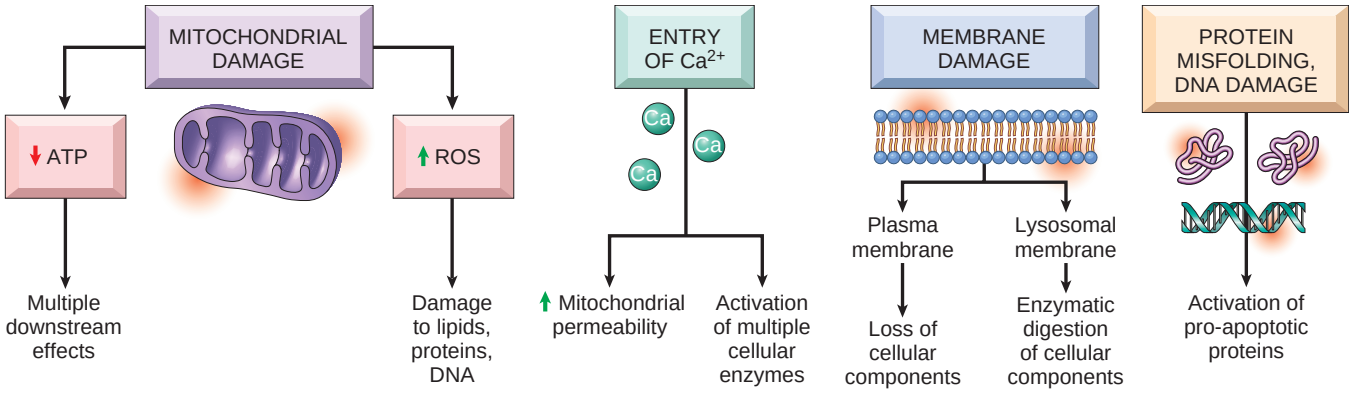

Figure 2-16 The principal biochemical mechanisms and sites of damage in cell injury. ATP, Adenosine triphosphate; ROS, reactive oxygen species.

result either in instantaneous cell death or in slow, irreversible injury leading in time to cell death.

- **The consequences of cell injury depend on the type, state, and adaptability of the injured cell.** The cell's nutritional and hormonal status and its metabolic needs are important in its response to injury. How vulnerable is a cell, for example, to loss of blood supply and hypoxia? When the striated muscle cell in the leg is deprived of its blood supply, it can be placed at rest and preserved; not so the striated muscle of the heart. Exposure of two individuals to identical concentrations of a toxin, such as carbon tetrachloride, may produce no effect in one and cell death in the other. This may be due to polymorphisms in genes encoding hepatic enzymes that metabolize carbon tetrachloride (CCl_4) to toxic by-products (Chapter 9). With the complete mapping of the human genome, there is great interest in identifying genetic polymorphisms that affect the responses of different individuals to various injurious agents.
- **Cell injury results from different biochemical mechanisms acting on several essential cellular components** (Fig. 2-16). These mechanisms are described individually in subsequent paragraphs. The cellular components that are most frequently damaged by injurious stimuli include mitochondria, cell membranes, the machinery of protein synthesis and packaging, and DNA. Any injurious stimulus may simultaneously trigger multiple interconnected mechanisms that damage cells. This is one reason why it is difficult to ascribe cell injury in a particular situation to a single or even dominant biochemical derangement.

The following section describes the biochemical mechanisms that may be activated by different injurious stimuli and that contribute to cell injury and necrosis. Apoptosis is described next, and finally necroptosis, which shares features with necrosis and apoptosis, is discussed.

Depletion of ATP

Reduction in ATP levels is fundamental cause of necrotic cell death. ATP depletion and decreased ATP synthesis are frequently associated with both hypoxic and chemical (toxic) injury (Fig. 2-17). ATP is produced in two ways. The major pathway in mammalian cells is oxidative phosphorylation of adenosine diphosphate, in a reaction that results in reduction of oxygen by the electron transfer system of mitochondria. The second is the glycolytic pathway, which can generate ATP in the absence of oxygen using glucose derived either from body fluids or from the hydrolysis of glycogen. *The major causes of ATP depletion are reduced supply of oxygen and nutrients, mitochondrial damage, and the actions of some toxins (e.g., cyanide).*

High-energy phosphate in the form of ATP is required for virtually all synthetic and degradative processes within the cell. These include membrane transport, protein synthesis, lipogenesis, and the deacylation-reacylation reactions necessary for phospholipid turnover. *Depletion of*

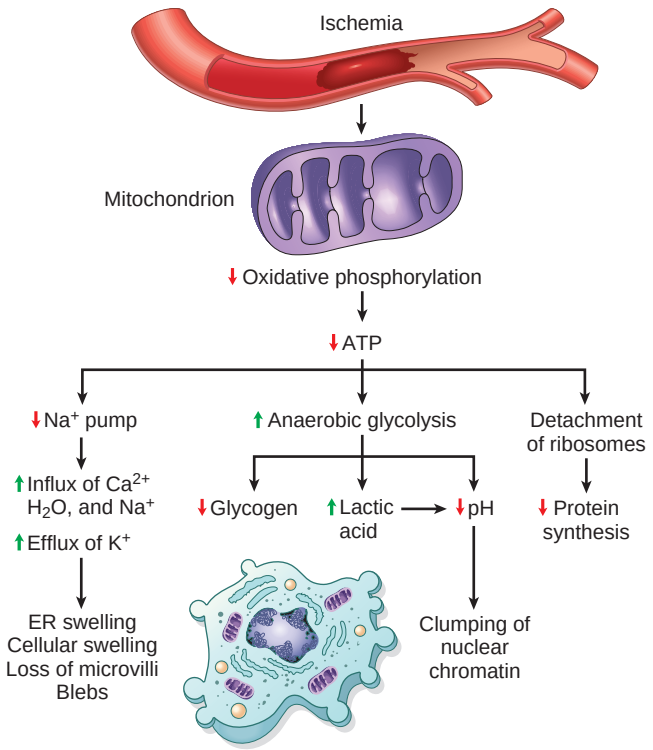

Figure 2-17 Functional and morphologic consequences of decreased intracellular adenosine triphosphate (ATP) during cell injury. The morphologic changes shown here are indicative of reversible cell injury. Further depletion of ATP results in cell death, typically by necrosis. ER, Endoplasmic reticulum.