Waste Disposal: Lysosomes and Proteasomes

As already mentioned in brief, **cellular waste disposal depends on the activities of lysosomes and proteasomes** (Fig. 1-9).

- **Lysosomes** are membrane-bound organelles containing roughly 40 different acid hydrolases (i.e., enzymes that function best in acidic pH ≤ 5); these hydrolases include proteases, nucleases, lipases, glycosidases, phosphatases, and sulfatases. Lysosomal enzymes are initially synthesized in the ER lumen and then tagged with a mannose-6-phosphate (M6P) residue within the Golgi apparatus. Such M6P-modified proteins are subsequently delivered to lysosomes through trans-Golgi vesicles that express M6P receptors. The other

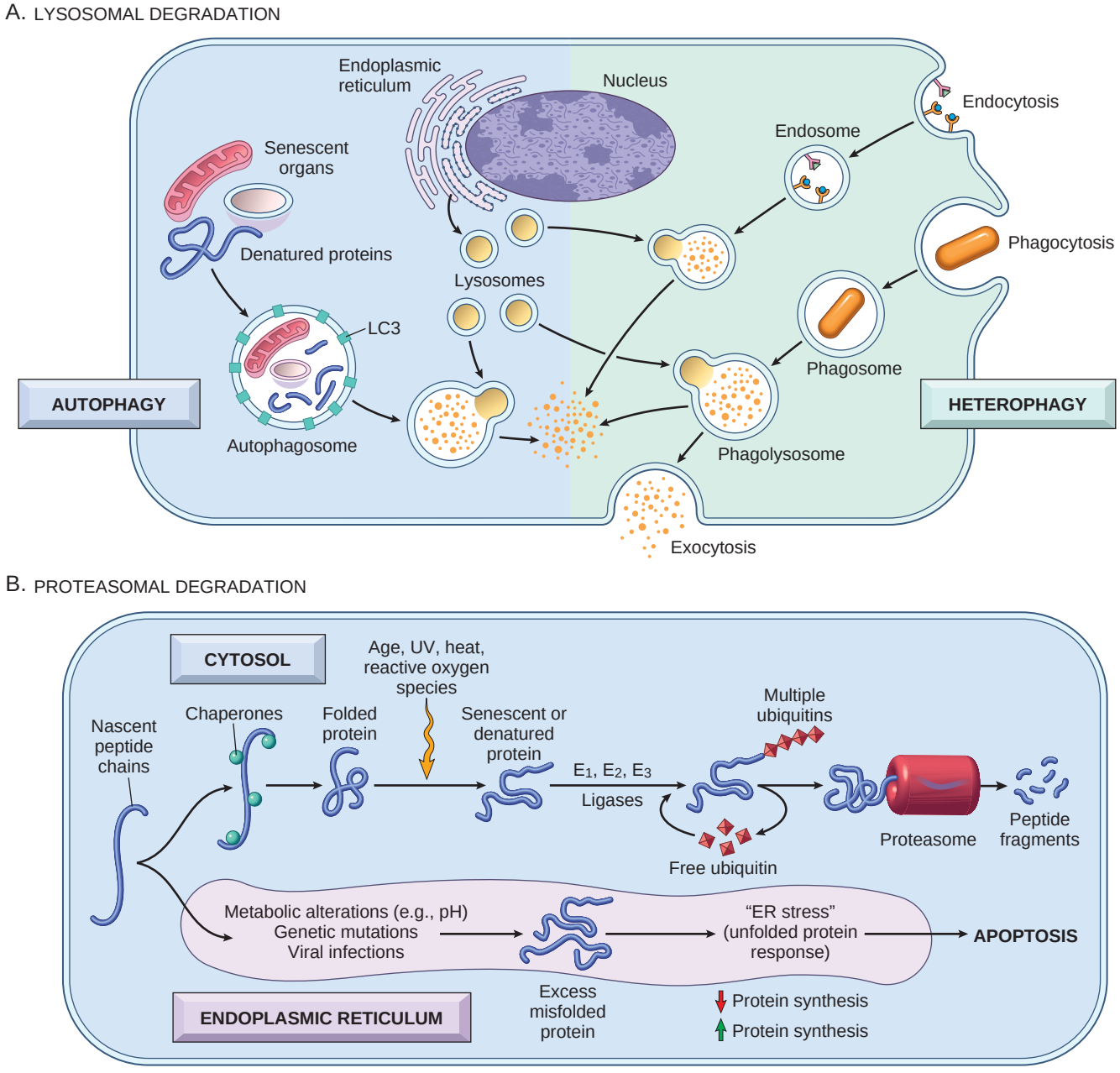

Figure 1-9 Intracellular catabolism. **A,** Lysosomal degradation. In *heterophagy* (right side), lysosomes fuse with endosomes or phagosomes to facilitate the degradation of their internalized contents (see Fig. 1-7). The end-products may be released into the cytosol for nutrition or discharged into the extracellular space (*exocytosis*). In *autophagy* (left side), senescent organelles or denatured proteins are targeted for lysosome-driven degradation by encircling them with a double membrane derived from the endoplasmic reticulum and marked by LC3 proteins (microtubule-associated protein 1A/1B-light chain 3). Cell stressors such as nutrient depletion or certain intracellular infections can also activate the autophagocytic pathway. **B,** Proteasome degradation. Cytosolic proteins destined for turnover (e.g., transcription factors or regulatory proteins), senescent proteins, or proteins that have become denatured due to extrinsic mechanical or chemical stresses can be tagged by multiple ubiquitin molecules (through the activity of E_1, E_2, and E_3 ubiquitin ligases). This marks the proteins for degradation by proteasomes, cytosolic multi-subunit complexes that degrade proteins to small peptide fragments. High levels of misfolded proteins within the endoplasmic reticulum (ER) trigger a protective *unfolded protein response*—engendering a broad reduction in protein synthesis, but specific increases in chaperone proteins that can facilitate protein refolding. If this is inadequate to cope with the levels of misfolded proteins, apoptosis is induced.