Biochemistry – Cholesterol Metabolism

CVS Block

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430 Biochemistry Team

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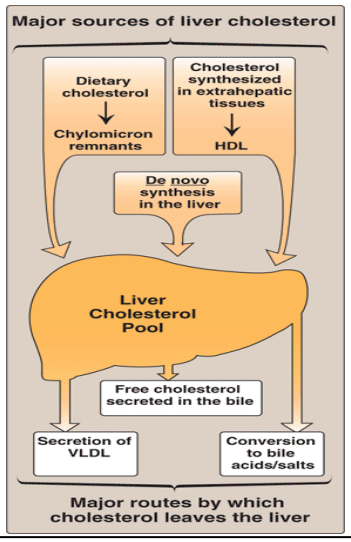
Cholesterol:

- Most important animal steroid
- Maintains membrane fluidity
- Insulating effect on nerve fibers
- Cholesterol is the parent molecule for:
  - Bile acids and bile salts (metabolism)
  - Steroid hormones and
  - Vitamin D_3

Liver plays a central role in the regulation of cholesterol homeostasis

*Explanation: Cholesterol enters the liver by a number of sources including dietary cholesterol or cholesterol synthesized from the liver itself and extra hepatic tissue. From here it could be secreted into unmodified cholesterol (free cholesterol) which is secreted in the bile. Or it could be converted to bile salts. cholesterol could also be converted into VLDL which will eventually leads to deposition of cholesterol in the endothelial lining of blood vessels. If present in high amount s, it can cause atherosclerosis)



Source of cholesterol (influx):

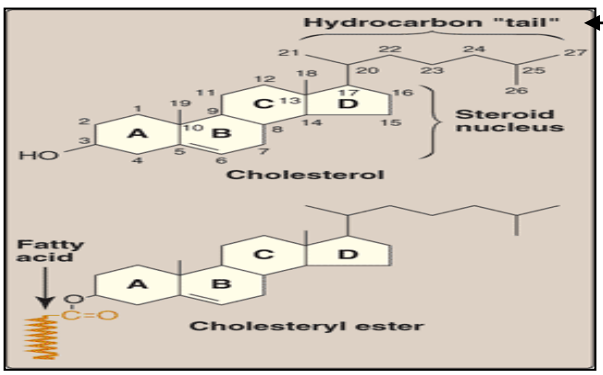
1- dietary.
2- synthesize in the body:

A- in extrahepatic tissue.

B- de novo synthesize in the liver (De novo mean something synthesized in the body).

The eflux:

1- secretion of VLDL.
2- free cholesterol secreted in the bile then to the intestine where it's modified then secreted
3- conversion to bile acid/ salt



Cholesterol Structure

Chemical structure is formed of 4 rings and branched carbon chains

2 form :
1- cholesteryl ester (hydrocarbon tail+ steroid nucleus with fatty acid)
2- cholesterol (hydrocarbon tail+ steroid nucleus which form of 4 rings with OH in carbon number 3)
We do not have to remember the structure.

Cholesteryl esters (in plasma):

- 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 (Because it has a fatty acid so it carried by lipoprotine).
- Cholesteryl esters must be accompanied by by a protein in order to enter the liver.

Cholesterol synthesis:

- Synthesized in all tissues.
- Major sites for synthesis: liver, adrenal cortex, testes, ovaries and intestine

We can divided to :

1- secretary organ(adrenal cortex, testes, ovaries)
2- 2-liver +intestine.

- For synthesizing we need:

1- building block from acetyl CoA.
2- enzyme.

- 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

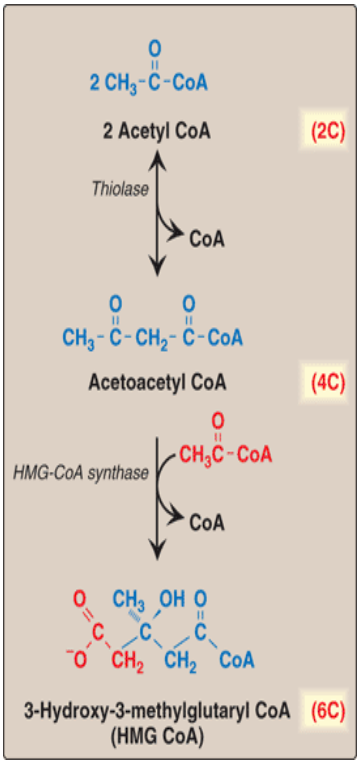
- HMG CoA is present in both cytosol and mitochondria of liver

Thiolase first converts 2 condensed acetyl CoA into Acetoacetyl CoA, next a third molecule of acetyl CoA is added in the presence of HMG-CoA synthases

- Mitochondrial- ketogenesis
  (synthesize keton body)

- Cytosolic – cholesterol synthesis

The enzyme HMG CoA reductase is present in both mitochondria and cytosol. In cytosol it synthesizes cholesterol. However, in mitochondria, it is responsible for the production of ketones.

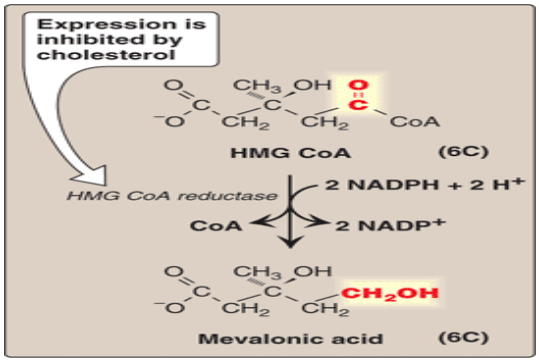


From picture we should know that
3 molecul of acetyl CoA give us 1 HMG CoA(6C)

Synthesis of mevalonic acid

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

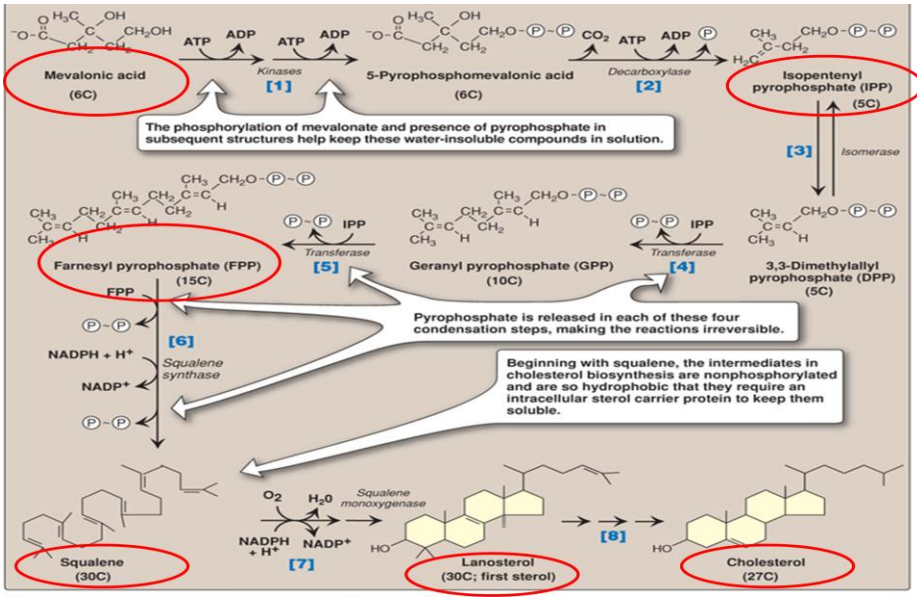
HMG CoA is catalyzed by HMG CoA reductase and reduced by 2 NADPH into Mevalonic acid.



HMG CoA is reduced to mevalonic acid which is also 6C by HMG CoA reducetase in the presence of NADPH.
Synthesis of mevalonic acid is the most important step because it is the only rate limiting step(it help in controlling cholesterol biosynthesis, so it is used in order to increase or decrease cholesterol level)

Further steps in synthesis:

- Production of a 5-carbon unit:
- Isopentinyl pyrophosphate (IPP) (the first 5C)
- Condensation of 5-carbon units to form a 30-carbon compound- Squalene (it is an open ring)
  (6 IPP=1 Squalene because each IIP contain 5C so 6IPPX5 =30 the number of Squalene carbon)
  Cyclization of squalene to 30C lanosterol
  (the first steroid to be formed)
- Cutting to size (because cholesterol contain 27C)- 27-Carbon cholesterol (defect in this leads to Smith-Lemli-Opitz Syndrome) (congenital syndrome)

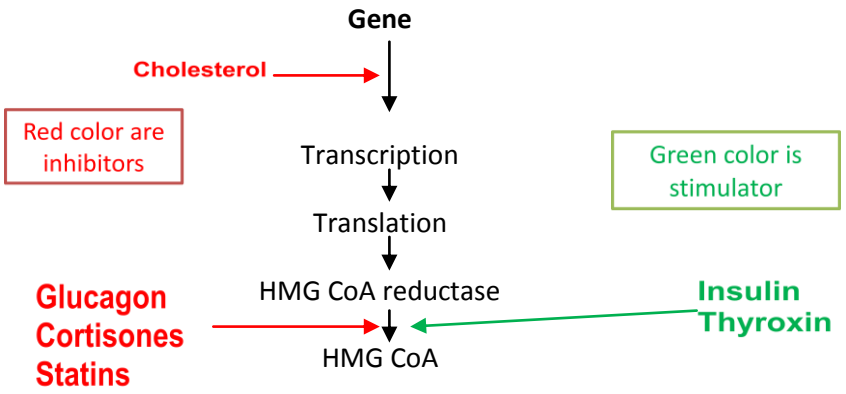


You don't have to go into the details. correlate this diagram with previous slide.

Regulation of Cholesterol Synthesis:

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

HMG CoA Reductase Regulation:

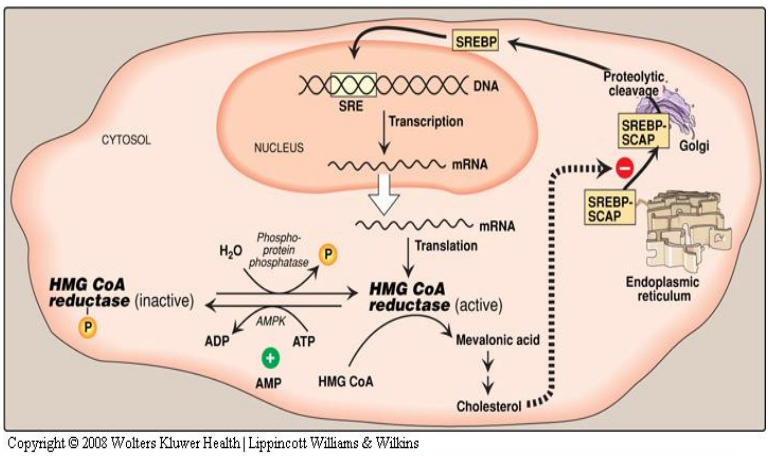


HMG CoA Reductase Regulation (here are the main **METHODS** in which HMG CoA is regulated inside the CYSTOSOL)

- Sterol-dependent regulation of gene expression
- Sterol-accelerated enzyme degradation "if cholesterol levels are high, it will degrade the enzyme, as a result, cholesterol levels will decrease" **(sterol dependent)**
- Sterol-independent phosphorylation/dephosphorylation
- Hormonal regulation **(sterol independent)**

Sterol-dependent regulation of gene expression of HMG CoA:

- When sufficient cholesterol is present, transcription is suppressed and vice versa.
- 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 (SREBP controlled by SCAP).



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When sterol levels are low, SREBP-SCAP complex is sent out from ER into golgi. then SREBP-SCAP complex is then acted on by proteases which makes the SREBP break off and move into the nucleus which will binds to SRE → HMG CoA reductase production increases → cholesterol increases. ***However*** if sterol is high, SCAP will bind to a third protein called insigs . This binding will prevent the SREBP-SCAP complex from being sent to golgi

Sterol-dependent regulation:

Cholesterol High	Cholesterol Low
• SCAP binds to insigs (ER membrane proteins) • SCAP-SREBP is retained in the ER • Down regulation of cholesterol synthesis	• SCAP-SREBP moves to Golgi bodies • SCAP is removed from SREBP • SREBP binds to SRE in DNA • HMG CoA gene is activated

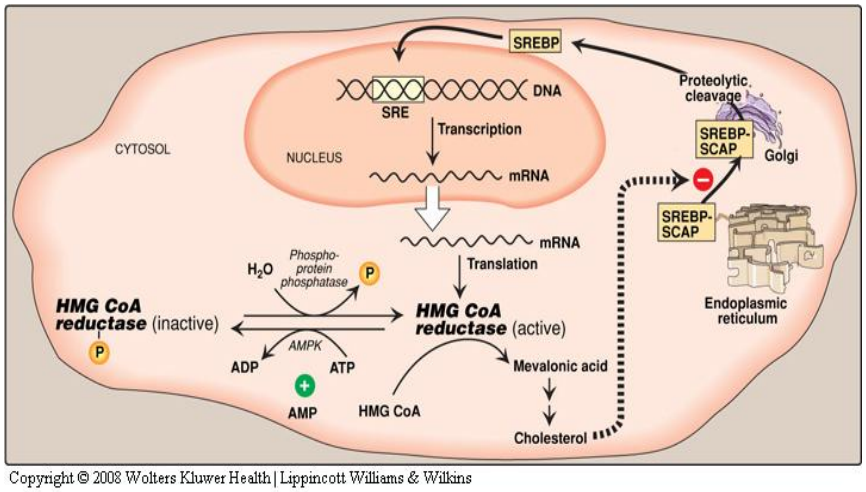
Sterol-accelerated enzyme degradation:

- When cholesterol is high, HMG CoA reductase itself binds to insigs
- Leading to degradation of enzyme

Enzyme phosphorylation and dephosphorylation:

- AMP- activated protein kinase (AMPK) for phosphorylation
- Phosphorylated form of enzyme is inactive
- Dephosphorylated form is active
- High ATP → cholesterol synthesis stops
- Low ATP → cholesterol synthesis starts

*(So when there enough cholesterol the enzyme will be inactive by phosphorylation, But when the level of cholesterol decrease this lead to dephosphorylation of enzyme to be active)



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High ATP → cholesterol synthesis stops
Low ATP → cholesterol synthesis starts

Cholesterol increases > ATP increases > HMG CoA reductase phosphorylated (in active) > cholesterol production inhibited

Hormonal Regulation:

- Insulin (increase after eating) and thyroxine increase up-regulation of enzyme expression. (they lead to increase cholesterol levels)
- Glucagon (increase in fasting) and cortisol have opposite effect (decrease it).

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 into coprostanol and cholestanol before excretion

Excretion of cholesterol in 3 form:
1- bile acids and bile salts.
2- coprostanol.
3- cholestanol

Hypercholesterolemia:

- High concentration of cholesterol in blood
- It Leads to atherosclerosis
- Statin drugs (attack HMG) are used to decrease plasma cholesterol levels to the normal level
- Statins are structural analogs of HMG CoA
- Statins inhibit enzyme activity by competitive inhibition irreversibly. (it competes with the substrate to bind with the enzyme. when they are bound there will be no cholesterol synthesize)

Example of statin drugs: simvastatin, lovastatin

Beta-Sitosterols/ Phytosterols:

- Plant sterols are poorly absorbed by humans
- Beta-sitosterols / phytosterols Block the absorption of dietary cholesterol
- They are Clinically useful in the dietary treatment of hypercholesterolemia
- Commercially available as – trans fatty acid-free margarine