Cholesterol Synthesis

Main function: formation of steroid nucleus
Substrate: cytoplasmic acetyl CoA
Endproduct: cholesterol
Location: cytoplasm

Regulation of cholesterol synthesis pathway

- HMG CoA reductase catalyzes the rate-limiting step.
- The synthesis and the activity of the HMG-CoA reductase enzyme is controlled in the liver cell.

Cholesterol biosynthesis

cyto. acetyl CoA → HMG CoA → mevalonate
isopentenyl PP (5C) → farnesyl PP (15C) → squalene (30C) → cholesterol

Cholesterol synthesis pathway

\[
\begin{align*}
\text{cyto. acetyl CoA} & \rightarrow \\
\text{HMG CoA} & \rightarrow \\
\text{mevalonate} & \rightarrow \\
\text{isopentenyl PP (5C)} & \rightarrow \\
\text{farnesyl PP (15C)} & \rightarrow \\
\text{squalene (30C)} & \rightarrow \\
\text{cholesterol} & \rightarrow
\end{align*}
\]

HMG CoA reductase

\[
\begin{align*}
\text{HMG-CoA} & \rightarrow \\
\text{mevalonate} & \rightarrow \\
\text{OH} & \rightarrow \\
\text{CH}_3\text{C-COO} & \rightarrow \\
\text{CH}_2\text{C-} & \rightarrow \\
\text{S-CoA} & \rightarrow
\end{align*}
\]

Regulation of HMG CoA reductase activity

- cholesterol and mevalonate directly inhibit HMG-CoA reductase activity
- insulin binding indirectly stimulates HMG-CoA reductase activity
- glucagon binding indirectly inhibits HMG-CoA reductase activity
Inhibition of HMG CoA reductase synthesis

1. Cholesterol esters in blood bind to Low Density Lipoprotein (LDL-cholesterol complex).
2. LDL-cholesterol complex binds LDL receptor protein in liver cell membrane.

LDL membrane receptors

Inhibition of HMG CoA reductase synthesis

• 3. LDL-cholesterol-ester complex is transported into liver cell by LDL receptor protein in liver cell membrane.
• 4. LDL-cholesterol drops off LDL receptor protein and binds to cytoplasmic receptor protein.

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Control of enzyme synthesis

5. Cholesterol derivative and cytoplasmic receptor protein enter nucleus, bind to DNA and prevent RNA polymerase from transcribing the gene coding for HMG-CoA reductase.

Controlling enzyme synthesis

Hormonal regulation of cholesterol synthesis

• Glucagon binds to receptor in liver cell membrane, stimulating cAMP formation
• cAMP activates PROTEIN KINASE which inactivates rate-limiting HMG CoA reductase enzyme, decreasing cholesterol synthesis
Hormonal regulation of cholesterol synthesis

- Insulin binds to its receptor protein in liver cell membrane, and stimulates irs-1 formation.
- irs-1 activates HMG CoA reductase enzyme, increasing rate of cholesterol synthesis.

Hormone action

**Insulin binding**
- Insulin binds to cell stimulates cholesterol synthesis
- Insulin binding decreases [cAMP] in cell

**Glucagon binding**
- Glucagon binds to cell decreases cholesterol synthesis

HMG CoA reductase

- active form
- inactive form
- protein kinase
- cAMP
- ATP
- AMP
- P

Glucagon binding results in cAMP formation

- Protein kinase
- HMG CoA reductase
- [cAMP]
- no product

Insulin binding to cell stimulates cholesterol synthesis

- HMG ~ S-CoA
- mevalonate + 2 NADP+ + H+
Activated isoprenes

mevalonate $\rightarrow$ isopentyl pyrophosphate $\rightarrow$ dimethylallyl pyrophosphate

Condensation of activated isoprenes

geranyl PP + $\cdots$ $\rightarrow$ cholesterol palmitate

Derivatives of cholesterol pathway intermediates

- ubiquinone
- retinal (Vit. A)
- cholecalciferol (Vit.D)
- menadione (Vit. K)

cholesterol

cholesterol ester

CH$_3$ - (CH$_2$)$_{14}$ - C - O

cholesterol palmitate
Steroid hormones

Testosterone

Cholesterol

Progesterone

Estradiol

Bile acids

- Bile acids are derivatives of cholic acid

- Bile acids are secreted from liver and stored in the gall bladder

- Glycine is condensed through COO- to produce glycocholic acid

- 80% of cholesterol made in liver is converted to bile acids and stored in gall bladder

Function of bile acids

- Glycocholic acid (bile acid) emulsifies triglycerides in the small intestine

- Fatty acids in blood stream cause gall bladder to contract, releasing bile.

- Glycocholic acid (bile acid) emulsifies triglycerides in the small intestine

- Fatty acids absorbed into blood through stomach wall stimulate gall bladder to contract, releasing bile.
**Gall stones**
- Gall stones are cholesterol & bile acids.
- Stones pass into hepatic duct.
- Passage of large gall stones is extremely painful.

**hypercholesterolemia**
(too much cholesterol in blood stream)

High cholesterol levels may be due to:
1. defective gene for LDL receptor protein
   - Affected individuals are slow to clear cholesterol from blood stream.
2. Other factors: smoking, age, inactivity.

**Atherosclerosis**
- Atherosclerosis is the formation of plaques in arteries and arterioles.
- Plaques are complex deposits of cholesterol esters and dead cells embedded in walls of arterioles.

**Atherosclerosis**
- Damaged regions in arteriole walls trigger inflammatory response.
- Plaques form at these inflamed areas more often in persons with high blood cholesterol.
- Plaques form and remain when circulation of blood is sluggish.

**Plaque formation**

- Damage & inflammation of arteriole wall
- Healthy vessel
- 90% blocked
**Pentose shunt**
(phosphogluconate pathway)
- Main function: formation of NADP:H and pentose PO₄
- Location in cell: enzymes found in cytoplasm
- Regulation: 1st enzyme, glu-6-P DHase catalyzes rate-limiting step

**Substrate:** glucose - 6 - P
**End-product:** depends on cell needs
- in adipose cells, NADP:H is required for lipid synthesis
- in rapidly dividing cells, pentose -PO₄’s are required for DNA synthesis

![Chemical reaction diagrams](image)

**Hereditary deficiency of G-6-P DH**
- at least 2 different G-6-P DHase isozymes in humans
- one isozyme is absent in many persons whose ancestors lived in malarial regions (S. Italy, parts of Africa, S.E. Asia)
- these individuals are asymptomatic until large demand for NADP:H