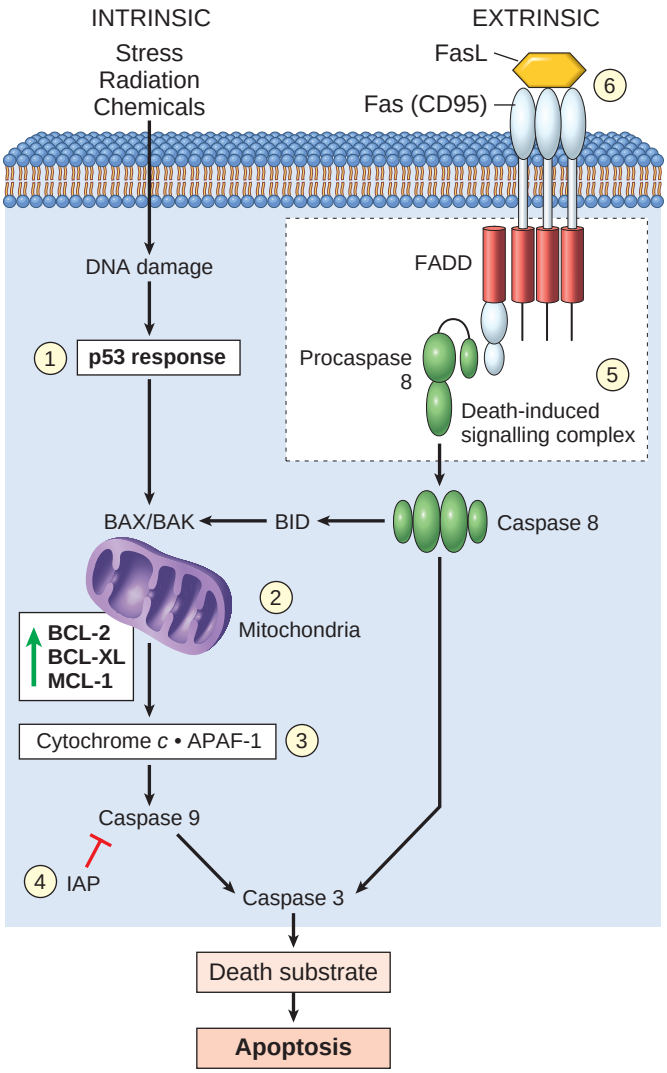

Figure 7-33 Intrinsic and extrinsic pathways of apoptosis and mechanisms used by tumor cells to evade cell death. (1) Loss of p53, leading to reduced function of pro-apoptotic factors such as BAX. (2) Reduced egress of cytochrome *c* from mitochondria as a result of upregulation of anti-apoptotic factors such as BCL2, BCL-XL, and MCL-1. (3) Loss of apoptotic peptidase activating factor 1 (APAF1). (4) Upregulation of inhibitors of apoptosis (IAP). (5) Reduced CD95 level. (6) Inactivation of death-induced signaling complex. FADD, Fas-associated via death domain.

contribute to malignancy if the cells remained viable. A cell with genomic injury can be induced to die, eliminating the chance that such a cell might go on to give rise to a neoplasm. A variety of signals, including DNA damage, deregulation of some of the most potent oncoproteins such as MYC, and loss of adhesion to the basement membrane (termed *anoikis*), can trigger apoptosis. Thus, apoptosis is a barrier that must be surmounted for cancer to develop and progress.

Biochemical Pathways That Lead To Programmed Cell Death. As discussed in Chapter 2, there are two distinct programs that activate apoptosis, the extrinsic and intrinsic pathways. Figure 7-33 shows, in simplified form, the sequence of events that lead to apoptosis by signaling through the death receptor CD95/Fas (extrinsic pathway) and by DNA damage (intrinsic pathway). **Of these two pathways, it is the intrinsic apoptotic pathway (sometimes referred to as the mitochondrial pathway) that is most frequently disabled in cancer.**

- Recall that the intrinsic pathway of apoptosis is triggered by a variety of stimuli, including withdrawal of survival factors, stress, and injury. Activation of this pathway leads to permeabilization of the mitochondrial outer membrane, with resultant release of molecules, such as cytochrome *c,* that initiate apoptosis. The integrity of the mitochondrial outer membrane is regulated by pro-apoptotic and anti-apoptotic members of the BCL2 family of proteins. The pro-apoptotic proteins BAX and BAK are required for apoptosis and directly promote mitochondrial permeabilization. Their action is inhibited by the anti-apoptotic members of this family, which are exemplified by BCL2, BCL-XL, and MCL1. A third set of proteins (so-called BH3-only proteins), including BAD, BID, and PUMA, sense death-inducing stimuli and promote apoptosis by neutralizing the actions of anti-apoptotic proteins like BCL2 and MCL1. When the sum total of all BH3 proteins expressed "overwhelms" the anti-apoptotic BCL2/BCL-XL/MCL1 barrier, BAX and BAK are activated and form pores in the mitochondrial membrane. Cytochrome *c* leaks into the cytosol, where it binds to APAF1, activating caspase 9. Caspase 9 then activates downstream caspases such as caspase 3, a typical *executioner caspase* that cleaves DNA and other substrates to cause cell death. Caspases are held in check in healthy cells by members of the *inhibitors of apoptosis protein* (IAP) family.
- The extrinsic pathway is initiated when CD95/Fas binds to its ligand, CD95L/FasL, leading to trimerization of the receptor and its cytoplasmic *death domains*, which attract the intracellular adaptor protein FADD. This protein recruits procaspase 8 to form the death-inducing signaling complex. Procaspase 8 is activated by cleavage into smaller subunits, generating caspase 8. Like caspase 9, caspase 8 then activates downstream executioner caspases. Additionally, caspase 8 can cleave and activate the BH3-only protein BID, activating the intrinsic pathway as well.

Within this framework it is possible to illustrate the multiple ways in which apoptosis is frustrated by cancer cells (Fig. 7-33). Of all these mechanisms, one of the best established is the role of BCL2 in protecting malignant lymphoid cells from apoptosis. As discussed later, approximately 85% of B-cell lymphomas of the follicular type (Chapter 13) carry a characteristic (14;18)(q32;q21) translocation. Recall that 14q32, the site where immunoglobulin heavy chain (IgH) genes are found, is also involved in the pathogenesis of Burkitt lymphoma. Juxtaposition of this transcriptionally active locus with *BCL2* (located at 18q21) causes overexpression of the BCL2 protein. This in turn protects lymphocytes from apoptosis and contributes to the survival of transformed B cells. Mice that are engineered to overexpress BCL2 in their B cells develop mainly lymphoid hyperplasia and autoimmune disorders and only infrequently get lymphoma; thus, overexpression of BCL2 must cooperate with other alterations (e.g., constitutive expression of MYC) to augment cancer development.