6.1: Cholesterol synthesis

Cholesterol is a key component of cell membranes and is an essential precursor for steroid hormone synthesis. All twenty-seven carbons are derived from acetyl-CoA, and the initial synthesis involves the condensation of acetyl-CoA to mevalonate (figure 6.1).

![Figure 6.1: Structure of cholesterol.](https://med.libretexts.org/Bookshelves/Basic_Science/Cell_Biology_Genetics_and_Biochemistry_for_Pre-Clinical_Students/0...)

Cholesterol synthesis takes place in the cytosol, and the acetyl-CoA needed can be obtained from several sources such as β-oxidation of fatty acids, the oxidation of ketogenic amino acids, such as leucine and lysine, and the pyruvate dehydrogenase reaction (acetyl-CoA shuttled out of the mitochondria is in the form of citrate, which is cleaved into acetyl-CoA and pyruvate by citrate lyase). The process of cholesterol synthesis involves four stages (figure 6.2); however, only the first stage is regulated and will be focused on here.
Synthesis of mevalonate from acetyl-CoA

The first stage of cholesterol synthesis leads to the production of the intermediate mevalonate. The synthesis of mevalonate is the committed, rate-limiting step in cholesterol formation. In this reaction, two molecules of acetyl-CoA condense, forming acetoacetyl-CoA, which then condenses with a third molecule of acetyl-CoA to yield the six-carbon compound \( \beta \)-hydroxy-\( \beta \)-methylglutaryl-CoA (HMG-CoA) (figure 6.3) (the cytosolic HMG-CoA synthase in this reaction is distinct from the mitochondrial HMG-CoA synthase that catalyzes a similar reaction involved in production of ketone bodies). The committed step and major point of regulation of cholesterol synthesis involves reduction of HMG-CoA to mevalonate, in a reaction that is catalyzed by HMG-CoA reductase.

\[
\begin{align*}
\beta \text{-hydroxy-}\beta \text{-methyl-glutaryl-CoA} \\
(\text{HMG-CoA})
\end{align*}
\]

![Figure 6.3: Regulatory step catalyzed by HMG-CoA reductase.](https://med.libretexts.org/Bookshelves/Basic_Science/Cell_Biology_Genetics_and_Biochemistry_for_Pre-Clinical_Students/0...

The subsequent steps of the pathway proceed largely unregulated, and mevalonate is used to synthesize isoprenoid units (five-carbon units). These five-carbon chains are joined in a head-to-tail fashion generating squalene, thirty-carbons, which undergoes a cyclization reaction after epoxidation. The cyclized product, lanosterol, undergoes several reactions to generate the final product, cholesterol.

Regulation of cholesterol synthesis

The major regulatory enzyme for cholesterol synthesis is HMG-CoA reductase. This enzyme is tightly controlled by many different types of regulation and can be influenced by hormonal changes as well as cellular needs (figure 6.4). This is also one of the primary pharmacological targets for the management of hypercholesterolemia. The statins are direct inhibitors of this enzyme.
Transcriptional control

![Diagram of transcriptional control]

Figure 6.4: Regulation of cholesterol synthesis.

The rate of synthesis of HMG-CoA reductase messenger RNA (mRNA) is controlled by one of the family of sterol-regulatory element-binding proteins (SREBPs). SREBPs are integral proteins of the endoplasmic reticulum (ER). When cholesterol levels in the cell are high, the SREBP is bound to SCAP (SREBP cleavage activating protein) in the ER membrane. When cholesterol levels drop, the sterol leaves its SCAP-binding site, and the SREBP:SCAP complex is transported to the Golgi apparatus. Within the Golgi, two proteolytic cleavages occur, which release the N-terminal transcription factor domain from the Golgi membrane. Once released, the active amino terminal component travels to the nucleus to bind to sterol-regulatory elements (SREs). Binding to this upstream element enhances transcription of the HMG-CoA reductase gene. The soluble SREBPs are rapidly turned over and need to be continuously produced to stimulate reductase mRNA transcription effectively. As cholesterol levels in the cell increase, due to de novo synthesis, cholesterol will bind to SCAP and prevent translocation of the complex to the Golgi, leading to a decrease in transcription of the reductase gene and thus less reductase protein being produced (figure 6.4).

Proteolytic degradation of HMG-CoA reductase

The amount of HMG-CoA reductase can also be influenced by proteolytic degradation. The membrane domains of HMG-CoA reductase contain sterol-sensing regions, which are similar to those in SCAP. As levels of cholesterol (or its derivatives) increase in the cell, this causes a change in the oligomerization state of the membrane domain of HMG-CoA reductase, rendering the enzyme more susceptible to proteolysis. This, in turn, decreases the activity of the enzyme.

Regulation by covalent modification

Much like other anabolic enzymes, the activity of HMG-CoA reductase can be influenced by phosphorylation. Elevated glucagon levels increase phosphorylation of the enzyme, thereby inactivating it, whereas hyperinsulinemia increases the activity of the reductase by activating phosphatases, which dephosphorylate the reductase. Increased levels of intracellular sterols may also increase phosphorylation of HMG-CoA reductase, thereby reducing its activity as well.
Adenosine monophosphate (AMP)-activated protein kinase can also phosphorylate and inactivate HMG-CoA reductase. Thus, cholesterol synthesis decreases when ATP levels are low and increases when ATP levels are high, similar to what occurs with fatty acid synthesis (recall that acetyl-CoA carboxylase is also phosphorylated and inhibited by the AMP-activated protein kinase; section 4.4.)

**Several fates of cholesterol**

Almost all mammalian cells are capable of producing cholesterol. Most of the biosynthesis of cholesterol occurs within liver cells, although the gut, the adrenal cortex, and the gonads (as well as the placenta in pregnant women) also produce significant quantities of the sterol. A small portion of hepatic cholesterol is used for the synthesis of hepatic membranes, but the bulk of synthesized cholesterol is secreted from the hepatocyte as one of three compounds: cholesterol esters, biliary cholesterol (cholesterol found in the bile), or bile acids.

**Cholesterol esterification and transport**

Lecithin (PC) reacts with free cholesterol to form cholesterol ester in the presence of lecithin:cholesterol acyltransferase (LCAT). The esterified cholesterol is then transported to the liver through the bloodstream. The final step in this process is the removal of cholesterol ester from the liver through the bile system.
Figure 6.5: Esterification of cholesterol by LCAT.

Cholesterol is an amphipathic molecule (containing both polar and nonpolar regions), and in its native state it can freely diffuse through membranes. In order to be stored in cells, cholesterol must be modified by increasing its hydrophobicity. Cholesterol ester production in the liver is catalyzed by acyl-CoA–cholesterol acyl transferase (ACAT). ACAT catalyzes the transfer of a fatty acid from coenzyme A to the hydroxyl group on carbon 3 of cholesterol. (This is similar to the reaction catalyzed by lecithin:cholesterol acyltransferase within the plasma associated with HDLs; figure 6.5.) Regardless of whether the additional group is an acyl chain or phosphatidylcholine, the resulting cholesterol esters are more hydrophobic than free cholesterol. The liver packages some of the esterified cholesterol into the hollow core of lipoproteins, primarily VLDL. VLDL is secreted from the hepatocyte into the blood and transports the cholesterol esters (triacylglycerols, phospholipids, apoproteins, etc.) to the tissues that require greater amounts of cholesterol than they can synthesize de novo. These tissues then use the cholesterol for the synthesis of membranes, the formation of steroid hormones, and the biosynthesis of vitamin D.

Synthesis of specialized products

The hepatic cholesterol pool serves as a source of cholesterol for the synthesis of the relatively hydrophilic bile acids and their salts. These derivatives of cholesterol are effective detergents because they contain both polar and nonpolar regions. They are introduced into the biliary ducts of the liver. They are stored and concentrated in the gallbladder and later discharged into the gut in response to the ingestion of food. Finally, cholesterol is the precursor of all five classes of steroid hormones: glucocorticoids, mineralocorticoids, androgens, estrogens, and progestins. Cholesterol and steroid hormones are transported through the blood from their sites of synthesis to their target organs. Because of their hydrophobicity, they must be complexed with a serum protein. Serum albumin can act as a nonspecific carrier for the steroid hormones, but there are specific carriers as well (section 2.1).

References and resources

Text


Figures

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Lieberman M, Peet A. Figure 6.4 Regulation of cholesterol synthesis. Adapted under Fair Use from Marks’ Basic Medical Biochemistry. 5th Ed pp 647. Figure 32.6 Regulation of 3-hydroxymethylglutaryl coenzyme A (HMG-CoA reductase activity. 2017. Added squiggle by Made by Made from the Noun Project and ion channel by Léa Lortal from the Noun Project.