Cholesterol Synthesis

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Cholesterol Synthesis Pathway

Konrad Bloch

Feodor Lynen
A sterol with 27 carbon molecules with an -OH group at the # 3 position

Sterols are waxy insoluble substances or lipids synthesized from acetyl coenzyme A (CoA). They are steroid-based alcohols having a hydrocarbon (aliphatic) side chain of 8–10 carbons at the 17 position and a hydroxyl group (-OH) at the 3 position (making it an alcohol). Because of the hydrophilicity at the -OH end and hydrophobicity at the hydrocarbon side chain, sterols can be incorporated into the lipid bilayers of the cytoplasmic membrane.
Four Stages of Cholesterol Biosynthesis

The liver is responsible for about 15% of cholesterol synthesis and the remainder is extrahepatic.

Cholesterol synthesis is a **four-step process** starting from its precursor acetate: \( \text{CH}_3\text{COO}^- \).
In the first step, two molecules of acetyl-CoA upon the action of thiolase reversibly forms acetoacetyl-CoA.
Cholesterol Synthesis: Stage 1

- Acetyl-CoA condenses with acetoacetyl-CoA upon the action of cytosolic hydroxymethylglutaryl (HMG) synthase and becomes HMG-CoA.
The catalytic action (rate-limiting state) of HMG-CoA reductase, an integral part of the smooth endoplasmic reticulum, irreversibly forms mevalonate (a five-carbon intermediate) with NADPH serving as the reductant. HMG-CoA reductase transcription is tightly regulated by a membrane-bound transcription factor designated as sterol regulatory element-binding protein-2 (SREBP-2).

Different from mitochondrial HMG-CoA which plays a role in ketosis.
In the second step, mevalonate is phosphorylated from ATP to isoprene units or isoprenoids, namely isopentyl pyrophosphate, which can isomerize or interconvert to dimethylallyl pyrophosphate.
Cholesterol Synthesis: Stage 3

Isoprenoids react with each other to form geranyl pyrophosphate.

Condensation with another isopentyl-PP yields farnesyl pyrophosphate.

Squalene synthase catalyzes the condensation of two molecules of farnesyl-PP with reduction by NADPH to make squalene.
Cholesterol Synthesis: Stage 4

The fourth step involves conversion of the linear squalene molecule to the four-ringed steroid nucleus.

A series of reactions - oxidation, cyclization, and loss of three methyl groups - results in conversion of squalene to cholesterol.
Cholesterol Synthesis

Acetate → Acetoacetyl-CoA → HMG synthase → HMGCoA → HMG CoA reductase → Mevalonate → Dimethylallyl-PP → isomerization → Isopentyl-pyrophosphate → condensation → Farnesyl-pyrophosphate → Squalene synthase → Squalene → Isoprenoids → Lanosterol → Cholesterol

4 ringed structure
19-20 reactions including Desmosterol, Lathosterol

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Natural Products Derived from Activated Isoprene Units

Isoprene units or Isoprenoids are a class of largely hydrophobic or nonpolar compounds related by being constructed biosynthetically from five-carbon units.