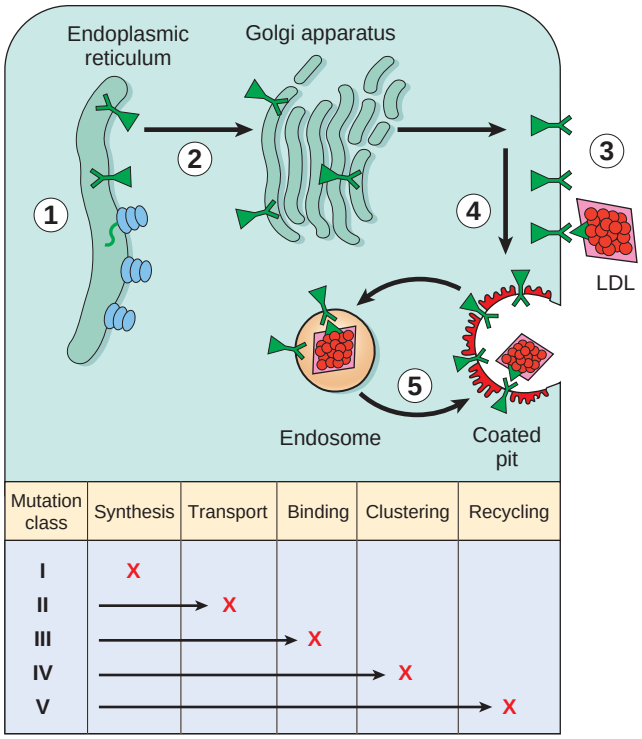

Figure 5-8 Classification of LDL receptor mutations based on abnormal function of the mutant protein. These mutations disrupt the receptor's synthesis in the endoplasmic reticulum, transport to the Golgi complex, binding of apoprotein ligands, clustering in coated pits, and recycling in endosomes. Each class is heterogeneous at the DNA level.(Modified with permission from Hobbs HH, et al: The LDL receptor locus in familial hypercholesterolemia: mutational analysis of a membrane protein. Annu Rev Genet 24:133-170, 1990. © 1990 by Annual Reviews.)

They bind LDL normally, but they fail to localize in coated pits, and hence the bound LDL is not internalized. *Class V mutations* encode proteins that are expressed on the cell surface, can bind LDL, and can be internalized; however, the pH-dependent dissociation of the receptor and the bound LDL fails to occur. Such receptors are trapped in the endosome, where they are degraded, and hence they fail to recycle to the cell surface.

The discovery of the critical role of LDL receptors in cholesterol homeostasis has led to the rational design of drugs that lower plasma cholesterol by increasing the number of LDL receptors. One strategy is based on the ability of certain drugs (statins) to suppress intracellular cholesterol synthesis by inhibiting the enzyme HMG CoA reductase. This, in turn, allows greater synthesis of LDL receptors (Fig. 5-8). Statins have been widely and successfully used for secondary prevention of ischemic heart disease. They exemplify rational design of drugs based on an understanding of pathophysiology.

KEY CONCEPTS

Familial Hypercholesterolemia

- Familial hypercholesterolemia is an autosomal dominant disorder caused by mutations in the gene encoding the LDL receptor.
- Patients develop hypercholesterolemia as a consequence of impaired transport of LDL into the cells.
- In heterozygotes, elevated serum cholesterol greatly increases the risk of atherosclerosis and resultant coronary artery disease; homozygotes have an even greater increase in serum cholesterol and a higher frequency of ischemic heart disease. Cholesterol also deposits along tendon sheaths to produce xanthomas.

Disorders Associated with Defects in Enzymes

Lysosomal Storage Diseases

Lysosomes are key components of the "intracellular digestive tract." They contain a battery of hydrolytic enzymes, which have two special properties. First, they function in the acidic milieu of the lysosomes. Second, these enzymes constitute a special category of secretory proteins that are destined not for the extracellular fluids but for intracellular organelles. This latter characteristic requires special processing within the Golgi apparatus, which merits brief discussion.

Similar to all other secretory proteins, lysosomal enzymes (or *acid hydrolases*, as they are sometimes called) are synthesized in the endoplasmic reticulum and transported to the Golgi apparatus. Within the Golgi complex they undergo a variety of posttranslational modifications including the attachment of terminal mannose-6-phosphate groups to some of the oligosaccharide side chains. The phosphorylated mannose residues serve as an "address label" that is recognized by specific receptors found on the inner surface of the Golgi membrane. Lysosomal enzymes bind these receptors and are thereby segregated from the numerous other secretory proteins within the Golgi. Subsequently, small transport vesicles containing the receptor-bound enzymes are pinched off from the Golgi and proceed to fuse with the lysosomes. Thus, the enzymes are targeted to their intracellular abode, and the vesicles are shuttled back to the Golgi (Fig. 5-9). As indicated later, genetically determined errors in this remarkable sorting mechanism may give rise to one form of lysosomal storage disease.

The lysosomal enzymes catalyze the breakdown of a variety of complex macromolecules. These large molecules may be derived from the metabolic turnover of intracellular organelles (autophagy), or they may be acquired from outside the cells by phagocytosis (heterophagy). An inherited deficiency of a functional lysosomal enzyme gives rise to two pathologic consequences (Fig. 5-10):

- Catabolism of the substrate of the missing enzyme remains incomplete, leading to the accumulation of the partially degraded insoluble metabolite within the lysosomes. This is called "primary accumulation". Stuffed with incompletely digested macromolecules, lysosomes become large and numerous enough to interfere with normal cell functions.
- Since lysosomal function is also essential for autophagy, impaired autophagy gives rise to "secondary accumulation" of autophagic substrates such as polyubiquinated proteins and old and effete mitochondria. The absence of this quality control mechanism causes accumulation of dysfunctional mitochondria with poor calcium buffering capacity and altered membrane potentials. This can trigger generation of free radicals and apoptosis.