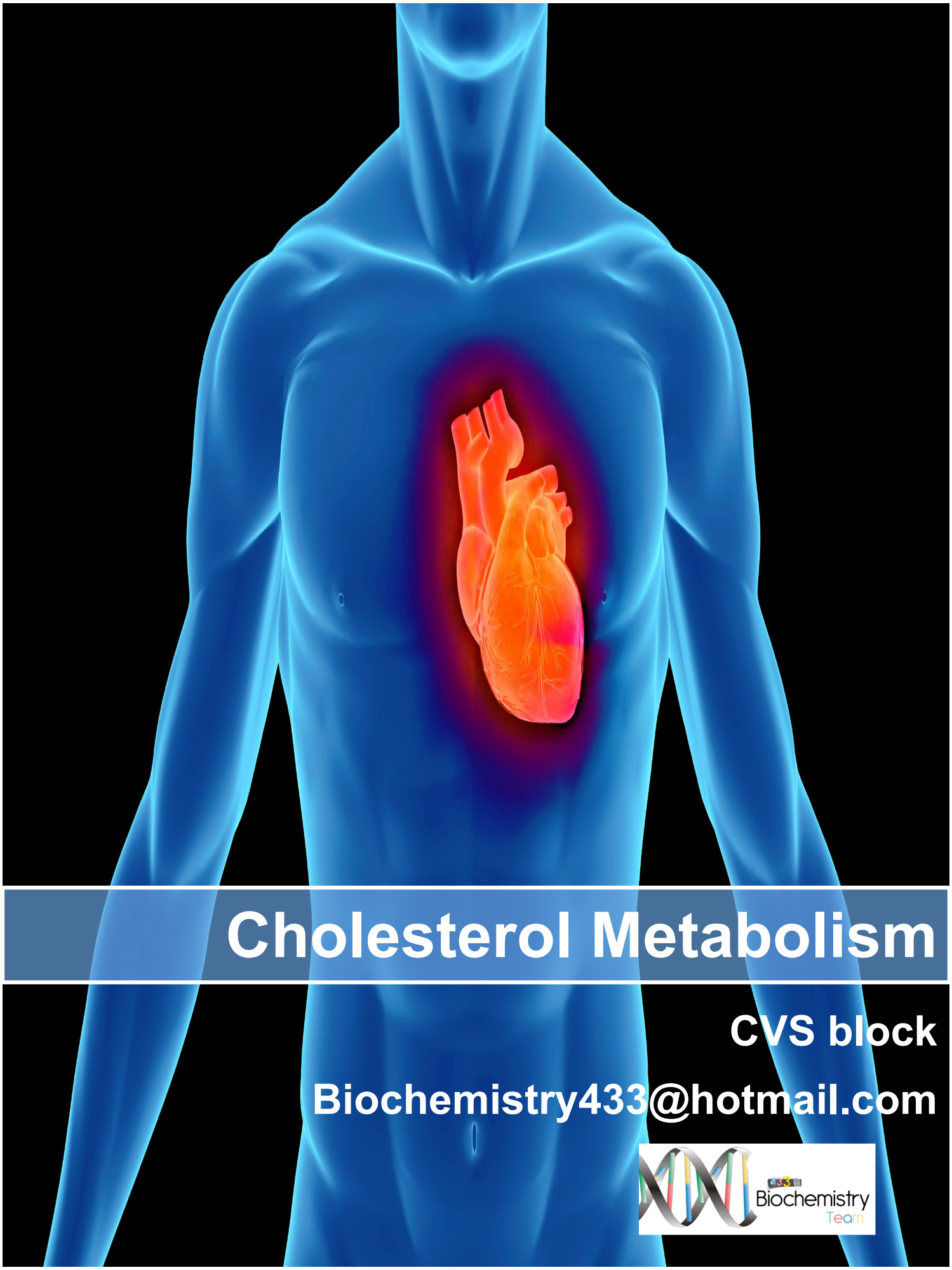

# Cholesterol Metabolism

CVS block

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Biochemistry Team

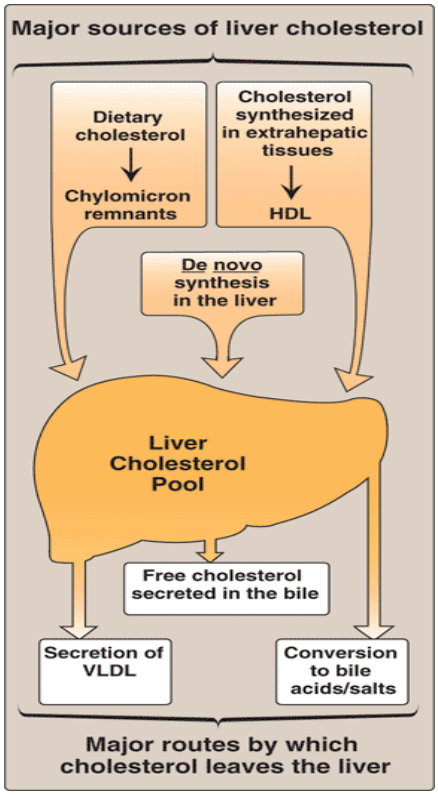
# Objectives:

- 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

# abbreviations:

- CE: cholesterol esters.
- ER: Endoplasmic Reticulum.
- HMG CoA: 3-Hydroxy 3-Methylglutaryl CoA.

# cholesterol

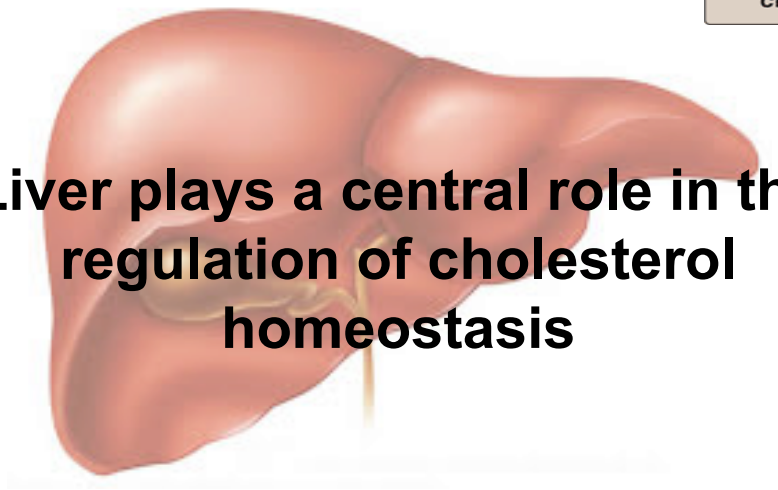



- Most important animal steroid
- Maintains membrane fluidity
- Insulating effect on nerve fibres
- Cholesterol is the parent molecule for

➲ Bile acids and bile salts

➲ Steroid hormones

➲ Vitamin D3

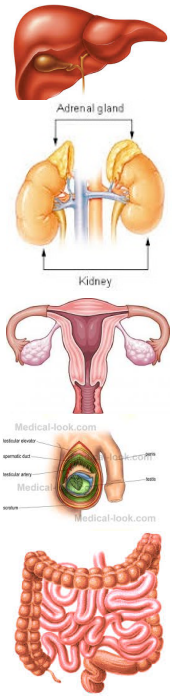


Liver plays a central role in the regulation of cholesterol homeostasis

# 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



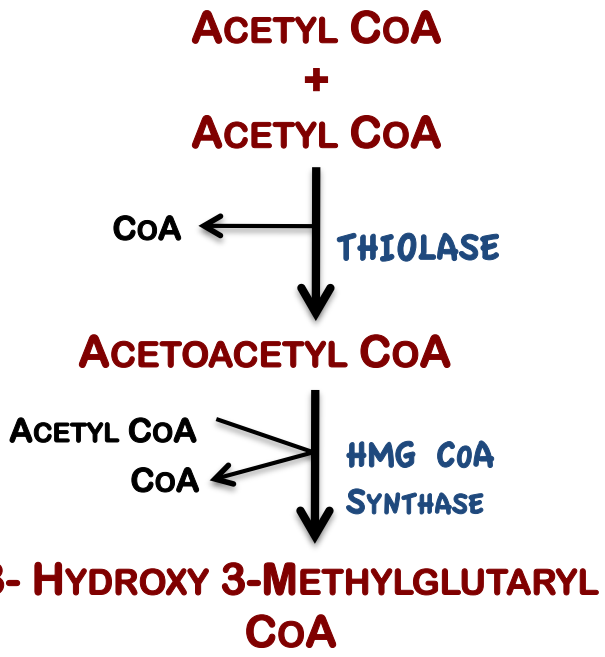

- Synthesized in ALL TISSUES
- MAJOR SITES for synthesis: liver, adrenal cortex, testes, ovaries and intestine
- All carbon atoms are derived from acetyl CoA
- Enzymes involved in biosynthesis are partly located in ER and partly in cytoplasm

# HMG CoA

• Present in both cytosol and mitochondria of liver:

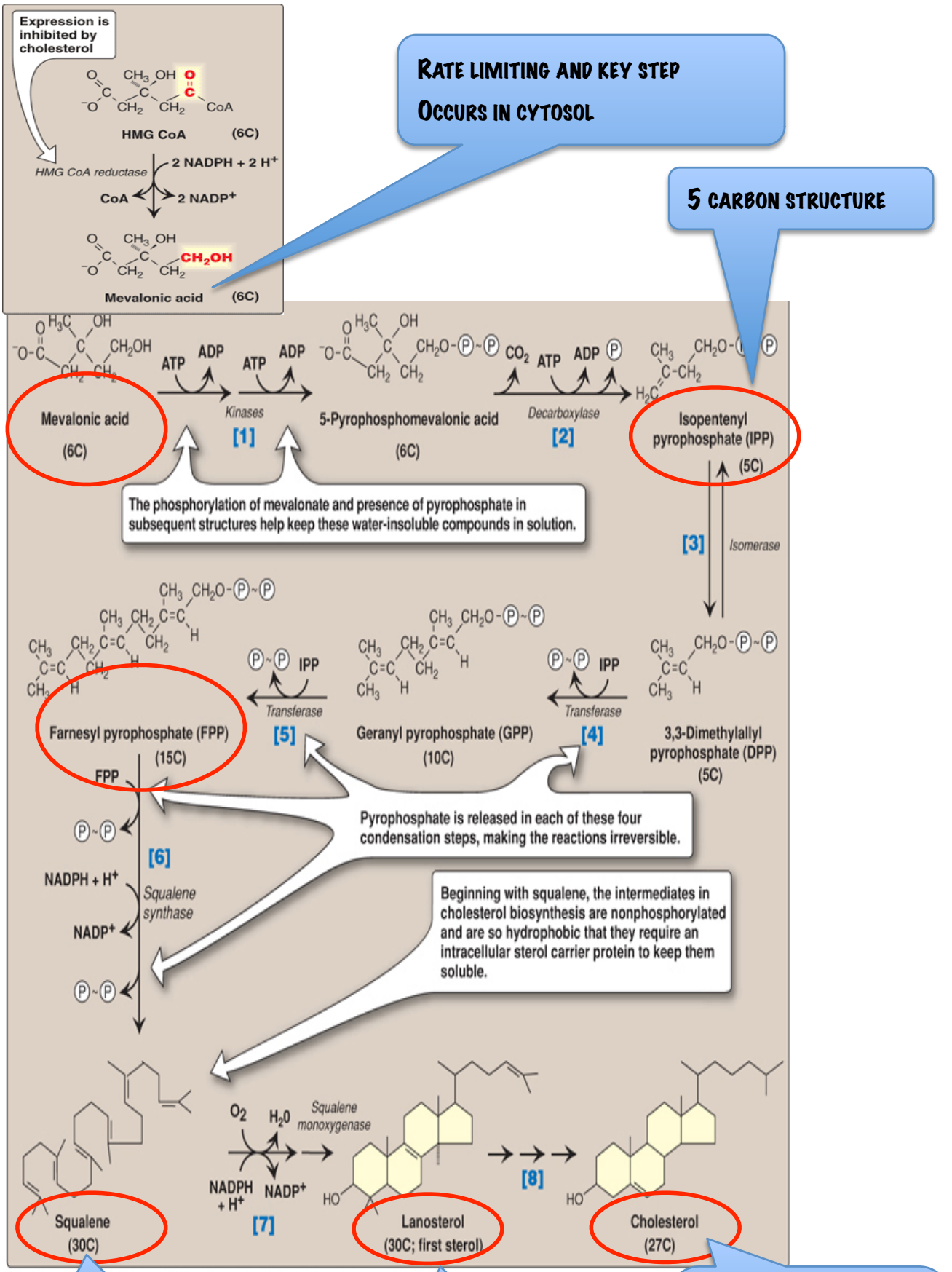
➲ Mitochondrial- involved in ketogenesis.

➲ Cytosolic - involved in cholesterol synthesis.




# Synthesis of mevalonic acid

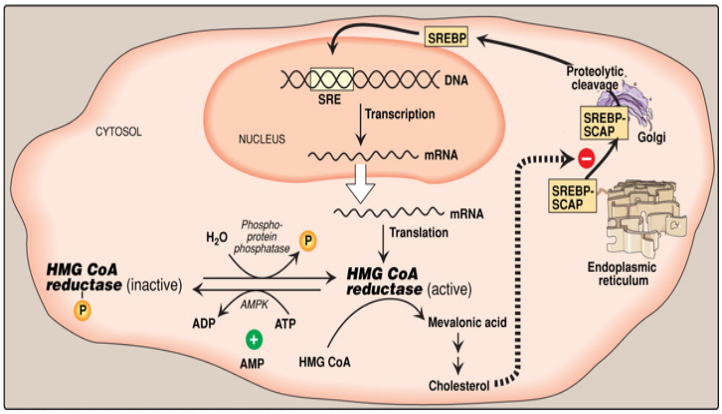
- RATE LIMITING AND KEY STEP
- Occurs in cytosol
- HMG CoA reductase is an ER membrane enzyme with catalytic unit hanging in the cytosol, it is also is the rate-limiting enzyme of cholesterol synthesis


Expression is inhibited by cholesterol
HMG CoA (6C)
HMG CoA reductase
2 NADPH + 2 H+
CoA
2 NADP+
Mevalonic acid (6C)
Rate limiting and key step
Occurs in cytosol
5 carbon structure
ATP
ADP
Kinases
[1]
Mevalonic acid (6C)
5-Pyrophosphomevalonic acid (6C)
CO2
Decarboxylase
[2]
Isopentenyl pyrophosphate (IPP) (5C)
The phosphorylation of mevalonate and presence of pyrophosphate in subsequent structures help keep these water-insoluble compounds in solution.
[3]
Isomerase
Farnesyl pyrophosphate (FPP) (15C)
Transferase
[5]
Geranyl pyrophosphate (GPP) (10C)
[4]
3,3-Dimethylallyl pyrophosphate (DPP) (5C)
Pyrophosphate is released in each of these four condensation steps, making the reactions irreversible.
[6]
NADPH + H+
Squalene synthase
NADP+
Beginning with squalene, the intermediates in cholesterol biosynthesis are nonphosphorylated and are so hydrophobic that they require an intracellular sterol carrier protein to keep them soluble.
O2
H2O
Squalene monoxygenase
NADPH + H+
NADP+
[7]
[8]
Squalene (30C)
Lanosterol (30C; first sterol)
Cholesterol (27C)
Condensates to a 30 carbon structure
Cyclization of squalene to 30C lanosterol
Synthesis of 27-Carbon cholesterol (defect in this leads to Smith-Lemli-Opitz Syndrome)

# HMG CoA Reductase Regulation

## THE REGULATION INCLUDES:

- STEROL-DEPENDENT REGULATION OF GENE EXPRESSION:
  - 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-ACCELERATED ENZYME DEGRADATION
- STEROL-INDEPENDENT PHOSPHORYLATION/DEPHOSPHORYLATION
- HORMONAL REGULATION:





Gene

Cholesterol →

↓

Transcription

↓

Translation

↓

HMG CoA Reductase

Glucagon
Cortisones
Statins → ↓ ← Insulin
Thyroxin

↓

HMG CoA → Cholesterol

STEROL-DEPENDENT REGULATION : WHEN SUFFICIENT CHOLESTEROL IS PRESENT, TRANSCRIPTION IS SUPPRESSED AND VICE VERSA

HORMONAL REGULATION:

- INSULIN AND THYROXINE INCREASE UPREGULATION OF ENZYME EXPRESSION
- GLUCAGON AND CORTISOL HAVE OPPOSITE EFFECT

# Sterol-dependent regulation

## Cholesterol High

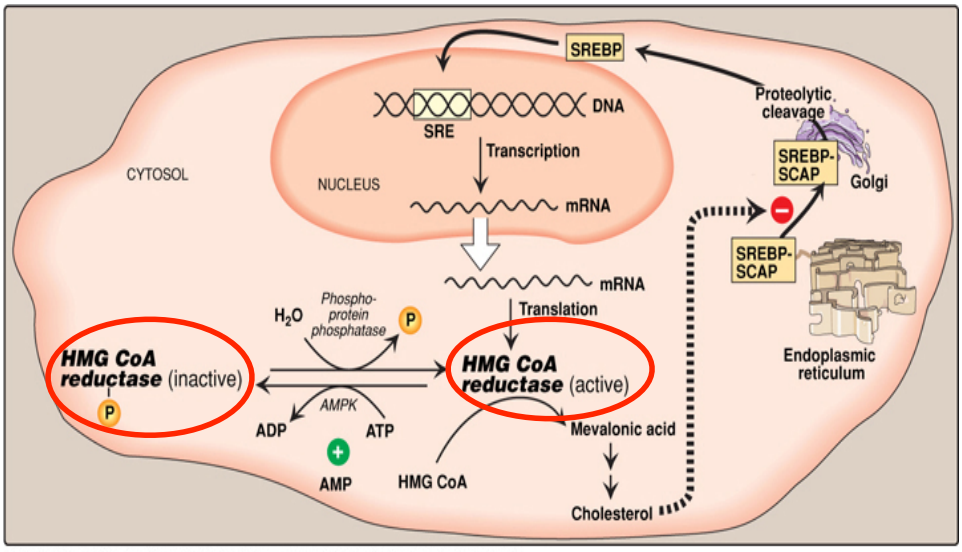
- SCAP binds to INSIG protein (insulin-induced protein) in ER membrabe
- SCAP-SREBP is retained in the ER
- Down regulation of cholesterol synthesis

## Cholesterol Low

- SCAP-SREBP moves to Golgi bodies
- SCAP is removed 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



## 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
- They are structural analogs of HMG CoA reductase and inhibit the 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

# QUIZ YOURSELF!!

1- STATIN DRUGS INHIBIT THE SYNTHESIS OF THE ENZYME HMG COA REDUCTASE BY:
A- COMPETITIVE INHIBITION
B- IRREVERSIBLE INHIBITION
C- UNCOMPETITIVE

2- CHOLESTEROL IS SYNTHESIZED IN:
A- LIVER AND INTESTINE
B- TESTES AND OVARIES
C- A&B
D- ALL TISSUES

3- SMITH-LEMLI-OPITZ SYNDROME IS A RESULT OF A DEFECT WHICH OF THE FOLLOWING?
A- CYCLIZATION OF SQUALENE TO 30C LANOSTEROL
B- SYNTHESIS OF 27-CARBON CHOLESTEROL
C- SYNTHESIS OF 20-CARBON CHOLESTEROL

4- IN STEROL DEPENDANT REGULATION, WHEN CHOLESTEROL IS HIGH:
A- SCAP-SREBP MOVES TO GOLGI BODIES
B- SREBP BINDS TO SRE IN DNA
C- SCAP BINDS TO INSIG PROTEIN

5- WHICH OF THE FOLLOWING IS CORRECT IN HYPERCHOLESTEROLEMIA:
A- HIGH CONC. OF CHOLESTEROL IN BLOOD .
B- LEADS TO ATHEROSCLEROSIS.
C- A & B .

ANS: 1- A 2- D 3- B 4- C 5- C

# GOOD LUCK!!

## FROM OUR TEAM MEMBERS:

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AMJAD ALBATILI
LAYAN ALTAWEEL

AHMAD ALHUSSAIN
ZIYAD ALAJLAN