26.2.1. The Synthesis of Mevalonate, Which Is Activated as Isopentenyl Pyrophosphate, Initiates the Synthesis of Cholesterol

The first stage in the synthesis of cholesterol is the formation of isopentenyl pyrophosphate from acetyl CoA. This set of reactions, which takes place in the cytosol, starts with the formation of 3-hydroxy-3-methylglutaryl CoA (HMG CoA) from acetyl CoA and acetoacetyl CoA. This intermediate is reduced to *mevalonate* for the synthesis of cholesterol (Figure 26.7). Recall that mitochondrial 3-hydroxy-3-methylglutaryl CoA is processed to form ketone bodies (Section 22.3.5).

The synthesis of mevalonate is the committed step in cholesterol formation. The enzyme catalyzing this irreversible step, *3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase),* is an important control site in cholesterol biosynthesis, as will be discussed shortly.

$$\text{3-Hydroxy-3-methylglutaryl CoA} + 2\ \text{NADPH} + 2\ \text{H}^+ \longrightarrow \text{mevalonate} + 2\ \text{NADP}^+ + \text{CoA}$$

HMG-CoA reductase is an integral membrane protein in the endoplasmic reticulum.

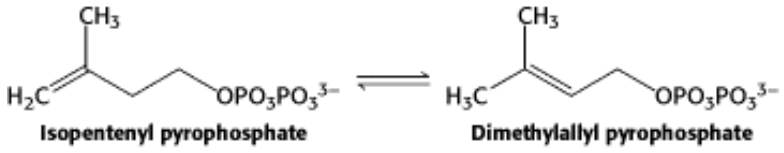
Mevalonate is converted into *3-isopentenyl pyrophosphate* in three consecutive reactions requiring ATP (Figure 26.8). Decarboxylation yields isopentenyl pyrophosphate, an activated isoprene unit that is a key building block for many important biomolecules throughout the kingdoms of life. We will return to a discussion of this molecule later in the chapter.

26.2.2. Squalene (C_{30}) Is Synthesized from Six Molecules of Isopentenyl Pyrophosphate (C_5)

Squalene is synthesized from isopentenyl pyrophosphate by the reaction sequence

$$C_5 \longrightarrow C_{10} \longrightarrow C_{15} \longrightarrow C_{30}$$

This stage in the synthesis of cholesterol starts with the isomerization of *isopentenyl pyrophosphate* to *dimethylallyl pyrophosphate.*



These isomeric C_5 units condense to form a C_{10} compound: isopentenyl pyrophosphate attacks an allylic carbonium ion formed from dimethylallyl pyrophosphate to yield *geranyl pyrophosphate* (Figure 26.9). The same kind of reaction takes place again: geranyl pyrophosphate is converted into an allylic carbonium ion, which is attacked by isopentenyl pyrophosphate. The resulting C_{15} compound is called *farnesyl pyrophosphate.* The same enzyme, *geranyl transferase,* catalyzes each of these condensations.

The last step in the synthesis of *squalene* is a reductive tail-to-tail condensation of two molecules of farnesyl

26.3.6. The Clinical Management of Cholesterol Levels Can Be Understood at a Biochemical Level

Homozygous familial hypercholesterolemia can be treated only by a liver transplant. A more generally applicable therapy is available for heterozygotes and others with high levels of cholesterol. *The goal is to reduce the amount of cholesterol in the blood by stimulating the single normal gene to produce more than the customary number of LDL receptors.* We have already observed that the production of LDL receptors is controlled by the cell's need for cholesterol. Therefore, in essence, the strategy is to deprive the cell of ready sources of cholesterol. When cholesterol is required, the amount of mRNA for the LDL receptor rises and more receptor is found on the cell surface. This state can be induced by a two-pronged approach. First, the intestinal reabsorption of bile salts is inhibited. Bile salts are cholesterol derivatives that promote the absorption of dietary cholesterol and dietary fats (Section 22.1.1). Second, de novo synthesis of cholesterol is blocked.

The reabsorption of bile is impeded by oral administration of positively charged polymers, such as cholestyramine, that bind negatively charged bile salts and are not themselves absorbed. Cholesterol synthesis can be effectively blocked by a class of compounds called *statins* (e.g., lovastatin, which is also called mevacor; Figure 26.22). These compounds are potent competitive inhibitors (K_i < 1 nM) of HMG-CoA reductase, the essential control point in the biosynthetic pathway. Plasma cholesterol levels decrease by 50% in many patients given both lovastatin and inhibitors of bile-salt reabsorption. Lovastatin and other inhibitors of HMG-CoA reductase are widely used to lower the plasma cholesterol level in people who have atherosclerosis, which is the leading cause of death in industrialized societies.

Figure 26.14. HMG-CoA Reductase. The structure of a portion of the tetrameric enzyme is shown.

Table 26.1. Properties of plasma lipoproteins

Lipoproteins	Major core lipids	Apoproteins	Mechanism of lipid delivery
Chylomicron	Dietary triacylglycerols	B-48, C, E	Hydrolysis by lipoprotein lipase
Chylomicron remnant	Dietary cholesterol esters	B-48, E	Receptor-mediated endocytosis by liver
Very low density lipoprotein (VLDL)	Endogenous triacylglycerols	B-100, C, E	Hydrolysis by lipoprotein lipase

Intermediate-density lipoprotein (IDL)	Endogenous cholesterol esters	B-100, E	Receptor-mediated endocytosis by liver and conversion into LDL
Low-density lipoprotein (LDL)	Endogenous cholesterol esters	B-100	Receptor-mediated endocytosis by liver and other tissues
High-density lipoprotein (HDL)	Endogenous cholesterol esters	A	Transfer of cholesterol esters to IDL and LDL

Source: After M. S. Brown and J. L. Goldstein, *The Pharmacological Basis of Therapeutics.* 7th ed., A. G. Gilman, L. S. Goodman, T. W. Rall, and F. Murad, Eds. (Macmillan, 1985), p. 828.

Figure 26.15. Site of Cholesterol Synthesis. Electron micrograph of a part of a liver cell actively engaged in the synthesis and secretion of very low density lipoprotein (VLDL). The arrow points to a vesicle that is releasing its content of VLDL particles. [Courtesy of Dr. George Palade.]

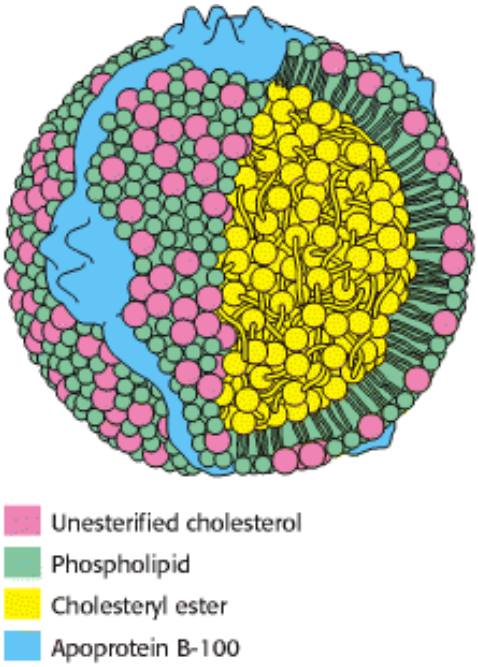


Figure 26.16. Schematic Model of Low-Density Lipoprotein. The LDL particle is approximately 22 nm (220 Å) in diameter.

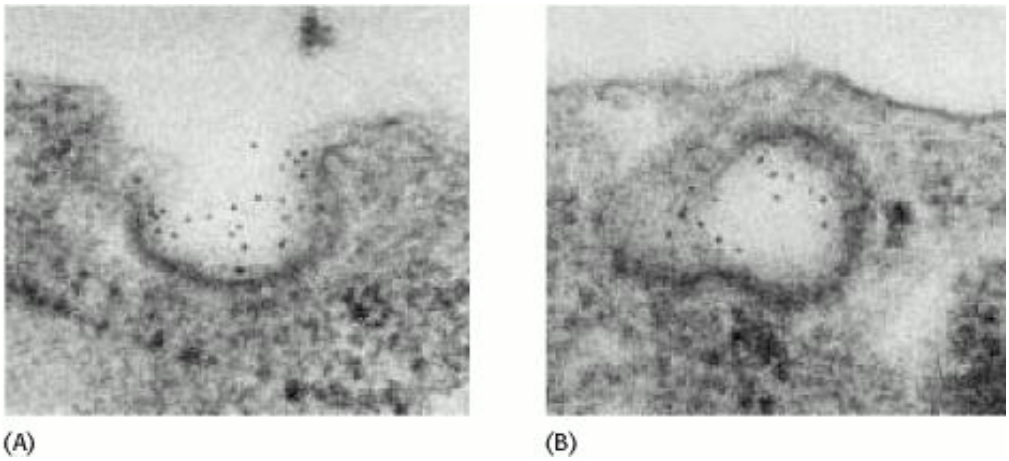


Figure 26.17. Endocytosis of LDL Bound to Its Receptor. (A) Electron micrograph showing LDL (conjugated to ferritin for visualization, dark spots) bound to a coated-pit region on the surface of a cultured human fibroblast cell. (B) Micrograph showing this region invaginating and fusing to form an endocytic vesicle [From R. G. W. Anderson, M. S. Brown, and J. L. Goldstein. *Cell* 10 (1977): 351.]

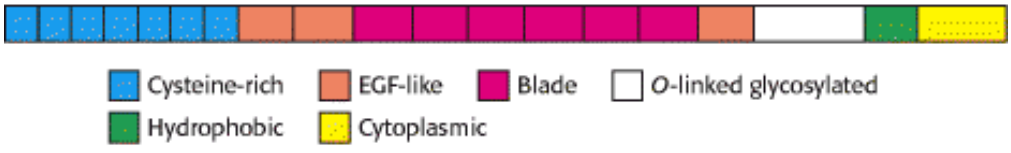


Figure 26.18. LDL Receptor Domains. A schematic representation of the amino acid sequence of the LDL receptor showing six types of domain.

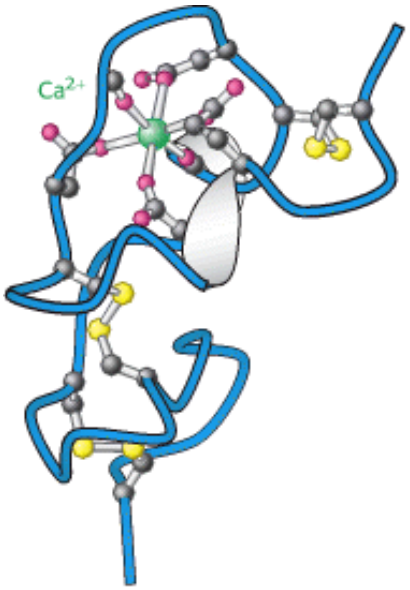


Figure 26.19. Structure of Cysteine-Rich Domain. This calcium-binding cysteine-rich domain is repeated seven times at the amino terminus of the LDL receptor.

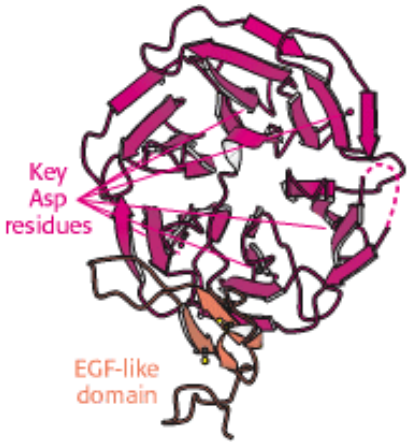


Figure 26.20. Structure of Propeller Domain. The six-bladed propeller domain and an adjacent EGF-like domain of the LDL receptor.

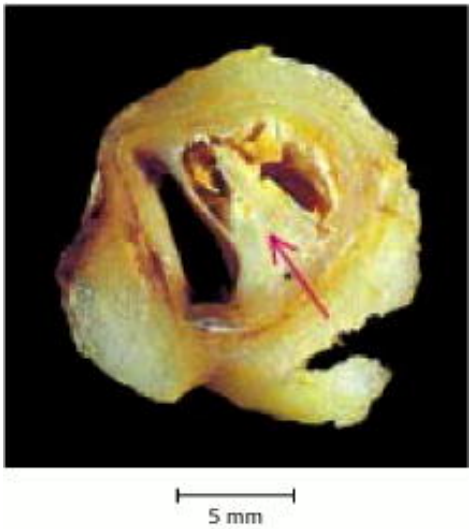


Figure 26.21. An Atherosclerotic Plaque. A plaque (marked by an arrow) blocks most of the lumen of this blood vessel. The plaque is rich in cholesterol. [Courtesy of Dr. Jeffrey Sklar.]

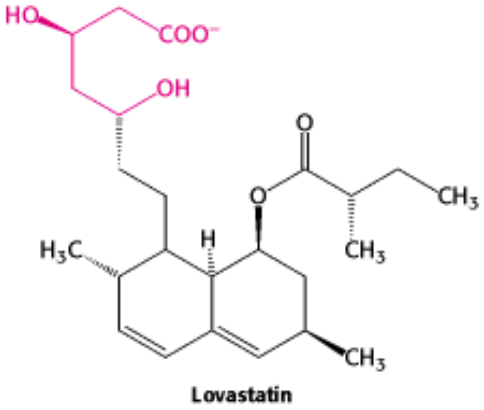


Figure 26.22. Lovastatin, a Competitive Inhibitor of HMG-CoA Reductase. The part of the structure that resembles the 3-hydroxy-3-methylglutaryl moiety is shown in red.

26.4. Important Derivatives of Cholesterol Include Bile Salts and Steroid Hormones

Cholesterol is a precursor for other important steroid molecules: the bile salts, steroid hormones, and vitamin D.

Bile Salts.

As polar derivatives of cholesterol, *bile salts* are highly effective *detergents* because they contain both polar and nonpolar regions. Bile salts are synthesized in the liver, stored and concentrated in the gall bladder, and then released into the small intestine. Bile salts, the major constituent of bile, *solubilize dietary lipids* (Section 22.1.1). Solubilization increases in the effective surface area of lipids with two consequences: more surface area is exposed to the digestive action of lipases and lipids are more readily absorbed by the intestine. Bile salts are also the major breakdown products of cholesterol.

Cholesterol is converted into trihydroxycoprostanoate and then into *cholyl CoA*, the activated intermediate in the synthesis of most bile salts (Figure 26.23). The activated carboxyl carbon of cholyl CoA then reacts with the amino group of glycine to form *glycocholate* or it reacts with the amino group of taurine ($H_2NCH_2CH_2SO_3^-$), derived from cysteine, to form *taurocholate. Glycocholate is the major bile salt.*