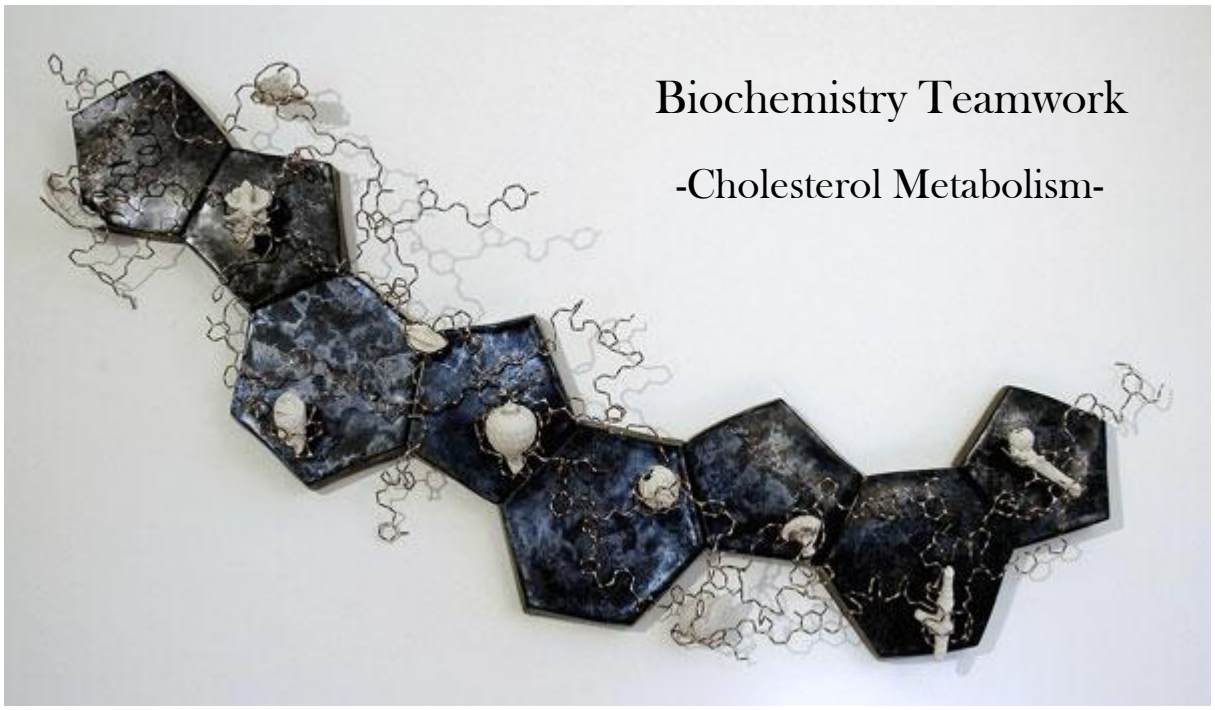

Team Leaders	
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Team Members	
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Reem AlMansour	Khalid Al-Khamis
Hadeel Helmi	
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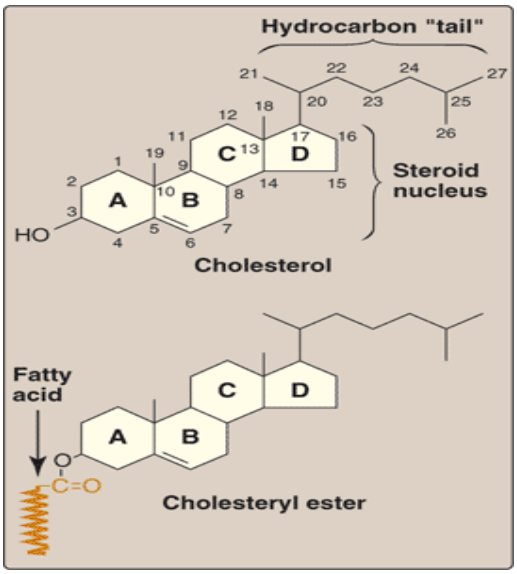
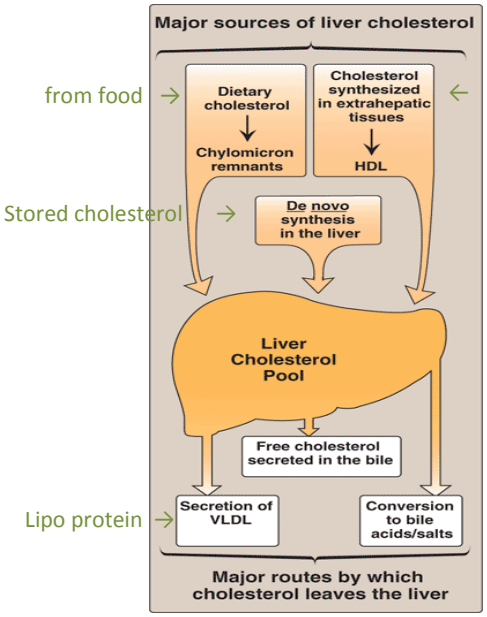
Cholesterol:

- 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 D_3



Cholesterol and Cholesteryl Ester structures:

- 4 fused carbon rings (steroid nucleus) with hydrocarbon chain 8C attached to ring "D"
- At 3rd carbon in "A" ring:
  - OH^- → Cholesterol – an alcohol (hydrophobic)
  - O-Fatty acid → Cholesteryl Ester (even more hydrophobic)



Liver plays a central role in the regulation of cholesterol homeostasis

Cholesterol esters:

- Most plasma cholesterol is esterified with a fatty acid
- Cholesterol Esters (ECs) are not present in cell membranes
- Present in small amounts in most cells
- More hydrophobic than cholesterol

Cholesterol Synthesis:

Dr. Sumbul mentioned that cholesterol synthesis occurs on the memberane of ER and in the cytosol. Not inside the ER.

- Synthesized in all tissues
- Major sites for synthesis: liver, adrenal cortex, testes, ovaries and intestine
- All carbon atoms (of cholesterol) are derived from acetyl CoA
- Enzymes involved in biosynthesis are partly located in ER and partly in cytoplasm

The Dr mentioned this:

Ketone bodies are bi-products of fatty acid oxidation. They are an important source of energy for the body in starvation.

Synthesis of HMG coA: (graph A)

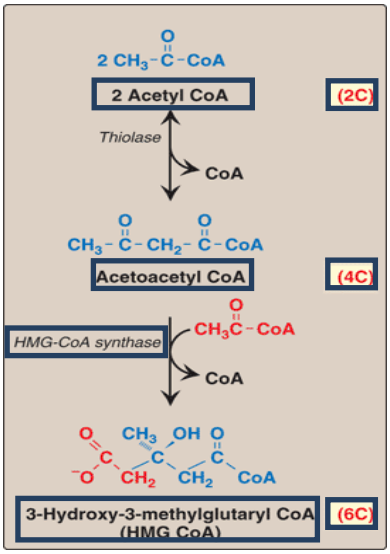
- HMG CoA is present in both cytosol and mitochondria of liver
- Mitochondrial HMG CoA – used for ketogenesis (formation of ketone bodies)
- Cytosolic HMG CoA – used for cholesterol synthesis

Synthesis of Mevalonic Acid: (graph B)

- Rate limiting and key step (the only rate limiting step or regulatory step)
- Occurs in cytosol
- HMG CoA reductase is an ER membrane enzyme with catalytic unit hanging in the cytosol. Bound to ER membrane but the part where the reduction happens is in the part of the enzyme that is hanging in the cytosol (catalytic unit) it reduces HMG CoA to Melvonic Acid.

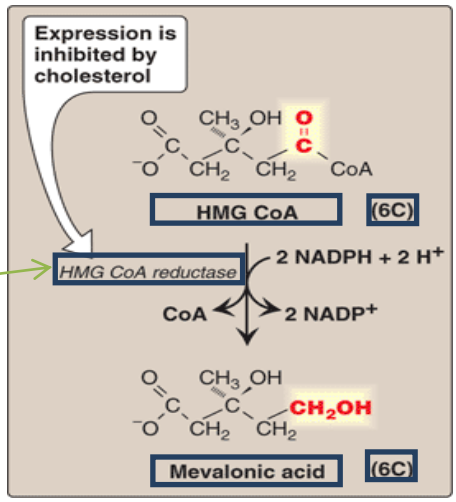
We join 2 acetyl CoA (2C) and get Acetoacetyl CoA (4C)

Then we add another Acetyl CoA and get HMG CoA (6C)



Graph A

This is the target of drugs if we need to reduce cholesterol production e.g Statins



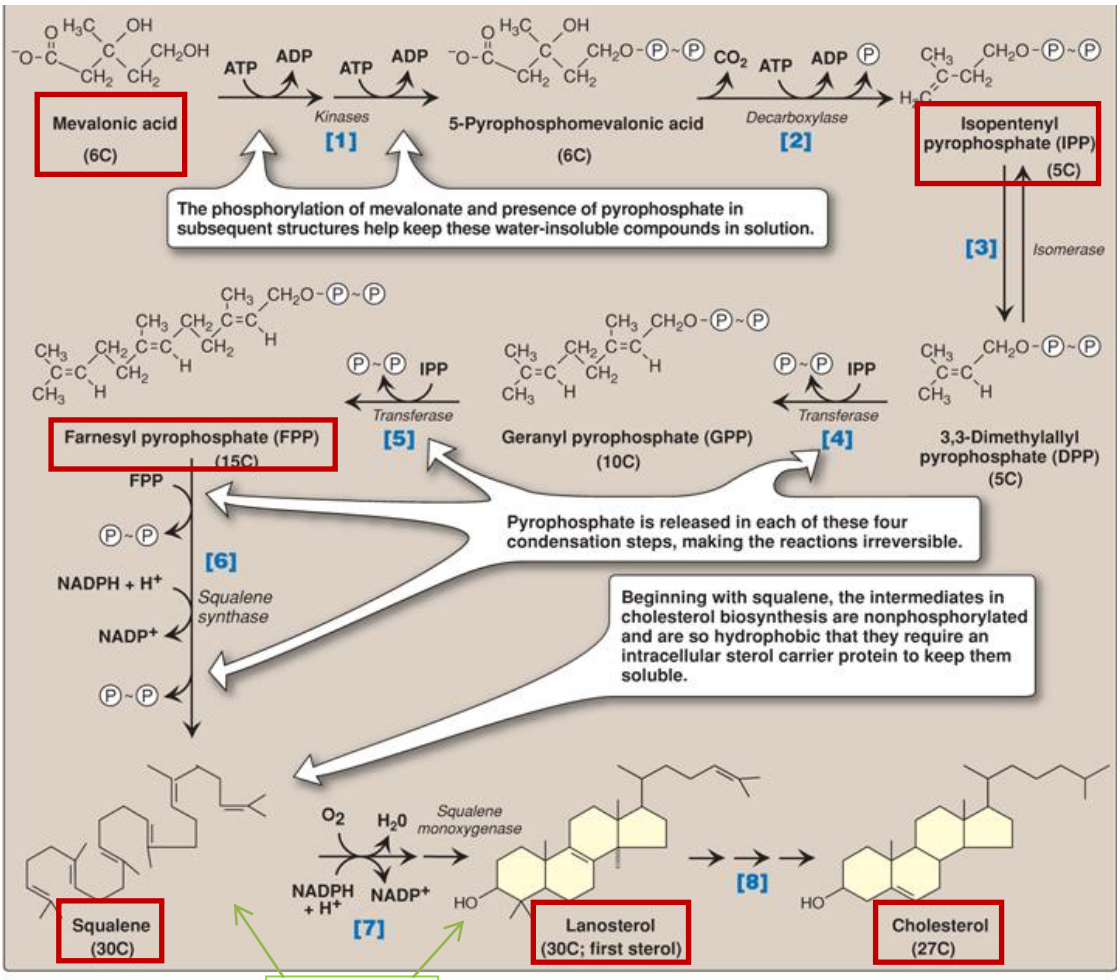
Graph B

Further steps in synthesis: (graph C)

The synthesis of the 27-C cholesterol from lanosterol is a long process which requires 17 enzymes. If any of them is deficient this leads to impaired cholesterol biosynthesis (Smith-Lemli-Optiz syndrome)

- Production of a 5-carbon unit:
  - Isopentinyl pyrophosphate (IPP)
- Condensation to a 30C compound: squalene [six IPP grouped together (6 x 5C = 30C < squalene)]
- Cyclization of squalene to 30C lanosterol (first sterol molecule to be formed, it has the steroid nucleus)
- Synthesis of 27-Carbon cholesterol (defect in this leads to Smith-Lemli-Opitz Syndrome)

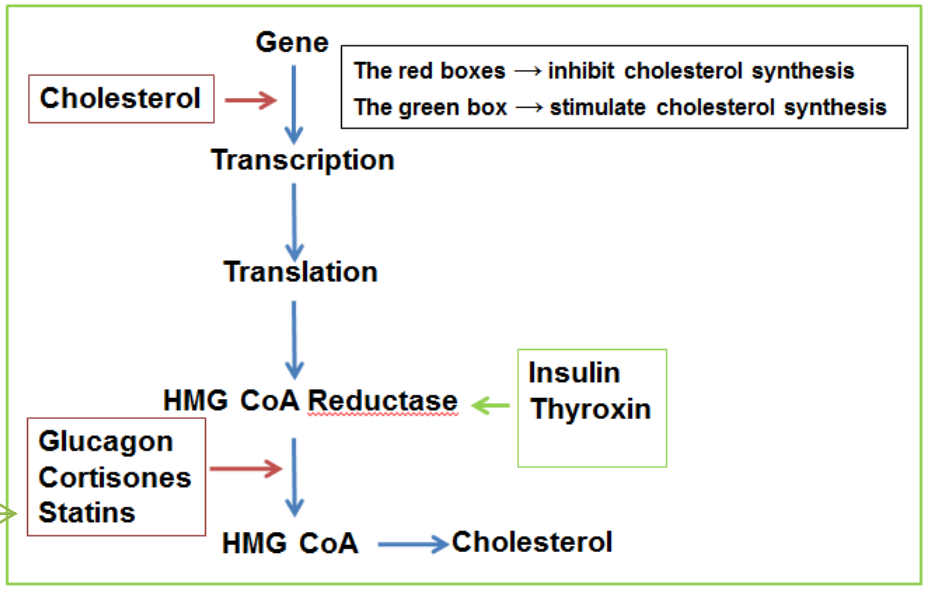
FPP is 3 IPP molecules and then we add another FPP molecule to it and get squalene 30C



cyclization

Regulation of Cholesterol Synthesis:

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



Statins are cholesterol reducing drugs

HMG CoA Reductase Regulation

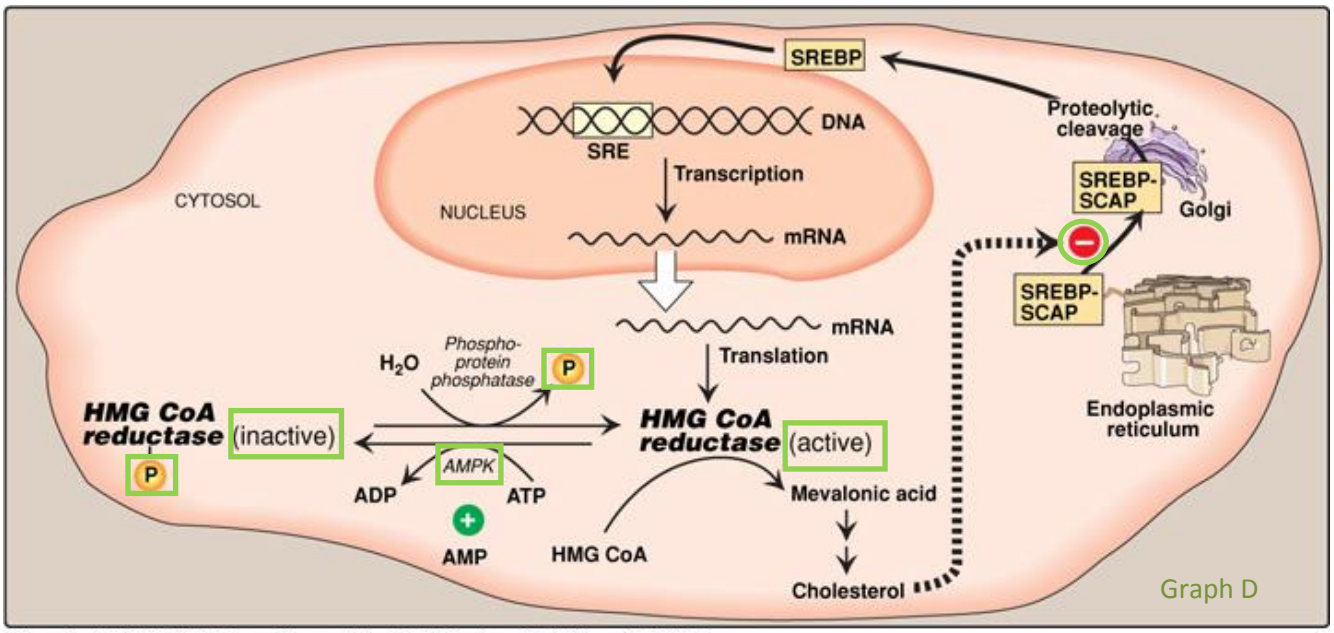
gene expression is the process by which information from a gene is used in the synthesis of a functional gene product

HMG CoA Reductase Regulation:

- Sterol-dependent regulation of gene expression
- Sterol-accelerated enzyme degradation (if ↑ cholesterol ↑ HMG CoA reductase degradation or if ↓ cholesterol ↓ HMG CoA reductase degradation)
- Sterol-independent phosphorylation/dephosphorylation (does not depend on cholesterol but on ATP)
- Hormonal regulation

Sterol-dependent regulation of gene expression of HMG CoA: (graph D)

- When sufficient cholesterol is present, transcription is suppressed and vice versa; when cholesterol is absent transcription is activated.
- Sterol Regulatory Element (SRE) is a recognition sequence in the DNA
- SREBP (SRE binding protein)(a transcription factor inside ER)(binding to SRE is essential for transcription of this gene. It binds to SCAP forming > SREBP-SCAP
- SREBP cleavage-activating protein (SCAP) is an intracellular cholesterol sensor



When SCAP senses that cholesterol is high or low it does the following:

Cholesterol High

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

Cholesterol Low

- SCAP-SREBP moves to Golgi bodies
- SCAP is removed/cleaved from SREBP by proteases
- SREBP binds to SRE in DNA
- HMG CoA gene is activated and starts transcription

Enzyme phosphorylation and dephosphorylation: (graph D)

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

Hormonal Regulation:

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

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

Hypercholesterolemia:

- High conc. of cholesterol in blood
- Leads to atherosclerosis
- Statin drugs are used to decrease plasma cholesterol levels
- Statins are structural analogs of HMG CoA reductase (analog: same in structure)
- Statins inhibit enzyme activity by competitive inhibition

β-Sitosterols/ Phytosterols:

- Plant sterols and are poorly absorbed by humans
- Block the absorption of dietary cholesterol
- Clinically useful in the dietary treatment of hypercholesterolemia

Plant sterols are absorbed by the intestine then thrown back taking with it some dietary cholesterol.

Questions:

1. **Where does the HMG CoA reductase gene transcription occur?**
    A. In the ER matrix
    B. In the ER membrane
    C. In the cytosol
    D. In the nucleus

2. **What happens if cholesterol concentration is high?**
    A. Gene transcription of HMG coA eductase is stimulated
    B. HMG CoA reductase is degraded
    C. Hypercholesterolemia
    D. B & C

3. **What is the funtion 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 condetions
    C. It is an HMG CoA reductase analog
    D. None of the above

4. **Which of the following about Cholesterol and Cholesteryl Ester is true**
    A. They are present in the cell membrane
    B. They are hydrophobic
    C. They share the same structure but deffer in the 3rd Carbon on the A ring, where one has an OH- and the other an O-fatty acid attached to it
    D. B & C

5. **What activates protein kinase (AMPK)?**
    A. Cholesterol
    B. Insulin
    C. AMP
    D. ATP

Answers: **D, D, B, D, C**