ATP to 5% to 10% of normal levels has widespread effects on many critical cellular systems:

- The activity of the *plasma membrane energy-dependent sodium pump* (ouabain-sensitive Na^+, K^+-ATPase) is reduced (Chapter 1). Failure of this active transport system causes sodium to enter and accumulate inside cells and potassium to diffuse out. The net gain of solute is accompanied by isosmotic gain of water, causing *cell swelling*, and dilation of the ER.
- *Cellular energy metabolism is altered*. If the supply of oxygen to cells is reduced, as in ischemia, oxidative phosphorylation ceases, resulting in a decrease in cellular ATP and associated increase in adenosine monophosphate. These changes stimulate phosphofructokinase and phosphorylase activities, leading to an increased rate of *anaerobic glycolysis*, which is designed to maintain the cell's energy sources by generating ATP through metabolism of glucose derived from glycogen. As a consequence *glycogen stores are rapidly depleted*. Anaerobic glycolysis results in the accumulation of *lactic acid* and inorganic phosphates from the hydrolysis of phosphate esters. This reduces the intracellular pH, resulting in decreased activity of many cellular enzymes.
- Failure of the Ca^{2+} pump leads to influx of Ca^{2+}, with damaging effects on numerous cellular components, described later.
- With prolonged or worsening depletion of ATP, structural disruption of the protein synthetic apparatus occurs, manifested as detachment of ribosomes from the rough ER and dissociation of polysomes, with a consequent *reduction in protein synthesis*.
- In cells deprived of oxygen or glucose, proteins may become misfolded, and accumulation of misfolded proteins in the endoplasmic reticulum (ER) triggers a cellular reaction called the *unfolded protein response* that may culminate in cell injury and even death (Chapter 1). This process is described further later in this chapter.
- Ultimately, there is irreversible damage to mitochondrial and lysosomal membranes, and the cell undergoes *necrosis*.

Mitochondrial Damage

Mitochondria are critical players in cell injury and cell death by all pathways. This should be expected because they supply life-sustaining energy by producing ATP. Mitochondria can be damaged by increases of cytosolic Ca^{2+}, reactive oxygen species (discussed later), and oxygen deprivation, and so they are sensitive to virtually all types of injurious stimuli, including hypoxia and toxins. In addition, mutations in mitochondrial genes are the cause of some inherited diseases (Chapter 5).

There are three major *consequences of mitochondrial damage*.

- Mitochondrial damage often results in the formation of a high-conductance channel in the mitochondrial membrane, called the *mitochondrial permeability transition pore* (Fig. 2-18). The opening of this conductance channel leads to the loss of mitochondrial membrane potential, resulting in failure of oxidative phosphorylation and progressive depletion of ATP, culminating in necrosis of the cell. One of the structural components of the mitochondrial permeability transition pore is the protein cyclophilin D, which is one of several cyclophilins that are targeted by the immunosuppressive drug cyclosporine (used to prevent graft rejection). In some experimental models of ischemia, cyclosporine reduces injury by preventing opening of the mitochondrial permeability transition pore—an interesting example of molecularly targeted therapy for cell injury. The role of cyclosporine in reducing ischemic myocardial injury in humans is under investigation.
- Abnormal oxidative phosphorylation also leads to the formation of *reactive oxygen species,* which have many deleterious effects, described later.
- The mitochondria sequester between their outer and inner membranes several proteins that are capable of activating apoptotic pathways; these include cytochrome c and proteins that indirectly activate apoptosis-inducing enzymes called *caspases*. Increased permeability of the outer mitochondrial membrane may result in leakage of these proteins into the cytosol and death by apoptosis (discussed later).

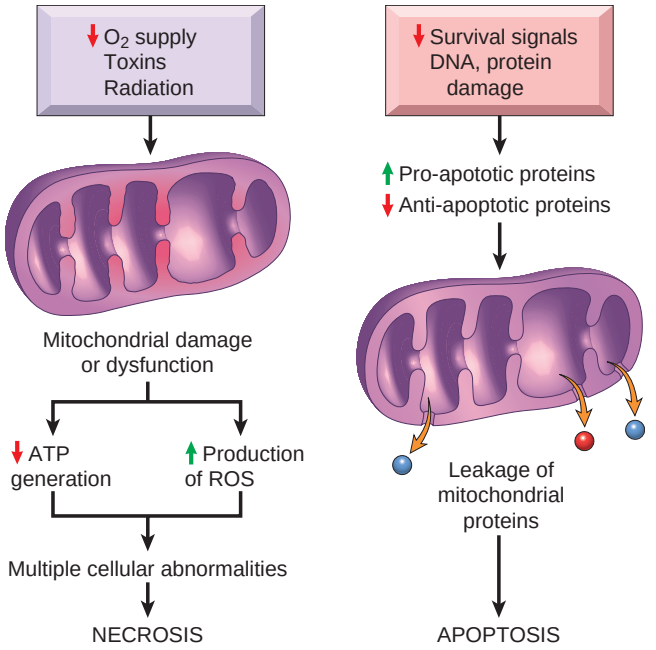

Figure 2-18 Role of mitochondria in cell injury and death. Mitochondria are affected by a variety of injurious stimuli and their abnormalities lead to necrosis or apoptosis. ATP, Adenosine triphosphate; ROS, reactive oxygen species.

Influx of Calcium and Loss of Calcium Homeostasis

Calcium ions are important mediators of cell injury. In keeping with this, depleting calcium protects cells from injury induced by a variety of harmful stimuli. Cytosolic free calcium is normally maintained at very low concentrations (~0.1 µmol) compared with extracellular levels of 1.3 mmol, and most intracellular calcium is sequestered in mitochondria and the ER. Ischemia and certain toxins cause an increase in cytosolic calcium concentration, initially because of release of Ca^{2+} from intracellular stores,