Lysosomes

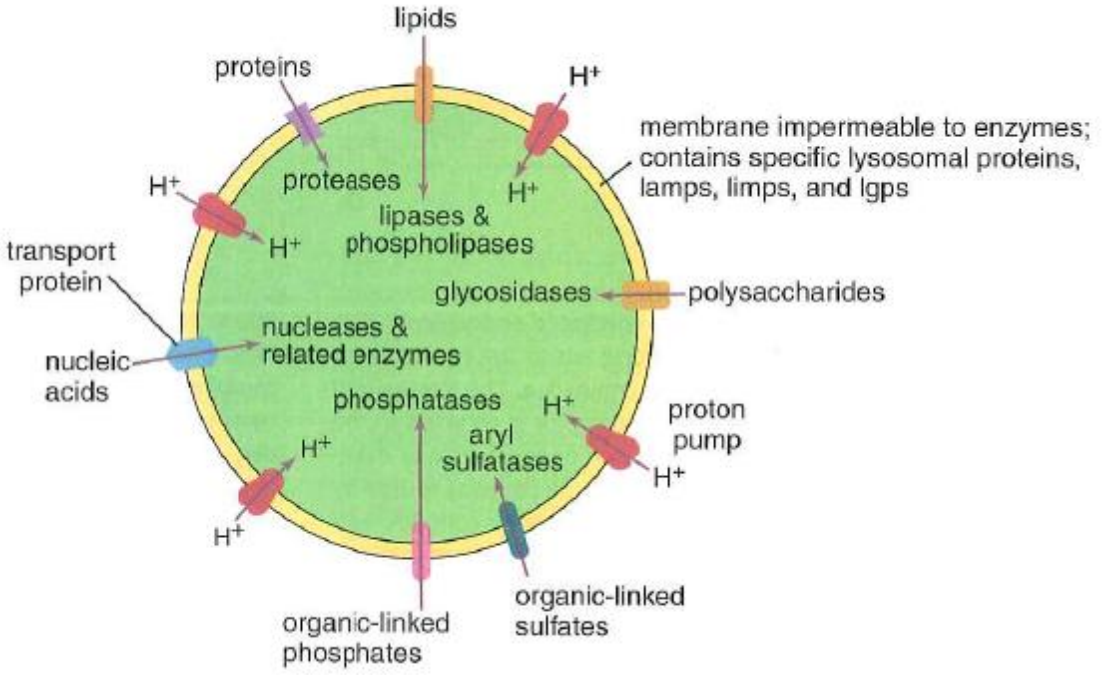
Lysosomes are digestive organelles that were recognized only after histochemical procedures were used to demonstrate lysosomal enzymes

Lysosomes are organelles rich in hydrolytic enzymes such as proteases, nucleases, glycosidases, lipases, and phospholipases. They are responsible for degradation of macromolecules derived from endocytotic pathways as well as from the cell itself in a process known as ***autophagy*** (removal of cytoplasmic components, particularly membrane-bounded organelles, by digesting them within lysosomes).

The first hypothesis for lysosomal biogenesis, formulated almost a half century ago, postulated that lysosomes arise as complete and functional organelles budding from the Golgi apparatus. These newly formed lysosomes were termed ***primary lysosomes,*** in contrast to ***secondary lysosomes,*** which had already fused with incoming endosomes. However, the primary and secondary lysosome hypothesis has proved to have little validity as new research data allow a better understanding of the details of protein secretory pathways and the fate of endocytotic vesicles.

Lysosomes have a unique membrane that is resistant to the hydrolytic digestion occurring in their lumen

Lysosomes contain a collection of hydrolytic enzymes and are surrounded by a unique membrane that resists hydrolysis by their own enzymes (Fig. 2.18). Most of the structural lysosomal membrane proteins are classified into ***lysosome-associated membrane proteins (lamps),***



lysosomal membrane glycoproteins (lgps), and *lysosomal integral membrane proteins (limps)*. The lamps, lgps, and limps represent more than 50% of the total membrane proteins in lysosomes and are highly glycosylated on the luminal surface. Sugar molecules cover almost the entire luminal surface of these proteins, thus protecting them from digestion by hydrolytic enzymes. The same family of proteins is also detected in late endosomes. In addition, lysosomes and late endosomes contain *proton (H^+) pumps* that transport H^+ ions into the lysosomal lumen, maintaining a low pH (~4.7). The lysosomal membrane also contains *transport proteins* that transport the final products of digestion (amino acids, sugars, nucleotides) to the cytoplasm, where they are used in the synthetic processes of the cell or are exocytosed. All membrane proteins destined for lysosomes (and late endosomes) are synthesized in the rER, transported to the Golgi apparatus, and reach their destination by one of two pathways:

- In the *constitutive secretory pathway*, limps that exit the Golgi apparatus are delivered to the cell surface. From here, they are endocytosed and, via the early and late endosomal compartments, finally reach lysosomes (Fig. 2.19). This pathway does not require the M-6-P receptor targeting mechanism.
- In the *Golgi-derived coated vesicle secretory pathway*, limps, after sorting and packaging, exit the Golgi apparatus in clathrin-coated vesicles (see Fig. 2.19). These vesicles are delivered to the early and/or late endosome in a manner similar to that described for soluble lysosomal enzymes; thus, the M-6-P targeting mechanism is required for this pathway (see page 29).

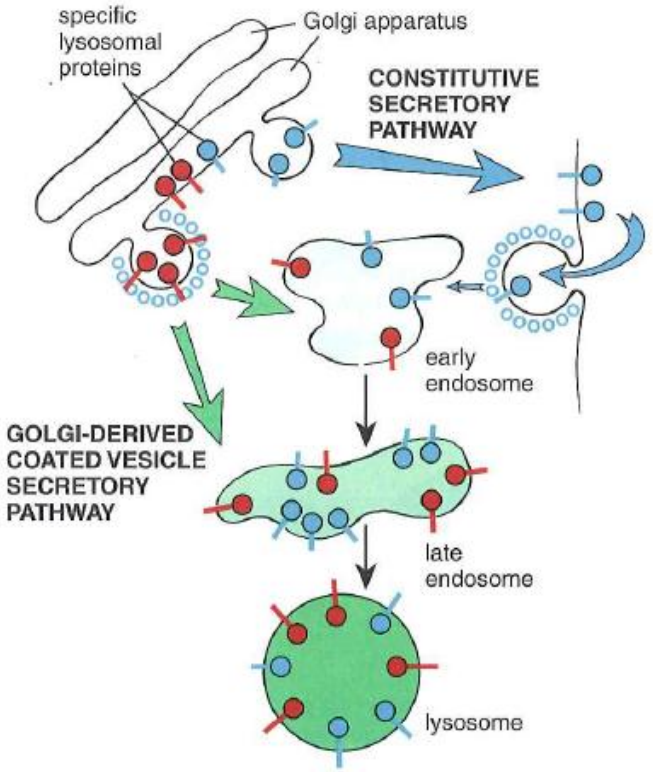


FIGURE 2.19
Lysosome biogenesis. This diagram shows regulated and constitutive pathways for delivery of lysosomal specific membrane proteins into early and late endosomes. The lysosomal membrane possesses highly glycosylated specific membrane proteins that protect the membrane from digestion by lysosomal enzymes. These lysosome-specific proteins are synthesized in the rER, transported to the Golgi apparatus, and reach their destination by two pathways. *Blue arrows* indicate the constitutive secretory pathway in which certain lysosomal membrane proteins exit the Golgi apparatus and are delivered to the cell surface. From there they are endocytosed and, via the early and late endosomal compartments, finally reach lysosomes. *Green arrows* indicate the endosomal Golgi-derived coated vesicle secretory pathway. Here, other lysosomal proteins, after sorting and packaging, exit the Golgi apparatus in clathrin-coated vesicles. These vesicles are delivered to the early and/or late endosome by use of the M-6-P targeting mechanism.

Three different pathways deliver material for intracellular digestion in lysosomes

Depending on the nature of the digested material, different pathways deliver material for digestion within the lysosomes (Fig. 2.20). In the digestion process, most of the digested material comes from endocytotic processes; however, the cell also uses lysosomes to digest its own obsolete parts, nonfunctional organelles, and unnecessary molecules. Three pathways for digestion exist:

- *Extracellular large particles* such as bacteria, cell debris, and other foreign materials are engulfed in the process of phagocytosis. A *phagosome*, formed as the material is internalized within the cytoplasm, subsequently fuses with a lysosome to create a *phagolysosome*.
- *Extracellular small particles* such as extracellular proteins, plasma membrane proteins, and ligand–receptor complexes are internalized by endocytosis and receptor-mediated endocytosis. These particles follow the endocytotic pathway through early and late endosomal compartments and are finally delivered to lysosomes for degradation.
- *Intracellular particles* such as entire organelles, cytoplasmic proteins, and other cellular components are isolated from the cytoplasmic matrix by endoplasmic reticulum membranes, transported to lysosomes, and degraded in the process called *autophagy* (see below).

In addition, some cells (e.g., osteoclasts involved in bone resorption and neutrophils involved in acute inflammation) may release lysosomal enzymes directly into the extracellular space to digest components of the extracellular matrix.

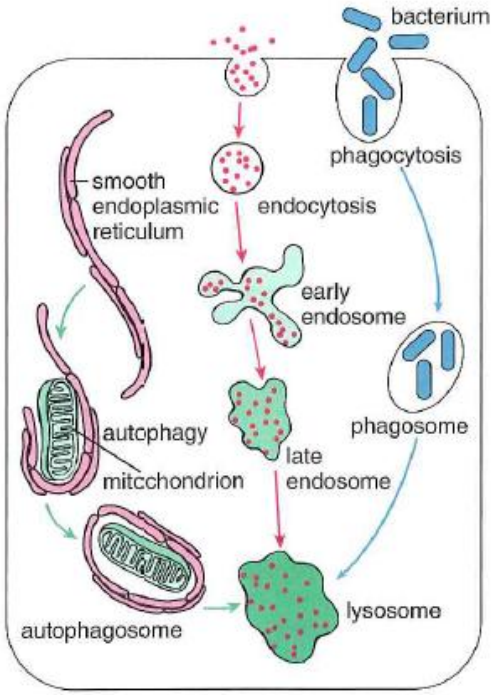


FIGURE 2.20
Pathways of delivery of materials for digestion in lysosomes. Most of the material to be digested comes from endocytotic pathways *(red arrows)*. It consists of small extracellular particles that are internalized by both endocytosis and receptor-mediated endocytosis. Large extracellular particles such as bacteria and cellular debris are delivered to lysosomes via the phagocytotic pathway *(blue arrows)*. The cell also uses lysosomes to digest its own proteins and other intracellular particles via the autophagic pathway *(green arrows)*. Intracellular particles are isolated from the cytoplasmic matrix by the membranes of the endoplasmic reticulum, transported to lysosomes, and subsequently degraded.

Cytoplasmic proteins and organelles are also substrates for lysosomal degradation in the process of autophagy

A number of cytosolic proteins, organelles, and other cellular structures can be degraded in the lysosomes (Fig. 2.21). Generally, this process can be divided into three well-characterized pathways:

- *Macroautophagy* is a nonspecific process in which a portion of the cytoplasm or an entire organelle is surrounded by an intracellular membrane of endoplasmic reticulum to form a vacuole called an *autophagosome*. After fusion with a lysosome *(autophagolysosome)*, the contents of the vacuole are degraded in a manner similar to that occurring within the phagolysosome. Macroautophagy occurs in the liver during the first stages of starvation (Fig. 2.22).
- *Microautophagy* is also a nonspecific process in which cytoplasmic proteins are degraded in a slow, continuous process under normal physiologic conditions. In microautophagy, small cytoplasmic soluble proteins are internalized into the lysosomes by invagination of the lysosomal membrane.
- *Chaperone-mediated direct transport* to lysosomes is the only selective process of protein degradation and requires assistance from a specific *chaperone protein* called *hsc73*. This process is activated during nutrient deprivation and requires the presence of targeting signals on the degraded proteins and a specific receptor on the lysosomal membrane. Chaperone-mediated direct transport resembles the process of protein import to various other cellular organelles: hsc73 binds to the protein

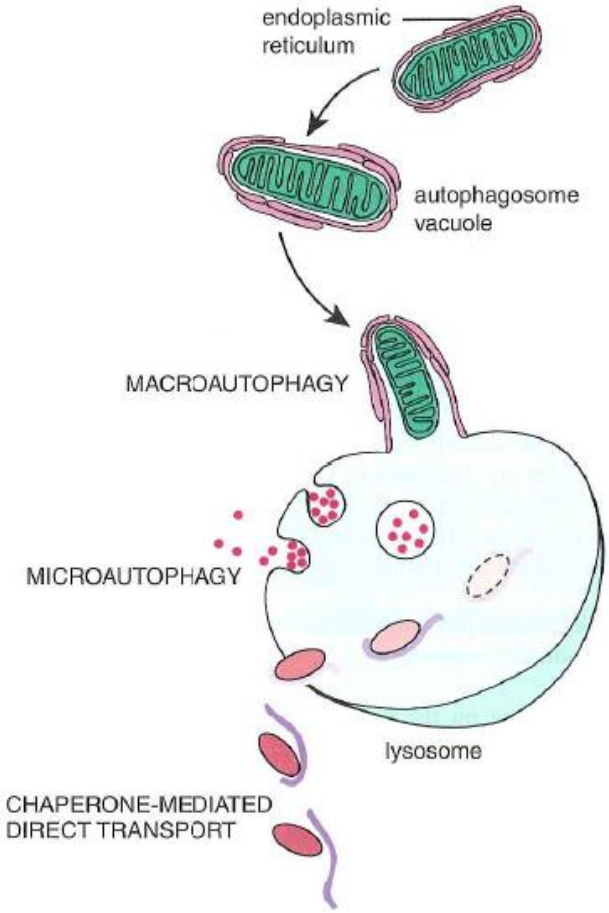


FIGURE 2.21
Three autophagic pathways for degradation of cytoplasmic constituents. In *macroautophagy*, a portion of the cytoplasm or an entire organelle is surrounded by an intracellular membrane of the endoplasmic reticulum to form an autophagosome vacuole. After fusion with a lysosome, the contents of the vacuole are degraded. In *microautophagy*, cytoplasmic proteins are internalized into lysosomes by invagination of the lysosomal membrane. *Chaperone-mediated direct transport* to lysosomes is the most selective process for degradation of specific cytoplasmic proteins. It requires assistance of proteins called chaperones. Chaperones bind to the protein and help transport it into the lysosomal lumen, where it is finally degraded.