macromolecules destined for catabolism in the lysosomes arrive by one of three other pathways (Fig. 1-9):

- Material internalized by *fluid-phase pinocytosis* or *receptor-mediated endocytosis* passes from plasma membrane to early endosome to late endosome, and ultimately into the lysosome. The early endosome is the first acidic compartment encountered, while proteolytic enzymes only begin significant digestion in the late endosome; late endosomes mature into lysosomes. During the maturation process, the organelle becomes progressively more acidic.
- Senescent organelles and large, denatured protein complexes are shuttled into lysosomes by a process called *autophagy*. Through poorly understood mechanisms, obsolete organelles are corralled by a double membrane derived from the endoplasmic reticulum; the membrane progressively expands to encircle a collection of structures and forms an *autophagosome* which then fuses with lysosomes and the contents are catabolized. In addition to facilitating the turnover of aged and defunct structures, autophagy is also used to preserve cell viability during nutrient depletion. Autophagy is discussed in more detail in Chapter 2.
- *Phagocytosis* of microorganisms or large fragments of matrix or debris occurs primarily in professional phagocytes (macrophages or neutrophils). The material is engulfed to form a *phagosome* that subsequently fuses with a lysosome.

- **Proteasomes** play an important role in degrading cytosolic proteins (Fig. 1-9); these include denatured or misfolded proteins (akin to what occurs within the ER), as well as any other macromolecule whose lifespan needs to be regulated (e.g., transcription factors). Many proteins destined for destruction are identified by covalently binding to a small 76–amino acid protein called *ubiquitin*. Poly-ubiquitinated molecules are then unfolded and funneled into the polymeric proteasome complex, a cylinder containing multiple different protease activities, each with its active site pointed at the hollow core. Proteasomes digest proteins into small (6 to 12 amino acids) fragments that can subsequently be degraded to their constituent amino acids and recycled.

Cellular Metabolism and Mitochondrial Function

Mitochondria evolved from ancestral prokaryotes that were engulfed by primitive eukaryotes about 1.5 billion years ago. Their origin explains why mitochondria contain their own DNA (circularized, about 1% of the total cellular DNA), encoding roughly 1% of the total cellular proteins and approximately 20% of the proteins involved in *oxidative phosphorylation*. Although their genomes are small, mitochondria can nevertheless carry out all the steps of DNA replication, transcription, and translation. Interestingly, the mitochondrial machinery is similar to present-day bacteria; for example, mitochondria initiate protein synthesis with N-formylmethionine and are sensitive to antibacterial antibiotics. Moreover, since the ovum contributes the vast majority of cytoplasmic organelles to the fertilized zygote, mitochondrial DNA is virtually entirely *maternally inherited*. Nevertheless, because the protein constituents of mitochondria derive from both nuclear and mitochondrial genetic transcription, mitochondrial disorders may be X-linked, autosomal, or maternally inherited.

Mitochondria provide the enzymatic machinery for oxidative phosphorylation (and thus the relatively efficient generation of energy from glucose and fatty acid substrates). They also have an important role in anabolic metabolism and play a fundamental role in regulating programmed cell death, so-called *apoptosis* (Fig. 1-10).

Energy Generation. Each mitochondrion has two separate and specialized membranes. The inner membrane contains the enzymes of the respiratory chain folded into *cristae*. This encloses a core *matrix space* that harbors the bulk of certain metabolic enzymes, such as the enzymes of the citric acid cycle. Outside the inner membrane is the *intermembrane space*, site of ATP synthesis, which is, in turn, enclosed by the *outer membrane*; the latter is studded with *porin* proteins that form aqueous channels permeable to small (<5000 daltons) molecules. Larger molecules (and even some smaller polar species) require specific transporters.

The major source of the energy to run all the basic cellular functions derives from oxidative metabolism. Mitochondria oxidize substrates to CO_2, transferring the high-energy electrons from the original molecule (e.g., sugar) to molecular oxygen, and generating the low-energy electrons of water. The oxidation of various metabolites drives *hydrogen ion (proton) pumps* that transfer H^+ from the core matrix into the intermembrane space. As the H^+ ions flow back down their electrochemical gradient, the energy released is used in the synthesis of *adenosine triphosphate (ATP)*.

It should be noted that the electron transport chain need not necessarily be coupled to ATP generation. Through the function of *thermogenin*, an inner membrane protein, the energy can be used to generate heat. Hence tissues with high levels of thermogenin, such as brown fat, can generate heat by non-shivering thermogenesis. As a natural (albeit usually low-level) byproduct of substrate oxidation and electron transport, mitochondria are also an important source of reactive oxygen species (e.g., oxygen free radicals, hydrogen peroxide); importantly, hypoxia, toxic injury, or even mitochondrial aging can lead to significantly increased levels of intracellular oxidative stress. Mitochondria are constantly turning over, with estimated half-lives ranging from 1 to 10 days, depending on the tissue, nutritional status, metabolic demands, and intercurrent injury.

Intermediate metabolism. As described in Chapter 7, pure oxidative phosphorylation produces abundant ATP, but also "burns" glucose to CO_2 and H_2O, leaving no carbon moieties suitable for use as building blocks for lipids or proteins. For this reason, rapidly growing cells (both benign and malignant) upregulate glucose and glutamine uptake and decrease their production of ATP per glucose molecule, a phenomenon called the Warburg effect. Both glucose and glutamine provide carbon moieties that prime

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