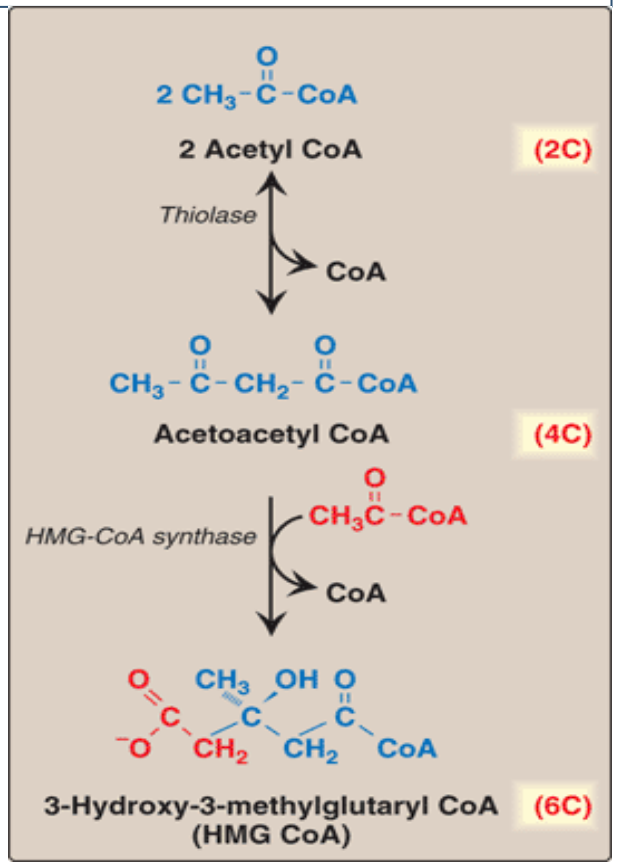
Starts with: Acetyl CoA ⟹ Acetoacetyl CoA ⟹ HMG CoA.

- Acetyl CoA has two carbon molecules
- NO need to memorize the structures
- 3 molecules of Acetyl CoA gives us a 6 carbon compound which is HMG CoA

HMG CoA is present in both cytosol and mitochondria of liver

Mitochondrial as: ketogenesis*

Cytosolic as: cholesterol synthesis



*endoplasmic reticulum.

*the process of breaking down fatty acid by Keton bodies.

Synthesis of mevalonic acid:

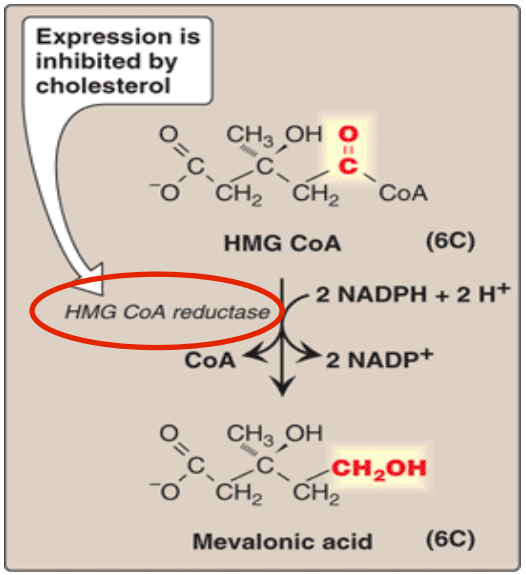
very important step

Rate limiting and key step. This is the step that we target if we want to limit the synthesis of mevalonic acid.

Occurs in cytosol

HMG CoA reductase* is an ER membrane enzyme with catalytic unit hanging in the cytosol

*Mevalonic acid is 6 carbon compound.



Further steps in synthesis

Production of a 5-carbon unit:

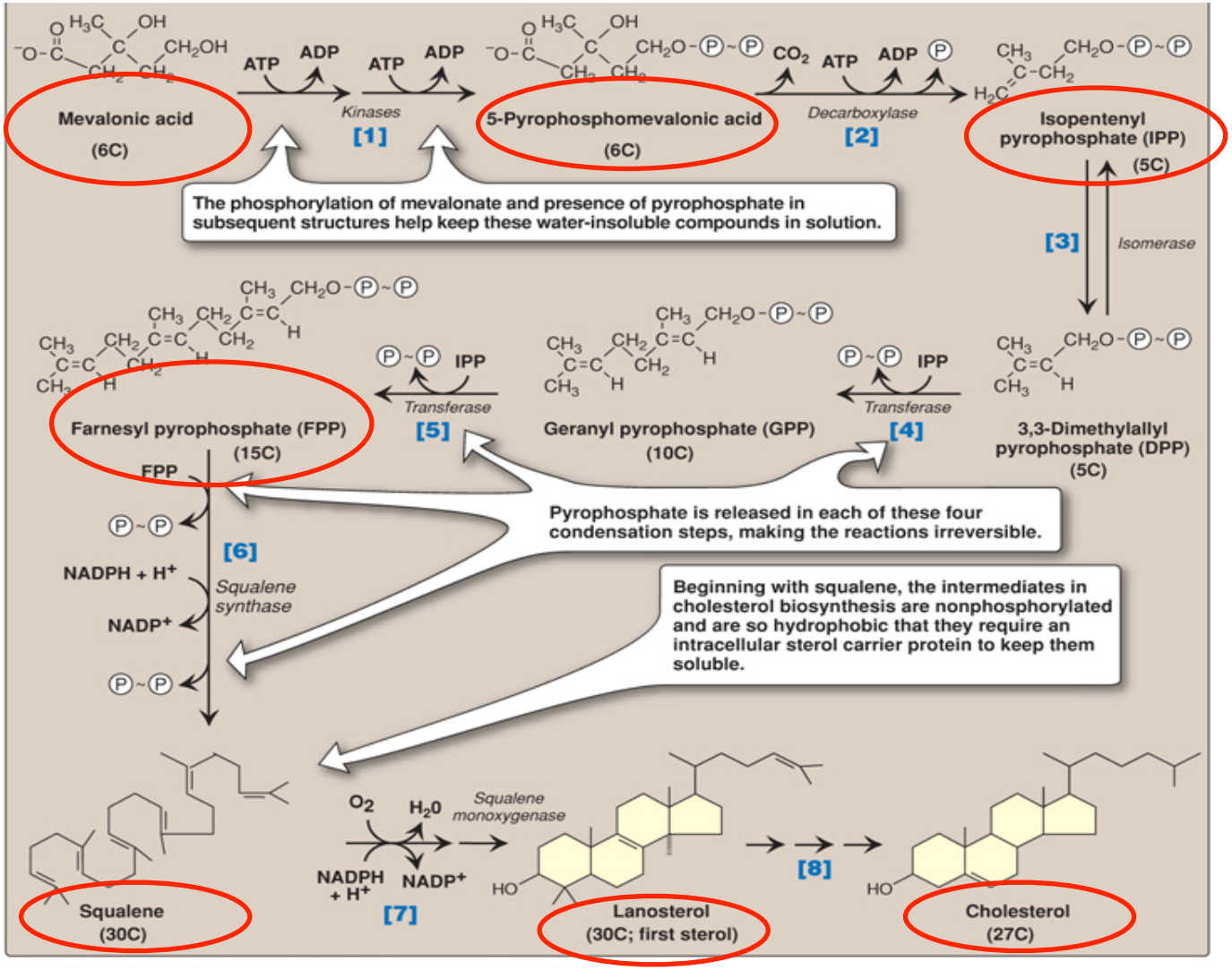
Isopentinyl pyrophosphate (IPP)

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).

*chlesterol synthesis depends on the activation of this enzyme.



Additional info for you:
FPP has an anchoring function.

Don't go into details of the steps

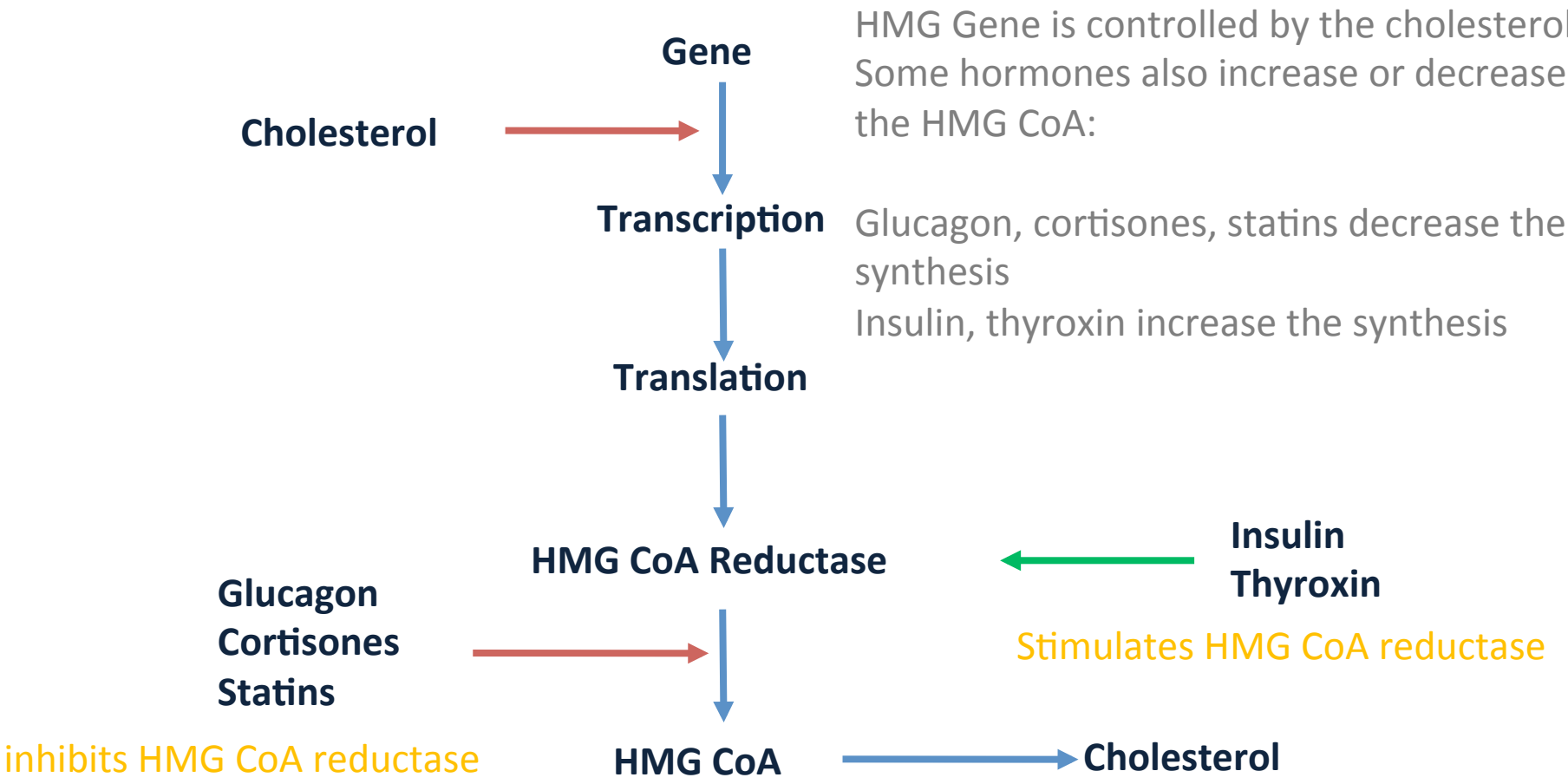
Notice that:

- 1st sterol made in the body is **Lanosterol**
- Partent molecule of cholesterol synthesis is **Acetyl CoA**

Regulation of Cholesterol Synthesis:

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

HMG CoA Reductase Regulation:



HMG Gene is controlled by the cholesterol
Some hormones also increase or decrease the HMG CoA:

Glucagon, cortisones, statins decrease the synthesis
Insulin, thyroxin increase the synthesis

NOTES :

- Before going deep to the details you should know the followings :
- HMG CoA reductase is the rate limiting enzyme in cholesterol synthesis so it is the site of regulation .
- SRE : stands for Sterol Regulatory Element (a special sequence of the DNA resembles the reductase gene)
- SREBP-2 stands for SRE binding protein is an integral ER membrane protein .
- SCAP stands for SREBP cleavage-activating protein is another ER membrane protein .
- Mechanism of regulation :

If the sterol levels are low(in the cell) :

1- the SREBP2 binds to SCAP

2- the SREBP2-SCAP complex moves to the Golgi

3- generating of a soluble fragments that enters the nucleus and binds to the SRE on the DNA . (transcription factor)

- **This results in increased synthesis of HMG CoA Reductase and so increase of cholesterol synthesis**

If the sterol levels are high (in the cell):

1- SCAP binds to anther ER proteins (insulin-induced protein) we'll talk about next slide)

2- prevention of SREBP2-SCAP complex formation

3- leads to down regulation of cholesterol synthesis .

by binding of HMG CoA to insig and then they will be recognised by proteolytic enzyme and then it will destroy the enzyme, and there will be no more cholesterol synthesis due to: inactivation of the enzyme.

HMG CoA Reductase Regulation:

Sterol-dependent regulation of gene expression.

Sterol-accelerated enzyme degradation.

Sterol-independent phosphorylation/ dephosphorylation.

Hormonal regulation.

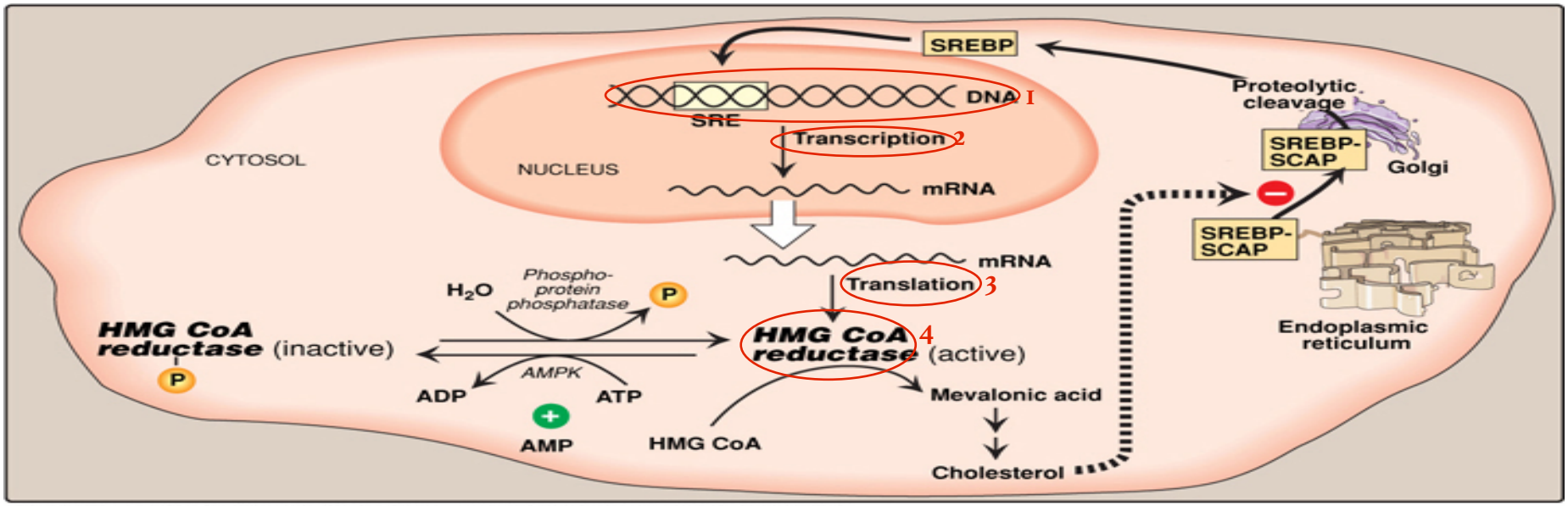
Sterol-dependent regulation of gene expression of HMG CoA:

When sufficient cholesterol is present, transcription is suppressed and vice versa.

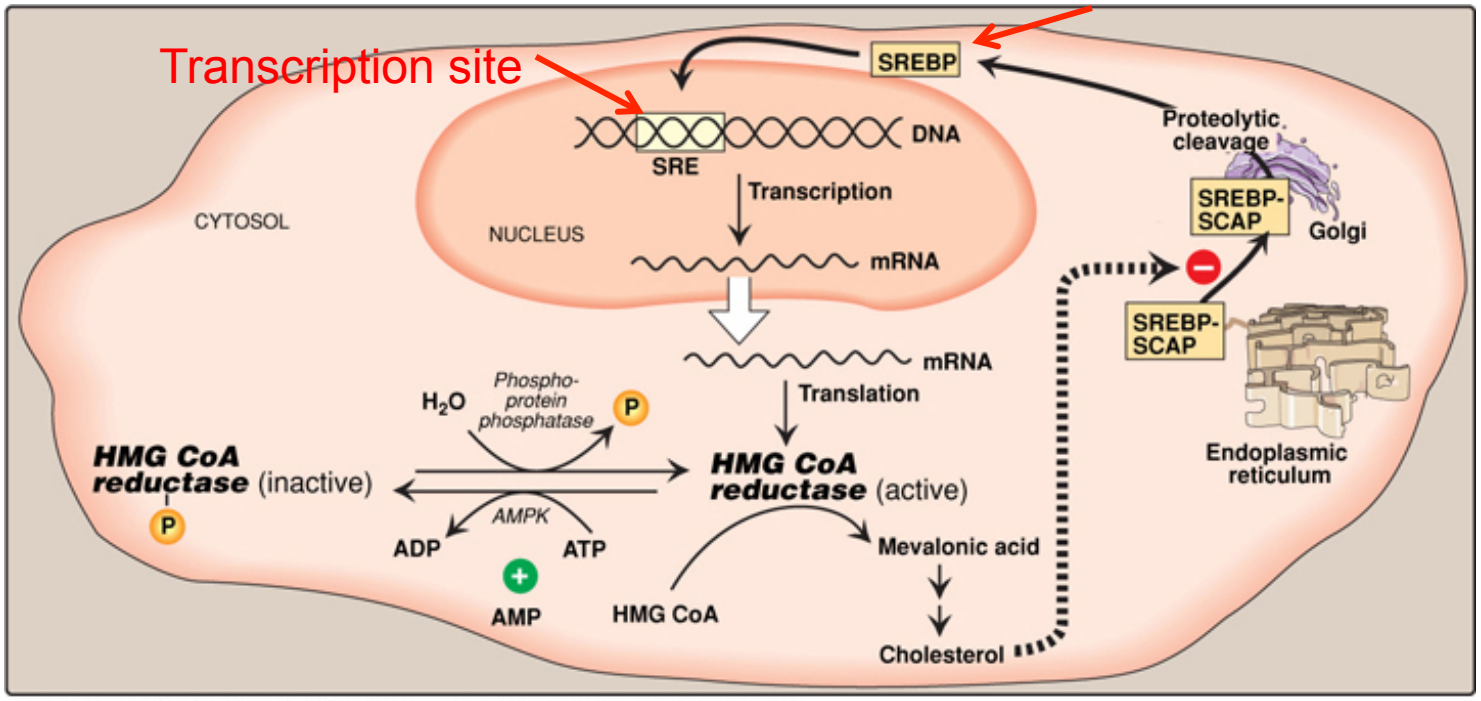
Sterol Regulatory Element (SRE) is a recognition sequence in the DNA.

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

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



Transcription factor is like a key



If cholesterol levels are low in the body:

Signals go to the ER and causes SREBP-SCAP complex to get sent to golgi

Usually SREBP is inactive because it's binding to SCAP

So when cholesterol levels are low, golgi breaks the SREBP-SCAP complex →SREBP becomes active, goes to the nucleus and starts the transcription → increases the amount of HMG CoA reductase

If cholesterol levels are high:

Signals are sent to ER

The SREBP-SCAP won't be sent to golgi because insig protein binds to the complex and keeps it in the ER

Sterol-dependent regulation

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

Ubiquitin is a small protein (like a flag) to mark a molecule such as (HMG CoA reductase) to get degraded by (proteasome)

Enzyme phosphorylation and dephosphorylation:

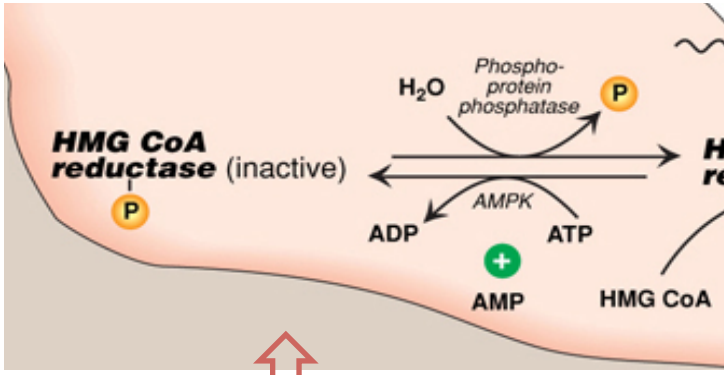
AMP- activated protein kinase (AMPK) for phosphorylation

Phosphorylated form of enzyme is inactive

Dephosphorylated form is active

Low ATP or High AMP → cholesterol synthesis decreases. **because of the phosphorylation.**

Phosphoprotein phosphatase removes phosphate group.



Phosphoprotein phosphatase removes phosphate group

Hormonal Regulation:

Insulin and thyroxine increase up-regulation of enzyme expression.

Glucagon and cortisol have opposite effect.

Cholesterol excretion:

By conversion into bile acids and bile salts- excreted in the feces.

Secretion of cholesterol in bile. **(mainly)**

Transported to intestine for elimination.

In the intestine, some cholesterol is converted by bacteria into coprostanol and cholestanol before excretion.

Hypercholesterolemia:

High conc. of cholesterol in blood.

Leads to atherosclerosis.

Statin drugs are used to decrease plasma cholesterol levels.

Statins are structural analogs of HMG CoA reductase.

Statins inhibit enzyme activity by competitive inhibition.

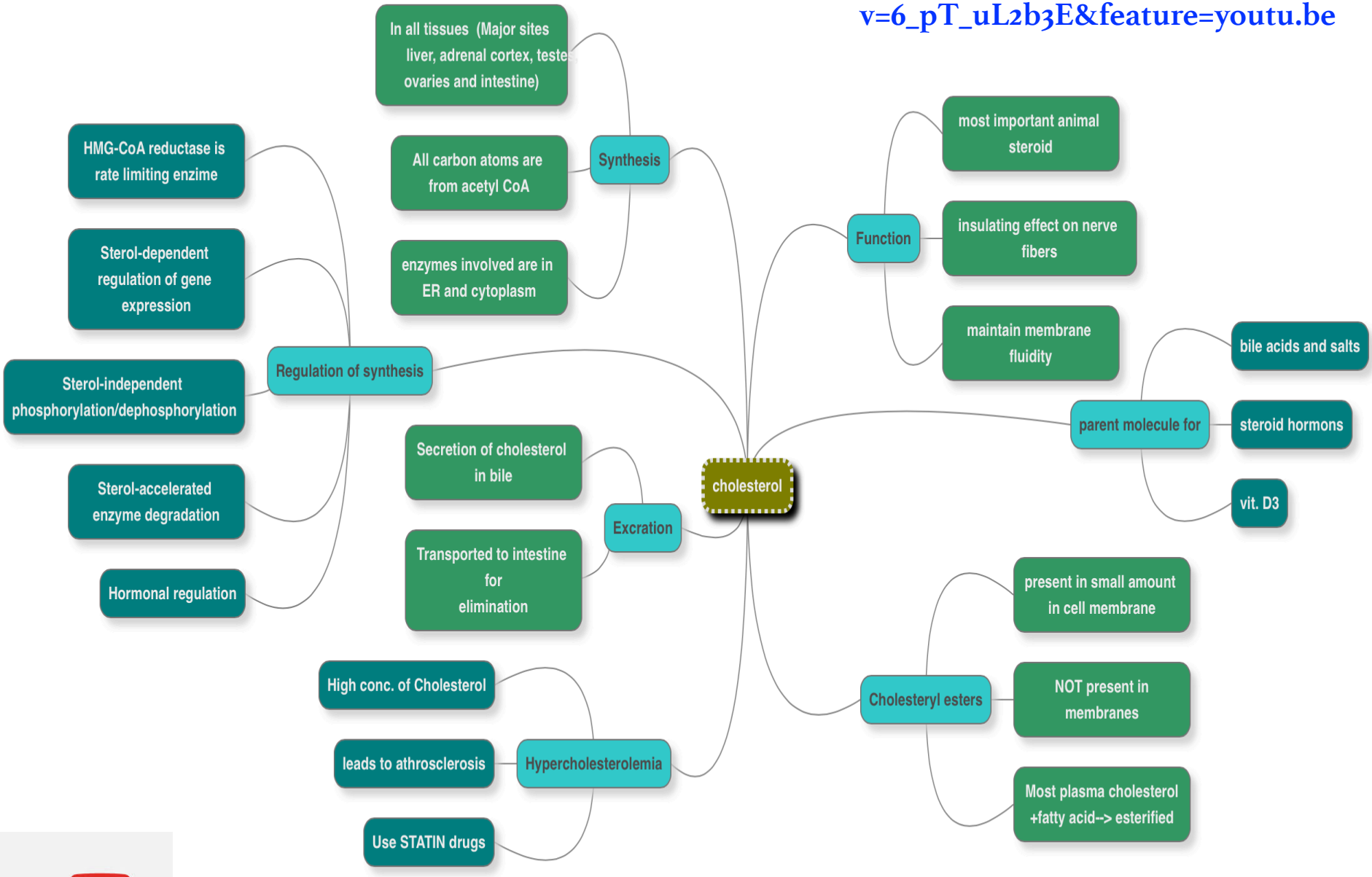
β-Sitosterols/ Phytosterols:

Plant sterols and are poorly absorbed by humans.

Block the absorption of dietary cholesterol.

Clinically useful in the dietary treatment of hypercholesterolemia.

https://www.youtube.com/watch?v=6_pT_uL2b3E&feature=youtu.be



Biosynthesis of Cholesterol

https://www.youtube.com/watch?v=u-JPWcGnJpk

1- STATIN DRUGS INHIBIT THE SYNTHESIS OF THE ENZYME HMG COA REDUCTASE BY:

A- IRREVERSIBLE INHIBITION
B- COMPETITIVE INHIBITION
C- UNCOMPETITIVE

2- Bile acid are derived from:

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

3- What happens if cholesterol concentration is high?

A. Gene transcription of HMG coA eductase is stimulated
B. HMG CoA reductase is degraded
C. Hypercholesterolemia
D. B & C

4- What is the funtion of insig proteins regarding cholesterol synthesis?

A. Moves SREBP-SCAP to golgi to cleave SCAP off
B. It is an HMG CoA reductase analog
C. Binds to SCAP and prevent it from exiting ER in certain condetions
D. None of the above

5- All carbons units of cholesterol are derived from:

A. Squalene
B. Mevalonic acid
C. Acetyl CoA

6- Increasing of AMP- activated protein kinase will lead to:

A. phosphorelation -> increase cholesterol synthesis.
B. Dephosphorelation ->cholesterol synthesis stopped.
C. phosphorelation -> cholesterol synthesis decreases
D. Dephosphorelation -> increase cholesterol synthesis.

Answers:

1-B	2-A	3-D	4-C	5-C	6-C

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