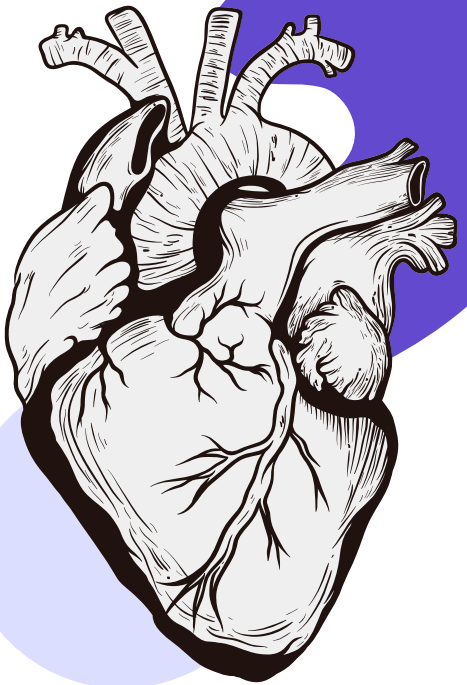
Cholesterol metabolism



Editing File

COLOR INDEX:
MAIN TEXT (BLACK)
FEMALE SLIDES (PINK)
MALE SLIDES (BLUE)
IMPORTANT (RED)
DR'S NOTE (GREEN)
EXTRA INFO (GREY)

Objective

01 Understand the structure and functions of cholesterol

02 Discuss the regulation of cholesterol homeostasis in the body

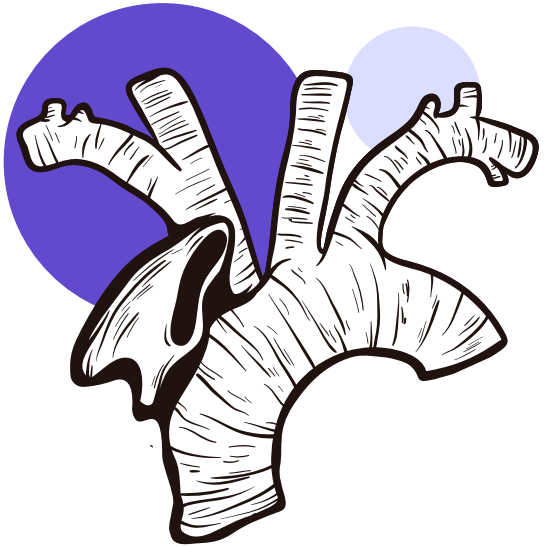
03 Comprehend the important steps of cholesterol synthesis pathway

04 Identify different levels of regulation of cholesterol synthesis

05 Discuss the association of hypercholesterolemia with abnormal cholesterol metabolism

06 Understand the role of statins in the treatment of hypercholesterolemia

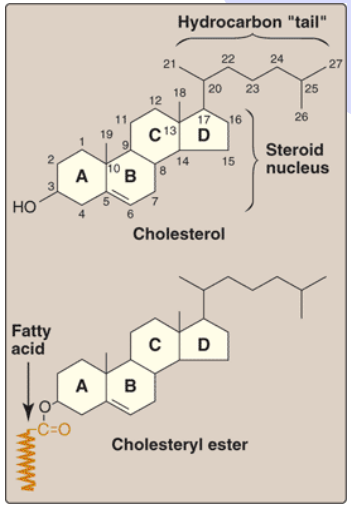
Overview



Cholesterol

Functions

- Most important animal steroid
- Maintains membrane fluidity
- Insulating effect on nerve fibres
- Cholesterol is the parent molecule for:
  - Bile acids and bile salts
  - Steroid hormones
  - Vitamin D3



Cholesterol Structure

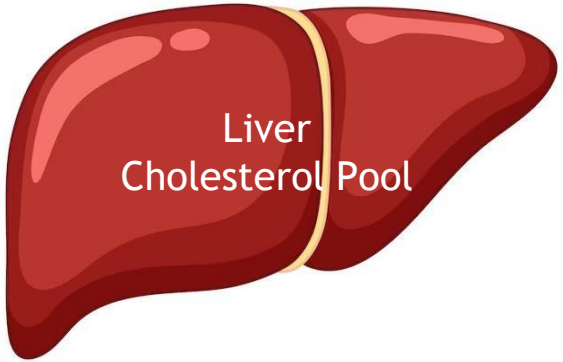
Dietary cholesterol → Chylomicron remnants → Liver

De novo synthesized in the liver

cholesterol synthesized in extrahepatic tissues →HDL → Liver

Major sources of liver cholesterol

Liver plays a central role in the regulation of cholesterol homeostasis



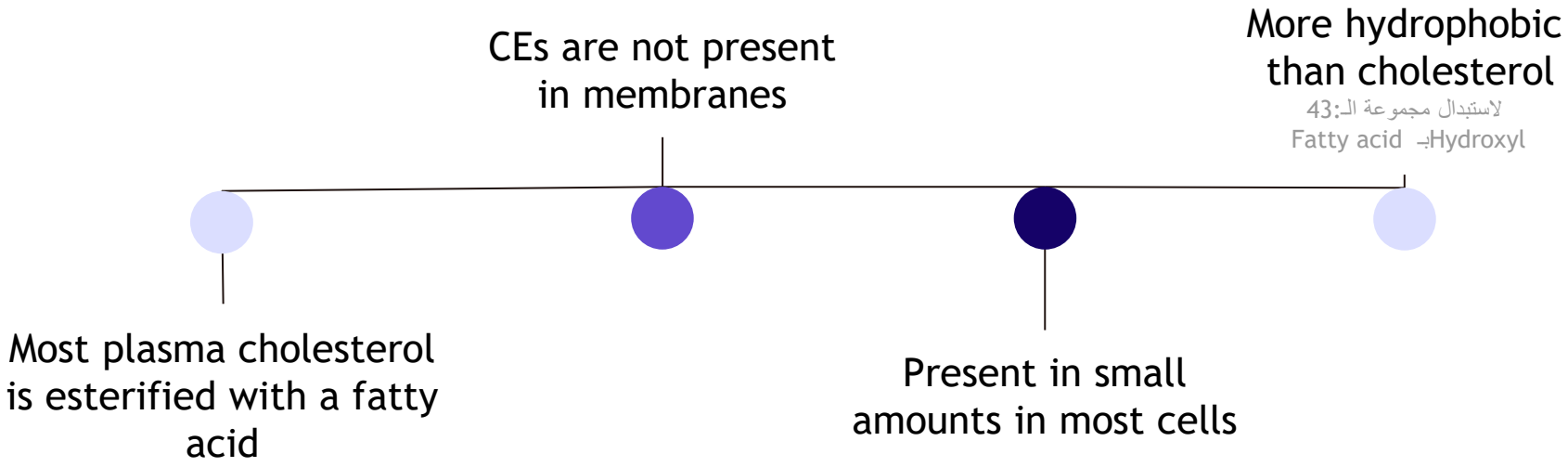
Major routes by which cholesterol leaves the liver

Secretion of VLDL

Free cholesterol secreted in the bile

Conversion to bile acids/salts

Cholesteryl esters



Cholesterol synthesis

Cholesterol synthesis

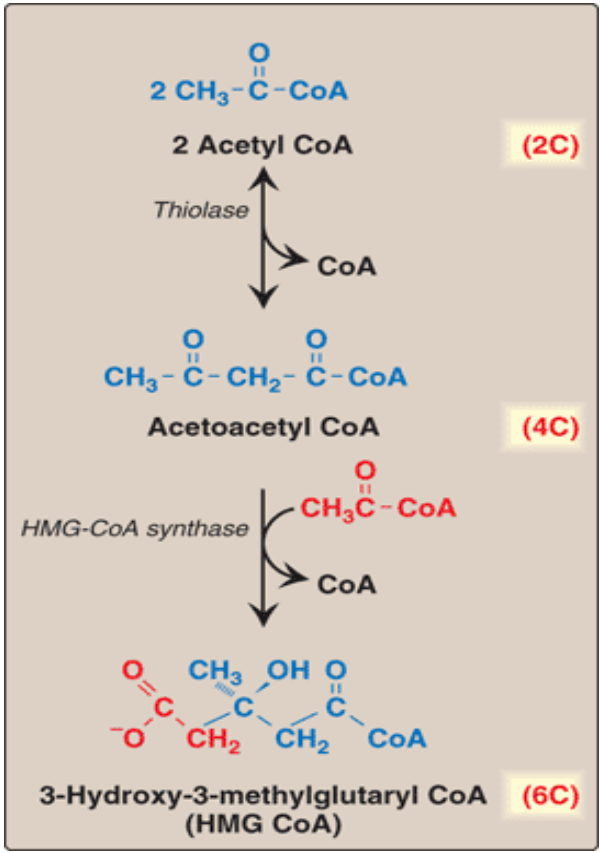
- Synthesized in all tissues
- Major sites for synthesis
  - Liver 
  - Adrenal Cortex 
  - Testes, Ovaries 
  - Intestine 
- All carbon atoms are derived from acetyl CoA
- Enzymes involved in biosynthesis are partly located in ER and partly in cytoplasm

Synthesis of HMG CoA

HMG CoA synthase is present in both cytosol (cholesterol synthesis) and mitochondria(Ketogenesis) of liver

Mitochondrial → ketogenesis

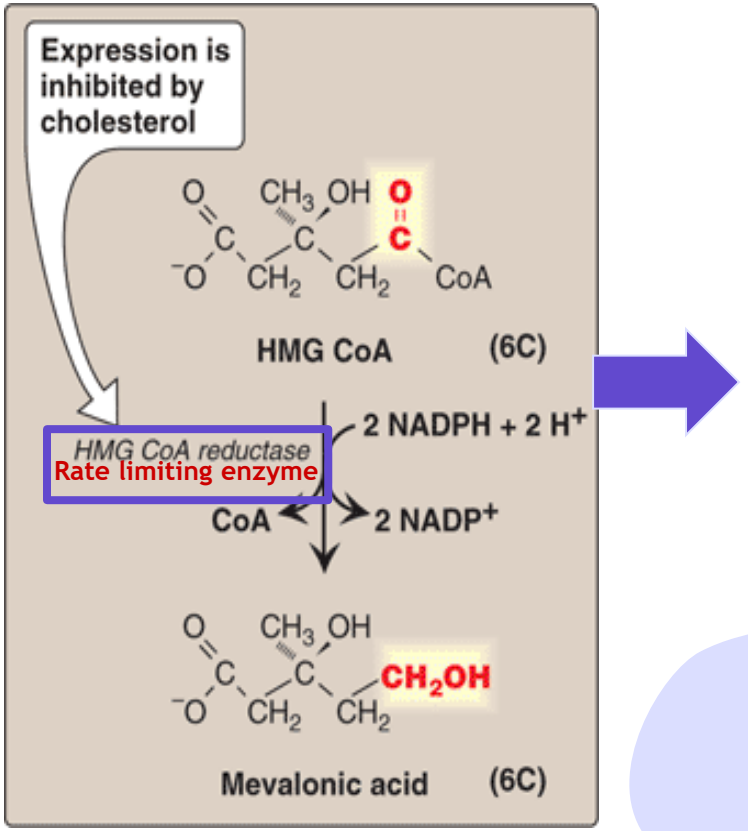
Cytosolic → cholesterol synthesis



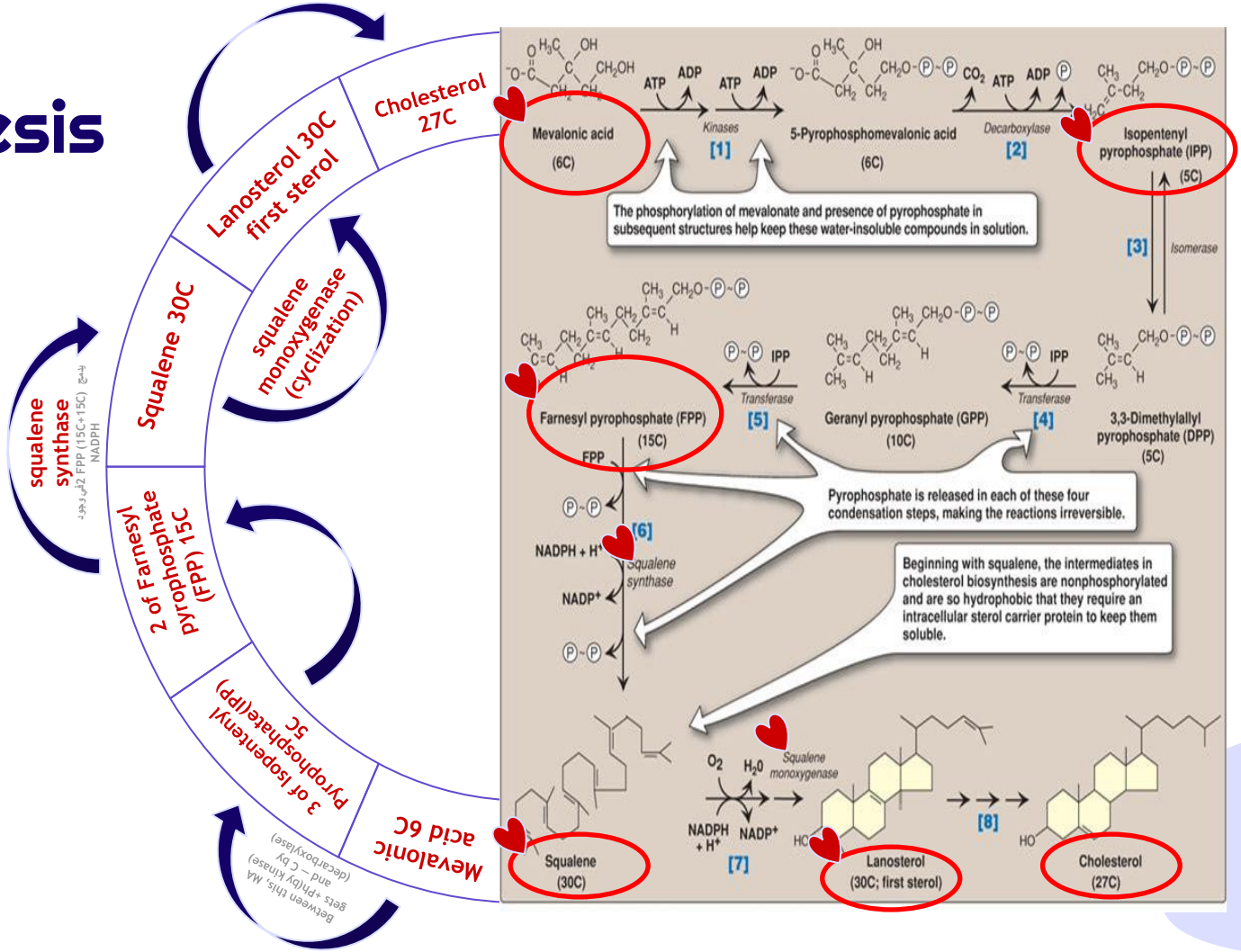
Synthesis of mevalonic acid

- Rate limiting and key step
- Occurs in cytosol
- **HMG CoA reductase** is an ER membrane enzyme with catalytic unit hanging in the cytosol

  Reductase and synthase مهم نفرق بين



Synthesis



Q: What is the first sterol in cholesterol synthesis pathway?

A: Lanosterol

Further steps in synthesis

01 Production of a 5-carbon unit: Isopentenyl pyrophosphate (IPP)

02 Condensation to a 30C compound: squalene

03 **Cyclization of squalene to 30C lanosterol**

04 Synthesis of 27-Carbon cholesterol (defect in this leads to **Smith-Lemli-Opitz Syndrome *SLO***)

Q: Defect in cholesterol synthesis?
A: SLO syndrome

HMG CoA Reductase Regulation

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

01 Sterol-dependent regulation of gene expression (Dependent)

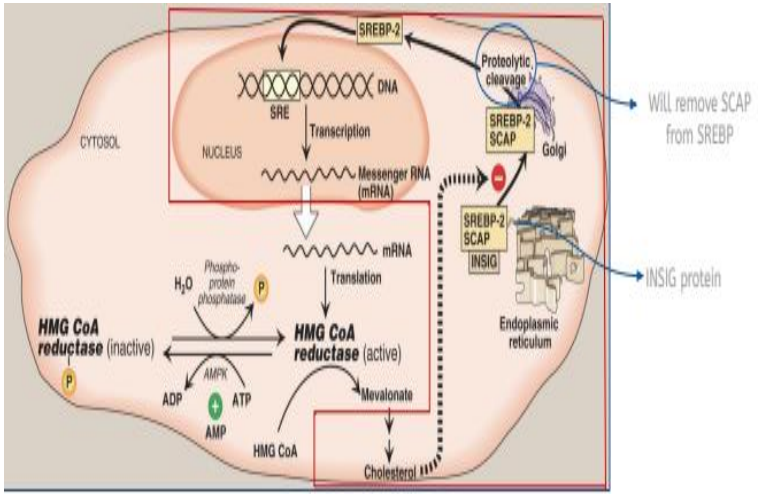
02 Sterol-accelerated enzyme degradation (Dependent)

03 Sterol-independent phosphorylation/dephosphorylation (Independent)

04 Hormonal regulation (Independent)

1- 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 DNA. SRE is a site found in DNA, there is a protein will bind to it.
- SRE Binding Protein (**SREBP**) will bind to **SRE**, is essential for transcription of this gene.
- SREBP Cleavage-Activating Protein (**SCAP**) is an intracellular cholesterol sensor. When cholesterol is low SCAP will take SREBP to Golgi bodies.



Sterol-dependent regulation

High Cholesterol

01 SCAP (already bound to SREBP) will bind to INSIG protein (insulin induced gene protein) in ER membrane.

02 SCAP-SREBP is retained in the ER. INSIG protein prevents them from leaving to Golgi bodies.

03 Down regulation of cholesterol synthesis. (HMG CoA reductase will be inhibited) It's the rate limiting enzyme.

Low Cholesterol

01 SCAP-SREBP moves to Golgi bodies

02 SCAP is removed from SREBP (by proteolytic cleavage found in Golgi bodies)

03 SREBP will bind to SRE in DNA

04 HMG CoA gene will be activated

Sterol-accelerated enzyme degradation

- The reductase itself is a sterol-sensing integral protein of SER.
- When sterol level is high- the enzyme binds to INSIG proteins- cytosolic translocation occurs followed by ubiquitination and proteasomal degradation of HMG CoA reductase.

2- Sterol-independent (enzyme) phosphorylation and dephosphorylation

HMG CoA reductase A rate limiting enzyme

We **need** energy (e.g.before Iftar) — ATP ↑ AMP ↓

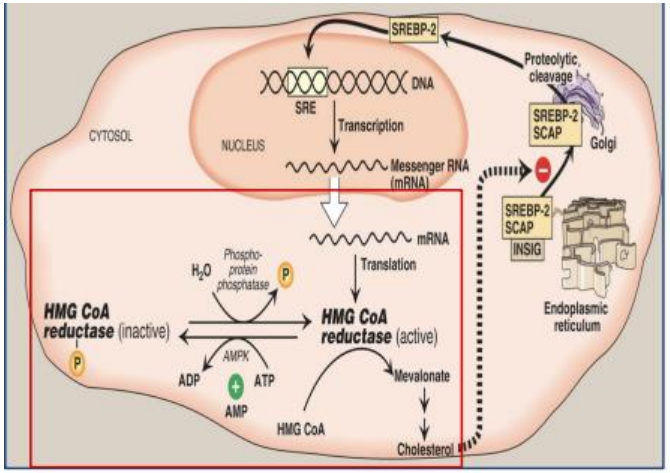
We **have** energy (e.g.after Iftar) — ATP ↓ AMP ↑

AMPK (AMP activated protein kinase) **is active**

→ **Phosphorylated form of enzyme is inactive** → stop making cholesterol

Phosphoprotein Phosphatase is active

→ **Dephosphorylated form of enzyme is active** → make cholesterol



439: High AMP = Low ATP which means the cell is in need of energy. Cholesterol synthesis needs energy (anabolic reaction) and therefore when the cell is running low on energy it inhibits the synthesis of Cholesterol through AMPK.

Remember in MSK Block we said that AMPK is activated by low energy states (e.g. exercise) This is one of the reasons we say exercise and lifestyle change is useful for lowering cholesterol in patients with hyperlipidemia.

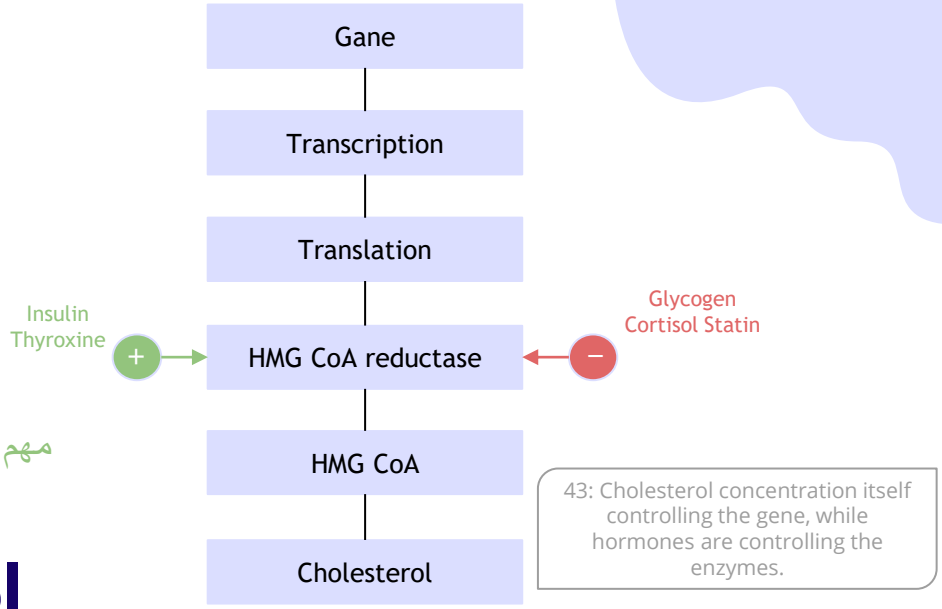
For extra reading on the effects of AMPK on the body: *AMPK and Exercise: Glucose Uptake and Insulin Sensitivity*.

By: Khalid Alohali 44

3-Hormonal regulation

01 Insulin (anabolic) and thyroxine increase **upregulation** of enzyme expression.

02 Glucagon (catabolic) and cortisol have opposite effect. (Down regulation) مهم أسماء الهرمونات و التأثير



Excretion of cholesterol

1) **Secretion** of cholesterol in **bile:**

- By conversion into → **bile acid** and **bile salts** → excreted in the **feces.**

2) **Transported** to **intestine** for elimination:

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

Hypercholesterolemia

High concentration of cholesterol in blood (More than 239 mg/dl), and can lead to atherosclerosis by depositing in blood vessels .

Statin drugs are used to **decrease** plasma cholesterol levels.	Statins are structural analogs (structurally similar) **of HMG CoA reductase.**	Statins inhibit enzyme activity by competitive inhibition.

β-Sitosterols/ Phytosterols

They are plant sterols, poorly absorbed by humans.

Block the absorption of dietary cholesterol.

Clinically useful in the dietary treatment of hypercholesterolemia.

Take home Messages

01 Cholesterol is important various body functions.

02 Liver plays a major role in the cholesterol homeostasis in the body.

03 HMG CoA reductase is a rate-limiting enzyme for cholesterol synthesis

Summary for Cholesterol Synthesis Pathway

Click here

Special thanks to Khalid Alohali 44

MCQ

1-A 2C- 3-D

Q1:the enzyme HMG-CoA reductase catalyse the conversion of which of the following?			
A-HMG-CoA to Mevalonic acid	B- Acetoacetyl CoA to HMG-CoA	C- HMG-CoA to Acetoacetyl CoA	D- Two Acetyl CoA to Acetoacetyl CoA
Q2:What are the hormones that increase the up regulation of HMG-CoA reductase synthesis?			
A-Glucagon and cortisol	B- Insulin and cortisol	C- Insulin and thyroxine	D-Glucagon and thyroxine
Q3:What is the rate limiting enzyme in cholesterol biosynthesis?			
A-HMG. CoA Synthase	B-Thiolase	C- HMG. CoA Dehydrogenase	D-HMG. CoA Reductase

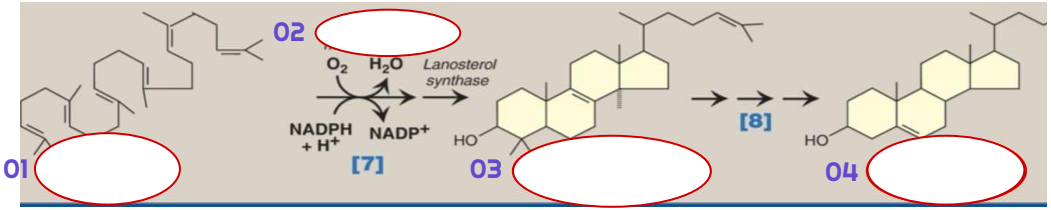
MCQ

4-A 5-C 6-B

Q4: Which one of the following is the form of cholesterol after being converted by intestinal bacteria before excretion?			
A-Coprostanol	B-Bile acid	C-Mevalonic acid	D-Amino acid
Q5:Which of the following is the intracellular cholesterol sensor?			
A-SRE	B-SREBP	C-SCAP	D-H202
Q6: Which one of the following is considered the first steroid compound in the cholesterol pathway?			
A-Squalene	B-Lanosterol	C-Mevalonic acid	D-Cholesterol

SAQ

Q1:complete the following reaction :



01: Squalene 30C
02: squalene monoxygenase
03: Lanosterol 30C; first sterol
04: Cholesterol 27C

Q2: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

A2:Statins, inhibit HMG-CoA activity by competitive reversible inhibition which leads to: 1) decreased hepatic cholesterol synthesis. 2) increased LDL-R expression → increased LDL clearance from blood

Q3: Which structures is cholesterol essential for their synthesis?

A3:Bile acids and bile salts, Steroid hormones, Vitamin D3.

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Lujain Darraj

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Osama Alotabib

Mays Altokhais

Shadin Alabbas

Khalid Alkanhal

Lana Alfouzan

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Waleed Alanazi

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