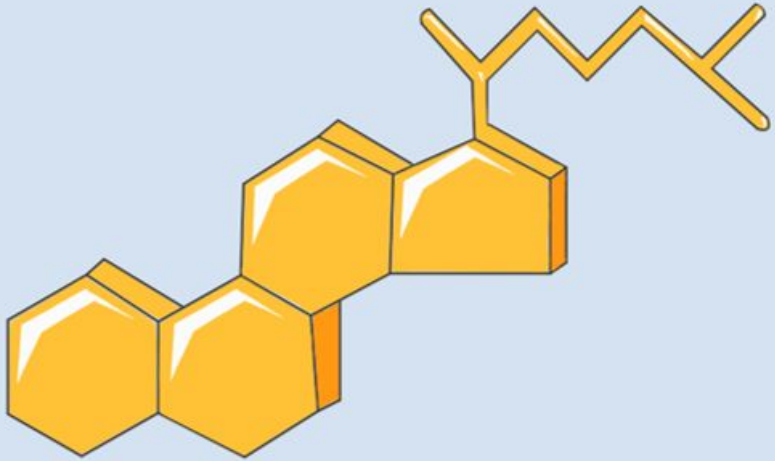
Revised & Reviewed by Abdulaziz & Bahammam Faye Wael Sendi

MED441
KING SAUD UNIVERSITY

2

Cardiovascular Block - KSU

Cholesterol Metabolism



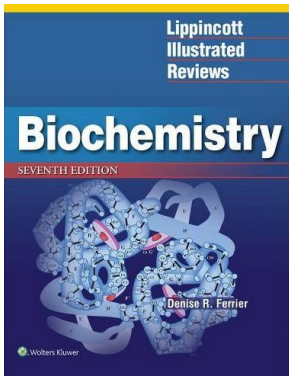
Main text
Important
Notes
Extra

Editing File

We recommend that to watch these videos below to make this lecture more easier & we suggest this book for you if you want more details

Metabolism | Cholesterol Metabolism
BY Ninja Nerd Lectures

Cholesterol Metabolism
BY Osmosis



Biochemistry Lippincott Illustrated Reviews 7th Edition
BY Denise R. Ferrier

Chapter 18
Pages 632-644

Objectives

- Understand the structure and functions of cholesterol
- Discuss the regulation of cholesterol homeostasis in the body
- Comprehend the important steps of cholesterol synthesis pathway
- Identify different levels of regulation of cholesterol synthesis
- Discuss the association of hypercholesterolemia with abnormal cholesterol metabolism
- Understand the role of statins in the treatment of Hypercholesterolemia

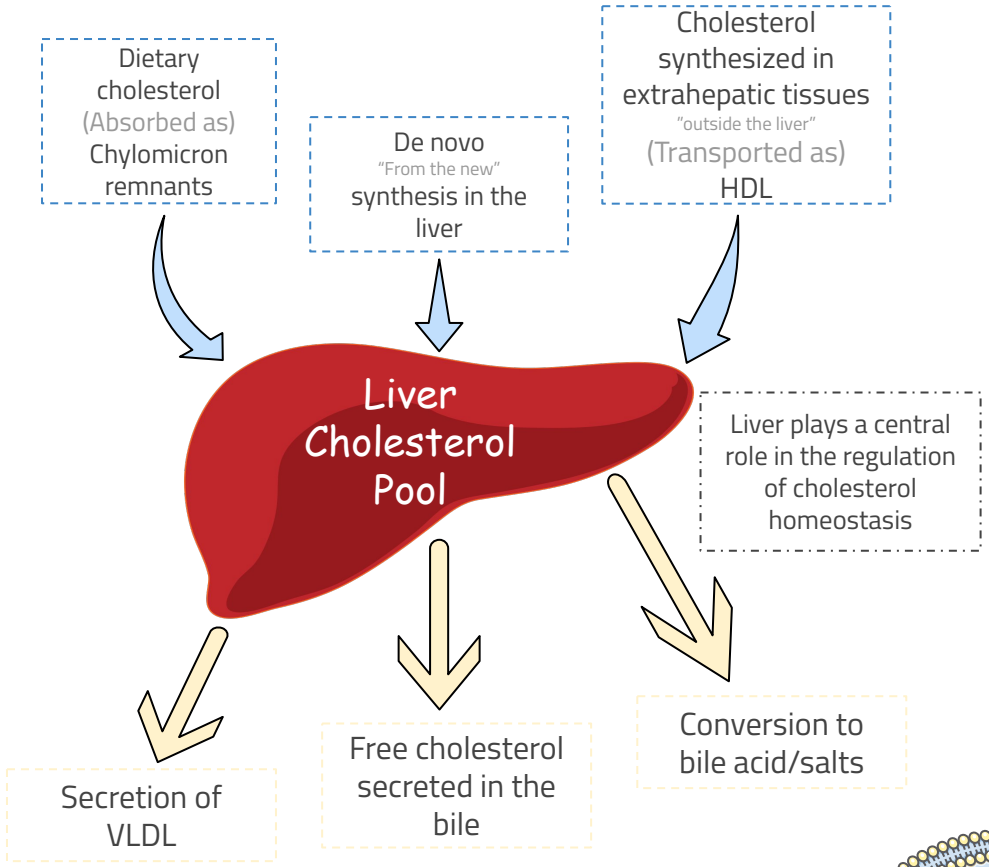
Cholesterol

- Most important animal steroid.

- **Functions :**

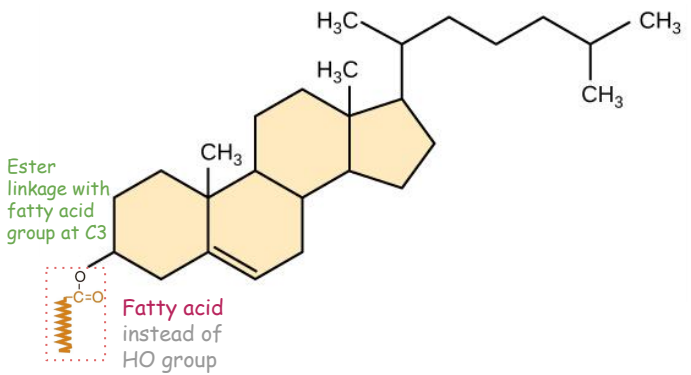
  - Maintains membrane fluidity (present between the phospholipids)
  - Insulating effect on nerve fibers
  - Cholesterol is the parent (precursor) molecule for :
    - Bile acids & bile salts
    - Steroid hormones
    - Vitamin D3

Major sources of liver cholesterol



Major routes by which cholesterol leaves the liver

Cholesteryl Ester (CEs)



Most plasma cholesterol is esterified with a **fatty acid**

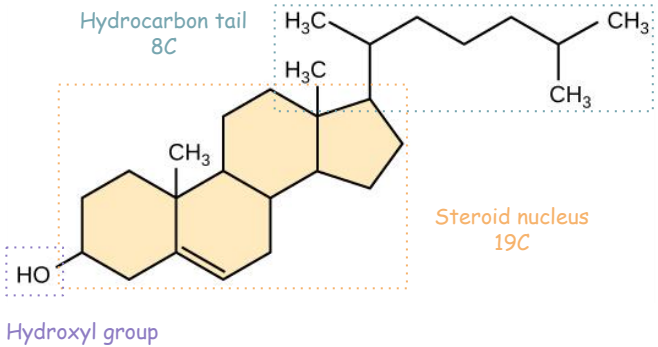
Present in **small** amounts in most cells

CEs are **not** present in membranes

More hydrophobic than cholesterol

Both can't move freely in the fluid, so to be transported they have to be carried usually by lipoprotein.

Cholesterol Synthesis



Synthesized in **all** tissues

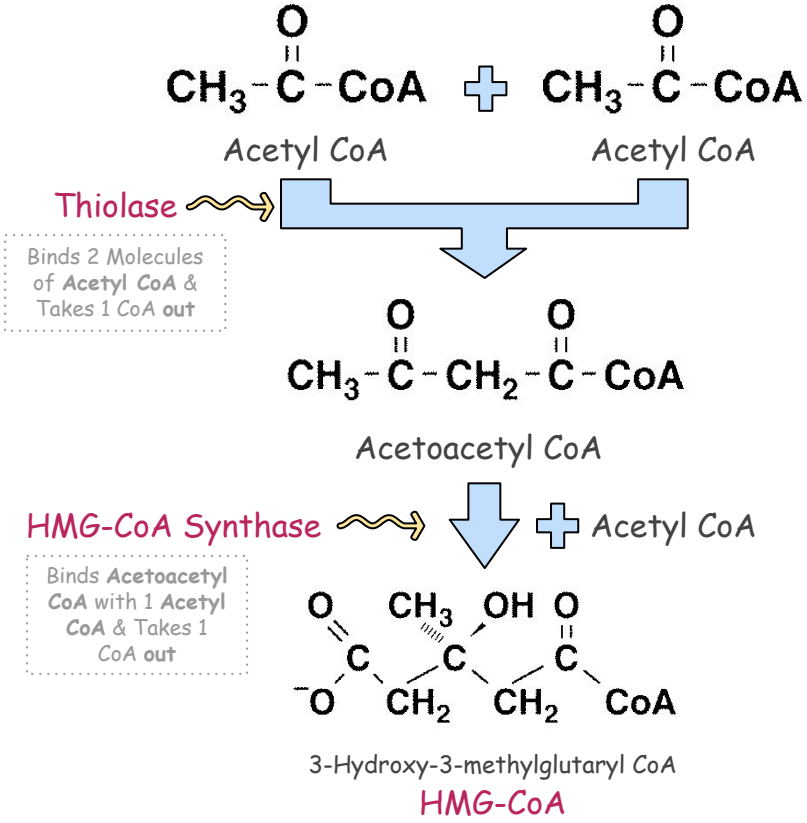
Major sites for synthesis where it gets modified to other molecules :

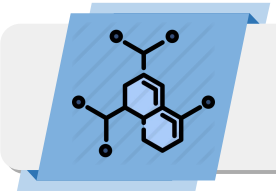
- liver
- adrenal cortex
- testes & ovaries
- intestine

All carbon atoms are derived from acetyl CoA

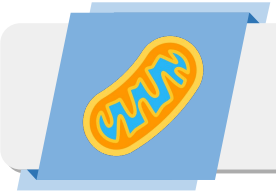
Enzymes involved in biosynthesis are partly located in ER and partly in cytoplasm

1- Synthesis of HMG-CoA

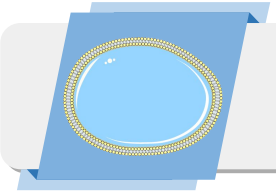




HMG-CoA synthase is present in both cytosol and mitochondria of liver (Isoenzymes)

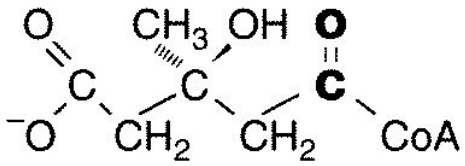


Mitochondrial enzyme participate in ketogenesis (ketone body synthesis)



Cytosolic enzyme participate in cholesterol synthesis

2- Synthesis of Mevalonic acid



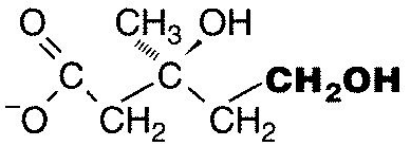
3-Hydroxy-3-methylglutaryl CoA

HMG-CoA

Expression is inhibited by cholesterol

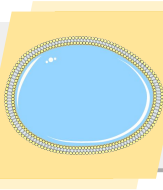
HMG-CoA Reductase

Reduction of HMG-CoA & Takes 1 CoA out

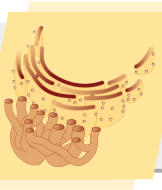


Mevalonic acid

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



Occurs in cytosol



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

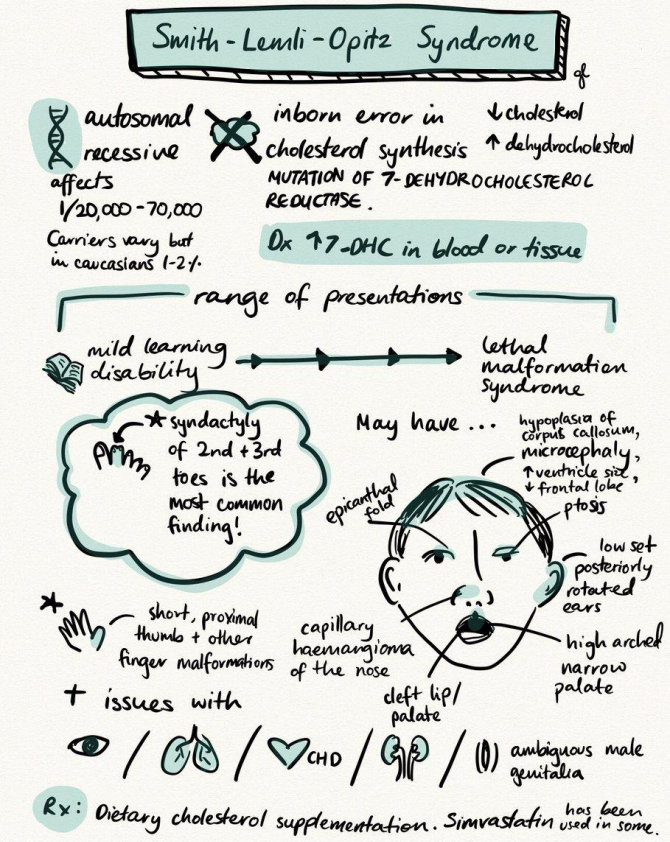
يعني إن هذا الإنزيم موجود في الـ Endoplasmic reticulum ولكن الجزء اللي يسوي عملية الإختزال طالع منه ومتواجد في الـ cytosol

Further steps in synthesis

3. Production of a 5-carbon unit: Isopentenyl pyrophosphate (IPP)
4. Condensation to a 30C compound squalene
5. Cyclization of squalene to 30C lanosterol
6. Synthesis of 27-Carbon cholesterol after a number of reactions (defect in this leads to Smith-Lemli-Opitz Syndrome)

See the picture in next slide

Smith-Lemli-Opitz syndrome (SLOS)



Mevalonic acid 6C

Steps you don't have to memorize

3 molecules of Isopentenyl Pyrophosphate (IPP) 5C

Steps you don't have to memorize

2 molecules of Farnesyl pyrophosphate (FPP) 15C

By squalene synthase

Squalene 30C

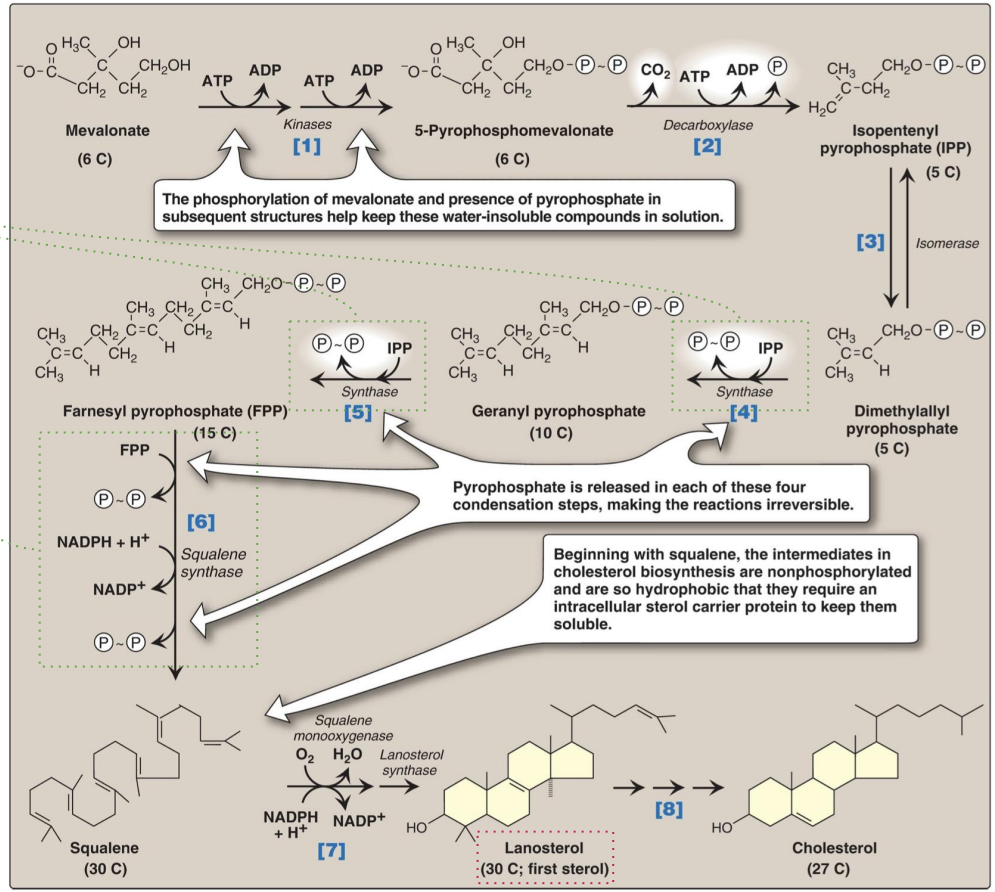
By cyclization

Lanosterol 30C; first sterol

By enzyme modification

Cholesterol 27C

Reactions in steps 4,5,6 are **irreversible**



First sterol in cholesterol synthesis

HMG CoA reductase regulation

1. **Sterol dependent regulation of gene expression**
   Cholesterol concentration in the body determine the gene expression

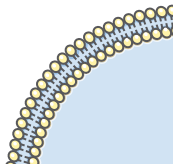
2. **Sterol-accelerated enzyme degradation**
   More cholesterol ⟹ Faster degradation

3. **Sterol-independent phosphorylation and dephosphorylation**

4. **Hormonal regulation**
   Depends on the hormone that stimulate or inhibit cholesterol synthesis
   E.g ⇧ insulin ⟹ ⇧ Enzyme expression

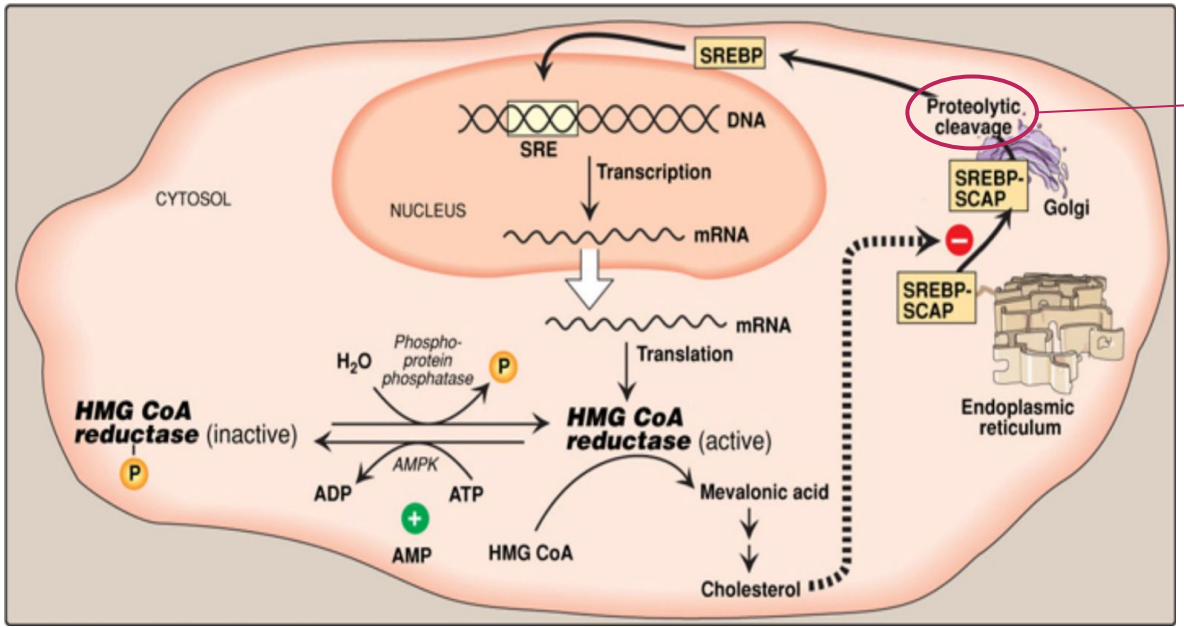
Dependent
Means it depends on the cholesterol concentration.

Independent
Means it doesn't depend on the cholesterol concentration.



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



Will remove SCAP from SREBP

This slide is important

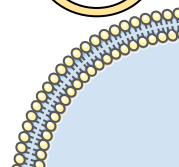
Sterol-dependent regulation

High cholesterol

- SCAP (already bound to SREBP) will bind to **INSIG protein** (insulin induced gene protein) in ER membrane
- SCAP-SREBP is retained تبقى in the ER.
  INSIG protein prevents them from leaving to Golgi bodies
- Down regulation of cholesterol synthesis
  (HMG CoA reductase will be inhibited)
  It's the rate limiting enzyme, remember?

Low cholesterol

- SCAP-SREBP moves to **Golgi bodies**
- SCAP is removed from SREBP
  (by proteolytic cleavage found in Golgi bodies)
- SREBP will bind to SRE in DNA
- HMG CoA gene will be activated



2) Sterol-independent (enzyme) phosphorylation and dephosphorylation

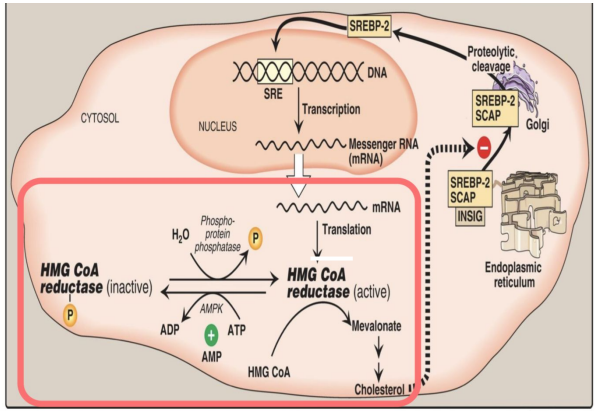
HMG CoA reductase
A rate limiting enzyme

↓ ATP ↑ AMP
AMPK is active

Phosphorylated form of enzyme is inactive

↑ ATP ↓ AMP
Phosphoprotein Phosphatase is active

Dephosphorylated form of enzyme is active



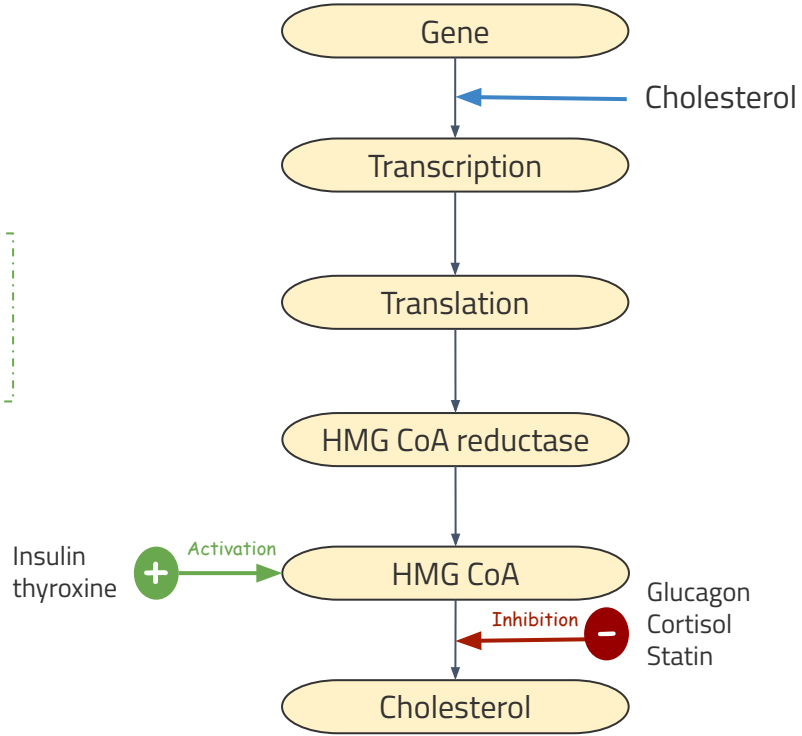
439: High AMP = Low ATP which means the cell is in need of energy. Cholesterol synthesis needs energy (anabolic reaction) and therefore when the cell is running low on energy it inhibits the synthesis of Cholesterol through AMPK.

3) Hormonal regulation

Insulin and thyroxine increase **upregulation** of enzyme expression.

Glucagon and cortisol have opposite effect. (Down regulation)

Cholesterol concentration itself controlling the gene, while hormones are controlling the enzymes



Excretion of cholesterol

- By conversion of **bile acid** 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** 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.

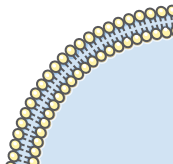
Statins are structural analogs (structurally similar) of HMG CoA reductase.

Statins inhibit enzyme activity by **competitive inhibition**

β-Sitosterols/ Phytosterols

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

- 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

Summary

Click HERE

Or

Scan the code for the amazing summary

Quiz

Q1: Which one of these is the rate limiting enzyme in cholesterol synthesis ?
A/ HMG-CoA synthase
B/ HMG-CoA reductase
C/ thiolase
D/ squalene synthase

Q2: Which of these hormones increase upregulation of HMG-CoA reductase expression ?
A/ glucagon
B/ insulin
C/ statin
D/ cortisol

Q3: Which one of these undergo cyclization in cholesterol synthesis ?
A/ mevalonic acid
B/ HMG-CoA
C/ squalene
D/ lanosterol

Q4: What is the first sterol during cholesterol synthesis pathway ?
A/ cholesterol
B/ squalene
C/ mevalonic acid
D/ lanosterol

Q5: Where does the synthesis of mevalonic acid occurs in ?
A/ cytosol
B/ ER
C/ golgi bodies
D/ mitochondria

Q6: Most plasma cholesterol is esterified with a ?
A/ fatty acid
B/ thyroxine
C/ phytosterols
D/ glycerol

Q: mention the 4 mechanisms of HMG-CoA reductase regulation ?

Slide 10

Q: mention 3 functions of cholesterol ?

Slide 4

Q: Mention 3 hormones can inhibit cholesterol synthesis ?

Slide 14

Click HERE for more questions Done by Qbank team!

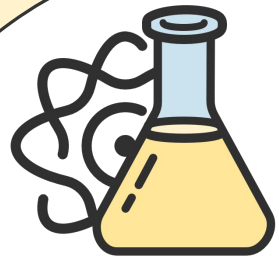
1)B 2)B 3)C 4)D 5)A 6)A

Children with SLOS, Study until you can help them all

YOU ARE A **DOCTOR** NOT A STUDENT!

YOU ARE THEIR HOPE!!!

Special Thanks to Mohammed Alwahibi!



Biochemistry 441

Girls

Leader: Wareef Almousa

Fay Alluhaidan
Manal Aldhirgham
Fatimah Albenmousa
Haya Alshaloob
Maram Alenzi
Futoon Almotairi

Organizer: Aisha Alhamed

Boys

Leader: Abdulrahman Alroqi

Sub-leader: Hamad Aljubayr

Anas Alharbi
Rayan Alahmari
Mohammed Aloufi
Faisal Alazmi
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Ali Almatri

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Special Thanks to Arwa Almobeirek
for the Great Theme!

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