Cholesterol (Greek for: ‘gall’ and ‘solid’) is a media star: For decades, no other biochemical substrate draws as much attention as cholesterol has. But what are the hard pre-clinical facts? How is cholesterol synthesized and degraded in the human body? How is cholesterol metabolism regulated? The following article presents you with useful information that will aid you in your exam preparation.

Cholesterol Structure & Function

Cholesterol is an amphiphilic molecule, consisting of four nonpolar hydrocarbon rings (A-D), a branched nonpolar hydrocarbon tail attached to carbon 17, and a polar alcohol group on carbon 3. Cholesterol’s polar structure allows it to fit inside the phospholipid bilayer and serve as a membrane fluidity buffer.

**Cholesteryl esters** are cholesterol molecules that have a fatty acid group attached to the alcohol group at position 3 in the “A-ring.” Esters are more hydrophobic than unesterified cholesterol and appear in bile components. Molecules of this type are too hydrophobic to serve as a membrane fluidity buffer; they are associated with lipoproteins.

Cholesterol Biosynthesis

Cholesterol is primarily synthesized in

- liver
The carbon skeleton that makes up its structure comes from Acetyl-CoA, whether derived from glucose or fatty acid oxidation. Synthesis takes place in the cytosol, and because this is an anabolic metabolic pathway, NADPH serves as the provider of reducing equivalents.

Cholesterol biosynthesis begins with the formation of mevalonate, which takes place in a sequence of three reactions: Thiolase (ACAT), HMG-CoA synthase (HMGCS), and HMG-CoA reductase (HMGC). In these reactions, CoA groups are cleaved off, with only the reductase step using reducing equivalents, in the form of 2 NADPH that is spent
to produce mevalonate. HMG-CoA Reductase is the rate-limiting step in the pathway, and also serves as the key regulatory enzyme to synthesize cholesterol.

**Note:** MG-CoA has an alternative metabolic fate. When blood glucose levels are low, Acetyl-CoA, produced from β-Oxidation of fatty acids, generates HMG-CoA, which can be converted to ketone bodies by the activity of HMG-CoA Lyase (HMGCL), β-hydroxybutyrate dehydrogenase, and Acetoacetate decarboxylase (AAD). Mevalonate Kinase (MVK) converts mevalonate to mevalonate-5-phosphate by hydrolyzing ATP. Then, Phosphomevalonate kinase (PMVK) phosphorylates mevalonate-5-phosphate a second time, producing mevalonate-5-pyrophosphate in a reaction that also uses ATP.

The ATP-dependent action of diphosphomevalonate decarboxylase (MVD) forms the starter unit of cholesterol synthesis, Δ^1-Isopentenyl-PP. Isopentenyl-P, Δ-isomerase (IDI-1) converts MVD to the repeating unit of cholesterol synthesis, dimethylallyl pyrophosphate. Dimethylallyl transferase (DMAT) combines the starter unit and repeat unit to form geranyl-pyrophosphate, which undergoes conversion to farnesyl-pyrophosphate by geranyl transferase.

This linkage of start and repeat units occurs by “head-to-tail” nucleophilic substitution, and the subsequently formed geranyl-pyrophosphate serves as the primer for an analogous condensation yielding farnesyl-pyrophosphate.

Squalene is formed from the “head-to-head” condensation of two farnesyl-pyrophosphate molecules by Squalene synthase (SQS), in a reaction that requires NADPH as a cofactor. Eukaryotic cells and prokaryotes differ in their sterol synthesis at this juncture. Our cells require oxygen (and NADPH) to fuel the reaction (squalene monooxygenase) that forms squalene-2, 3-epoxide. Prokaryotes anaerobically produce a compound called hopanoids, which is similar to cholesterol.

Lanosterol synthase produces lanosterol, which is the first compound on the way to cholesterol that has four closed defined rings. From this point, a sequence of 19 reactions removes three methyl groups to form zymosterol. Zymosterol’s double bonds are rearranged; eventually, one is removed, depending on the tissue in which the synthesis takes place. The conversion of lanosterol to zymosterol takes place by enzymes that require eleven NADPH. Cholesterol’s synthesis from zymosterol requires an additional two NADPH to rearrange/remove double bonds.

An important conversion of cholesterol that takes place is esterification with long-chain fatty acids (e.g., palmitic acid) in the endoplasmic reticulum, which blocks cholesterol’s polar head group and, thus, its inclusion as a membrane fluidity buffer.

Cholesterol degradation leads to bile acids, which occur in the liver and excrete bile into the small intestine. Bile acid amides form conjugates with taurine or glycine, which dissociate completely at physiological pH levels due to their low pKa values. Therefore, bile serves as a good anionic detergent for the body and forms cylindrical micelles. It emulsifies lipids in the intestine so the intestinal mucosa can resorb them.

**Regulation of Cholesterol Synthesis**

The formation of mevalonate by HMG-CoA Reductase is strictly regulated because it is the key reaction in the pathway leading to cholesterol. Glucagon (and thus cAMP) induces HMG-CoA Reductase Kinase to phosphorylate HMG-CoA, thereby inhibiting the enzyme. HMG-CoA will be shuttled to the mitochondria to produce ketone bodies instead.
When there is adequate glucose intake, insulin induces **HMG-CoA Reductase Phosphatase** to dephosphorylate the enzyme, which allows for the production of mevalonate and, eventually, cholesterol.

The transcription of HMG-CoA reductase is also under tight regulation so that the synthesis of cholesterol only takes place when the cell has adequate precursors to do so. When the cell needs to produce cholesterol, and there are plenty of precursors, **sterol regulatory element-binding protein (SREBP)** is released from the ER and translocates to the nucleus, where it binds the **sterol regulatory element (SRE)**. This increases the rate of HMG-CoA reductase transcription.

Conversely, when there are high levels of cholesterol, or the cell needs to use precursors to produce other metabolites, SREBP is prevented from translocating to the nucleus and binding to SRE, attenuating the production of HMG-CoA reductase.

HMG-CoA reductase is regulated at additional levels: Glucocorticoids (metabolites of cholesterol) and other compounds accelerate HMGCR mRNA breakdown. Also, HMG-CoA reductase is regulated by sterol-accelerated ubiquitination and degradation. However, no total blockade of the enzyme occurs since sufficient intermediates must be supplied to synthesize non-sterols. Similar regulation is exerted with HMG-CoA synthase and mevalonate kinase.

**Transport of Cholesterol**

**Lipoproteins** are spherical complexes of lipid and protein, which include **chylomicrons**, **very-low-density lipoproteins (VLDL)**, **low-density lipoproteins (LDL)**, and **high-density lipoproteins (HDL)**. They differ in their lipid and protein compositions, sizes, densities, and biosynthesis sites. Lipoproteins function in the transport of lipids between tissues. Cholesterol is one of the lipids that is transported. As a result of their less than perfect transport, cholesterol is deposited in tissues gradually. This could lead to a potentially life-threatening condition when plaques form in **blood vessels**.
Lipoproteins are composed of endogenous or exogenous triacylglycerol or cholesteryl esters, forming a core surrounded by a shell composed of apolipoproteins, phospholipids, or free cholesterol. The polar portions of the lipids are oriented so that they are on the surface of the lipoprotein, and this makes them soluble.
**Chylomicrons** are lipoprotein particles with the lowest density and largest size; in other words, they contain the highest percentage of lipid and the lowest percentage of protein. VLDLs and LDLs are successively denser, having higher ratios of protein to lipid. HDL particles are the densest.

The apolipoprotein portion associated with lipoprotein particles has several diverse functions, such as providing recognition sites for cell-surface receptors and activating lipoprotein metabolism. They are divided by structure and function into five major classes, A through E. Most of the classes have subclasses, for example, apolipoprotein (or apo) A-I and apo C-II.

**Elimination of Cholesterol**

After LDL enters the liver, cholesterol esters are hydrolyzed by lysosomal cholesterol esterase. The excess cholesterol produced in this way activates acetyl-CoA cholesterol acyl-transferase (ACAT), which re-estersifies cholesterol into cholesterol esters that can be deposited as lipid droplets or mobilized again to where it is needed.

**Hypercholesterolemia**

Disturbances in cholesterol metabolism cause various diseases. In familial hypercholesterolemia, the uptake of cholesterol into the cells by LDL receptors is diminished. Therefore, despite high plasma cholesterol concentration (intracellularly regulated), cholesterol synthesis still proceeds at high speed.

**References**


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