Biochemstry Team

If U find any mistake, plz contact us:
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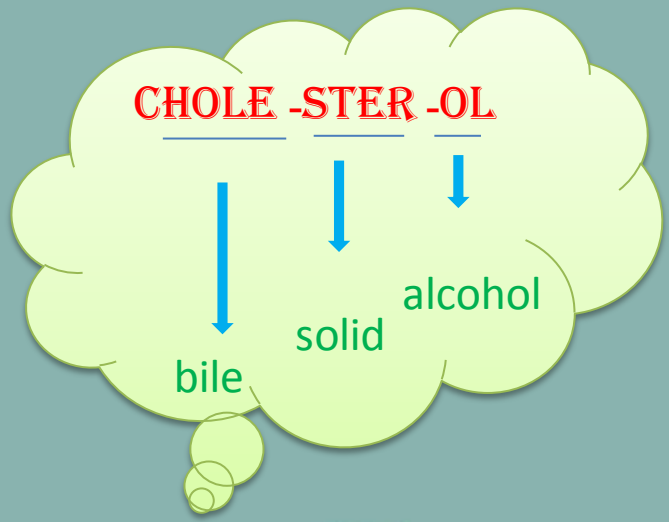
..CHOLESTEROL..



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Red = imp

Blue = explain

Green= addition notes

Most important animal steroid

..CHOLESTEROL

Cholesterol is the parent molecule for

- Bile acids and bile salts
- Steroid hormones
- vitamin D3

Function of Cholesterol

- Maintains membrane fluidity
- Has an insulating effect on nerve fibers

Liver plays a central role in the regulation of body's cholesterol homeostasis

CHOLESTEROL METABOLISM

Major sources of liver cholesterol

- diet
- Cholesterol Synthesized in extrahepatic tissue **by HDL***
- De novo synthesis in liver

LIVER

Major routes by which cholesterol leaves the liver

- Free cholesterol
- Conversion to bile acids & salts
- Secretion of **VLDL***

- High Density Lipoprotein *
- Very Low Density Lipoprotein * ، Lipoproteins are substances made of cholesterol

CHOLESTEROL STRUCTURE

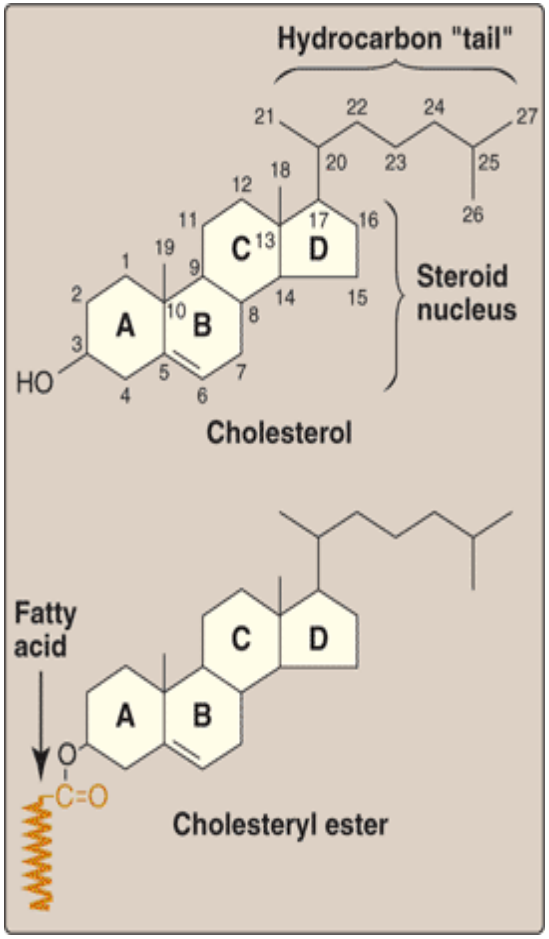
- It is consist of 3 rings A,B,C,D & at the level of D17 there is a hydrocarbon tail (8 Cs) &OH molecule.
- If we change the OH by fatty acid the result will be Cholesteryl esters.

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

More hydrophobic than cholesterol

CEs are not present in membranes and in small amounts in most cells

Most **membrane cholesterol is** free cholesterol



You do not have to memorize the structures

VLDL = very low density lipoprotein

CEs = Cholesteryl esters

ER= Endoplasmic reticulum

HDL = High density lipoprotein

CHOLESTEROL SYNTHESIS

Acetyl CoA(2c)+ Acetyl CoA(2c)

↓

Acetoacetyl CoA (4 C)

↓ HMG CoA synthase

HMG CoA (6 C)

↓ HMG CoA reductase — Reductase= reducing= adding H

Mevalonic acid (6 C)

↓

Isopentinyl pyrophosphate (IPP) (5 c)

↓

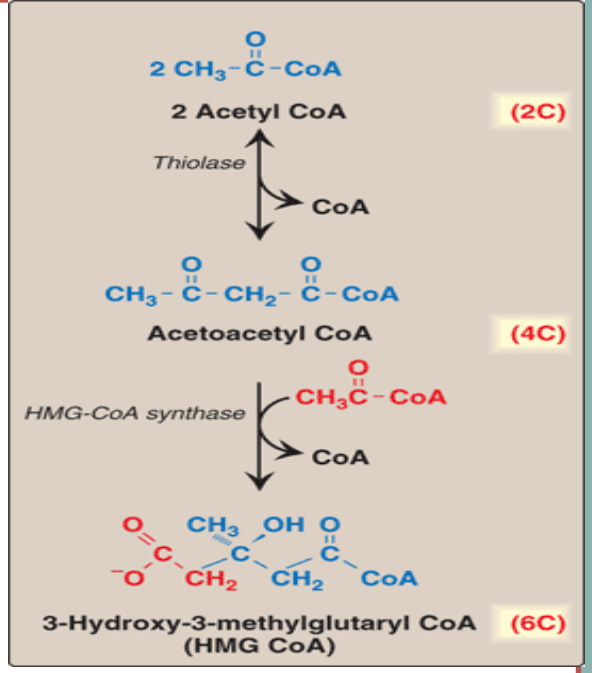
Adding of IPP ……6 times to form **Squalene**(30 Cs)

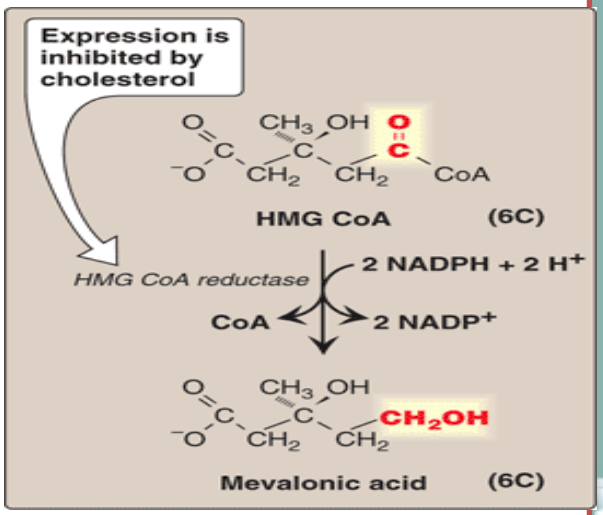
↓

lanosterol (30 Cs) the first sterole formed &parent molecule

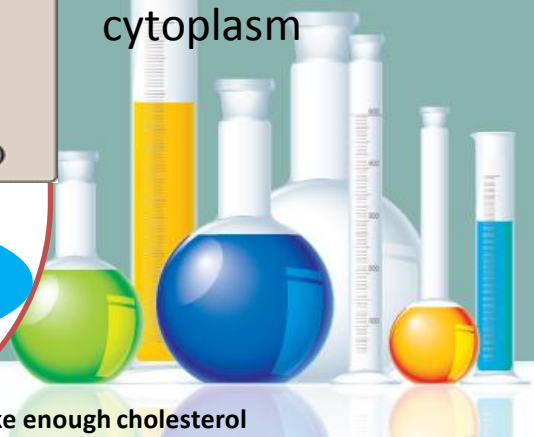
(defect in this leads to SLOS) *

Cutting to size- **27-Carbon cholesterol**





- Synthesized in all tissues but major sites liver, adrenal cortex, testes, ovaries and intestine
- All carbon atoms are derived from **acetyl CoA** which is 2 carbons.
- Enzymes involved in biosynthesis are partly located in ER and partly in cytoplasm



*Smith-Lemli-OpitzSyndrome = disorder where the body is unable to make enough cholesterol

HMG CoA synthase is present in

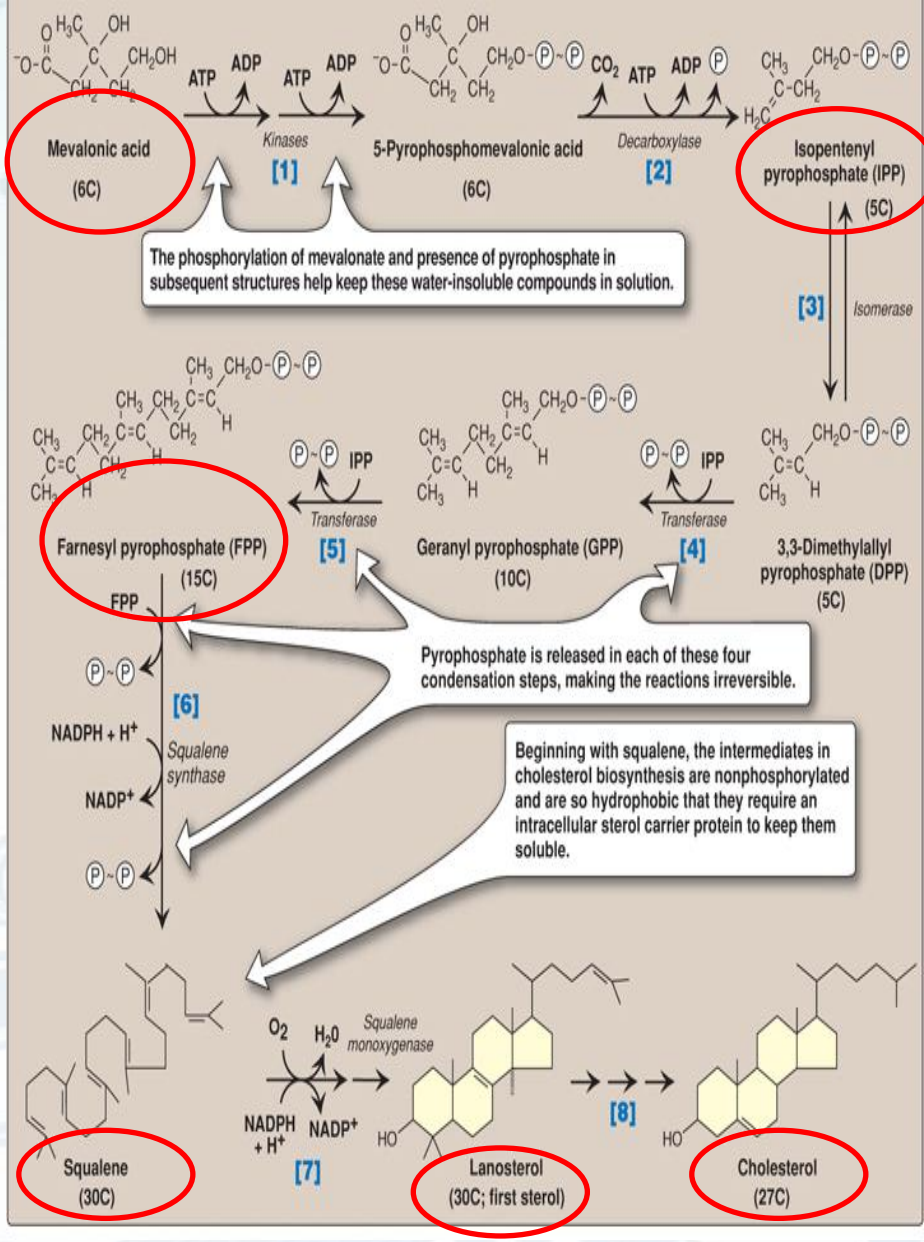
- Mitochondrial for ketogenesis
- Cytosolic for cholesterol synthesis

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

Rate limiting and key step

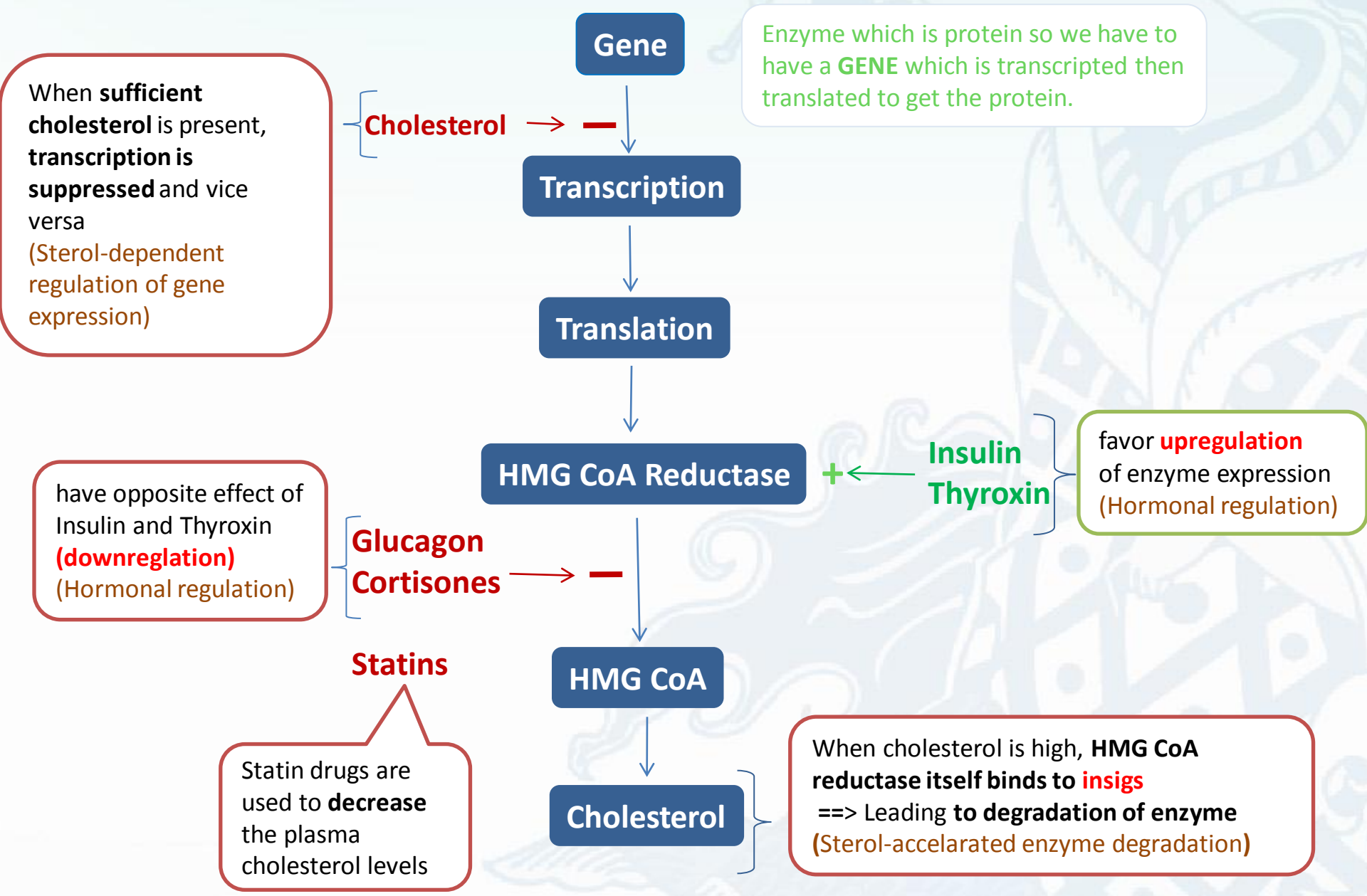
Occurs in cytosol

is the major control point



Just memorize the things in circles

HMG CoA Reductase Regulation



HMG CoA Reductase Regulation

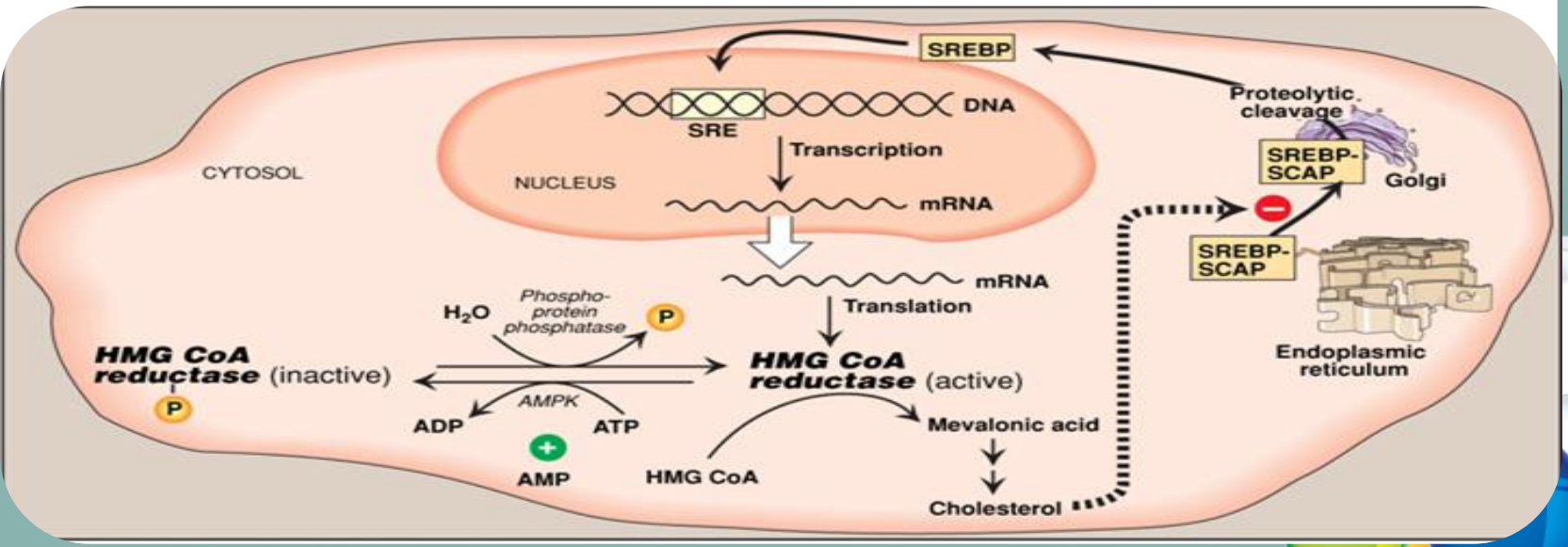
Sterol-dependent regulation of gene expression	Sterol-accelarated enzyme degradation	Sterol-independent phosphorylation/dephosphorylation	Hormonal regulation
- **Sterol Response Element** (SRE) is a recognition sequence in the DNA - SREBP (**SRE binding protein)** binding to SRE is essential for transcription of this gene -**SREBP cleavage activator protein** (SCAP) is an intracellular cholesterol sensor. -(we'll talk about it in the next slide).	Written in the diagram above.	- Phosphorylated form of enzyme is **inactive** - Dephosphorylated form – **active** - AMP- activated protein kinase (AMPK) for phosphorylation -**Phosphoprotein phosphatase** for dephosphorylation -Low ATP or High AMP => cholesterol synthesis decreases. ↑AMP-> phosphorelation -> inactivation-> cholesterol synthesis stopped.	Written in the diagram above.

Phosphorylation= adding phosphate group.
Dephosphorylation= removal of phosphate group.

Gene regulation=Long term
Enzyme regulation= Short term

Sterol-dependent regulation

Cholesterol High	Cholesterol Low
SCAP binds to **insigs** (ER membrane proteins) -> SCAP binds to SREBP -> SCAP-SREBP is retained in the ER (they stick inside the ER, they **don't** go to Golgi) -> **Downregulation** of cholesterol synthesis.	SCAP (the sensor of cholesterol level) go to the ER(where the SREBP found) -> SCAP escorts SREBP to Golgi bodies -> two proteases cleave SREBP to a soluble fragment that enters the nucleus and binds SRE -> **HMG CoA gene transcription is activated.**



Excretion of cholesterol

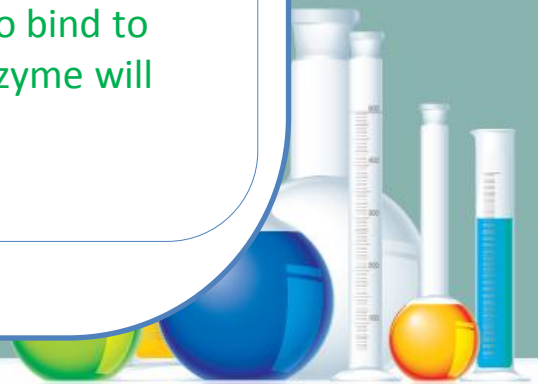
By conversion into bile acids and bile salts- excreted in the feces

By secretion of cholesterol in bile- transported to intestine for elimination

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

Hypercholesteremia

- High concentration of cholesterol **in blood**
- Leads to atherosclerosis
- Statin drugs are used to decrease the plasma cholesterol levels
- Statins are structural analogs of HMG CoA .(structural analog= has the same structure)
- Statins inhibit enzyme activity by competitive inhibition (Statin is going to bind to the active site of the enzyme and sense it's not the right substrate the enzyme will not do anything= become inactive enzyme)



Not cholesterol but similar in structure

B-Sitosterols/ Phytosterols

- Plant sterols and are **poorly absorbed by humans (we eat them for taste then we secrete them)**
- Block the absorption of dietary cholesterol
- Clinically useful in the dietary treatment of hypercholesteremia

(when it being absorbed by mucosal cells in the intestine -> it blocks the absorption of other dietary cholesterol -> when it being thrown by mucosal cells out(because it can't go to the circulation) -> it brings with it the cholesterol that was actually taking in by mucosal cells. So, it reduces the amount of cholesterol that is absorbed by the diet) .

- Commercially available as – trans fatty acid-free margarine

Imp Qs

1) Cholesterol metabolized mainly by

a) Liver b)adrenal cortex c) intestine

2) All carbons units of cholesterol are derived from

a) Squalene b) mevalonic acid c) Acetyl CoA

3) If we want to regulate cholesterol synthesis, which ONE of the following enzymes will be targeted

a) HMG CoA reductase b) HMG CoA synthesized c) lanosterol

4) The first sterol formed &parent molecule of all sterol

a) lanosterol b) Squalene c) HMG CoA

5) If cholesterol not synthesized propapry it can lead to

a) Smith-Lemli-Opitz Syndrome b) hypercholestremia

6) Which ONE of the following we give for a patient who has a hypercholestermia ?

a) Statin b) insigs c) Thyroxin

7) In the intestine cholesterol is converted by bacteria into

a) B-Sitosterols/ Phytosterols b) coprostanol and cholestanol

8) Increasing of AMP- activated protein kinase will lead to

a) phosphorelation -> increase cholesterol synthesis. b) Dephosphorelation ->cholesterol synthesis stopped.

c) phosphorelation -> cholesterol synthesis stopped d) Dephosphorelation -> increase cholesterol synthesis.

9) What is the function of insig proteins regarding cholesterol synthesis?

a) Moves SREBP-SCAP to Golgi to cleave SCAP off b) Binds to SCAP and prevent it from exiting ER in certain conditions

c) It is an HMG CoA reductase analog d) None of the above

Answers: 1-a 2-c 3-a 4-a 5-a 6-a 7-b 8-c 9-b