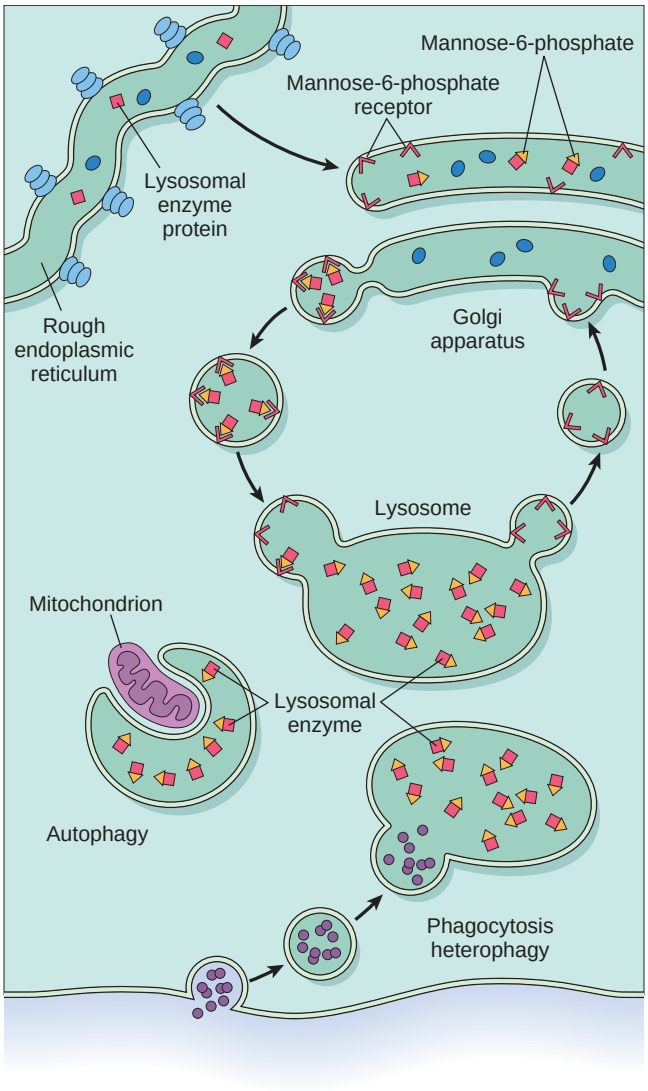

Figure 5-9 Synthesis and intracellular transport of lysosomal enzymes.

While details are still lacking it is clear that defects in autophagy are common in lysosomal storage diseases and play an important role in tissue damage.

There are three general approaches to the treatment of lysosomal storage diseases. The most obvious is enzyme replacement therapy, currently in use for several of these diseases. Another approach, the "substrate reduction therapy," is based on the premise that if the substrate to be degraded by the lysosomal enzyme can be reduced, the residual enzyme activity may be sufficient to catabolize it and prevent accumulation. A more recent strategy is based on the understanding of the molecular basis of enzyme deficiency. In many disorders, exemplified by Gaucher disease, the enzyme activity is low because the mutant proteins are unstable and prone to misfolding, and hence degraded in the endoplasmic reticulum. In such diseases an exogenous competitive inhibitor of the enzyme can, paradoxically, bind to the mutant enzyme and act as the "folding template" that assists proper folding of the enzyme and thus prevents its degradation. Such *molecular chaperone therapy* is under active investigation.

Several distinctive and separable conditions are included among the lysosomal storage diseases (Table 5-6). In general, the distribution of the stored material, and hence the organs affected, is determined by two interrelated factors: (1) the tissue where most of the material to be degraded is found and (2) the location where most of the degradation normally occurs. For example, brain is rich in gangliosides, and hence defective hydrolysis of gangliosides, as occurs in GM_1 and GM_2 gangliosidoses, results primarily in accumulation within neurons and consequent neurologic symptoms. Defects in degradation of mucopolysaccharides affect virtually every organ, because mucopolysaccharides are widely distributed in the body. Because cells of the mononuclear phagocyte system are especially rich in lysosomes and are involved in the

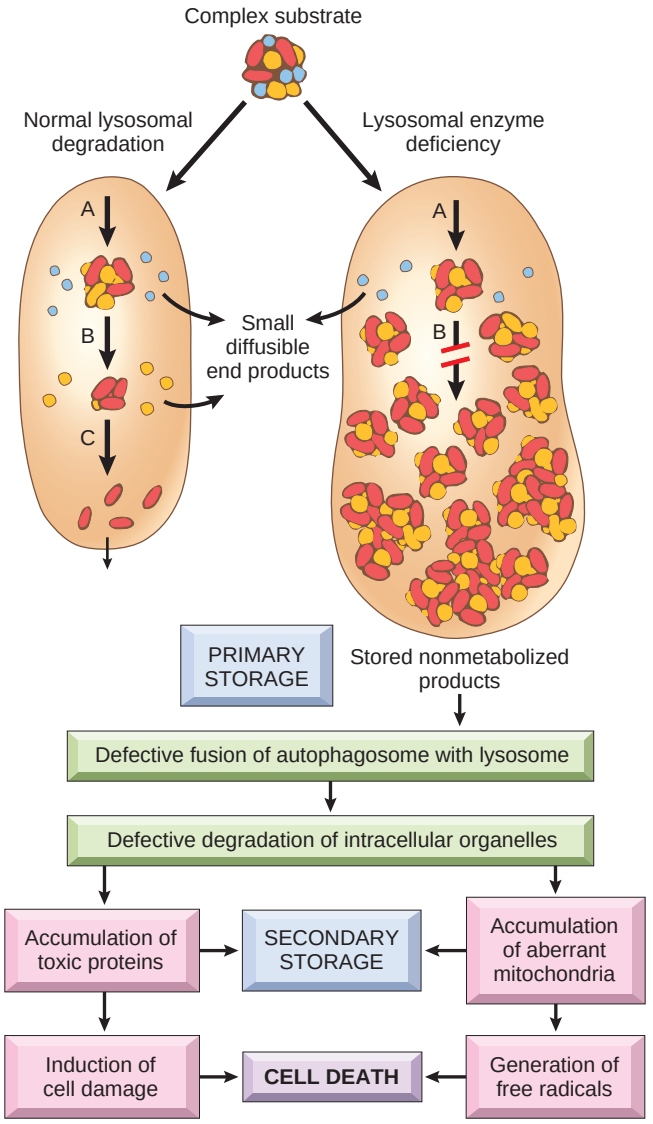

Figure 5-10 Pathogenesis of lysosomal storage diseases. In the example shown, a complex substrate is normally degraded by a series of lysosomal enzymes (A, B, and C) into soluble end products. If there is a deficiency or malfunction of one of the enzymes (e.g., B), catabolism is incomplete and insoluble intermediates accumulate in the lysosomes. In addition to this primary storage, secondary storage and toxic effects result from defective autophagy.

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