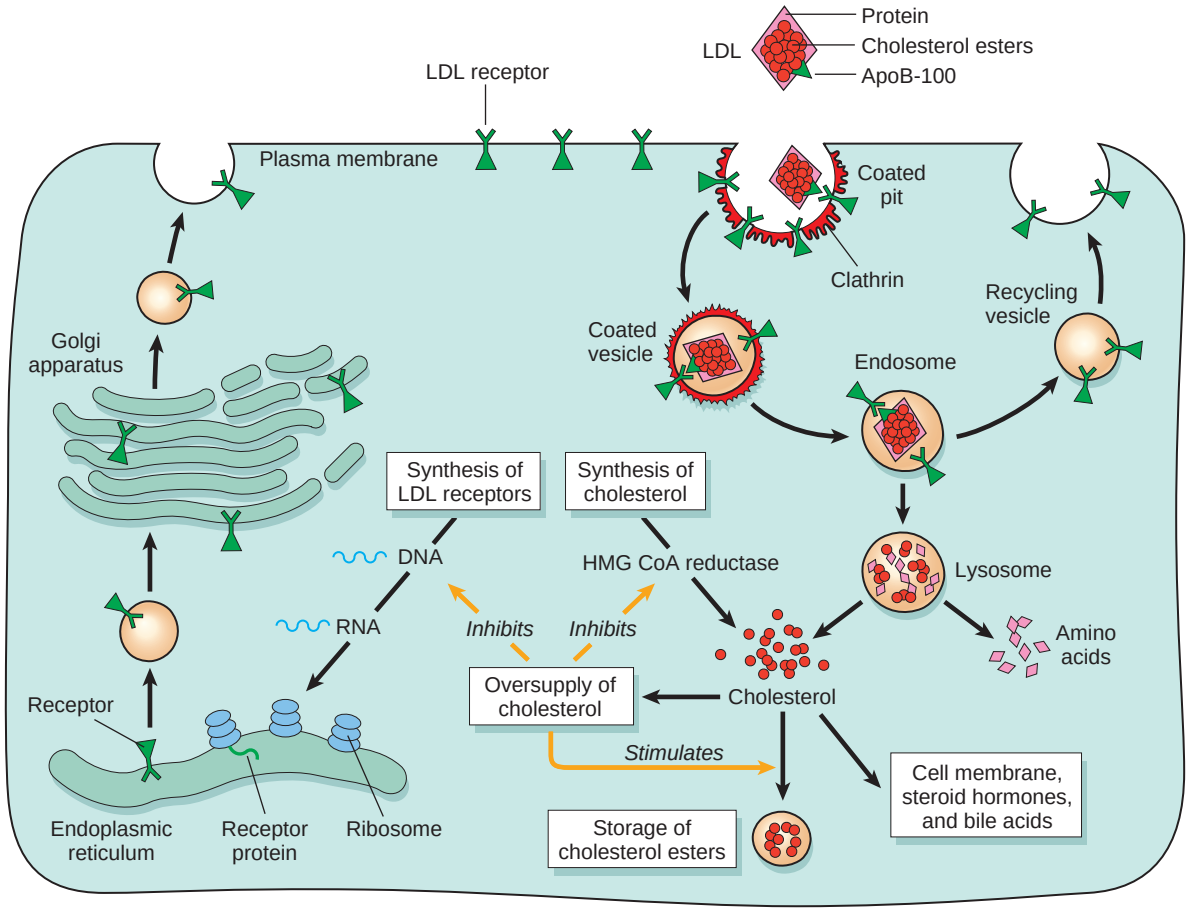

Figure 5-7 The LDL receptor pathway and regulation of cholesterol metabolism.

which is the rate-limiting enzyme in the synthetic pathway.

- Cholesterol *activates* the enzyme acyl-coenzyme A: cholesterol acyltransferase, favoring esterification and storage of excess cholesterol.
- Cholesterol *suppresses* the synthesis of LDL receptors, thus protecting the cells from excessive accumulation of cholesterol.

As mentioned earlier, familial hypercholesterolemia results from mutations in the gene encoding the receptor for LDL. Heterozygotes with familial hypercholesterolemia possess only 50% of the normal number of high-affinity LDL receptors, because they have only one normal gene. As a result of this defect in transport, the catabolism of LDL by the receptor-dependent pathways is impaired, and the plasma level of LDL increases approximately two-fold. Homozygotes have virtually no normal LDL receptors in their cells and have much higher levels of circulating LDL. In addition to defective LDL clearance, both the homozygotes and heterozygotes have increased synthesis of LDL. The mechanism of increased synthesis that contributes to hypercholesterolemia also results from a lack of LDL receptors (Fig. 5-6). IDL, the immediate precursor of plasma LDL, also uses hepatic LDL receptors (apoprotein B-100 and E receptors) for its transport into the liver. In familial hypercholesterolemia, impaired IDL transport into the liver secondarily diverts a greater proportion of plasma IDL into the precursor pool for plasma LDL.

The transport of LDL via the scavenger receptor seems to occur at least in part into the cells of the mononuclear phagocyte system. Monocytes and macrophages have receptors for chemically altered (e.g., acetylated or oxidized) LDL. Normally the amount of LDL transported along this scavenger receptor pathway is less than that mediated by the LDL receptor-dependent mechanisms. In the face of hypercholesterolemia, however, there is a marked increase in the scavenger receptor-mediated traffic of LDL cholesterol into the cells of the mononuclear phagocyte system and possibly the vascular walls (Chapter 11). This increase is responsible for the appearance of xanthomas and contributes to the pathogenesis of premature atherosclerosis.

The molecular genetics of familial hypercholesterolemia is extremely complex. More than 900 mutations involving the LDL receptor gene, including insertions, deletions, and missense and nonsense mutations, have been identified. These can be classified into five groups (Fig. 5-8): *Class I mutations* are relatively uncommon and lead to a complete failure of synthesis of the receptor protein (null allele). *Class II mutations* are fairly common; they encode receptor proteins that accumulate in the endoplasmic reticulum because their folding defects make it impossible for them to be transported to the Golgi complex. *Class III mutations* affect the LDL-binding domain of the receptor; the encoded proteins reach the cell surface but fail to bind LDL or do so poorly. *Class IV mutations* encode proteins that are synthesized and transported to the cell surface efficiently.