Cholesterol Synthesis

The process of cholesterol synthesis begins with two molecules of acetyl-CoA. These then condense to form acetoacetyl-CoA, which is then further combined with another acetyl-CoA molecule via the enzyme cytosolic HMG-CoA synthase to form HMG-CoA. The enzyme HMG-CoA reductase then forms mevalonate, which undergoes a complex series of reactions to finally form cholesterol.

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Pathway

Acetyl-CoA
Seagull Coin-purse
Endogenously synthesized cholesterol accounts for roughly 10% of total body cholesterol. Most of this synthesis occurs in the cytoplasm of liver cells. Acetyl-CoA functions as the substrate for the initiation of cholesterol synthesis.

Acetoacetyl-CoA
2 Seagulls Together with Coin-purse
In the first step of cholesterol synthesis, two acetyl-CoA molecules are condensed into a single acetoacetyl-CoA molecule.

Cytosolic HMG-CoA Synthase
Side-toe-sail Humming-bird with Coin-purse Synthase
The cytosolic isoenzyme of HMG-CoA synthase will add an additional acetyl-CoA molecule to acetoacetyl-CoA, forming HMG-CoA. It is important to note that this isoenzyme of HMG-CoA synthase is located in the cytoplasm, whereas the HMG-CoA synthase enzyme that plays a role in ketogenesis is located in the mitochondria.

HMG-CoA
Humming-bird with Coin-purse
HMG-CoA is a molecule formed from three acetyl-CoA molecules (one acetyl-CoA and one acetoacetyl-CoA) in the cytoplasm of hepatocytes. This molecule is an intermediate in cholesterol synthesis as well as ketogenesis.

HMG-CoA Reductase
Humming-bird with Coin-purse and Red-duck
HMG-CoA reductase catalyzes the rate-limiting step of cholesterol synthesis. This enzyme forms mevalonate from HMG-CoA. This enzyme's activity is upregulated by insulin and thyroxine, whereas its activity is downregulated by glucagon and catecholamines. Statins work by inhibiting this enzyme.

Mevalonate
My-Valentine
Mevalonate is synthesized from HMG-CoA by HMG-CoA reductase. This is the rate-limiting step in cholesterol synthesis, and is irreversible.

Cholesterol
Cholesterol-burger
In the final phase of cholesterol synthesis, mevalonate undergoes a multi-step process to finally form cholesterol. This resulting cholesterol can be used for steroid synthesis, stabilization of cellular membranes, or as a precursor to vitamin D.
