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Role of apoptosis in colon cancer biology, therapy, and prevention

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Abstract

Deregulation of apoptosis is a hallmark of human cancer and contributes to therapeutic resistance. Recent advances in cancer genomics reveal a myriad of alterations in key pathways that directly or indirectly increase tumor cell survival. This review will outline the pathways of apoptosis in mammalian cells, and highlight the common alterations of apoptosis regulators found in colon cancer, the role of apoptosis and underlying mechanisms in colon cancer treatment and prevention, including recent advances on investigational agents, such as kinase inhibitors, proteasome inhibitors, HSP90 inhibitors, BH3 mimetics, TRAIL, and IAP antagonists. Topics will also include novel concepts, as well as opportunities and challenges for drug discovery and combination therapy by exploring cancer-specific genetic defects, and therefore selective induction of apoptosis in cancer cells. Although the emphasis is on colon cancer, the main theme and many of the aspects are applicable to other solid tumors.

Keywords

apoptosis; colon cancer; Bcl-2 family; BH3-only protein; mitochondria; death receptor; TRAIL; EGFR; K-RAS; b-Raf; c-Myc; PI3K; IAPs; targeted therapies; sorafenib; regorafinib; vemurafenib; protesome inhibitors; Hsp90 inhibitors; autophagy; necrosis; BH3 mimetics; SMAC mimetics; NSAIDs; synthetic lethality

Introduction

Apoptosis, also known as programmed cell death, is an evolutionally conserved cell suicidal process essential for managing stress and maintaining tissue homeostasis in multi-cellular organisms. It consists of a series of well-ordered biochemical events which are regulated by a network of proteins containing distinctive functional domains. Apoptosis serves as a

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Compliance with Ethics Guidelines

Conflict of Interest

Lin Zhang has received compensation for U.S. patents 5,695,937; 5,866,330; 6,383,743; 6,746,845; and 6,333,152, and has received royalties from Johns Hopkins University for the preparation of genetically engineered cells.

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safeguard mechanism against tumorigenesis. During oncogenic transformation, neoplastic cells become resistant to apoptosis as a result of genetic and epigenetic alterations (1). Defective apoptosis regulation drives other tumorigenic events, such as extended lifespan, accumulation of further genetic mutations, growth under stress conditions, and tumor angiogenesis and metastasis, and contributes to therapeutic resistance (1). Colorectal cancer (CRC) is one of the most common cancers, with estimated 140,000 new cases and over 50,830 deaths in 2013 in the US, and over 1.2 million new cases and 600,000 deaths worldwide (2). Research in colon cancer has provided fundamental insights in cancer biology, treatment and prevention. This review provides an overview of the current understanding of the apoptotic pathways, and their deregulation in colon cancer. Discussions will cover advances in selective induction of apoptosis in neoplastic cells, and explore novel concepts such as crosstalk among cell death and survival pathways and synthetic lethality for cancer drug development and combination.

1. Apoptotic pathways

Apoptosis is initiated and executed by a series of well-ordered biochemical events and regulated by complex signaling networks. There are two major apoptotic pathways, termed as the extrinsic and intrinsic pathways (Figure 1), which are responsible for processing stress signals and executing cell demise in mammalian cells. Although distinctively regulated, these two pathways frequently cross-talk with each other.

The extrinsic apoptotic pathway is engaged upon binding of pro-apoptotic ligands to cell surface death receptors of the tumor necrosis factor receptor (TNFR) family. All death receptors contain a cysteine-rich extracellular domain for ligand binding, and an intracellular death domain for transmitting signals through the recruitment of effectors. Pro-apoptotic ligands belong to the extended cytokine TNF superfamily, and are either present on the cell surface or secreted into the extracellular space (3). Upon binding of proapoptotic ligands to their respective receptors, each receptor can independently form a death-inducing signaling complex (DISC) by recruiting the adapter protein FAS-associated death domain protein (FADD), along with pro-caspase-8 and pro-caspase-10 (Figure 1) (3). FADD recruitment and DISC formation lead to processing and activation of caspase-8 and caspase-10, and their release into the cytoplasm triggers subsequent activation of effector caspases to execute apoptosis (Figure 1) (3). FLICE-like inhibitory protein (FLIP) is a caspase-like protein lacking the catalytic function, which suppresses caspase-8 activation (4).

The intrinsic apoptotic pathway is triggered by stresses such as DNA damage, deregulated oncogenes or growth factor deprivation, and is largely regulated by the Bcl-2 family of proteins and mitochondria (5) (Figure 1). For example, DNA damage activates the tumor suppressor p53, which transmits death signals by inducing the expression of BH3-only proteins to allow for the activation of Bax and Bak. This in turn leads to mitochondrial outer membrane permeabilization (MOMP) (6), and release of several mitochondrial apoptogenic proteins, including cytochrome *c*, SMAC/Diablo, Omi/HtrA2, AIF (Apoptosis-inducing factor), and EndoG (Endonuclease G). Cytochrome *c* promotes the assembly of apoptosome and subsequent activation of caspase 9, which is facilitated by SMAC/Diablo and HtrA2/Omi, which antagonize the inhibitors of apoptosis (IAP) family of proteins. AIF and Endo G promote DNA degradation (7-8). In cells with low levels of DISC, caspase-8-dependent cleavage of the BH3-only protein Bid generates truncated Bid (tBid) to amplify apoptotic signaling via Bax/Bak and the mitochondria (Figure 1) (5).

2. Deregulation of apoptosis in cancer

Maintenance of tumor phenotypes is highly dependent on apoptosis suppression by certain pro-survival proteins, to evade the fate of cell killing imposed by “oncogenic stress” during

neoplastic transformation. Many key pathways controlling apoptosis and cell survival are therefore commonly altered in cancer (1, 9**). Genetic alterations are generally found in the more proximal components rather than the core apoptotic machinery or downstream effectors, suggesting a strong selective pressure during carcinogenesis to disable nodal points critical for apoptosis initiation, such as p53. Data from genetically manipulated mice also support apoptosis as an important mechanism for tumor suppression in the intestinal tract.

Alterations in the proximal regulators

Transcription factors: Apoptosis initiation is heavily regulated at the level of gene expression. The best studied and highly relevant to cancer are p53 and NF-κB transcription factors. p53 is essential for preventing inappropriate cell proliferation and for maintaining genome integrity following genotoxic stress, and is mutated or inactivated in over half of human cancers (6, 9). Tumor-derived p53 mutants are defective in transcription and apoptosis induction (6, 10). NF-κB plays a key role in cancer and inflammation, and its overexpression or activation is linked to chemoresistance (11). Upon stimulation by pro-inflammatory cytokines, cytoplasmic NF-κB is released from inhibitor of κB (IκB), and translocates into the nucleus to regulate gene expression. Well-known antiapoptotic targets of NF-κB include Bcl-2-like proteins, IAPs and c-FLIP (11).

Protein kinases: Kinases are key regulators of normal cell physiology and play critical roles in the development and progression of human cancer. Aberrant activation of receptor tyrosine kinases (RTKs) and non-RTKs ultimately contributes to tumor initiation and maintenance of tumor phenotypes such as cell survival, proliferation, migration, and tumor angiogenesis (1, 9), and confers resistance to cancer therapy (12**). Aberrant activation of RTKs, such as epidermal growth factor receptor (EGFR, erbB1), hepatocyte growth factor (HGF) receptor MET, platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR), engages intracellular kinase cascades such as Ras/b-Raf/ERK and phophotidylinositol-3-kinase (PI3K)/AKT/mTOR. Activation of these non-RTKs is also caused by gene mutations and amplifications in colon cancer (9).

Alterations in the Bcl-2 family of proteins—Antiapoptotic Bcl-2 family members are frequently overexpressed in solid tumors, while proapoptotic Bcl-2 family members are downregulated or mutated (5). In rare cases, homozygous deletions or inactivating mutations of *BAX* are found, particularly in DNA mismatch repair deficient colorectal tumors (13). The activities or levels of proapoptotic proteins are often suppressed by oncogenic kinases. For example, PI3K/AKT or ERK inactivates BAD by phosphorylation (14), and suppresses PUMA induction (15-17). *PUMA* ablation in mice leads to decreased apoptosis and increased tumor burden and invasiveness in the GI tract (18**).

Alterations in the extrinsic pathway and other apoptotic components—In contrast to the deregulation in the upstream regulators or Bcl-2 family, direct impairments of the extrinsic pathway and downstream apoptotic effectors by genetic alterations are generally rare in human cancer, while altered expression is common (3, 19-20). Overexpression of c-FLIP (4), particularly c-FLIP-L, functions as a survival factor in colon cancer (21). Elevated XIAP (22), cIAP2 (23) or reduced SMAC expression (24), are correlated with disease progression, metastasis or poor survival in colon cancer patients. SMAC levels were inversely correlated with cIAP2 levels and tumor grade, and its ablation accelerates cancer progression in mice (25). Lost expression or deletion of *DR4* and *DR5,* overexpression of decoy receptors DcR3 or DcR1 (3), *Caspase-8* (*CASP8)* polymorphisms or deletion have been reported in other cancers, however not in colon cancer.

3. Apoptosis induction in colon cancer treatment and resistance mechanisms

Induction of apoptosis is a major cytotoxic mechanism of anticancer therapies, including radiation, chemotherapy, and targeted therapies (Figure 1) (3, 5, 12, 26). Targeted therapies are expected to have improved specificity and reduced toxicity, and ultimately help move oncology practice toward personalized treatment (27). Cancer cells can develop various mechanisms to evade apoptosis. Deficiency in p53, Bax, PUMA, or caspase activation can cause resistance to radiation and chemotherapy, while overexpression of antiapoptotic proteins such as Bcl-X_L, c-FLIP and IAPs are frequently associated with therapeutic resistance. Mutations in kinases and their cross-talk modulate therapeutic responses to targeted therapies in patients.

Radiation and chemotherapy—Radiation and the majority of conventional chemotherapeutic agents induce DNA damage. Following DNA damage, p53 undergoes extensive post-translational modifications, including phosphorylation and acetylation, which stabilize p53 and enhance its transcriptional activities (6). p53 mediates DNA damage-induced apoptosis primarily via the intrinsic pathway, through the BH3-only protein PUMA, and Noxa to a lesser extent, in various cancer cells and normal tissues (28-30). In addition, DR5 and PIDDosome/caspase 2 (31) are implicated in 5-FU-induced apoptosis in colon cancer cells, which is partially dependent on p53 (32). Under some conditions, cytoplasmic p53 inactivates Bcl-2 like proteins at the mitochondria (33), though the significance and mechanisms are not well understood. Moreover, genotoxic stress can activate p53 family proteins such as p73 and p63, which share many proapoptotic targets with p53 (34).

On the other hand, p53 plays a key role in the pathologic apoptosis of tissue stem cells and acute side effects induced by radiation and chemotherapy in the bone marrow and GI tract (29-30, 35). Given the prevalence of p53 alterations in cancer (6), it is tempting to speculate that enhancement of p53-independent induction of apoptosis genes in cancer cells and/or suppression of p53-dependent apoptosis in normal tissues can be exploited to widen the therapeutic index.

Targeted therapies

Anti-EGFR therapy: EGFR-targeting agents, including tyrosine kinase inhibitors (TKIs) and monoclonal antibodies, have been used to treat different tumor types. EGFR TKIs are particularly useful in treating a subset of lung cancers harboring oncogenic EGFR mutations. Cetuximab and panitumumab, two anti-EGFR monoclonal antibodies, are effective in combination with chemotherapy or as single agents for the treatment of metastatic colon cancer. However, mutations in *K-RAS*, *b-Raf*, and *PIK3CA* are associated with resistance to anti-EGFR therapies (27). Apoptosis is induced by EGFR TKIs in a variety of tumor cells through the intrinsic pathway by modulating the BH3-only proteins, such as Bim or PUMA (17, 36-37). Clinical response to EGFR TKIs is correlated with induction of apoptosis in tumor cells, and defective apoptosis regulation contributes to resistance of EGFR-targeted therapy (38).

Anti-VEGF therapy: Bevacizumab (Avstin), a recombinant humanized monoclonal antibody against VEGF, is used in combination with conventional chemotherapy for treating metastatic colorectal cancer. Several studies suggest induction of apoptosis in tumor cells contributes to the therapeutic effect of Bevacizumab. In xenograft models, antitumor effects of Bevacizumab are correlated with hypoxia-induced apoptosis (39). Combined use of Bevacizumab and irinotecan (CPT-11) strongly induced apoptosis and improved therapeutic efficacy against lung metastasis from colon cancer cells (40). In Bevacizumab-treated metastatic colon cancer patients, the serum level of proapoptotic death receptor ligand

TRAIL (sTRAIL) was found to be elevated, which was correlated with patient survival (41-42).

Sorafenib/Regorafinib: Sorafenib (Nexavar) is the first FDA-approved oral multi-kinase inhibitor drug that targets the RAS/Raf/MEK/ERK pathway. Sorafenib inhibits c-Raf, b-Raf, PDGFR, and VEGFRs, and has been used for the treatment of advanced kidney and liver tumors (43-44). Regorafenib (BAY 73-4506, Stivarga), a Sorafenib analogue with an extra fluoro group, has been recently approved for the treatment of metastatic colorectal cancer and advanced gastrointestinal stromal tumors that are resistant to other therapies. The anticancer effects of Sorafenib/Regorafenib are thought to be mediated by apoptosis induction, in addition to its anti-proliferative and anti-angiogenic effects, and are enhanced when combined with cytotoxic agents (43-44). Sorafenib-induced apoptosis is associated with downregulation of Mcl-1 and inhibition of eIF4E (eukaryotic translation initiation factor 4E) phosphorylation (45-46), as well as the induction of PUMA through NF-κB in colon cancer cells (47*), and Bim in leukemia cells (48).

Other targeted therapies and investigational agents—Numerous investigational drugs are in the various stages of clinical development for colon cancer and found to stimulate apoptosis. Vemurafenib (PLX4032), a selective inhibitor of b-Raf V600E mutant, has shown significant activity in b-Raf mutant (V600E) melanomas, but only very limited efficacy in colon cancers with the same mutation. The intrinsic and acquired resistance to b-Raf inhibitors involves feedback activation of the PI3K/AKT, mTOR, or EGFR pathway, and can be overcome by the inhibitors of these pathways via apoptosis induction (49-51*). Non-selective kinase inhibitors such as UCN-01(15) or Sunitinib (52) induced PUMA-dependent, but p53-independent apoptosis in colon cancer cells. Met/ALK inhibitors such as crizotinib induced both p53-dependent and -independent apoptosis, and synergized with EGFR-TKI or Raf inhibitors to induce PUMA and apoptosis (53*). Additional inhibitors against Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR pathways are in development (12). Therefore, systematic approaches are needed to determine optimal use of these agents in the correct patients (see synthetic lethality).

In addition to kinase inhibitors, several other classes of agents also induce apoptosis in cancer cells. The proteasome inhibitor Bortezomib (Velcade), approved for treating multiple myeloma, triggers apoptosis alone or in combination with chemotherapy by modulating the Bcl-2 family and NF-κB pathway (54-55). Heat shock protein 90 (Hsp90) is one of the most abundant molecular chaperones in eukaryotes and expressed at much higher levels in tumor cells. Currently, over 17 Hsp90 inhibitors have entered clinical trials. These agents are found to induce apoptosis and overcome resistance to bRaf or PI3K/ATK/mTOR inhibitors in preclinical models (56). Several proapoptotic mechanisms, likely to be cell-type specific, have been suggested, including down-regulation of Hsp90 client oncoproteins such as mutant p53, Raf-1, AKT, NF-κB, Her2 (56), or activation of wild-type p53 (57).

4. Apoptosis and cancer prevention

Cancer prevention is expected to have a great impact on cancer mortality. Chemoprevention is a promising anti-cancer strategy, referring to the use of pharmacologic agents or natural products to intervene early in the process of tumor development (58). Epidemiological studies, clinical trials and animal studies have shown that the widely used non-steroidal anti-inflammatory drugs (NSAIDs) prevent intestinal cancer in human and mice, particularly in high-risk individuals who carry germ-line *APC* mutations (9, 59). NSAIDs are also useful in preventing other types of cancer, and as an adjuvant therapy (60).

Several anticancer mechanisms of NSAIDs and other cancer preventive agents have been described, such as inhibition of cyclooxygeneses (COXs) enzymes (60). and induction of apoptosis (61). Mechanistic studies demonstrated that Bax and SMAC/Diablo mediate the anti-cancer effects of NSAIDs by promoting apoptotic cell death (62-65*), likely by crosstalk between the death receptor and the mitochondrial apoptotic pathways (Figure 1). Manipulating apoptosis or using a combination of different classes of chemopreventive agents can enhance the effectiveness of NSAIDs (64), and reduce toxicity by lowering the doses (66).

One of the earliest events in colorectal tumorigenesis is genetic alterations in the *APC* tumor suppressor pathway leading to aberrant Wnt signaling and subsequent nuclear translocation of β-catenin, and activation of oncogenes such as *c-Myc* and *cyclin D1 (9)*, and likely targeting the intestinal stem cells (67). NSAID treatment selectively induced apoptosis to remove intestinal stem cells with aberrant Wnt signaling (65). Adenoma samples from patients taking NSAIDs were also found to have enhanced apoptosis induction in cells with expression of stem cell markers and aberrant Wnt signaling (65), suggesting that NSAIDs eliminate stem cells that have acquired oncogenic mutations to prevent intestinal tumorigenesis.

5. Apoptosis cross talk with other death and survival mechanisms

Although apoptosis is a major mode of cell death in response to anticancer agents, several alternative cell death pathways have recently been identified, in particular autophagy and programmed necrosis (Figure 1). These pathways are engaged in response to specific stimuli, upon a restricted condition, or within a time window during cell death. The interplay among different cell death pathways can sometimes play a critical role in determining therapeutic response and development of drug resistance, and is partially mediated by the competition of shared regulators or adaptors.

Autophagy—Autophagy is a self-eating process of cells that has recently emerged as an important stress response and cell death mechanism, and regulated by a group of evolutionarily conserved *autophagy-related genes* (*ATGs*) (68). It is characterized by the formation double membrane autophagosomes, which fuse with lysosomes to promote degradation of damaged organelles or cytosolic materials (69). Autophagy can either promote or inhibit cell death, and is often cytoprotective in cancer cells (70). Inhibition of autophagy sensitizes cancer cells to chemotherapy, and autophagy inhibitors such as hydroxychloroquine are being tested in a number of clinical trials (71). Autophagy interconnects with apoptosis in a number of ways (72). Bcl-2-interacting protein-1 (Beclin 1), a key regulator of autophagy, contains a BH3 domain that can interact with Bcl-2 and Bcl-X_L (73), which inhibit autophagy (74). Several ATG proteins, including Beclin 1, ATG5 and ATG4D, can be cleaved by caspases and other proteases during apoptosis (75-76). Specific ablation of caspase-8-mediated Beclin 1 cleavage restored autophagy in apoptotic cells, and enhanced cancer cell survival and therapeutic resistance (77*).

Necrosis—Necrosis is characterized by ATP depletion, swelling of organelles and spilling of cellular contents, and some forms of necrosis are found to be regulated. In the absence of cIAPs, TNFα stimulates the formation of a secondary cytoplasmic complex similar to DISC, leading to rapid activation of caspase 8 and subsequently apoptosis (64, 78-79), which is largely blocked by caspase inhibitors in most cell types. In some cells, caspase inhibitors or genetic ablation of caspase-8 can switch the apoptotic response to necrosis mediated by receptor-interacting protein kinase 1 (RIPK1 or RIP1) or RIPK3 (80-81*). Necrosis often leads to inflammation, whose significance in cancer biology and therapy and underlying mechanisms remain to be elucidated.

6. Apoptosis targeted agents in development for cancer therapy

Several strategies have been devised to induce cell killing by manipulating apoptotic regulators directly. Small-molecule or antisense inhibitors of pro-survival Bcl-2 family members or the IAP antagonists promote apoptosis by inhibiting antiapoptotic signaling within the cells. The protein-based agents trigger apoptosis from cell surface by stimulating death receptors. Most of these agents have limited toxicity to cancer cells as single agents, while potently synergize with radiation or conventional chemotherapy in preclinical studies.

Bcl-2 antagonists—Compared to peptidyl and small-molecule BH3 mimetics, antisense oligonucleotides against various antiapoptotic Bcl-2 family members have limited success. Only the Bcl-2 antisense oligo oblimersen advanced into clinic trials. Due to more desirable pharmacological properties, extensive preclinical studies have been conducted on various BH3 mimetics, including HA14-1, Antimycin A and analogs, BH3Is, gossypol and analogs, GX015-070 (82). The most promising BH3 mimetic is ABT-737, which potently inhibits Bcl-2 and Bcl-X_L, but not MCL-1, to induce Bax/Bak-dependent apoptosis (83-84). As a single agent, ABT-737 and most BH3 mimetics had limited efficacy in selective types of cancer cells (83), but they exhibited striking synergy with a variety of anticancer agents in colon cancers (15, 47, 52). ABT-263, an orally available derivative of ABT-737, is currently being evaluated in clinical trials (85).

Death receptor ligands or agonists—Recombinant human TRAIL (rhTRAIL) has shown promise in both preclinical and clinical studies, suggesting the importance of DR4 and DR5 in cancer cell killing (19). Deficiency in *CASP8* (3, 19), *BAX* (62) or *SMAC* (63) , but not p53 (3) is associated with TRAIL resistance. Mapatumumab (HGS-ETR1) is the only human agonistic antibody for DR4 that has advanced into clinical trials, showing some efficacy in combination regimens (3). The clinical outlook of FasL or TNF- is limited due to severe side effects associated with inflammation (3).

IAP antagonists—SMAC/Diablo and Omi/HtrA2 are endogenous IAP inhibitors, also called IAP antagonists, and relieve the antiapoptotic activities of several IAPs (20). The synthesis of SMAC mimetics that resemble either monomeric or dimeric N-terminal IAP-binding AVPI peptide of SMAC is a great example of structure-based drug design (20, 86). Both monovalent and divalent SMAC mimetics are currently in Phase I and Phase II trials (20, 86). As single agents, SMAC mimetics exert little or no toxicity in non-malignant human cells, and only induce apoptosis in a limited number of cancer cell lines via TNFα production (79). SMAC mimetics or forced SMAC expression sensitizes cancer cells to apoptosis induced by various classes of anticancer agents, including chemotherapeutics, radiation, death receptor agonists and kinase inhibitors, by enhancing caspase activation (64), release of endogenous SMAC (87) and cIAP1/2 degradation (20).

7. Exploring synthetic lethality in cancer therapy and prevention

The concept of synthetic lethality borrowed from yeast genetics has recently been used to discover new anticancer agents or targets based on cancer-specific genetic changes (88). Using isogenic cells combined with siRNA or small-molecule library screens has identified several synthetic lethal interactions in colon cancer cells. For example, *K-RAS* mutation is synthetic lethal with the inhibition of the mitotic machinery, proteasome (89), kinase *STK33* (90) and TAK1 (91), transcription factor GATA2, DNA replication factor CDC6 (92), and MEK/Bcl-X_L (93*). c-Myc overexpression is synthetic lethal with Aurora B kinase inhibition (94). Interestingly, TRAIL is synthetic lethal with either *RAS* or c-*Myc* (95-96). Cell killing in these settings is likely mediated through apoptosis. Synthetic lethal interactions with DNA repair deficiencies are of therapeutic interest, such as the PARP inhibitors with *BRCA1/2* deficiency in a subset of ovarian or breast cancer (97), and

mismatch repair proteins MSH2 and DNA polymerase (polβ), and MLH1 with polγ in colon cancer cells (98-99).

Discovery of novel synthetic lethal interactions has important implications in cancer treatment and prevention. *RAS* mutant tumors account for 40-50% of colon cancer, while c-Myc overexpression is an early and nearly universal event in colon cancer resulting from the loss of tumor suppressor *APC* (9). The advantages of this approach include reduction of side effects by using lower doses of conventional therapies, and increase in therapeutic efficacy through rationale combinations (100*). It is likely that cancer-driver mutations play a key role in the understanding of gene-gene, gene-drug interactions and therapeutic resistance as discussed before.

Conclusion

Apoptosis in mammalian cells is regulated by two major pathways. Integration of apoptotic signals is achieved through the cross-talk among many upstream signals and downstream effectors, influencing the decision between life and death. Alterations in the apoptotic pathways are complex, with genetic alterations found mostly in the upstream regulatory proteins, providing many potential targets for drug development. One of the main goals of cancer research is to develop safer and more effective therapies, which might capitalize on a better understanding of cancer genome as well as cancer-specific synthetic lethal interactions. A great challenge ahead is to understand in biochemical detail the integration modules and nodes of apoptotic pathways to help drug development and delineation of therapeutic resistance mechanisms. Another big challenge is to identify biomarkers that can help stratify patients for treatments and follow-up. Such efforts are expected to ultimately lead towards personalized medicine.

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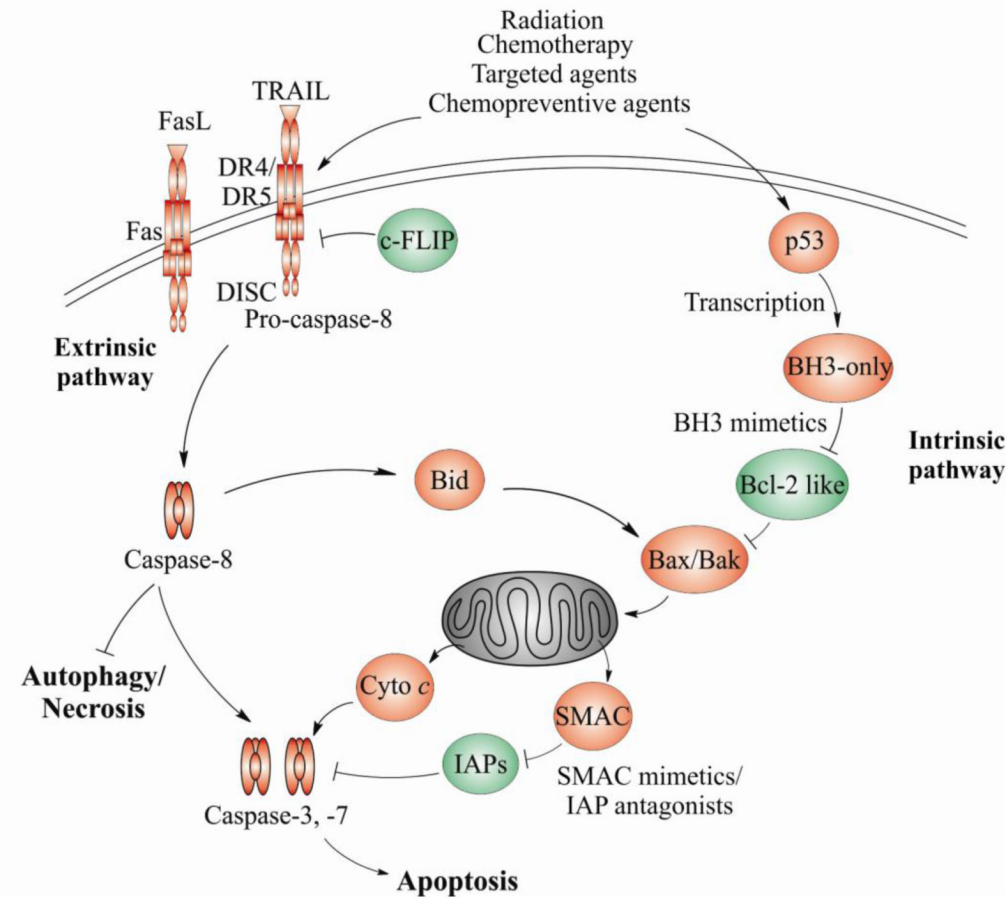

Figure 1. Coaxing cancer cells into apoptosis

Apoptosis in mammalian cells is mediated through the intrinsic and extrinsic pathways. The intrinsic pathway is predominantly regulated by the Bcl-2 family and mitochondria. The extrinsic pathway is engaged upon binding of proapoptotic ligands, such as TRAILor Fas to their respective death receptors on the cell surface. Apoptosis initiation is regulated by transcription as well as the cross-talk of two apoptotic pathways via Bid. Apoptosis is activated by anticancer agents, such as radiation, chemotherapy, kinase inhibitors, BH3 or Smac mimetics, and chemopreventive agents acting on both pathways and various players, to trigger a caspase activation cascade. Inhibition of apoptosis or certain caspases such as caspase-8 can lead to increased autophagy or necrosis, providing additional targets for drug development. Antiapoptotic proteins are colored in green while proapoptotic proteins are colored in red. Cyto *c*, cytochrome *c*.