

Cholesterol Metabolism



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

Overview

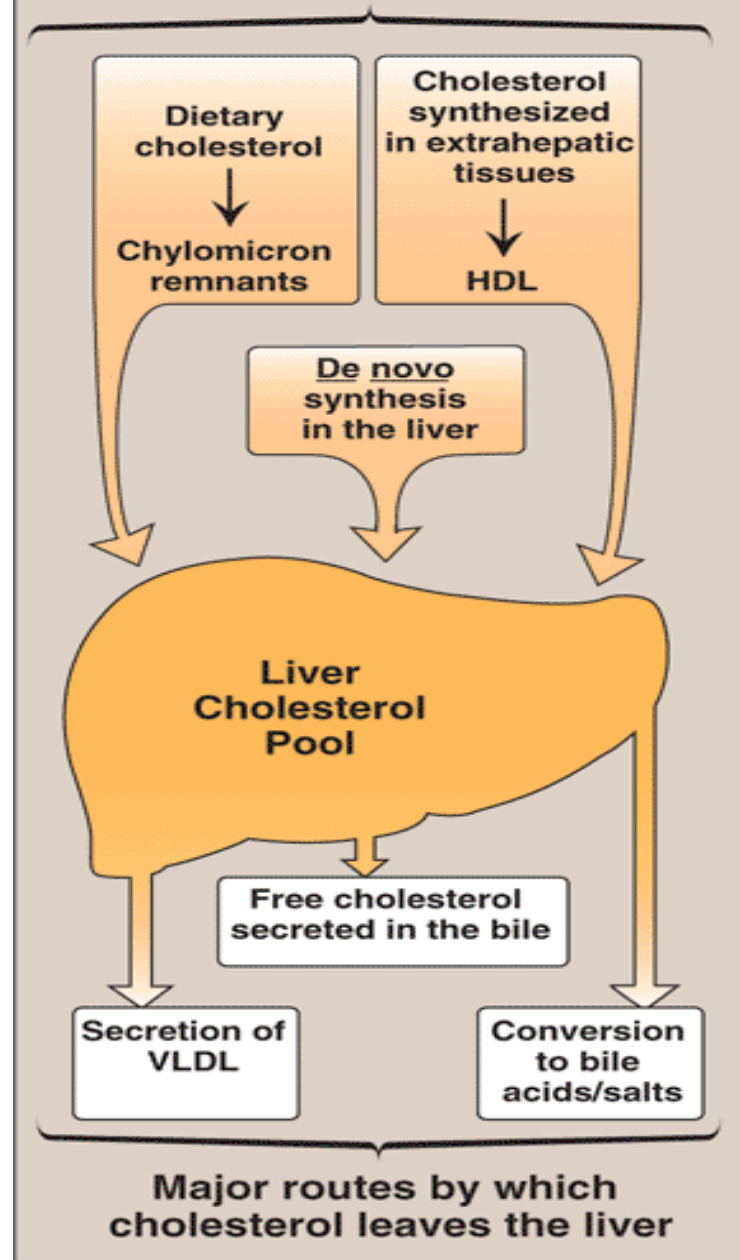
- Introduction
- Cholesterol structure
- Cholesteryl esters
- Cholesterol synthesis
- Rate limiting step
- Regulation of cholesterol synthesis
- Regulation of HMG CoA reductase
- Excretion of cholesterol
- Hypercholesterolemia and **treatment**

Cholesterol

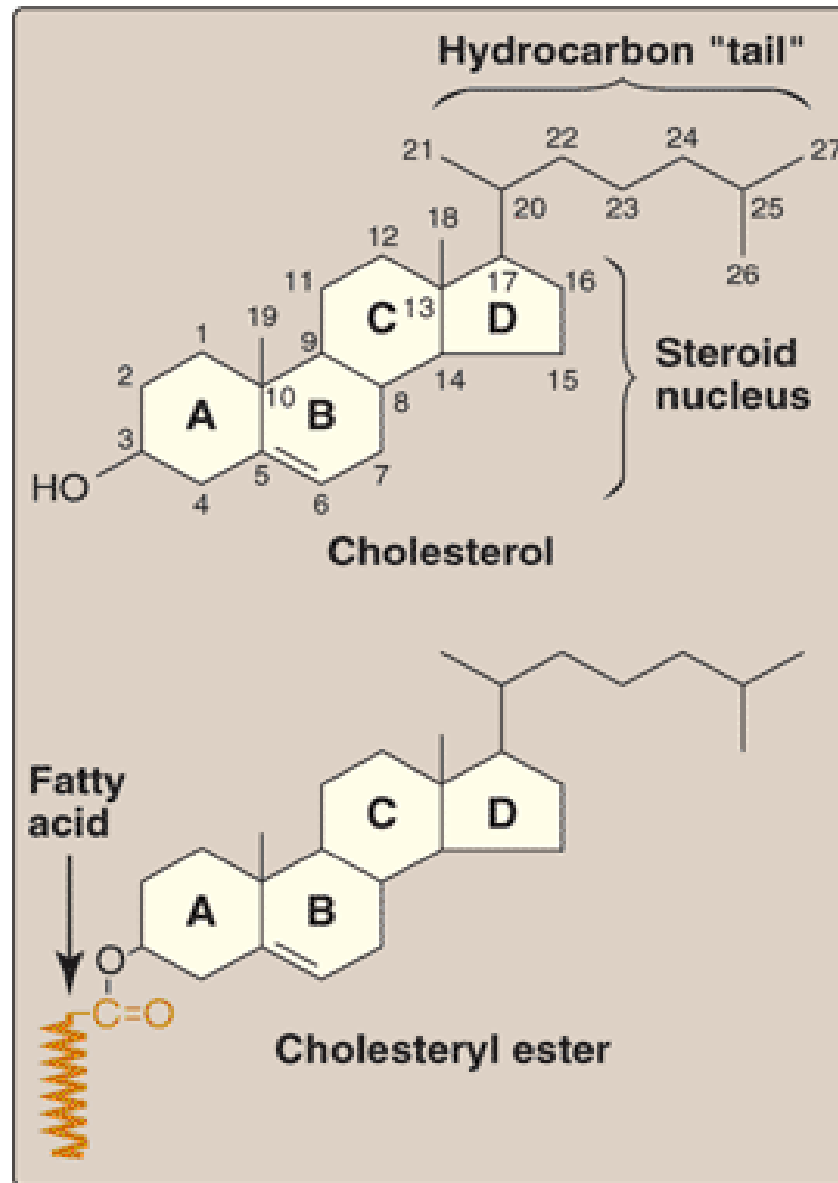
- Most important animal steroid
- Maintains membrane fluidity
- Insulating effect on nerve fibres
- Cholesterol is the parent molecule for
 - Bile acids and bile salts
 - Steroid hormones
 - Vitamin D₃

**Liver plays a central role
in the regulation of
cholesterol homeostasis**

Major sources of liver cholesterol



Cholesterol Structure



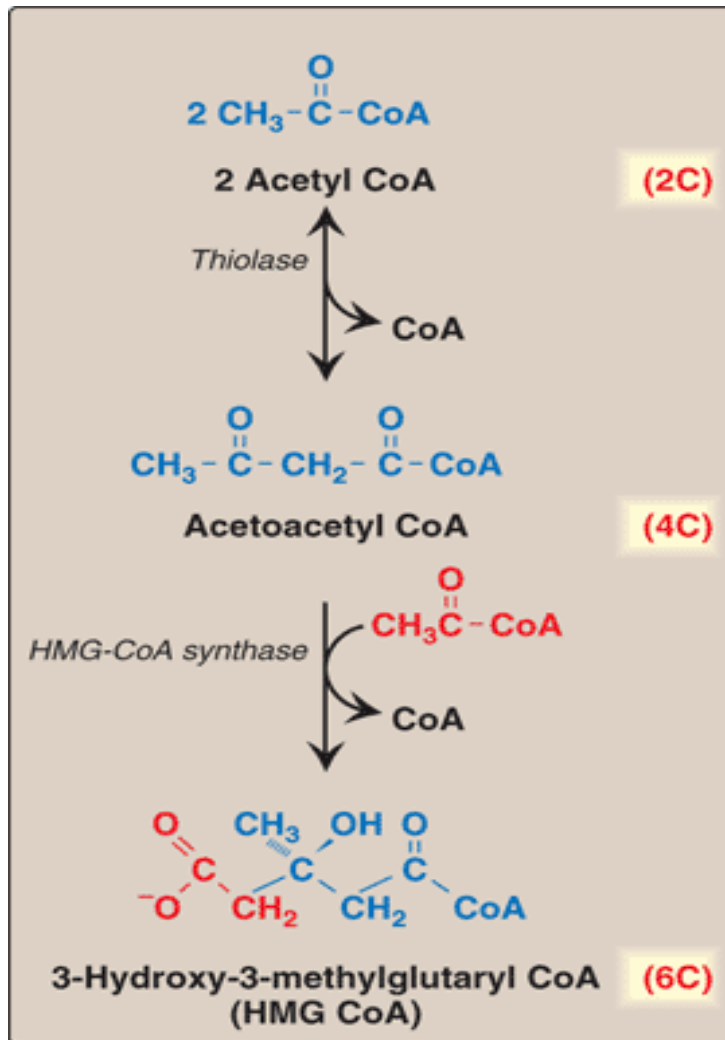
Cholesteryl esters

- 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

Cholesterol synthesis

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

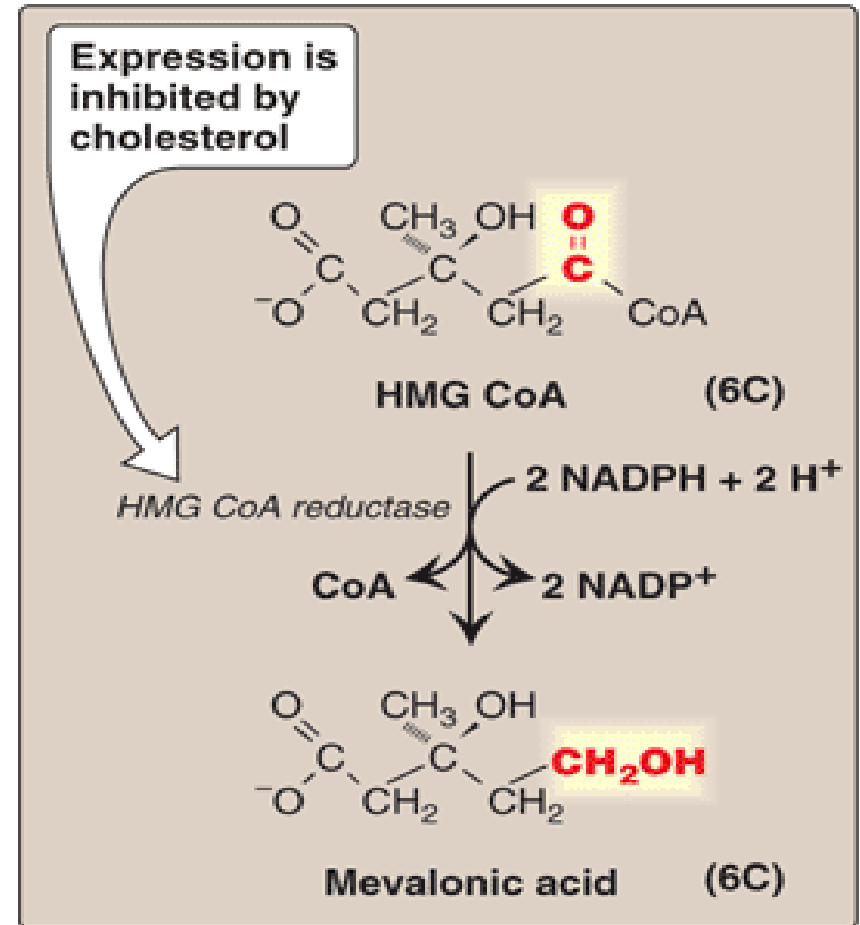
Synthesis of HMG CoA



- HMG CoA is present in both cytosol and mitochondria of liver
- Mitochondrial-ketogenesis
- Cytosolic – cholesterol synthesis

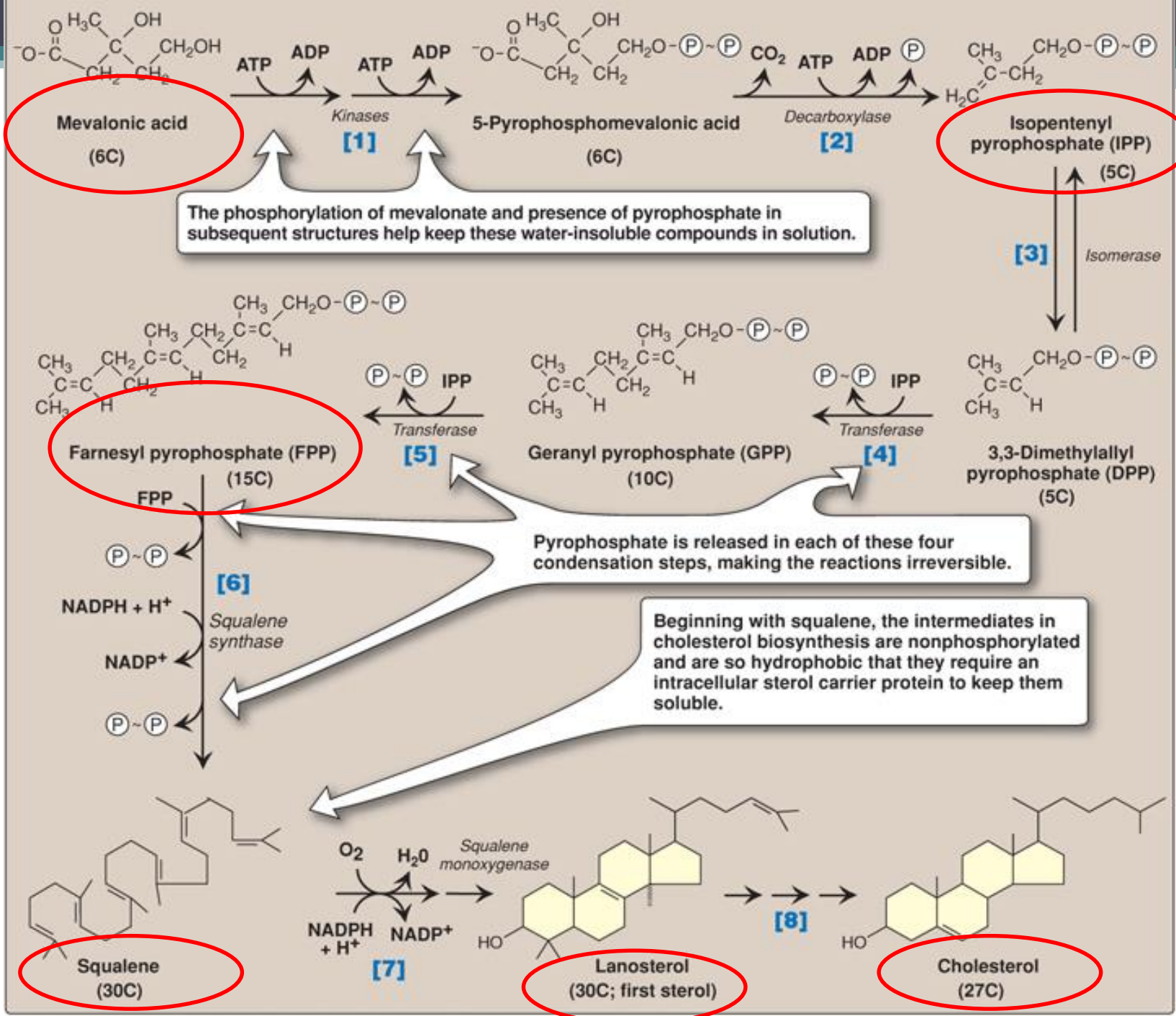
Synthesis of mevalonic acid

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



Further steps in synthesis

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



Regulation of Cholesterol Synthesis

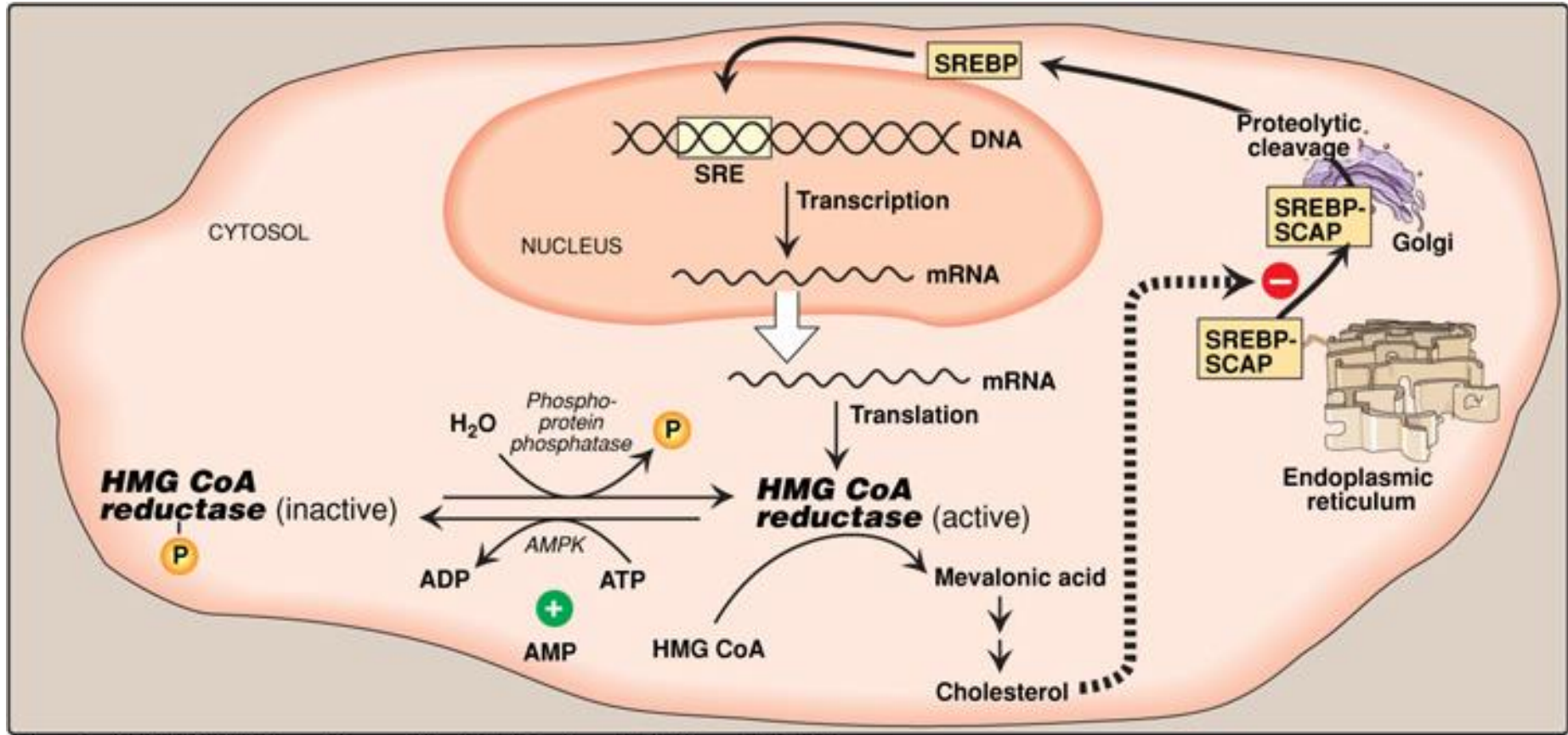
- HMG CoA reductase is the rate-limiting enzyme of cholesterol synthesis

HMG CoA Reductase Regulation

- Sterol-dependent regulation of gene expression
- Sterol-accelerated enzyme degradation
- Sterol-independent phosphorylation/dephosphorylation
- Hormonal regulation

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 the DNA
- SREBP (SRE binding protein) binding to SRE is essential for transcription of this gene
- SREBP cleavage-activating protein (SCAP) is an intracellular cholesterol sensor



Sterol-dependent regulation

Cholesterol High

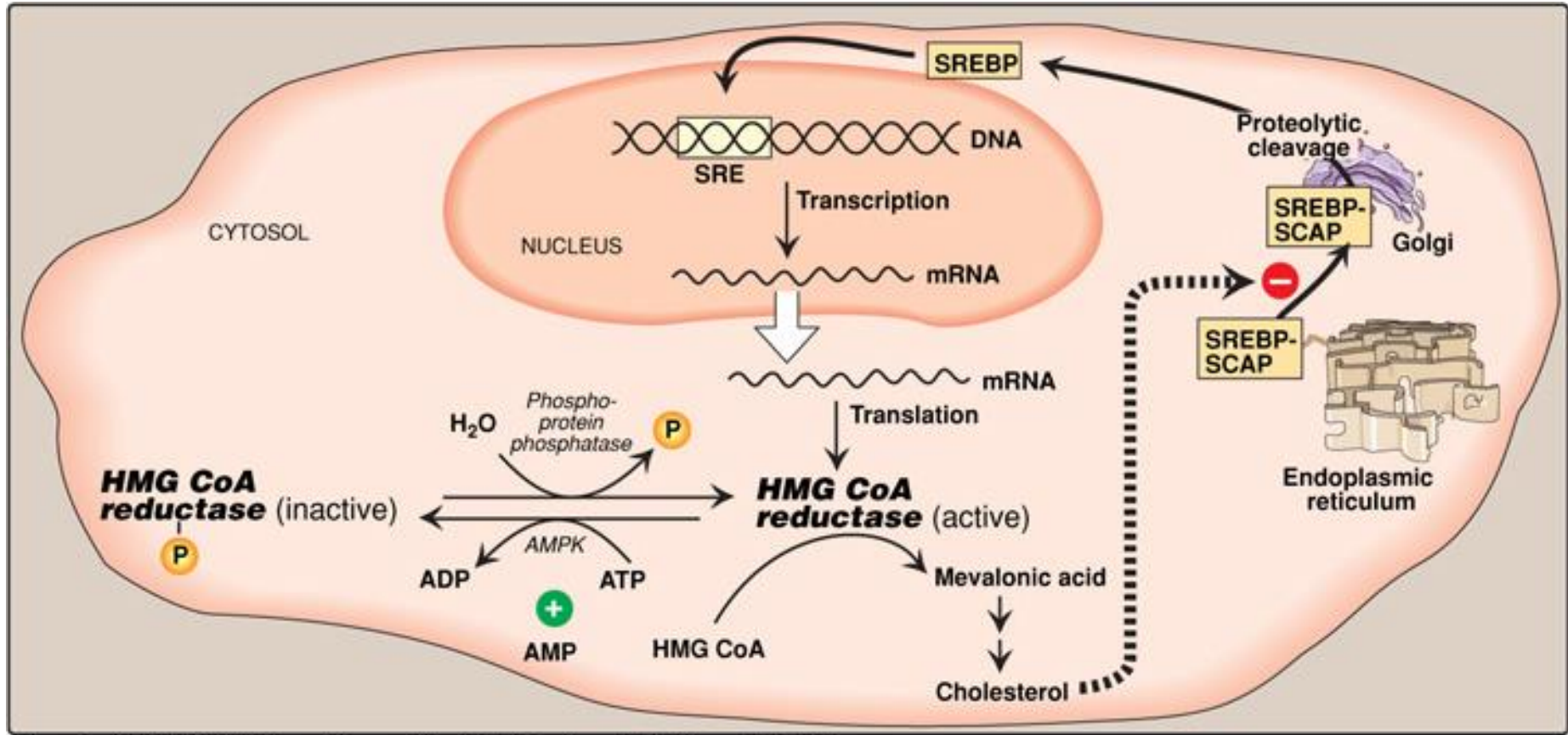
- SCAP binds to insig protein (insulin-induced protein) in ER membrane
- SCAP-SREBP is retained in the ER
- Down regulation of cholesterol synthesis

Cholesterol Low

- SCAP-SREBP moves to Golgi bodies
- SCAP is removed from SREBP
- SREBP binds to SRE in DNA
- HMG CoA gene is activated

Enzyme phosphorylation and dephosphorylation

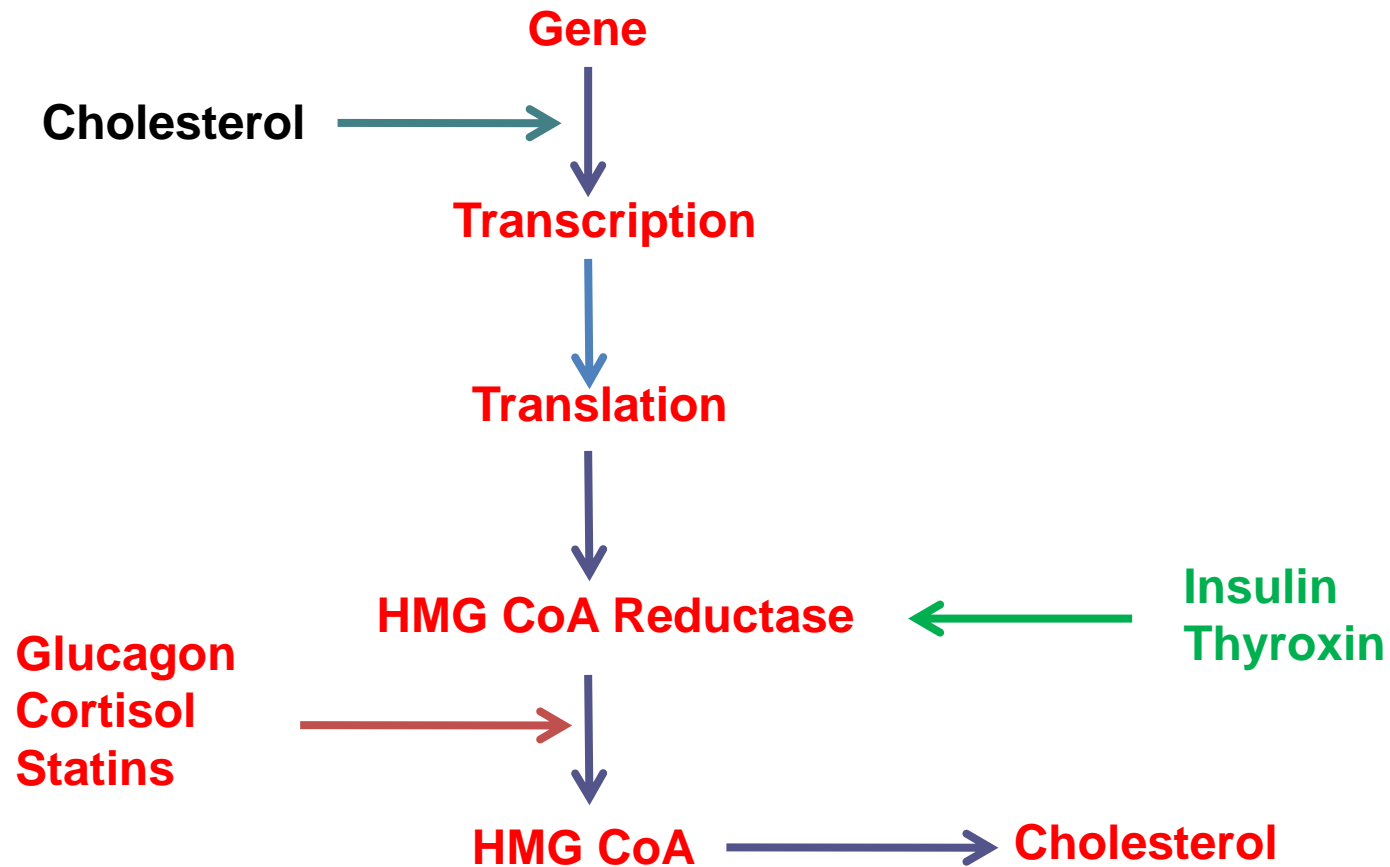
- AMP- activated protein kinase (AMPK) for phosphorylation
- Phosphorylated form of enzyme is inactive
- Dephosphorylated form is active
- Low **ATP** or High **AMP** → cholesterol synthesis decreases



Hormonal Regulation

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

HMG CoA Reductase Regulation



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
- Statins inhibit enzyme activity by competitive inhibition

β -Sitosterols/ Phytosterols

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

Take home message

- 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

References

- Lippincott's Biochemistry 5th Edition, Chapter 18, pp 219–224