in causing cervical cancer produces the protein E6 that binds and inactivates the apoptosis promoter p53. This protein, called the "guardian of the genome," is involved in the induction of apoptosis, cell cycle regulation, development, differentiation, gene amplification, DNA recombination, chromosomal segregation, and cellular senescence.[158] It has a dual and conflicting role in the regulation of autophagy because nuclear p53 promotes the transcriptional activation of autophagy-related genes, whereas cytoplasmic p53 acts as a repressor of autophagy. Epstein–Barr virus, which causes mononucleosis and is associated with some lymphomas, inhibits cell apoptosis by producing a protein similar to Bcl-2 and another that causes the cell to increase its own production of Bcl-2. Cancer cells may avoid apoptosis without the participation of viruses. For example, some B-cell leukemias and lymphomas express high levels of Bcl-2, which block the apoptotic signals that they may receive; melanoma cells avoid apoptosis by inhibiting the expression of the gene encoding APAF-1; and other cancer cells secrete elevated levels of a soluble "decoy" molecule that binds to FasL, avoiding the binding of this ligand to Fas receptors. Alternatively, cancer cells may express high levels of FasL that activate the Fas receptors of cytotoxic T lymphocytes that try to kill them.

The IAPs are endogenous inhibitors of caspase activity. They are a group of structurally and functionally similar proteins characterized by the presence of a baculovirus IAP repeat (BIR) protein domain. The binding of these BIR domains to caspases promotes their degradation, or keeps them away from their substrates. Dysregulated IAP expression has been reported in many cancers, and the overexpression of XIAP (also known as BIRC4), which occurs in many NSCLCs, and survivin has been associated with resistance against a variety of apoptosis-inducing conditions.[159] XIAP is the most potent inhibitor of the intrinsic and extrinsic pathways of apoptosis, mainly by binding and inhibiting upstream caspase-9 and the downstream caspases-3 and -7, being highly expressed in many human tumor cell lines.[160] Survivin, also called baculoviral inhibitor of apoptosis protein repeat-containing 5 (BIRC5), is another crucial target in cancer therapy.[161] Its name reflects its ability to promote cell survival in cancer by blocking programmed cell death.[162] With a single BIR domain, it is the smallest IAP, and its levels and localization can be regulated by changes in transcription, physical association with chaperones, altering proteosomal degradation, and other post-translational mechanisms. Survivin inhibits apoptosis by interacting with multiple regulators of both intrinsic and extrinsic apoptosis pathways, including caspase-dependent and caspase-independent mechanisms. Because IAPs suppress apoptosis, enhance survival signaling, and are upregulated in many cancer types, they may be excellent therapeutic targets, opening the possibility that IAP antagonists might specifically target cancer cells over normal cells (Figure 11.32).

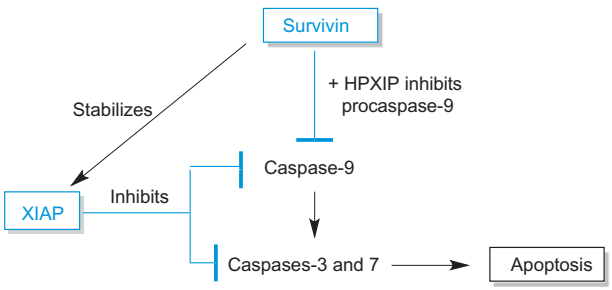

FIGURE 11.32

Apoptosis inhibition by survivin.