



FIGURE 11.31

Some drug targets in apoptotic pathways.

A third, less well-known initiation pathway is the intrinsic endoplasmic reticulum (ER) pathway,¹⁵⁵ which is believed to be caspase-12-dependent and mitochondria-independent. In this case, when the ER is injured by cellular stress, protein synthesis is reduced, many proteins unfold, and the adaptor protein known as TNF receptor-associated factor 2 (TRAF2) dissociates from procaspase-12, resulting in activation of the latter.

Caspases are a group of specific proteases produced as inactive zymogens (pro-enzymes) that are activated and cleave their substrates by a hydrolysis reaction at Asp sites, inducing proteolytic cascade processes. They are central to the mechanism of apoptosis, being both its initiators and its executioners. Low levels of caspases or impairment in caspase function may lead to a decrease in apoptosis and carcinogenesis. However, most caspases and related proteins are not typical drug targets, and small-molecule drugs are of limited value.

Mitochondria are indispensable for energy production and hence for the survival of eukaryotic cells, but they are also crucial regulators of the intrinsic pathway of apoptosis. Internal stimuli, such as irreparable genetic damage, hypoxia, extremely high concentrations of cytosolic Ca^{2+} , and severe