Because of the duality of these features, necroptosis is sometimes called *programmed necrosis* to distinguish it from the more usual forms of necrosis driven passively by toxic or anoxic injury to the cell. *In sharp contrast to apoptosis, the genetic program that drives necroptosis does not result in caspase activation* and hence it is also sometimes referred to as "caspase-independent" programmed cell death.

The process of necroptosis starts in a manner similar to that of the extrinsic form of apoptosis, that is, by ligation of a receptor by its ligand. While ligation of TNFR1 is the most widely studied model of necroptosis, many other signals, including ligation of Fas, and yet to be identified sensors of viral DNA and RNA, as well as genotoxic agents, can also trigger necroptosis. Since TNF can cause both apoptosis and necroptosis, the mechanisms underlying these effects of TNF are especially illustrative (Fig. 2-27).

While the entire set of signaling molecules and their interactions is not known, necroptosis involves two unique kinases called receptor associated kinase 1 and 3 (RIP1 and RIP3). As indicated in Fig. 2-27, ligation of TNFR1 recruits RIP1 and RIP3 into a multiprotein complex that also contains caspase-8. While events downstream of RIP1 and RIP3 kinase activation are still murky, it is clear that unlike in apoptosis, caspases are not activated and as in necrosis the terminal events include permeabilization of lysosomal membranes, generation of ROS, damage to the mitochondria, and reduction of ATP levels. *This explains the morphologic similarity of necroptosis with necrosis initiated by other injuries.*

Necroptosis is being recognized as an important death pathway both in physiologic and pathologic conditions. For example, necroptosis occurs during the formation of the mammalian bone growth plate; it is associated with cell death in steatohepatitis, acute pancreatitis, reperfusion injury, and neurodegenerative diseases such as Parkinson disease. Necroptosis also acts as a backup mechanism in host defense against certain viruses that encode caspase inhibitors (e.g., cytomegalovirus).

Before closing this discussion, we should briefly mention another form of programmed cell death called *pyroptosis,* so called because it is accompanied by the release of fever inducing cytokine IL-1 and because it bears some biochemical similarities with apoptosis.

As is well known, microbial products that enter the cytoplasm of infected cells are recognized by cytoplasmic innate immune receptors and can activate the multiprotein complex called the *inflammasome* (Chapter 6). The function of the inflammasome is to activate caspase-1, (also known as interleukin-1β converting enzyme) which cleaves a precursor form of IL-1 and releases its biologically active form. IL-1 is a mediator of many aspects of inflammation, including leukocyte recruitment and fever (Chapter 3). Caspase-1 and, more importantly, the closely related caspase-11 also induce death of the cells. Unlike classical apoptosis, this pathway of cell death is characterized by swelling of cells, loss of plasma membrane integrity, and release of inflammatory mediators. Pyroptosis results in the death of some microbes that gain access to the cytosol and promotes the release of inflammasome-generated IL-1.

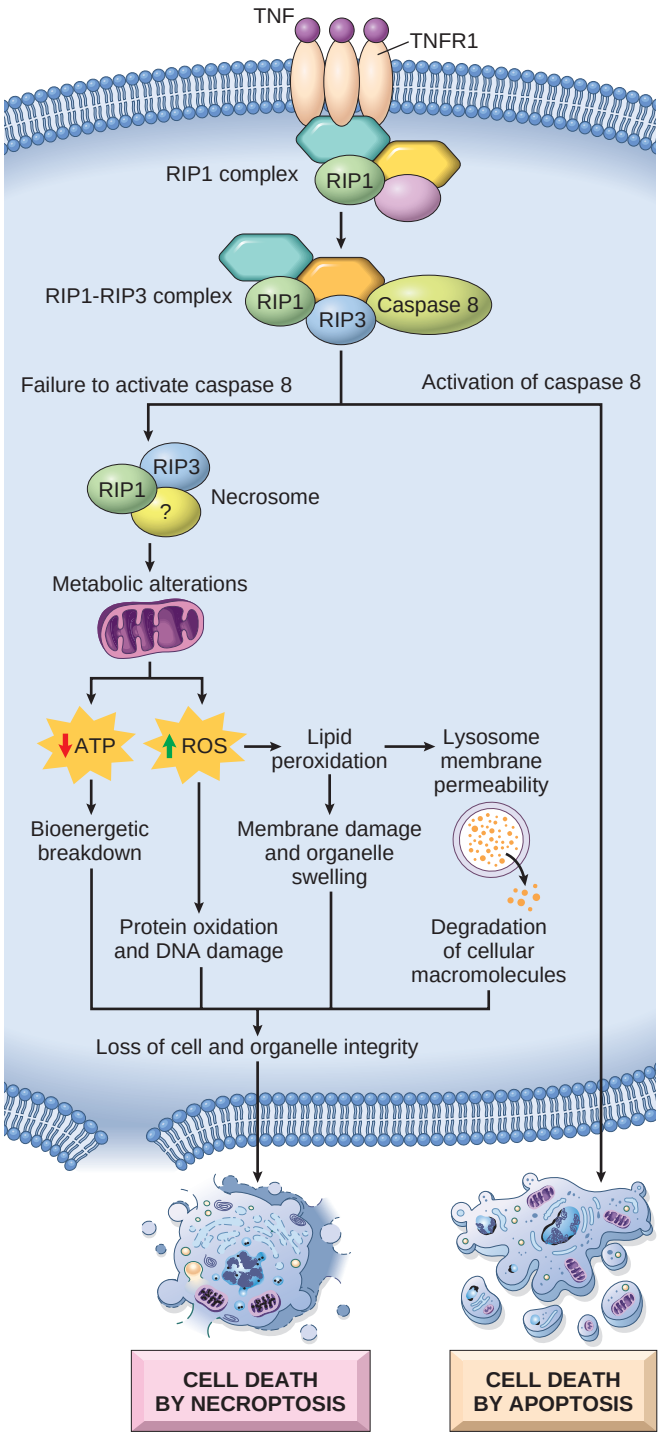

Figure 2-27 Molecular mechanism of TNF-mediated necroptosis. Cross-linking of TNFR1 by TNF causes recruitment of RIP1 and RIP3 along with caspase 8. Activation of the caspase leads to apoptosis as described in the text. Inhibition of caspase 8, as may occur in some viral infections, allows RIP1 and RIP3 to initiate signals that affect mitochondrial generation of ATP and ROS. This is followed by events typical of necrosis. (Adapted from Galluzi L, et al: Programmed necrosis from molecules to health and disease. Int Rev Cell Molec Biol 289:1, 2011.)