Disorders Associated with Defects in Receptor Proteins

Familial Hypercholesterolemia

Familial hypercholesterolemia is a "receptor disease" that is the consequence of a mutation in the gene encoding the receptor for LDL, which is involved in the transport and metabolism of cholesterol. As a consequence of receptor abnormalities there is a loss of feedback control and elevated levels of cholesterol that induce premature atherosclerosis, leading to a greatly increased risk of myocardial infarction.

Familial hypercholesterolemia is one of the most frequently occurring Mendelian disorders. Heterozygotes with one mutant gene, representing about 1 in 500 individuals, have from birth a two-fold to three-fold elevation of plasma cholesterol level, leading to tendinous xanthomas and premature atherosclerosis in adult life (Chapter 11). Homozygotes, having a double dose of the mutant gene, are much more severely affected and may have five-fold to six-fold elevations in plasma cholesterol levels. Skin xanthomas and coronary, cerebral, and peripheral vascular atherosclerosis may develop in these individuals at an early age. Myocardial infarction may occur before age 20 years. Large-scale studies have found that familial hypercholesterolemia is present in 3% to 6% of survivors of myocardial infarction.

Normal Process of Cholesterol Metabolism and Transport

Approximately 7% of the body's cholesterol circulates in the plasma, predominantly in the form of LDL. As might be expected, the amount of plasma cholesterol is influenced by its synthesis and catabolism, and the liver plays a crucial role in both these processes (Fig. 5-6). The first step in this complex sequence is the secretion of very-low-density lipoproteins (VLDLs) by the liver into the bloodstream. VLDL particles are rich in triglycerides, but they contain lesser amounts of cholesteryl esters. When a VLDL particle reaches the capillaries of adipose tissue or muscle, it is cleaved by lipoprotein lipase, a process that extracts most of the triglycerides. The resulting molecule, called *intermediate-density lipoprotein (IDL)*, is reduced in triglyceride content and enriched in cholesteryl esters, but it retains two of the three apoproteins (B-100 and E) present in the parent VLDL particle (Fig. 5-6). After release from the capillary endothelium, the IDL particles have one of two fates. Approximately 50% of newly formed IDL is rapidly taken up by the liver by receptor-mediated transport. The receptor responsible for the binding of IDL to the liver cell membrane recognizes both apoprotein B-100 and apoprotein E. It is called the *LDL receptor*, however, because it is also involved in the hepatic clearance of LDL (described later). In the liver cells, IDL is recycled to generate VLDL. The IDL particles not taken up by the liver are subjected to further metabolic processing that removes most of the remaining triglycerides and apoprotein E, yielding cholesterol-rich LDL particles. *IDL is the immediate and major source of plasma LDL.* There seem to be two mechanisms for removal of LDL from plasma, one mediated by an LDL receptor and the other by a receptor for oxidized LDL (scavenger receptor), described later.

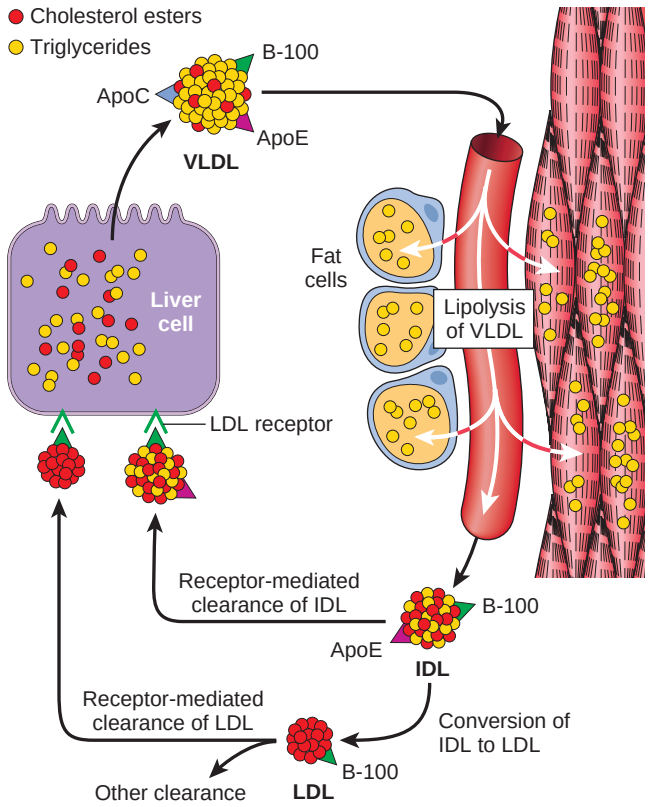

Figure 5-6 Low-density lipoprotein (LDL) metabolism and the role of the liver in its synthesis and clearance. Lipolysis of very-low-density lipoprotein (VLDL) by lipoprotein lipase in the capillaries releases triglycerides, which are then stored in fat cells and used as a source of energy in skeletal muscles. See text for explanation of abbreviations used.

Although many cell types, including fibroblasts, lymphocytes, smooth muscle cells, hepatocytes, and adrenocortical cells, possess high-affinity LDL receptors, approximately 70% of the plasma LDL is cleared by the liver, using a quite sophisticated transport process (Fig. 5-7). The first step involves binding of LDL to cell surface receptors, which are clustered in specialized regions of the plasma membrane called *coated pits* (Chapter 1). After binding, the coated pits containing the receptor-bound LDL are internalized by invagination to form coated vesicles, after which they migrate within the cell to fuse with the lysosomes. Here the LDL dissociates from the receptor, which is recycled to the surface. In the lysosomes the LDL molecule is enzymatically degraded; the apoprotein part is hydrolyzed to amino acids, whereas the cholesteryl esters are broken down to free cholesterol. This free cholesterol, in turn, crosses the lysosomal membrane to enter the cytoplasm, where it is used for membrane synthesis and as a regulator of cholesterol homeostasis. The exit of cholesterol from the lysosomes requires the action of two proteins, called NPC1 and NPC2 (see "Niemann-Pick Disease Type C"). Three separate processes are affected by the released intracellular cholesterol, as follows:

- Cholesterol *suppresses* cholesterol synthesis within the cell by inhibiting the activity of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase,