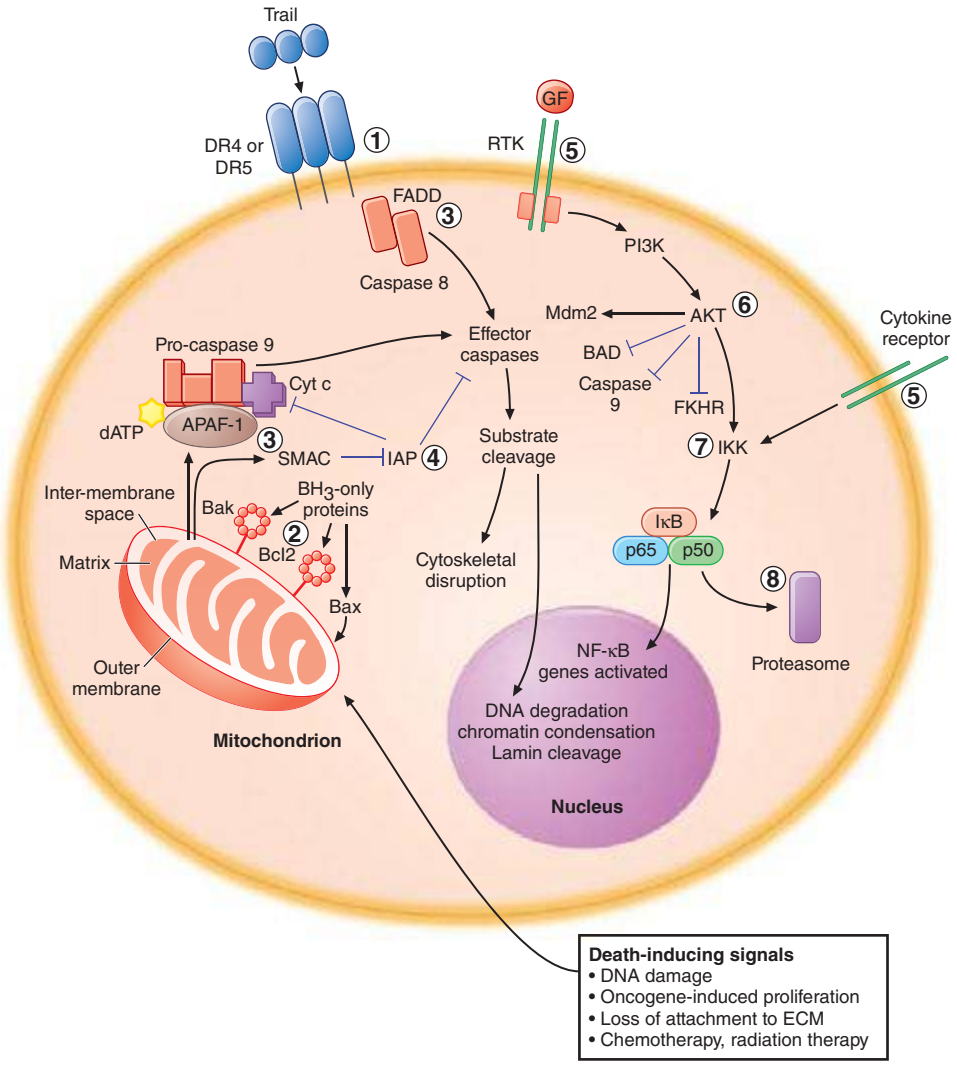

FIGURE 102e-5 **Therapeutic strategies to overcome aberrant survival pathways in cancer cells.** ***1.*** The extrinsic pathway of apoptosis can be selectively induced in cancer cells by TRAIL (the ligand for death receptors 4 and 5) or by agonistic monoclonal antibodies. ***2.*** Inhibition of antiapoptotic Bcl-2 family members with antisense oligonucleotides or inhibitors of the BH_3-binding pocket will promote formation of Bak- or Bax-induced pores in the mitochondrial outer membrane. ***3.*** Epigenetic silencing of APAF-1, caspase-8, and other proteins can be overcome using demethylating agents and inhibitors of histone deacetylases. ***4.*** Inhibitor of apoptosis proteins (IAP) blocks activation of caspases; small-molecule inhibitors of IAP function (mimicking SMAC action) should lower the threshold for apoptosis. ***5.*** Signal transduction pathways originating with activation of receptor tyrosine kinase receptors (RTKs) or cytokine receptors promote survival of cancer cells by a number of mechanisms. Inhibiting receptor function with monoclonal antibodies, such as trastuzumab or cetuximab, or inhibiting kinase activity with small-molecule inhibitors can block the pathway. ***6.*** The Akt kinase phosphorylates many regulators of apoptosis to promote cell survival; inhibitors of Akt may render tumor cells more sensitive to apoptosis-inducing signals; however, the possibility of toxicity to normal cells may limit the therapeutic value of these agents. ***7*** and ***8.*** Activation of the transcription factor NF-κB (composed of p65 and p50 subunits) occurs when its inhibitor, IκB, is phosphorylated by IκB kinase (IKK), with subsequent degradation of IκB by the proteasome. Inhibition of IKK activity should selectively block the activation of NF-κB target genes, many of which promote cell survival. Inhibitors of proteasome function are Food and Drug Administration approved and may work in part by preventing destruction of IκB, thus blocking NF-κB nuclear localization. NF-κB is unlikely to be the only target for proteasome inhibitors.

mitochondrial activator of caspases) from the mitochondrial intermembrane space in response to a variety of noxious stimuli, including DNA damage, loss of adherence to the extracellular matrix (ECM), oncogene-induced proliferation, and growth factor deprivation. Upon release into the cytoplasm, cytochrome *c* associates with dATP, procaspase-9, and the adaptor protein APAF-1, leading to the sequential activation of caspase-9 and effector caspases. SMAC binds to and blocks the function of inhibitor of apoptosis proteins (IAP), negative regulators of caspase activation.

The release of apoptosis-inducing proteins from the mitochondria is regulated by pro- and antiapoptotic members of the Bcl-2 family. Antiapoptotic members (e.g., Bcl-2, Bcl-XL, and Mcl-1) associate with the mitochondrial outer membrane via their carboxyl termini, exposing to the cytoplasm a hydrophobic binding pocket composed of Bcl-2 homology (BH) domains 1, 2, and 3 that is crucial for their activity. Perturbations of normal physiologic processes in specific cellular compartments lead to the activation of BH3-only proapoptotic family members (such as Bad, Bim, Bid, Puma, Noxa, and others) that can alter the conformation of the outer-membrane proteins Bax and Bak, which then oligomerize to form pores in the mitochondrial outer membrane resulting in cytochrome *c* release. If proteins composed only of BH3 domains are sequestered by Bcl-2, Bcl-XL, or Mcl-1, pores do not form and apoptosis-inducing proteins are not released from the mitochondria. The ratio of levels of antiapoptotic Bcl-2 family members and the levels of proapoptotic BH3-only proteins at the mitochondrial membrane determines the activation state of the intrinsic pathway. The mitochondrion must therefore be recognized not only as an organelle with vital roles in intermediary metabolism and