

Apoptotic pathways as a therapeutic target for colorectal cancer treatment

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Author contributions: Abraha AM and Ketema EB contributed equally to this work; both authors wrote, read, revised and approved the final manuscript.

Conflict-of-interest statement: Authors declare that there is no conflict of interests for this article.

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Manuscript source: Unsolicited manuscript

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Received: February 11, 2016

Peer-review started: February 12, 2016

First decision: March 23, 2016

Revised: April 15, 2016

Accepted: June 14, 2016

Article in press: June 16, 2016

Published online: August 15, 2016

Abstract

Colorectal cancer is the second leading cause of death from cancer among adults. The disease begins as a benign adenomatous polyp, which develops into an advanced adenoma with high-grade dysplasia and then progresses

to an invasive cancer. Appropriate apoptotic signaling is fundamentally important to preserve a healthy balance between cell death and cell survival and in maintaining genome integrity. Evasion of apoptotic pathway has been established as a prominent hallmark of several cancers. During colorectal cancer development, the balance between the rates of cell growth and apoptosis that maintains intestinal epithelial cell homeostasis gets progressively disturbed. Evidences are increasingly available to support the hypothesis that failure of apoptosis may be an important factor in the evolution of colorectal cancer and its poor response to chemotherapy and radiation. The other reason for targeting apoptotic pathway in the treatment of cancer is based on the observation that this process is deregulated in cancer cells but not in normal cells. As a result, colorectal cancer therapies designed to stimulate apoptosis in target cells would play a critical role in controlling its development and progression. A better understanding of the apoptotic signaling pathways, and the mechanisms by which cancer cells evade apoptotic death might lead to effective therapeutic strategies to inhibit cancer cell proliferation with minimal toxicity and high responses to chemotherapy. In this review, we analyzed the current understanding and future promises of apoptotic pathways as a therapeutic target in colorectal cancer treatment.

Key words: Colorectal cancer; Apoptotic pathways; Drug resistance; Colorectal cancer therapies; Apoptosis

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Core tip: Evasion of apoptosis has been established as a prominent hallmark of several human cancers, contributing to both tumor progression and chemo-resistance. In colorectal cancer development, the balance between the rates of cell growth and apoptosis that maintains intestinal epithelial cell homeostasis is impaired progressively. Recent studies indicated that failure of apoptosis may be an important factor in the evolution of colorectal cancer and its poor response to chemotherapy

and radiation. We herein discussed the mechanisms of apoptosis, abnormal expression of apoptosis-related genes and future promises of apoptotic pathways as a therapeutic target for colorectal cancer chemoprevention and treatment.

Abraha AM, Ketema EB. Apoptotic pathways as a therapeutic target for colorectal cancer treatment. *World J Gastrointest Oncol* 2016; 8(8): 583-591 Available from: URL: <http://www.wjgnet.com/1948-5204/full/v8/i8/583.htm> DOI: <http://dx.doi.org/10.4251/wjgo.v8.i8.583>

INTRODUCTION

Colorectal is the second driving reason for death from malignancy among adults^[1]. The diseases starts as a benign adenomatous polyp, which changes into a propelled adenoma with high-rate dysplasia that advances to aggressive tumor^[2]. The development of colorectal cancer (CRC) shows that tumor is a multistep procedure. The continuous process of cell division and differentiation of intestinal epithelium can be subverted by genetic alteration that switch the progenitor cells into tumor cells. This change is not prompt but occurs progressively through various stages as the cells get increasingly mutated, depending on the activation of oncogenes and the inactivation of tumor suppressors^[3]. The aim of this review was to summarize evidences on the role of apoptotic pathways in the initiation and progression of CRC and their potentials as a therapeutic target.

APOPTOSIS AND ITS ROLE IN CANCER

Apoptosis is an implicit cell suicide pathway that helps to remove cells that are no more required or have extreme injury to their DNA and cytoskeleton^[4]. Since defined by Kerr *et al.*^[5] in the 1970's, apoptosis remains amongst the most explored topics in biologic investigation. Being a very selective process, apoptosis is vital both in normal and pathological processes.

Mainly three fundamental sorts of biochemical changes are seen in apoptosis: (1) stimulation of caspases; (2) DNA and protein degradation; and (3) membrane alterations and detection by phagocytic cells. Specific morphological changes of apoptotic cells comprises nuclear compression and disintegration, cell contraction, active membrane blebbing, and loss of linkage to extracellular lattices or to neighboring cells. These alterations involve chromosomal DNA cleavage into internucleosomal rubbles, translocation of phosphatidylserine, and stimulation of proteases distinguished as the caspases^[6,7].

The unique characteristics of apoptosis is the activation various enzymes that are cysteine protease families called caspases^[7]. Activated caspases slice several key cellular proteins and degraded the nuclear

scaffold and the cytoskeleton. They additionally stimulate DNAase, which advances nuclear DNA degradation processes^[8].

MECHANISMS OF APOPTOSIS

Since they are both the initiators and destroyers, caspases play a key role in apoptotic processes. Caspases are initiated by three separate pathways: The intrinsic (or mitochondrial), the extrinsic (or death receptor) and the intrinsic endoplasmic reticulum pathways^[9]. The extrinsic pathway is initiated by triggering cell death receptors on the cell surface which leads to activation of the intracellular apoptotic machinery. The signals are originated from the activation of specific proapoptotic membrane receptors, a subclass of tumour necrosis factor (TNF) receptor family, through ligands, for example, FasL23/CD95L (receptor Fas/CD95) and Apo2 ligand TNF-linked apoptosis-initiating binding groups (Apo2L/TRAIL) (receptors DR4 and DR5)^[10]. These receptors have an internal components that mobilize core proteins including TNF receptor-associated death domain (TRADD) and fas-associated death domain (FADD)^[11]. Upon binding of the ligand to its receptor, the death-inducing signaling complex (DISC) that causes stimulation of caspase 8 formed^[9]. Thusly, caspase 8 activate the remaining downstream caspase enzymes. In some group of cells, the stimulation of caspase 8 could be the only prerequisite conditions to accomplish death, but in other cell types; caspase 8 cooperates with the intrinsic apoptotic processes by splitting Bid (a proapoptotic member of the Bcl-2 protein), causing the successive release of cytochrome-c^[12,13].

As the name suggests, the intrinsic pathway starts inside the cell. Intracellular stimuli such as irreversible genetic impairment, hypoxia, high calcium (Ca^{2+}) concentrations and elevated oxidative stress are amongst the triggers of intrinsic mitochondrial pathway. Irrespective of the inducers, this pathway caused an increase in mitochondrial porousness and the discharge of cytochrome-c and other proapoptotic proteins into the cytosol^[14]. This process is strictly controlled by Bcl-2 family proteins, termed after the *Bcl-2* gene originally detected at the chromosomal breakpoint of the translocation of chromosome 18 to 14 in follicular non-Hodgkin lymphoma^[15]. There are two classes of the Bcl-2 proteins: The pro-apoptotic proteins (such as Bax, Bakand, Bad, Bcl-Xs, Bid, Bik, Bimand Hrk) and the anti-apoptotic proteins (such as Bcl-2, Bcl-XL, Bcl-W, Bfl-1 Mcl-1). While anti-apoptotic proteins control apoptosis by delaying the mitochondrial release of cytochrome-c, the pro-apoptotic proteins accomplish by stimulating such releases. It is not the total amount, but rather the equilibrium between the pro- and anti-apoptotic proteins that regulate whether apoptosis should be started or not^[16]. Additional apoptotic factors that are released from the mitochondria into the cytosol contains apoptosis-inducing factor (AIF), second mitochondria-derived activator of caspase (SMAC), inhibitor of apoptosis

proteins (IAP), binding protein with low pI (DIABLO) and Omi/high-temperature requirement protein A (HtrA2). The cytoplasmic release of cytochrome c stimulates caspase 3 through the formation of a complex called apoptosome made up of cytochrome c, apoptotic protease activating factor 1 (APAF-1) and caspase 9. Active caspase-9 then activates caspase-3, which continually triggers the remaining of the caspase cascade and resulted in apoptosis^[17]. On the other hand, SMAC/DIABLO or Omi/HtrA2 stimulates caspase activation by binding to inhibitor of apoptosis proteins (IAPs) which then leads to disturbance in the interaction of IAPs with caspase 3 or 9^[16]. The intrinsic and extrinsic apoptotic pathways come together at caspase-3, which splits the inhibitor of the caspase-activated deoxyribonuclease, and the caspase-activated deoxyribonuclease causes nuclear apoptosis. The triggered enzymes cleave regulatory and structural molecules, ending in the death of the cell^[9]. Caspases also disturb the cytoskeletal structure, cell cycle and signaling process, eventually leading to the morphological indicators of apoptosis, for instance, DNA condensation and disintegration, and membrane blebbing^[4]. In early stage of apoptosis, there is expression of phosphatidylserine (PS) in cell membrane, which is overturned from the inside. This lets prompt detection of deceased cells by macrophages, causing phagocytosis without the release of pro-inflammatory mediators^[18].

The equilibrium between pro- and anti-apoptotic pathways comprises a vital role in the control of cell death, and disturbances in the balance between proteins have been associated in increased carcinogenesis by reducing apoptosis in tumor cells^[19,20].

ABNORMAL EXPRESSIONS OF GENES CONTROLLING APOPTOSIS IN CRC

CRC development is defined by the consecutive accumulation of mutations in genes controlling epithelial cell growth and differentiation^[21]. Genomic instability (gene mutations) and epigenetic alterations are the major mechanisms for CRC development^[22]. Approximately 60%-80% of CRC display genomic instability^[23]. In CRC, genomic instability takes several forms each with a different cause including mutations in specific genes that control mitosis, sequential inactivation of tumor-suppressor genes, such as adenomatous polyposis coli (*APC*) (chromosome 5q), *P53* (chromosome 17p), and deleted in CRC (*DCC*), mothers against decapentaplegic homolog 2 (*SMAD2*), and *SMAD4* (chromosome 18q) through numerous changes in chromosomal copy number and structure^[21]. The loss of genomic stability can initiate the evolution of CRC by enabling the acquisition of different cancer-related mutations^[24]. The building up of genomic modifications may bring changes in the level of apoptotic cell death, and many of these genes have been found to control apoptosis. Tumor-suppressor genes and oncogenes genes commonly associated with apoptosis

and CRC development are the tumor suppressor genes: Adenomatous polyposis coli (*APC*), *P53* and the proto-oncogene *Bcl-2*.

ADENOMATOUS POLYPOSIS COLI

Changes in the adenomatous polyposis coli (*APC*) gene have been linked to about 60% of colorectal neoplasia signifying that *APC* mutations may be a central event in the development of colorectal carcinogenesis^[25-27]. *APC* protein is synthesized in normal epithelial cells as they moved towards the uppermost part of the crypt. Interruption of normal *APC* function distracts the equilibrium between new cell development at the bottom of the crypts and cell death at the top of the crypts, promoting the expansion of the descendants of *APC*-mutant cells^[28,29].

The absence of functional *APC* leads to an inappropriately and constitutively activation of the Wnt signaling pathway, thereby promoting colorectal tumor initiation^[30,31]. Stimulation of the Wnt pathway overwhelms the phosphorylation of the onco-protein β -catenin, causing its stabilization and nuclear translocation. β -catenin then cooperates with T-cell factor/lymphocyte enhancer factor (TCF/LEF) to induce expression of Wnt target pro-proliferative and anti-apoptotic genes. In normal cells, where Wnt signaling is controlled, cytoplasmic β -catenin is phosphorylated by the glycogen synthase kinase 3 β (GSK-3 β) within a complex comprising *APC* and Axin, leading to the degradation of β -catenin via the ubiquitin proteasome pathway. The complex also activates transcription of TCF target genes such as c-myc, cyclin-D1, and peroxisome proliferator-activated receptor delta which are known to influence cell proliferation and apoptosis^[32-34]. *APC*, as constituent of this multifaceted complex, not only contributes to the β -catenin degradation but also hinders its nuclear positions, thereby abrogating transcription of Wnt target genes^[35].

P53 GENE

The tumor suppressor gene, *P53* functions to assimilate a diversity of cellular strains into an array of reactions that include apoptosis. Its product attaches to particular sequences in DNA and control transcription of various pro-apoptotic genes such as Bax and the BH3 only proteins puma and noxa^[36]. These genes and proteins inactivate anti apoptotic proteins Bcl-2 and Bcl-xL and cause the release of cytochrome c from mitochondria. *P53* also promotes the synthesis of apoptosis effector proteins such as APAF-1 and caspase 6^[37]. Moreover, *P53* has main components of the extrinsic apoptosis pathway such as the death receptor Fas and DR5 as well as the BH3 only protein Bid that couples the extrinsic pathway to the intrinsic pathway^[38]. Although not adequately investigated, *P53* repress the key inhibitor of apoptosis proteins (*IAP*) gene, which may stop caspase activity. *P53* also blocks survival pathways including the PI3 kinase/AKT survival pathway that neutralize

apoptosis by promoting transcription of the PI₃ kinase inhibitor, phosphatase and tensin homolog (PTEN) and in doing so prevents inhibition of P53 by mouse double minute 2 homolog (MDM2)^[39]. Furthermore, P53 can pledge cell cycle detention, DNA healing, and senescence, besides apoptosis. The P53 protein may possibly also react to DNA injury by activating either growth seizure at G1 or G2 phase of the cell cycle, or automated cell decease. By similar fashion, P53 defend the cells from scheduled to duplicate injured DNA^[37]. Thus, deletion of P53 gene through the CIN pathway is undutiful to cause the transition of adenoma to carcinoma in CRC^[24]. It has also been documented that P53 efficiently affects reactions to chemotherapeutic medications utilized as a part of CRC treatment^[40].

Reports showed that P53 of gene deletions and mutations has been noticed in up to 85% of colorectal tumors and typically occurs throughout the transition from adenoma to adenocarcinoma^[41]. Cells with mal-functional P53 are tolerant to chromosomal instability coming from telomere restriction and have an influential selection benefit. The adenoma/carcinoma shift of CRC is amongst occasions where failure of apoptosis is pivotal in the progression of malignant clones. In contrast, few immune-histochemical studies did not back the main role of mutant P53 protein as an inhibitor of apoptosis in CRC progression^[42].

BCL-2 PROTEINS

As mentioned above, the intrinsic pathway is tightly controlled by Bcl-2 family proteins^[43]. Bcl-2 protein is regularly expressed only in the bottom half of the crypts of the colon, consistent to the stem cell compartment, where Bcl-2 is supposed to defend stem cells from apoptosis^[44]. Most colonic adenomas express Bcl-2 protein at abnormal states all through the neoplastic epithelium while non-neoplastic polyps have regular Bcl-2 expression. In this manner, overexpression of Bcl-2 may contribute to the switch between hyperplastic epithelium and adenomas. Bcl-2 protein expression in colorectal carcinomas is greater than in ordinary mucosa but lesser than in adenomas^[45-47]. On the other hand, tumor necrosis factor (TNF)- α could promote the expression of nuclear factor (NF)- κ B and triggers anti-apoptotic Bcl-2 proteins^[4]. High expression of Bcl-2 leads to resistance to chemotherapeutic drugs and radiation therapy, whereas diminished Bcl-2 expression promotes apoptotic reactions to chemotherapeutic drugs. Furthermore, overexpression of Bcl-2 could lead to gathering of cells in the G0 phase of cell cycle and subsidizing to chemo-resistance^[48]. Additionally, overproduction of Bcl-2 in the intrinsic pathway may perhaps inhibit extrinsic mediated apoptosis. Subsequently, the *Bcl-2* gene could be one of the genes that regulate the occurrence of apoptotic cell death in colorectal neoplasms. Certainly, alterations in the expression of other members of the Bcl-2 proteins has been revealed during evolution of colorectal tumors, such as the anti-apoptotic proteins Bcl-XL, mcl-1 and the

pro-apoptotic protein Bak, that may be more important than Bcl-2^[49].

TARGETING APOPTOSIS PATHWAYS IN CRC TREATMENT

Proper apoptotic signaling is basically central to conserve a healthy balance between cell death and survival and in keeping genome stability^[50]. As a rule, it is thought that the equilibrium between the rates of cell growth and apoptosis sustains intestinal epithelial cell homeostasis, and this stability gets disturbed during cancer expansion^[51,52]. In accordance with this, there is an expanding proof to support the speculation that failure of apoptosis might be an essential component in the expansion of colorectal tumor and its poor response to chemotherapy and radiation.

Interruption of apoptosis causes an irregularity in typical tissue homeostasis by promoting cell development. It additionally permits the survival of hereditarily modified cells, adding to both tumor growth and progression^[53]. Thus, apoptotic pathways can be modified by tumor cells transcriptionally, translationally, and post-translationally. Altogether, these mechanisms are not limited and tumor cells can utilization various strategies to escape apoptosis^[54]. The other explanation behind focusing on apoptosis in the treatment of malignancy depends on the perception that this procedure is dysregulated in tumor cells yet not in ordinary cells^[4]. Tumor cells have acquired blocks to apoptosis but are continually driven to recruit it by genomic and other aberrations. Accordingly, if proapoptotic pathways could be invigorated, these cells would be more helpless to death than ordinary cells^[55].

Researchers are actively searching on a targets in every single defect in the apoptotic pathways to re-establish the apoptotic signaling pathways and eradicate tumor cells^[56]. Study of apoptosis has hinted the basis for novel targeted therapies that can bring death in malignant cells or prepare them to proven cytotoxic agents and radiation therapy^[55]. Consequently, the activation of apoptosis is emerging as a key approach to treat colorectal tumor^[57] and substantial effort has been devoted in isolating pro-apoptotic and apoptotic targets comprising the extrinsic and/or intrinsic pathways with therapeutic potential^[58]. Directed stimulation of the extrinsic pathway by pro-apoptotic receptors, inactivation of Bcl-2 proteins, caspase modulation, and IAP inhibition are amongst these methods.

EXTRINSIC PATHWAY AS A THERAPEUTIC TARGET

Several members of the extrinsic apoptotic pathway hold potential biomarkers and therapeutic targets in colorectal malignancy. The death receptor Fas (CD95), tumor necrosis family receptor (TNFR), and its ligand are assumed to be participated in colorectal tumor progression. Aberrations in these death-signaling

pathways are described in the circumvention of the extrinsic apoptotic pathway. This could be as a result of FasL overexpression in colon cancer cells, that enables these cells to escape cell death by the immune reactions^[59]. The pro-apoptotic Fas ligand possesses strong cytotoxic activity towards various types of tumors cells; despite, hepatotoxic side effects limit its usage. In contrast, activation of the pro-apoptotic receptors DR4 and DR5 by enhanced soluble recombinant human Apo2L/TRAIL (rhApo2L/TRAIL) signifies a better approach, providing effective antitumor activity but marginal cytotoxicity in healthy cells^[55]. Besides, tumor cells that are not amenable to apoptosis induced through FasL are sensitive to Apo2L/TRAIL^[60]. These directed therapies play a key role in cancer therapy by increasing the extent of apoptotic cell death through stimulation of TRAIL receptor. From the candidates, recombinant TRAIL and monoclonal agonist antibodies directed against the TRAIL receptors are highly promising targets^[61]. There are limited studies investigating the role of TRAIL and its receptors DR4 and DR5 as colon cancer biomarkers. In contrast to colorectal tumors and matched normal mucosa, reports indicated that tumor expression of TRAIL is often lesser in normal mucosa^[62,63]. The results of preliminary studies verified the ability of Apo2L/TRAIL to act synergistically with common chemotherapies in a wide variety of malignancies and are especially convincing^[64]. This interaction may be ascribed to the additional activation of the caspase cascade by the extrinsic and intrinsic pathways^[65]. Besides, Apo2L/TRAIL has been found to overcome tumor cell confrontation to chemotherapy in some experimental models^[66] and to work together with chemotherapy even in cells lacking P53. Based on these facts, numerous pro-apoptotic receptor agonists (PARAs) are in clinical trial^[67]. Since the extrinsic pathway activates apoptosis independently, treatments that initiate this mechanism have also the potential to induce cell death in cancers with a variety of responses to common drugs^[57].

INTRINSIC MITOCHONDRIAL PATHWAY AND BCL-2 FAMILY PROTEINS AS A THERAPEUTIC TARGETS

Common cancer treatments seem to trigger apoptosis mainly by the intrinsic pathway, and failure of this pathway could contribute to the development of drug resistance^[68]. So far, approaches targeting the intrinsic apoptosis pathway were focusing on Bcl-2 family proteins^[69]. Bcl-2 was initially qualified as a compelling anticancer target in studies that revealed its capacity to cooperate with the *myc* oncogene in driving B cell lymphomas in mice^[55]. The disequilibrium between pro- and anti-apoptotic Bcl-2 proteins can promote cancer cell survival^[20]. This can be due to an under-expression or over-expression of the pro-apoptotic proteins and anti-apoptotic proteins, respectively, or a combination of both^[70,71]. About 30%-94% of human CRC has been

found to over-express Bcl-2^[72]. Overexpression of anti-apoptotic Bcl-2 family proteins is often correlated with aggressive cancer, recurrence, poor prognosis, and chemo-resistance to cancer therapeutics^[73]. In addition, Bcl-2 and Bax are inversely correlated in colon cancer and over-expression of Bcl-2 in primary CRC specimens is a negative prognostic factor^[72]. Accordingly, these proteins are labeled as exceedingly promising therapeutic targets to design pharmacological manipulation of cell death by inactivating anti-apoptotic Bcl-2 family proteins^[20]. Recent studies found that inactivation of Bcl-2 proteins through small interfering RNAs (siRNAs) caused induction of cell apoptosis and then a decrease in tumor growth. Consequently, several microRNAs such as miR-195, miR-24-2, and miR-365-2 have been identified. These miRNAs regulates Bcl-2 expression, act as negative regulators of Bcl-2 *via* direct binding to the 3'-UTR of the *Bcl-2* gene, showing their therapeutic potentials^[20,74].

An additional approach to improve the response of apoptotic stimuli could be stimulation of pro-apoptotic protein expression. Drugs that simulate the action of the BH3 domain by binding to Bcl-2 like proteins and triggering apoptosis are under investigation^[75]. Both genetic and epigenetic alterations of several pro-apoptotic members of the Bcl-2 family have been described^[20]. Under the physiological condition, the pro-apoptotic and anti-apoptotic members of the Bcl-2 family can cooperate to maintain a dynamic balance. Small molecule inhibitors of Bcl-2 such as HA14-1 or Bcl-2 antisense Oblimersen have been tested in experimental therapy for CRC. Preliminary data suggest that Oblimersen alone only had limited therapeutic efficacy, but this agent can significantly sensitize cancer cells to other therapeutic agents induced apoptosis^[72].

TARGETING P53

Inhibition of P53 is one of common mutations, arising in more than half of tumors, and gives a key resistance machinery that supports these tumor cells to escape apoptosis initiation in response to various injuries caused by common therapies^[68]. P53 serves as a transcription factor controlling downstream genes that have role in stopping cell cycle, DNA reparation, and apoptosis. The main role that P53 plays is shown by the numerous tumors that have mutation in this gene. Impairment of *P53* gene in several tumors resulted in genomic instability, impaired cell cycle control, and inhibition of apoptosis. When DNA damages, P53 keeps the cell at a checkpoint until the damage is reversed. If the damage is permanent, apoptosis is activated^[76]. One of the most crucial roles of P53 is its capacity to activate apoptosis by both transcription-dependent and transcription-independent means. The disturbance of this process can cause tumor progression and chemo-resistance^[20,77].

There are various methods that targets P53 to activate apoptosis, such as targeting P53 family proteins, inactivation of P53-MDM2 contact, returning mutated

P53 back to their normal function, removing mutant P53, producing P53-based vaccines, and gene therapy to repair P53 mutation^[20,78]. The role of P53 is adversely controlled by onco-proteins such as MDM2 (known as HDM2 in humans) and MDMX by an interaction with the P53 transactivation domain (P53TAD)^[20,79]. Hence, one of the key targets for cancer therapy is inactivation of the P53TAD-MDM2/MDMX contact by the small molecule MDM2 antagonist that maintain P53 by avoiding its interaction with MDM2 and selectively brings senescence in tumor cells. Some of these small-molecule MDM2 inhibitors, for example R7112 (Nutlin-3, analogs of cis-imidazole) and JNJ-26854165 (a tryptamine derivative) are now under clinical investigations^[20,80,81].

TARGETING INTRACELLULAR CASPASE INHIBITORS

Since caspases are important initiator and executor of apoptosis, it seems reasonable to consider that impairment in caspase activity could reduce apoptosis and lead to carcinogenesis. Down-regulation of different caspases has been observed in different cancers^[20,82]. Strategies targeting caspase includes modification of intracellular caspase inhibitors, for example, the IAPs and FLICE (FADD-like ICE) inhibitory protein or c-FLIP which are intracellular inhibitors of extrinsic apoptosis signaling. In recent times, compounds that reduce the expression of c-FLIP and sensitize cells to Apo2L/TRAIL-induced apoptosis have been identified^[83].

Overexpression of IAPs has been associated with resistance of cancers to apoptosis^[84]. One of the encouraging anticancer approach comprises the use of small molecules that bind IAPs and stop their inhibitory effect on caspases. On the other hand, small molecule caspase activators that possessed arginine-glycine-aspartate motif decrease the activation threshold of caspase. This initiates auto-activation of procaspase-3, and finally, sensitizes cancer cells to chemotherapeutic agents^[20,85]. Several drugs have been designed to activate caspases. For example, apoptin is a caspase activator agent which employs a tumor-preferential apoptotic action and specifically initiate apoptosis in cancer but not healthy cells^[86]. Polyphenylurea XIAP chelators have been found to overcome the inhibitory effects of XIAP on caspase 3 and 7, promoting apoptosis in wide variety of malignant cells with minimal toxicity to ordinary cells^[11]. In addition, they sensitized tumor cells to apoptosis initiated through cancer drugs or *via* Apo2L/TRAIL. Alternatively, small molecule drugs simulate the effect of Smac by attaching to IAPs and stop their action. Particularly, Smac mimetics can synergize with Apo2L/TRAIL to initiate increased levels of caspase activation and apoptosis^[87].

An additional possibility to deplete IAP expression is through RNA interference (RNAi), which consists of producing and transferring small interfering RNA (siRNA) into tumor cells to avoid the overexpression of IAPs or similar other molecules. Treatment with XIAP siRNA

along with conventional chemotherapy can powerfully reduce XIAP synthesis and initiate cellular apoptosis^[38]. On the other hand, healthy cells are less dependent on IAPs, thus providing an significant advantage for these novel agents^[88].

CONCLUSION

Although non-steroidal anti-inflammatory drugs (NSAIDs) are currently the most widely used agents for chemo-prevention in CRC, the significant toxicity associated with long-term NSAID use, such as gastrointestinal bleeding, limits the complete advantage of NSAID-treatment in high-risk patients^[89]. This obliges the design of nontoxic agents that could initiate apoptosis with minimal toxicity and reduce the opportunity for acquired drug resistance. CRC treatments developed to stimulate apoptosis might play a critical effect in limiting the development and progression of CRC^[90]. As a result, a better understanding of the apoptotic signaling pathways and the instruments by which colorectal tumor cells escape apoptotic death could lead to potent treatment tactics to limit cancer cell growth. Currently, direct activation of the extrinsic pathway by pro-apoptotic receptors, inactivation of Bcl-2 proteins, caspase modification, and IAP inhibition are amongst the promising candidates. Identification of further chemotherapeutic targets that explicitly initiate apoptosis could provide new approaches to prevent colonic tumors. In the future, strategies that use apoptotic pathways will create new effective remedies with minimal toxicity.

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