editing file

Cholesterol Metabolism

Color Index:

- Original content
- Important
- Extra info, Dr's notes

Objectives:

Slide (3,4)	Understand the structure and functions of cholesterol
Slide No. 3	Discuss the regulation of cholesterol homeostasis in the body
Slides (5-7)	Comprehend the important steps of cholesterol synthesis pathway
Slide No. 8	Identify different levels of regulation of cholesterol synthesis
	Discuss the association of hypercholesterolemia with abnormal cholesterol metabolism
Slide No. 12	Understand the role of statins in the treatment of hypercholesterolemia

Overview:

- Introduction
- Cholesterol structure
- Cholesteryl esters
- Cholesterol synthesis
- Rate limiting step
- Regulation of cholesterol synthesis
- Regulation of HMG CoA reductase
- Excretion of cholesterol
- Hypercholesterolemia and treatment

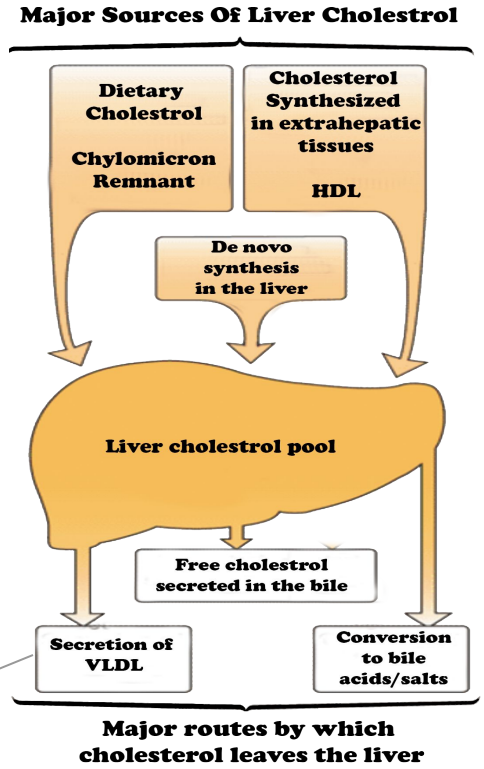
Cholesterol

1. Most important animal steroid
   - in eukaryotic cell membrane
   - Ingestion of animal products ↑cholesterol levels
2. Maintains membrane fluidity
   - facilitate easy transport along the membrane e.g. Electron transport chain
3. Insulating effect on nerve fibres
4. Cholesterol is the parent molecule (precursor) for:
   - Bile acids and bile salts
   - Steroid hormones
   - Vitamin D3

In the tissue gets transformed into

transform into VLDL in the circulation

Liver plays a central role in the regulation of cholesterol homeostasis



* Important for fat digestion

Cholesterol Structure

1. **Steroid nucleus**

four fused hydrocarbon rings

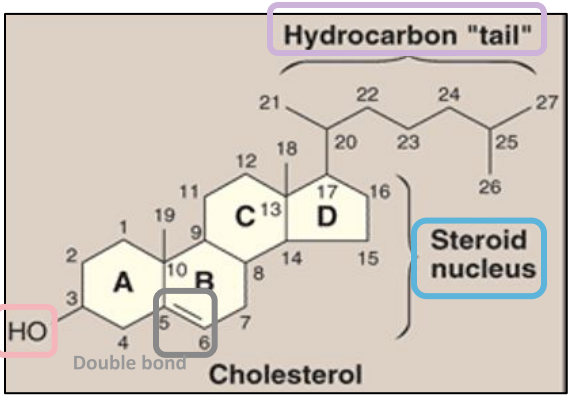
2. **Hydrocarbon tail**

branched hydrocarbon chain attached to carbon 17

3. **Hydroxyl group**

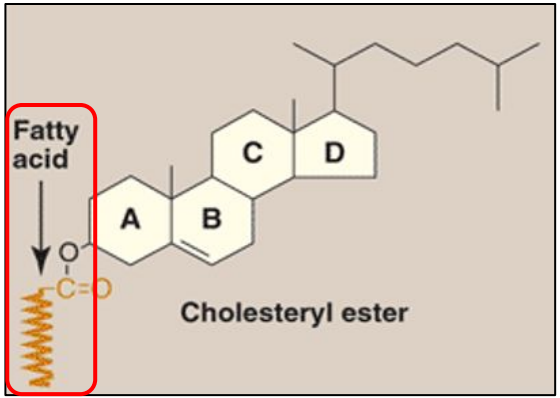
at carbon 3

"makes it **less** hydrophobic, whereas cholesteryl ester has a fatty acid instead of an OH"



Cholesteryl esters

- Most plasma cholesterol is esterified with a fatty acid
- Cholesteryl esters are not present in membranes "free cholesterol is"
- Present in small amounts in most cells
- More hydrophobic than cholesterol



☆ Because of their hydrophobicity, cholesterol and its esters must be transported in association with protein as a component of a lipoprotein particle

Cholesterol synthesis

Synthesized in all tissues

Major sites for Synthesis:

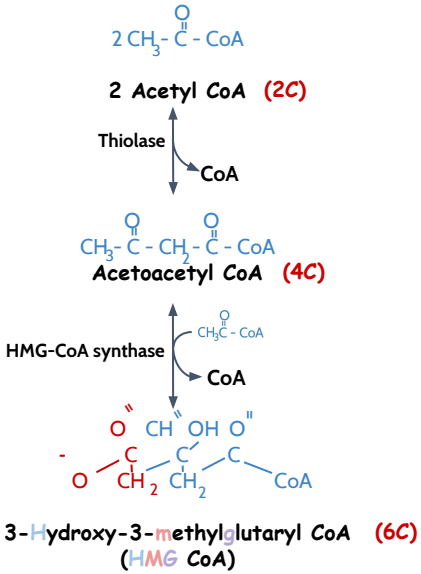
- Liver
- Adrenal cortex
- Testes, ovaries (gonads)
- Intestine

All carbon atoms are derived from acetyl CoA

Enzymes involved in biosynthesis are partly located in Endoplasmic reticulum and partly in cytoplasm

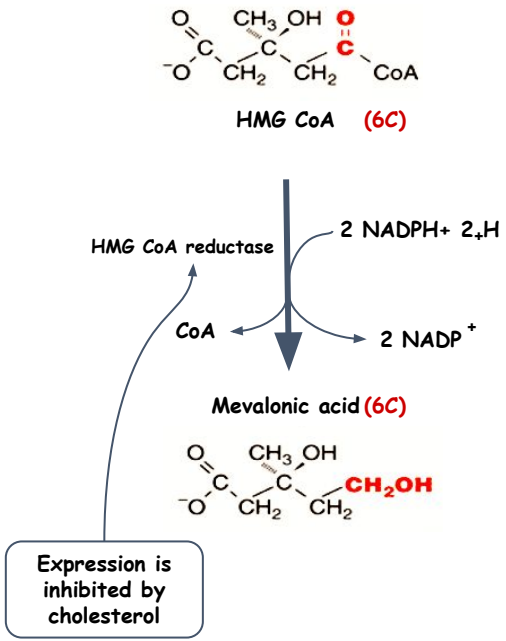
Synthesis of HMG CoA

HMG CoA synthase		
Location	Mitochondria	Cytosol (Cytosolic)
function	ketogenesis	cholesterol synthesis



☆ These first two reactions in the cholesterol biosynthetic pathway are similar to those in the pathway that produces ketone bodies
☆ HMG CoA → 3-Hydroxy-3-Methylglutaryl CoA

Synthesis of mevalonic acid



Rate limiting and key step

☆ Target for drugs controlling cholesterol levels

Occurs in cytosol

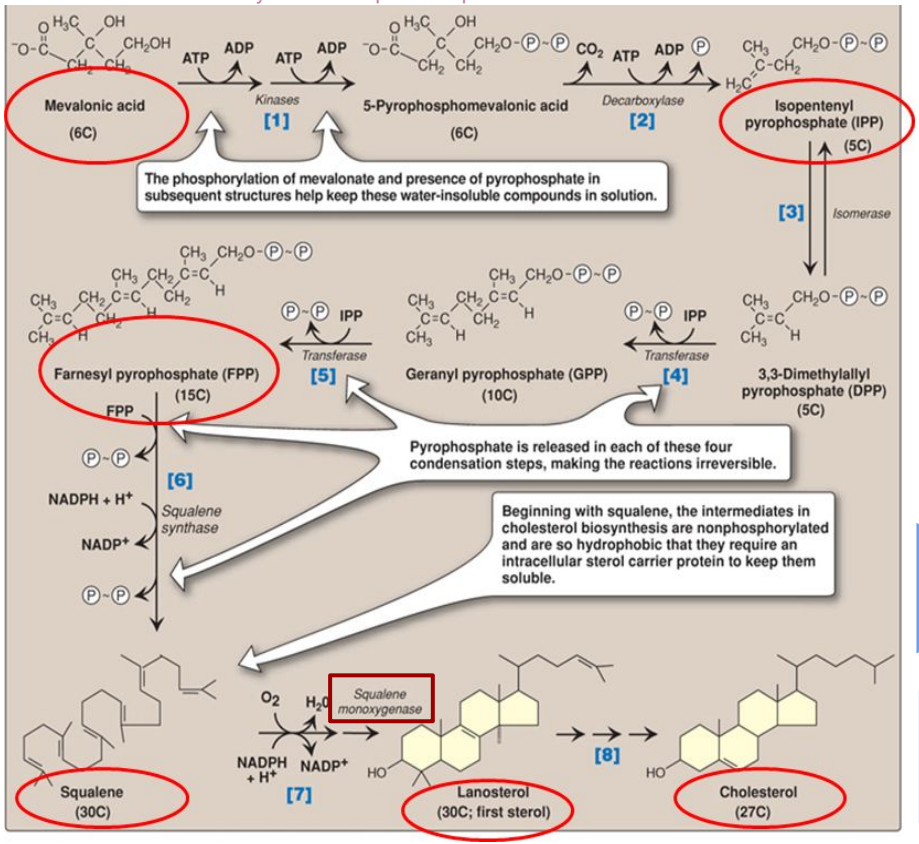
HMG CoA reductase

- Endoplasmic reticulum membrane enzyme
- Catalytic unit hanging in the cytosol

☆ All Cholesterol synthesis occurs in the cytosol. Even with the enzymes found in ER. How? Their responsible domains are hanging out of the ER.

Further steps in synthesis

☆ Female doctor note: only the circled part is important.



1. Production of a 5-carbon unit: Isopentinyl pyrophosphate (IPP)

↓ x3

2. Condensation to a 15-carbon compound: Farnesyl pyrophosphate (FPP)

↓ x2

3. ★ Condensation to a 30-carbon compound: squalene

4. Cyclization of squalene to: lanosterol

↓ -3

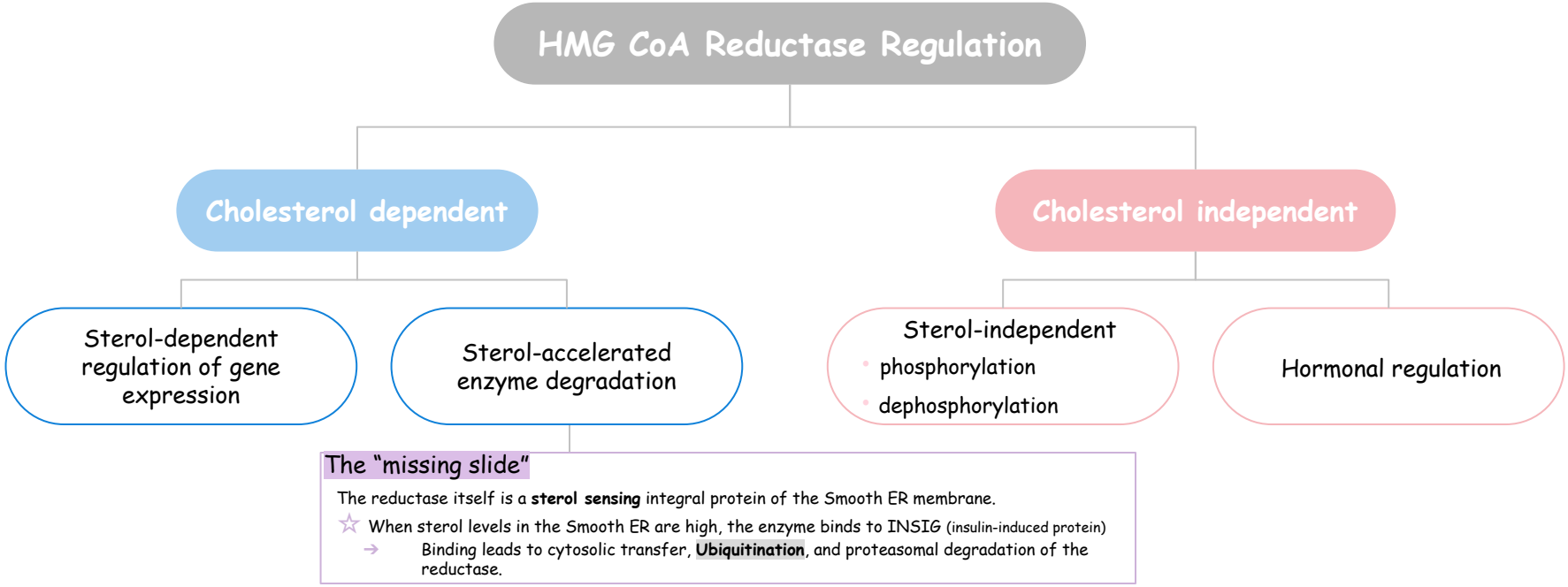
5. Synthesis of 27-Carbon cholesterol (deficiency leads to Smith-Lemli-Opitz Syndrome)

☆ Smith-Lemli-Opitz Syndrome

Autosomal-recessive multisystem, embryonic malformation syndrome, is caused by a partial deficiency in 7-dehydrocholesterol-7-reductase, the enzyme that reduces the **double bond** in 7-dehydrocholesterol (7-DHC), converting it to cholesterol.

Regulation of Cholesterol Synthesis

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



☆ **Ubiquitination:** The "kiss of death"

Process In which a protein is inactivated by attaching ubiquitin to it. Ubiquitin is a small molecule. It acts as a tag that signals the protein-transport machinery to ferry the protein to the proteasome for degradation.

Sterol-dependent regulation of gene expression of HMG CoA

Sterol Regulatory Element (SRE):

recognition sequence in the DNA.

☆ Where transcription happens

SREBP (SRE binding protein)

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

SREBP cleavage-activating protein (SCAP):

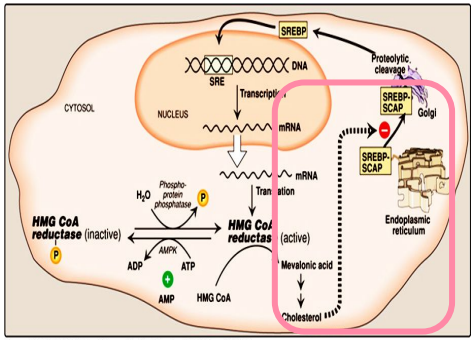
Intracellular cholesterol sensor.

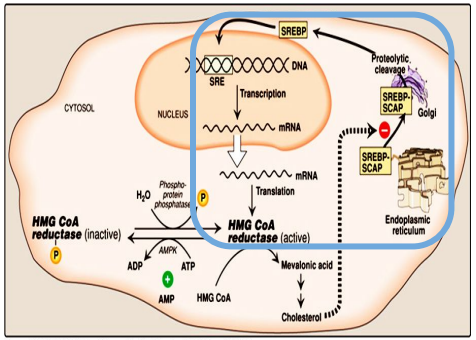
High Cholesterol

- SCAP binds to insig protein (insulin-induced protein) in ER membrane
- SCAP-SREBP is retained in the ER
- transcription is suppressed
- Down regulation of cholesterol synthesis

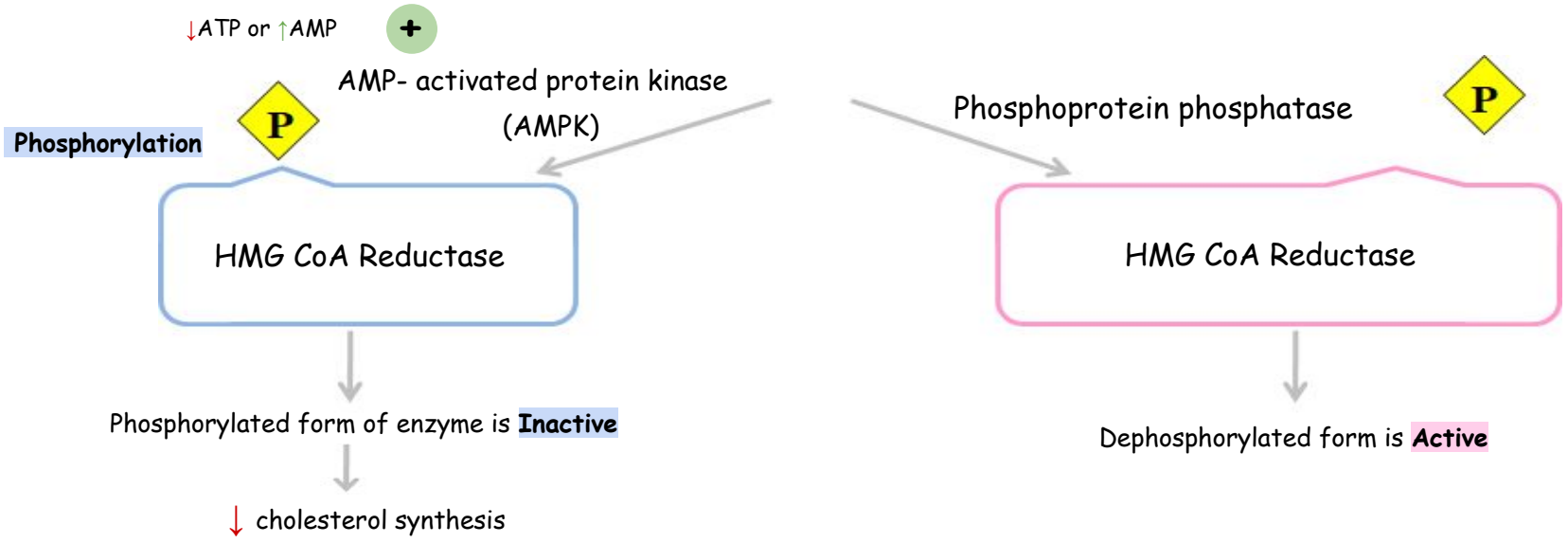
Low Cholesterol

- SCAP-SREBP moves to Golgi bodies
- SCAP is removed from SREBP
- SREBP binds to SRE in DNA
- HMG CoA gene is activated
- transcription is Activated





Enzyme phosphorylation & dephosphorylation

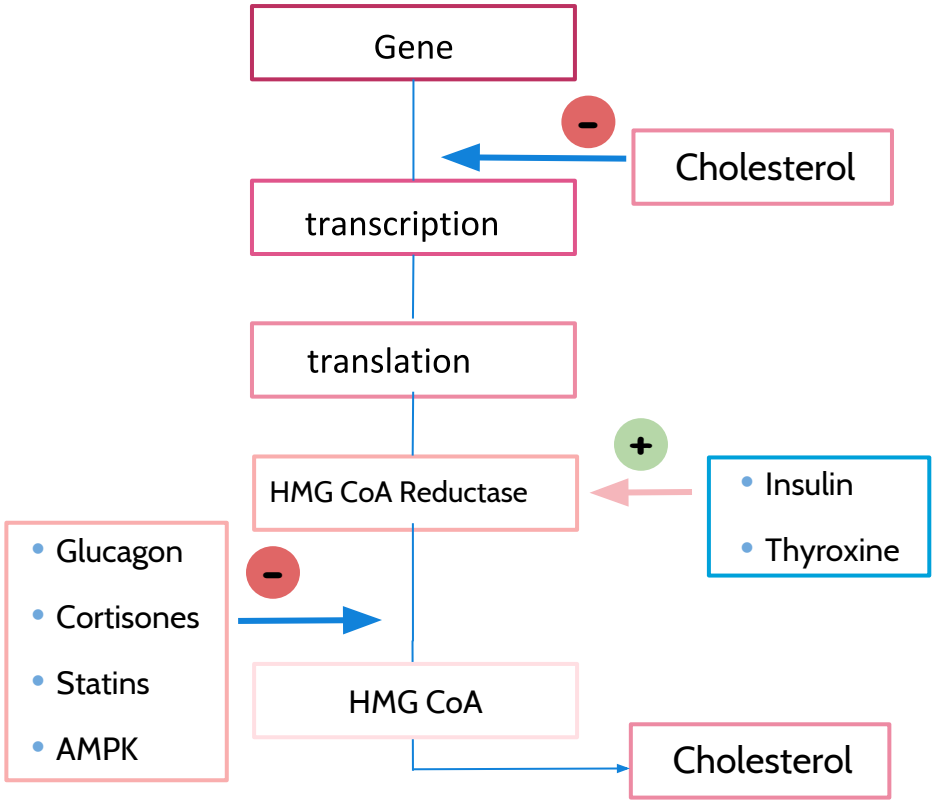


☆ AMPK is activated by AMP because cholesterol synthesis, like any other anabolic pathway consumes energy so it's decreased when ATP availability is decreased.

hormonal regulation

- Insulin and thyroxine increase upregulation of enzyme expression
- Glucagon and cortisol have the opposite effect

HMG CoA Reductase Regulation



Excretion of cholesterol

- By conversion into bile acids and bile salts- excreted in the feces
  - Secretion of cholesterol in bile
  - Transported to intestine for elimination
- In the intestine, some cholesterol is converted by bacteria before excretion into:
  - Coprostanol
  - Cholestanol

Hypercholesterolemia

Definition

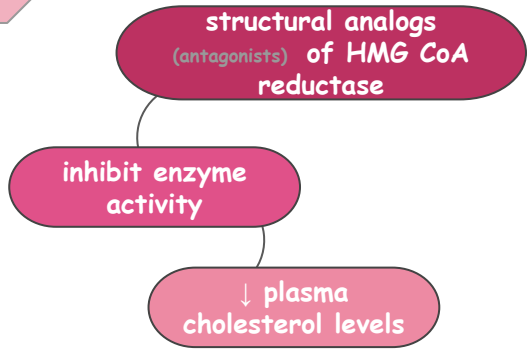
High conc. of cholesterol in blood

Complications

Atherosclerosis

Treatment

Statin drugs
"competitive inhibition"

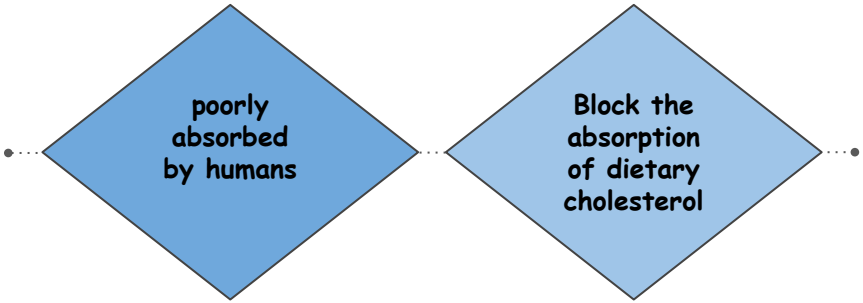


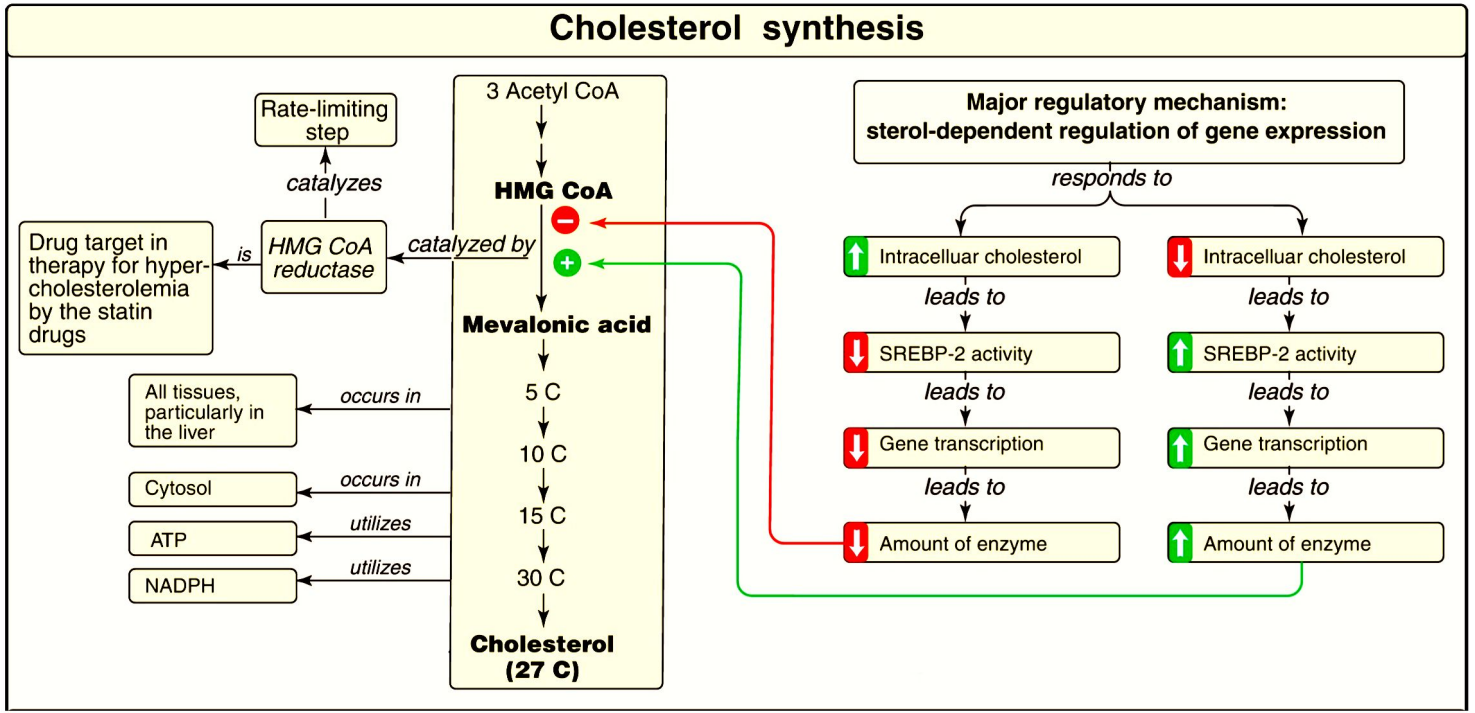
β-Sitosterols/ Phytosterols

Plant sterols *e.g. in avocados*

Clinically useful in:

dietary treatment of hypercholesterolemia





Take home message

- Cholesterol is important various body functions.
- Liver plays a major role in the cholesterol homeostasis in the body.
- HMG CoA reductase is a rate-limiting enzyme for cholesterol synthesis.

Quiz

MCQs

Q1: A four fused rings molecule with OH at the third Carbon is called:
a) Cholesterol **b)** Steroid nucleus **c)** Hydrocarbon tale **d)** Ketone

Q2: Enzymes involved in the biosynthesis of cholesterol are found in:
a) Mitochondria **b)** Endoplasmic reticulum **c)** Cytoplasm **d)** Both b and c

Q3: Which of these statements is true when cholesterol levels are low?
a) SCAP binds to SREBP **b)** SREBP binds to SRE **c)** SCAP binds to SRE

Q4: Which of these is the rate limiting enzyme of cholesterol synthesis?
a) HMG CoA Reductase **b)** HMG CoA Synthase **c)** Thiolase **d)** HMG CoA Oxidase

Q5: Which of the following is the most abundant cholesterol in the plasma?
a) Esterified cholesterol **b)** Free cholesterol **c)** Lanosterol **d)** Squalene

Q6: Which type of inhibition is the MOA of statins?
a) Covalent modification **b)** Competitive **c)** Regulation of gene expression

Q7: Mice were genetically engineered to contain hydroxymethylglutaryl coenzyme A reductase in which serine 871, a phosphorylation site, was replaced by alanine. Which of the following statements concerning the modified form of the enzyme is most likely to be correct?
a) The enzyme is nonresponsive to ATP depletion.
b) The enzyme is nonresponsive to statin drugs.
c) The enzyme is nonresponsive to the SRE-SREBP system.
d) The enzyme is unable to be degraded by the ubiquitin-proteasome system.

SAQs

Q1: Where does the synthesis of mevalonic acid occur?

Q2: Name the enzyme that convert FPP to Squalene

Q3: A patient presented to the ER with high cholesterol level which lead to atherosclerosis, what can you give him to decrease his plasma cholesterol level? + mention the MOA

Q4: Which structures is cholesterol essential for their synthesis?

★ **MCQs Answer key:**

1) B 2) D 3) B 4) A 5) A 6) B 7) A

★ **SAQs Answer key:**

1) In the cytosol.

2) Squalene synthase.

3) Statins, inhibit enzyme activity by competitive inhibition.

4) Bile acids and bile salts, Steroid hormones, Vitamin D3.

Team members

Girls team :

- Ajeed Al-rashoud
- ★ Alwateen Albalawi
- Elaf Almusahel
- ★ Haifa Alessa
- Lama Alassiri
- Lina Alosaimi
- Nouf Alhumaidhi
- Noura Alturki
- Nouran Arnous
- Reem Algarni
- ★ Shahd Alsalamh
- Taif Alotaibi

Boys team :

- Abdullah Altuwaijri
- Alkaseem binobaid
- Fares Aldokhayel
- Naif Alsolais
- Sultan Alhammad

Team leaders

Deema Almaziad **Mohannad Alqarni**

★ This lecture was done by

★ سيَأتي الحلْم في مِشكاة فجرٌ وعند الصّبح!
تبتسمُ الأماني.

438 BIOCHEMISTRY TEAM