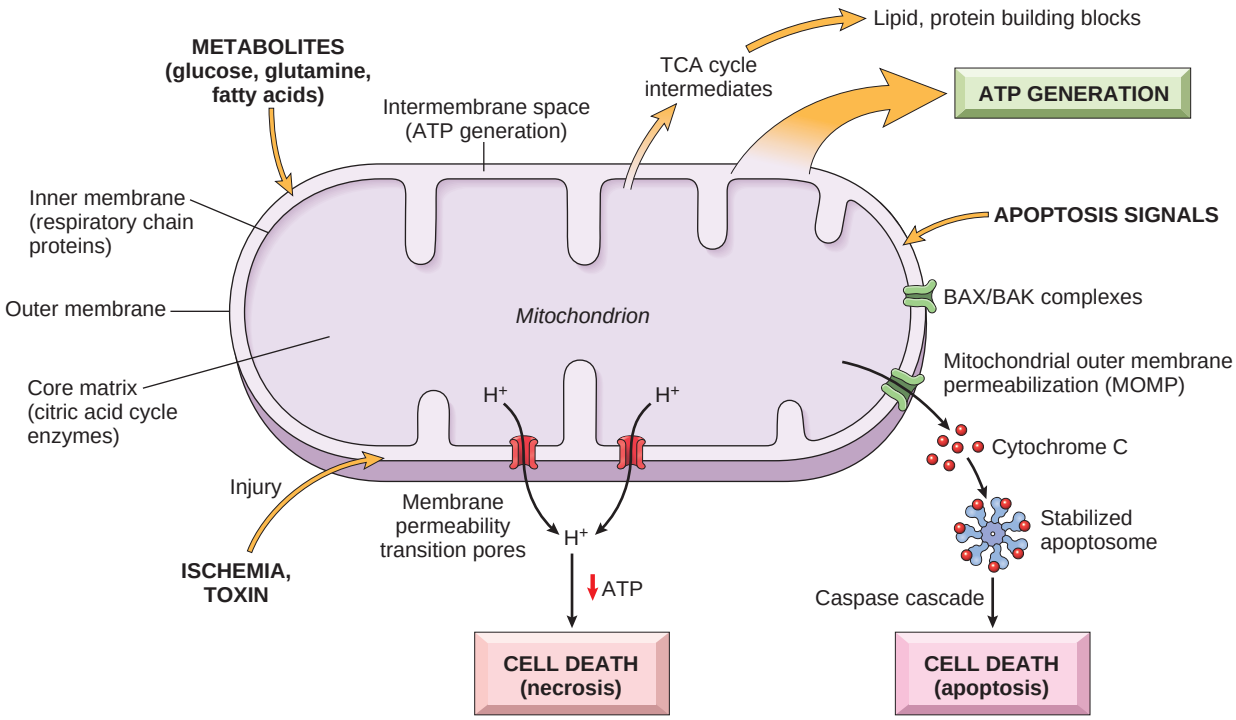

Figure 1-10 Roles of the mitochondria. Besides the efficient generation of ATP from carbohydrate and fatty acid substrates, mitochondria have an important role in intermediary metabolism, serving as the source of molecules used to synthesize lipids and proteins, and are also are centrally involved in cell life-and-death decisions.

the mitochondrial TCA cycle, but instead of being used to make ATP, intermediates are "spun-off" to make lipids, nucleic acids, and proteins . Thus, depending on the growth state of the cell, mitochondrial metabolism can be modulated to support either cellular maintenance or cellular growth. Ultimately, these metabolic decisions are governed by growth factors, nutrient and oxygen supplies, and cellular signaling pathways and sensors that respond to these exogenous factors.

Cell Death. In addition to providing ATP and metabolites that enable the bulk of cellular activity, mitochondria also regulate the balance of cell survival and death. There are two major pathways of cell death (Chapter 2):

- *Necrosis*: External cellular injury (toxin, ischemia, trauma) can damage mitochondria, inducing the formation of mitochondrial permeability transition pores in the outer membrane. These channels allow the dissipation of the proton potential so that mitochondrial ATP generation fails and the cell dies.
- *Apoptosis*: Programmed cell death is a central feature of normal tissue development and turnover and can be triggered by extrinsic signals (including cytotoxic T cells and inflammatory cytokines), or intrinsic pathways (including DNA damage and intracellular stress). Mitochondria play a central role in the intrinsic pathway of apoptosis. If mitochondria are damaged (a sign of irreversible cell injury or stress) or the cell cannot synthesize adequate amounts of survival proteins (because of deficient growth signals), mitochondria become leaky. Cytochrome c, which is normally sequestered inside the mitochondria, leaks into the cytosol, where it forms a complex with other proteins that ultimately activate caspases, the enzymes that induce apoptosis. This process is described in more detail in Chapter 2. Failure of apoptosis can contribute to malignancy (Chapter 7) and too much apoptosis can lead to premature cell death, as occurs in some neurodegenerative disorders (Chapter 28).

Although mitochondria were discovered well over 100 years ago, the secrets of their functions continue to be unraveled.

Cellular Activation

Cell communication is critical in multicellular organisms. At the most basic level, extracellular signals determine whether a cell lives or dies, or whether it remains quiescent or is stimulated to perform its specific function. Intercellular signaling is clearly important in the developing embryo, and in maintaining tissue organization; it is also important in the intact organism, assuring that tissues respond in an adaptive and effective fashion to various threats, such as local tissue trauma or a systemic infection. Loss of cellular communication and the "social controls" that maintain normal relationships of cells can variously lead to unregulated growth (cancer) or an ineffective response to an extrinsic stress (as in shock).

Cell Signaling

An individual cell is chronically exposed to a remarkable variety of signals, which it must sort through and integrate

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