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**Mechanisms of drug resistance in colon cancer and its therapeutic strategies**

Hu T *et al.* Drug resistance in colon cancer

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**Abstract**

Drug resistance develops in nearly all patients with colon cancer, leading to the decrease of therapeutic efficacies of anticancer agents. This review provides an up-to-date summary on overexpression of ATP-binding cassette (ABC) transporters and evasion of apoptosis, two representatives of transport based and non-transport based mechanisms of drug resistance as well as their therapeutic strategies. Different ABC transporters were found to be up-regulated in colon cancer, which can facilitate the efflux of anticancer drugs out of cancer cells and decrease their therapeutic effects. Inhibition of ABC transporters by suppressing their protein expressions or co-administration of modulators was proved to be an effective approach to sensitize drug-resistant cancer cells to anticancer drugs *in vitro*. On the other hand, evasion of apoptosis observed in drug-resistant cancers also results in drug resistance to anticancer agents especially to apoptosis inducers. Restoration of apoptotic signals by BH3 mimetics or epidermal growth factor receptor inhibitors and inhibition of cancer cell growth by alternative cell death pathways such as autophagy are effective means to treat such resistant cancer type. Given that the drug resistance mechanisms are different among colon cancer patients and may change even in a single patient at different stages, personalized and specific combination therapy is supposed to be more effective and safer for the reversal of drug resistance in clinics.

**Key words:** Colon cancer; Drug resistance; ATP-binding cassette transporters; Evasion of apoptosis; Autophagy

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**Core tip:** Drug resistance in colon cancer is still an obstacle to successful chemotherapy**.** This review focuses on overexpression of ATP-binding cassette transporters and evasion of apoptosis, two representatives of transport based and non-transport based mechanisms of drug resistance as well as their therapeutic strategies. Given that the drug resistance mechanisms are different among colon cancer patients and may change even in a single patient at different stages, personalized and specific combination therapy is supposed to be more effective and safer for the reversal of drug resistance in clinics.

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**INTRODUCTION**

Colon cancer, a disease during which malignant tumors form in the tissues of colon, is the third most frequently diagnosed cancer and one of the leading causes of cancer-related deaths in the world[[1-3](#_ENREF_1)]. Currently, surgery and chemotherapy are the two main treatment options for colon cancer, depending on the cancer stages and tumor location at diagnosis as well as individual characteristics of the patients[[4](#_ENREF_4)]. Generally, chemotherapy can be used at different stages during the treatment and is often given after surgery as an adjuvant therapy for patients with advanced colon cancer. It is also used before surgery as neoadjuvant chemotherapy to shrink the tumor before removal[[5](#_ENREF_5)]. Due to the availability of various chemotherapy regimens, the overall survival of patients with advanced colon cancer has been improved over the past decades. However, even though the response rate to current systemic chemotherapies is up to 50%, drug resistance developed in nearly all patients with colon cancer limits the therapeutic efficacies of anticancer agents and finally leads to chemotherapy failure[[6](#_ENREF_6)].

Drug resistance is the reduction in effectiveness of drugs including antibiotics, antiviral and chemotherapeutic agents during the treatment of various diseases[[7](#_ENREF_7)]. Cancer drug resistance has been extensively investigated since the discovery of a novel type of resistance correlated with P-glycoprotein (P-gp) in several Chinese hamster ovary cell lines in 1976[[8](#_ENREF_8)]. It refers to the resistance to a variety of structurally and functionally unrelated chemotherapeutic agents after exposure to a single cytotoxic compound. Till now, multidrug resistance in cancer is still an obstacle to successful chemotherapy[[9](#_ENREF_9)]. In fact, most of the cancer-related deaths are due to chemotherapy failure caused by drug resistance that occurs during the course of cancer progression and chemotherapy. Thus, investigation on the mechanisms of drug resistance and their reversal strategies plays an important role in the success of cancer chemotherapy.

A number of underlying mechanisms conferring drug resistance have been described in the past decades, which were broadly classified into two categories: the non-cellular and cellular resistance mechanisms. Non-cellular mechanisms refer to the extracellular factors such as limited vascular accessibility and tumor microenvironment[[10](#_ENREF_10)]. Cellular mechanisms, on the other hand, are mainly concerned with the drug targets, enzymes and transport systems inside the cancer cells[[11](#_ENREF_11)], which are further divided into two categories: classical/transport based and non-classical/non-transport based mechanisms[[11](#_ENREF_11)]. Since the experimental models can be easily generated by *in vitro* selection with cytotoxic compounds, cellular mechanisms of drug resistance in cancer have been intensively studied so far[[12](#_ENREF_12)]. Given the accumulating literature regarding this field, the present review will focus on cellular mechanisms of drug resistance in colon cancer and its reversal strategies, with an emphasis on the overexpression of drug efflux transporters and evasion of apoptosis, two representatives of transport based and non-transport based cellular mechanisms, respectively.

**TRANSPORT BASED CELLULAR MECHANISMS**

The transport based cellular mechanisms of drug resistance mainly refer to the efflux of drugs out of cancer cells through a variety of membrane transporters, thereby leading to decreased intracellular accumulation of anticancer drugs and chemotherapy failure. Membrane transporters are a group of membrane associated proteins that control the transport of their substrates into and out of the cells[[13](#_ENREF_13)]. To date, more than 400 membrane transporters have been annotated in the human genome, and they are divided into two major superfamilies: ATP-binding cassette (ABC) and solute carrier (SLC) transporters. Representative ABC transporters include P-gp, breast cancer resistant protein (BCRP) and multidrug resistance-associated proteins (MRPs). Whereas transporters such as organic anion transporters, organic cation transporters and organic anion transporting polypeptides belong to the SLC superfamily[[13](#_ENREF_13),[14](#_ENREF_14)]. In fact, the most commonly observed mechanism conferring drug resistance in cancer cells is the overexpression of ABC transporters on plasma membrane[[15](#_ENREF_15)].

***ABC transporters***

The ABC transporter superfamily includes a number of transporters located on the cellular plasma membrane that mediate the efflux of endogenous and exogenous substances using energy provided by ATP hydrolysis[[13](#_ENREF_13)]. There are at least 48 known human ABC transporters. Based on their amino acid sequences, they are grouped into 7 subfamilies designated A though G[[13](#_ENREF_13)]. It has been recognized that several members of three ABC subfamilies, in particular P-gp of the ABCB subfamily, MRP1 of the ABCC subfamily and BCRP of the ABCG subfamily, play pivotal roles in the transport of anticancer drugs out of cells as well as in the development of drug resistance.

P-gp, a 170 kDa protein encoded by human *ABCB1* gene, is one of the most well characterized ABC transporters. As an ATP-dependent drug efflux pump, the functional unit of P-gp consists of two nucleotide-binding domains (NBDs) and two transmembrane domains (TMDs) containing 12 (2 × 6) membrane-spanning alpha helices (Figure 1)[[16](#_ENREF_16)]. The two NBDs form a common binding site where the energy of ATP is harvested to promote the efflux of substrates through a pore that is delineated by the transmembrane helices[[17](#_ENREF_17)]. P-gp preferentially transports relatively large, lipophilic and positively charged molecules[[13](#_ENREF_13)]. The 190 kDa MRP1, encoded by *ABCC1* in humans, has a P-gp like core structure containing two NBDs and two TMDs, and an additional third TMD (TMD0) with 5 predicted transmembrane segments and an extra N-terminus (Figure 1)[[18](#_ENREF_18)]. Generally, the substrates of MRP1 are unconjugated and conjugated organic anions. The conjugation of drugs with glutathione, glucuronate, phosphate or sulfate by phase II drug-metabolizing enzymes usually makes them better substrates of MRP1[[13](#_ENREF_13)]. Different from P-gp and MRP1, however, BCRP is a 72-kDa "half transporter" encoded by *ABCG2* in humans, consisting of only one NBD and one TMD (Figure 1)[[19](#_ENREF_19)]. BCRP also transports a broad range of endogenous and exogenous substrates across cellular plasma membrane[[13](#_ENREF_13)].

Physiologically, ABC transporters are expressed in important biological barriers in the body such as small intestine, liver, kidney, blood-brain barrier, choroid plexus, testis and placenta, functioning to pump their substrates out of the cells and protecting the body against endogenous toxins and xenobiotics[[13](#_ENREF_13)]. These biological barriers are also important tissues involved in the disposition of various drugs in the body. Thus, from a pharmacokinetic point of view, ABC transporters play pivotal roles in the absorption, distribution and excretion of anticancer drugs, and thereby affect their efficacy and safety profiles.

***Overexpression of ABC transporters in cancer cells***

In addition to their physiological roles in host detoxification and pharmacokinetics, dysregulation of ABC transporters is associated with a variety of diseases. ABC transporters in particular the P-gp, MRP1 and BCRP have been reported to be up-regulated in different tumors and overexpressed in various cancer cells cultured under specific microenvironments such as insult by different cytotoxic agents[[20-22](#_ENREF_20)].

The involvement of P-gp in clinical tumors has been extensively characterized. Approximately 50% of human cancers express P-gp at levels sufficient to confer drug resistance[[23](#_ENREF_23)]. Colon cancer is insensitive to most chemotherapeutic agents from the beginning of therapy. Indeed, high expression of P-gp has been observed at the time of colon cancer diagnosis, which is associated with the intrinsic resistance of various colon cancer cell lines to anticancer drugs derived from natural products[[24-26](#_ENREF_24)]. P-gp expression is also inducible by chemotherapeutic agents in cancer cells. For instance, its expression level was up-regulated by 5 folds in Caco-2 cells after chronic exposure to imatinib[[27](#_ENREF_27)]. Using HCT15 colon cancer cells, nuclear factor- kappaB (NF-ĸB) activation was reported to induce P-gp expression, and inhibition of NF-ĸB or P-gp increased the level of apoptosis induced by daunomycin[[28](#_ENREF_28)]. Hypoxia-inducible factor-1α (HIF-1α) was also reported to be associated with the expression of P-gp in human colon carcinoma tissues and colon cell lines including HCT116, HT29, LoVo and SW480[[29](#_ENREF_29)]. Downregulation of P-gp by HIF-1α inhibition reversed the drug resistance in LoVo multicellular spheroids[[30](#_ENREF_30)]. Besides, suppression of P-gp via inhibition of transient receptor potential channel 5 also reversed the resistance of human colon cancer HCT8 and LoVo cells to 5-fluorouracil (5-FU), the first-line drug used for colon cancer therapy[[31](#_ENREF_31)]. Thus, multiple signaling pathways are involved in the regulation of P-gp in cancer cells.

Increased expression of MRP1 also occurs early in the colorectal carcinogenesis in humans[[32](#_ENREF_32)]. Upregulation of MRP1 was found during the development of drug resistance in colon cancer cells HT29[[33](#_ENREF_33)]. Besides, MRP1 and MRP3 were induced by nonsteroidal anti-inflammatory drugs (NSAIDs) in human colon cancer cells HCT15, HT29 and HCA7[[34](#_ENREF_34)]. The activities of MRP1 and BCRP were increased in HT29 cells treated with hypericin and in turn affected the accumulation of hypericin in cancer cells[[35](#_ENREF_35)]. Like P-gp, MRP1 gene can also be induced by HIF-1α in LoVo cells[[36](#_ENREF_36)]. The induction of MRP1 gene expression by interleukin-1beta in HT29 cells was related to nitric oxide related signaling pathways[[37](#_ENREF_37)].

Induction of BCRP was also observed during the acquirement of resistance to anticancer drugs. In fact, it was cloned from human colon carcinoma cells S1-M1-80 after selection with mitoxantrone[[38](#_ENREF_38)]. Dramatically overexpressed BCRP mRNA was also detected in HT29 cells selected with mitoxantrone[[39](#_ENREF_39)]. The resistance of HT29 cells to doxorubicin was also mediated by elevated BCRP expression, which was associated with c-MET/PI3K signaling[[40](#_ENREF_40)]. In Caco-2 cells after chronic exposure to imatinib, BCRP expression was found to be up-regulated by 17 folds[[27](#_ENREF_27)]. The mRNA expression of BCRP in SW1116 cells resistant to hydroxycamptothecin, a topoisomerase I inhibitor, was 200 folds higher than its level in the parental SW1116 cells[[41](#_ENREF_41)]. Upregulation of MRP2 and BCRP was also involved in the cisplatin-induced drug resistance in colon cancer cells Caco-2 and LS174T[[42](#_ENREF_42)]. In HCT8 cells with BCRP expression, the intracellular accumulation of CI1033, a tyrosine kinase inhibitor and BCRP substrate, was reduced. By inhibition of BCRP-mediated drug efflux, CI1033 enhanced the cytotoxicities of SN-38 and topotecan in HCT8 cells[[43](#_ENREF_43)]. Besides, expression of P-gp and BCRP was significantly higher in side population (SP) colon cancer cells than non-SP cells, which confers the higher resistance of SP cells to 5-FU and irinotecan[[44](#_ENREF_44)].

Besides P-gp, MRP1 and BCRP, several other ABC transporters could also be induced by anticancer drugs in colon cancer cells and play roles in the drug resistance. For instance, ABCB5 expression was substantially increased in clinical colorectal cancers after 5-FU-based chemotherapy and contributed to the resistance to 5-FU[[45](#_ENREF_45)]. Based on an analysis of 45 patients, MRP2 was reported to be important for the resistance of colon cancer to cisplatin treatment[[46](#_ENREF_46)], and its level was also increased in SW620 and LoVo cells selected by oxaliplatin[[20](#_ENREF_20)]. MRP4 and MRP5 were also induced in WiDr and COLO-205 cells treated with celecoxib at a clinically relevant concentration[[47](#_ENREF_47)]. Taken together, these findings suggest that overexpression of ABC transporters could be induced by various anticancer drugs and ABC transporters contribute to both intrinsic and acquired drug resistance in colon cancer.

As shown in Figure 2, the overexpression of ABC transporters can facilitate the efflux of their substrate anticancer drugs out of cancer cells, which consequently decreases the drug intracellular concentrations and therapeutic effects, giving rise to drug resistance[[48](#_ENREF_48)]. So far, a number of clinically used anticancer drugs have been identified as the substrates of ABC transporters. A non-exhaustive list is shown in Table 1. Some of the anticancer drugs such as 5-FU, oxaliplatin and irinotecan are often used alone or as combination therapy for the treatment of advanced colon cancer. Thus, efflux of these drugs by ABC transporters can decrease their therapeutic efficacies for colon cancer. In terms of the transport of chemotherapeutic agents, of note, the substrate specificity of ABC transporters overlaps extensively, which increases the barrier function of these efflux transporters and makes the chemotherapy of drug resistant cancer more difficult.

***Modulation of ABC transporters to reverse drug resistance***

Given that overexpression of ABC transporters is one of the most commonly observed mechanisms contributing to drug resistance in cancer cells, inhibition of these transporters is supposed to be an effective approach to sensitize drug resistant cancer cells to chemotherapeutic agents[[15](#_ENREF_15)]. One method to suppress the ABC transporters is to regulate their expression levels. Different antisense oligonucleotides, ribozymes and small interfering RNAs have been reported to successfully reduce the expression levels of ABC transporters and reverse the drug resistance in cancer cells overexpressing these transporters[[49-53](#_ENREF_49)]. Besides the regulation of protein expression, another important method to inhibit ABC transporters is the co-administration of their inhibitors, of which the P-gp inhibitors will be discussed in detail in this review.

Since the discovery of P-gp inhibition by verapamil in 1981, at least three generations of P-gp inhibitors have been identified[[54](#_ENREF_54)]. The first generation P-gp inhibitors including quinidine, verapamil and cyclosporine A have relatively low affinity for P-gp, which requires the treatment of high doses and leads to severe side effects when co-administrated with anticancer drugs[[54](#_ENREF_54)]. Most of the second generation P-gp inhibitors are derivatives of the first-generation modulators, such as dexverapamil, valspodar and biricodar. As compared with the first generation, the second generation inhibitors are more specific for P-gp, with greater potency and less toxicity. However, they also inhibit the metabolism and excretion of co-administrated drugs, resulting in unpredictable pharmacokinetic interactions[[54](#_ENREF_54)]. To overcome this drawback, the third generation of P-gp inhibitors was investigated, most of which have been developed by combinatorial chemistry. Some representatives include tariquidar, zosuquidar and laniquidar, and a number of new tariquidar derivatives have also showed potent inhibition on P-gp in cell-based studies[[55](#_ENREF_55)]. They are more specific for P-gp without affecting the activity of cytochrome P450 enzymes[[54](#_ENREF_54), [56](#_ENREF_56)].

All three generations of P-gp inhibitors have been reported to dramatically sensitize various drug-resistant cancer cells to the known P-gp substrate anticancer drugs *in vitro*[[57](#_ENREF_57)]. Some of them, such as verapamil, cyclosporine A, dexverapamil, valspodar and tariquidar have also been studied as chemosensitizers in clinical trials[[58-62](#_ENREF_58)]. However, so far none of them has been used in clinics because of undesirable drawbacks including poor selectivity, low potency, high toxicity and unpredictable pharmacokinetic interactions[[54](#_ENREF_54)]. In order to develop novel P-gp inhibitors with good safety and efficacy profiles, nowadays, a lot of research work is focused on the natural products and subsequent structural modifications, owing to their versatile applications and relatively low toxicities[[63](#_ENREF_63)].

The P-gp modulators from natural products belong to the fourth generation of P-gp inhibitors[[64](#_ENREF_64)]. In fact, more than 70% of the inhibitors reported in the last decade were natural products and their synthetic derivatives[[65](#_ENREF_65)]. Some of them were able to sensitize the drug-resistant colon cancer cells. For instance, cryptotanshinone and dihydrotanshinone, the two tanshinones from *Salvia miltiorrhiza*, were reported to inhibit P-gp function and enhance the cytotoxicities of doxorubicin and irinotecan in SW620 Ad300 cells overexpressing P-gp[[66](#_ENREF_66)]. Sipholenol A, a marine-derived triterpene, also specifically reversed P-gp-mediated drug resistance in SW620 Ad300 cells[[67](#_ENREF_67)]. Using *in situ* cancerous colon perfusion model in rat, curcumin was showed to increase the permeability of irinotecan via inhibition of P-gp function[[68](#_ENREF_68)].

In addition to P-gp inhibitors, modulators of other ABC transporters have also been identified and showed ability to sensitize drug-resistant cancer cells. Selective inhibitors of P-gp, MRP1 and BCRP are summarized in Table 1. However, most of the current findings were obtained from cell-basedstudies, and the *in vivo* effects of these potential candidates have not been well investigated[[69](#_ENREF_69)]. Thus, pre-clinical and clinical trials including both pharmacodynamic and pharmacokinetic studies should be carried out for their further development as chemosensitizers. Nevertheless, the development of novel inhibitors of ABC transporters is an important approach to overcome drug resistance in various cancers including colon cancer.

**NON-TRANSPORT BASED MECHANISMS**

The non-transport based mechanisms of drug resistance are often associated with altered activities of specific enzymes and alterations in various cell death signaling pathways. For instance, overexpression of glutathione S-transfereases (GSTs), the phase II metabolic enzymes involved in drug metabolism, can facilitate the anticancer drug detoxification in cancer cells and decrease their therapeutic effects[[70](#_ENREF_70),[71](#_ENREF_71)]. Downregulation of topoisomerases, enzymes that regulate the process of DNA replication, can also cause drug resistance of cancer cells to the anticancer drugs such as doxorubicin and etoposide[[72](#_ENREF_72)]. In addition to the change of enzymes, another important non-transport based mechanism of drug resistance is the alterations in cell death signaling pathways, in particular apoptosis, the type I programmed cell death[[73](#_ENREF_73)]. This type of drug resistance develops with the overexpression of proteins that inhibit cell death and/or with the loss of proteins required for cell death[[74-76](#_ENREF_74)]. Most of the conventional anticancer drugs such as doxorubicin, cisplatin, oxaliplatin and cyclophosphamide are apoptosis inducers[[77](#_ENREF_77)], therefore, defects in the apoptotic signaling pathways could protect cancer cells from this type of programmed cell death, leading to drug resistance to chemotherapy in clinics.

***Programmed cell death: apoptosis and autophagy***

Programmed cell death, which has been recognized since the 1960s, is any type of cell death in which the cell uses specialized intracellular machinery to kill itself[[78](#_ENREF_78)]. Apoptosis, the best-described type of programmed cell death, is triggered by different extracellular and intracellular [signals](http://en.wikipedia.org/wiki/Cell_signalling) and characterized by cell shrinkage, chromatin condensation, DNA laddering and nuclear fragmentation[[79](#_ENREF_79)]. The extracellular signals include [hormones](http://en.wikipedia.org/wiki/Hormone), [nitric oxide](http://en.wikipedia.org/wiki/Nitric_oxide), [growth factors](http://en.wikipedia.org/wiki/Growth_factor), [cytokines](http://en.wikipedia.org/wiki/Cytokine), [toxins](http://en.wikipedia.org/wiki/Toxin) and chemotherapeutic agents. Whereas the intracellular apoptotic signals are often initiated in response to various stresses, such as radiation, heat, hypoxia, viral infection, nutrient deprivation and increased intracellular calcium concentration[[79](#_ENREF_79)]. Through elimination of damaged, unnecessary and old cells, apoptosis plays an important role in the body growth and development as well as in maintaining the health of the body. Impaired apoptosis is involved in a diverse range of diseases such as viral infections, inflammatory diseases, autoimmune diseases and cancers[[80](#_ENREF_80),[81](#_ENREF_81)].

Macroautophagy (hereafter referred to as autophagy), type II programmed cell death, is characterized by the degradation of cellular components including Golgi apparatus, mitochondria, polyribosomes and endoplasmic reticulum as well as the formation of numerous autophagosomes[[82](#_ENREF_82)]. Autophagy is activated in response to stressful stimuli, including starvation, hypoxia and high temperature or intracellular stress such as damaged organelles and mutant proteins. During the cellular process of autophagy, the redundant, damaged or aged organelles and cells are sequestered, degraded and recycled[[83](#_ENREF_83)]. One important function of autophagy is to overcome stress conditions and keep cellular homeostasis. Conversely, excessive activation of autophagy may lead to cell death by destroying major proportions of the cytoplasm[[84](#_ENREF_84)]. Impaired autophagy is also involved in various diseases including neurodegeneration, cardiovascular diseases, autoimmune diseases, aging, rheumatoid arthritis, infection and cancers[[85](#_ENREF_85)]. Currently, the role of autophagy in tumorigenesis is still controversial. Autophagy can promote the survival of rapidly growing cancer cells by targeting damaged or aged organelles for degradation and recycle. On the other hand, its death-promoting effect may lead to growth inhibition of cancer cells and suppress tumorigenesis[[86](#_ENREF_86)]. As a double-edged sword in cancer, the function of autophagy may differ at different stages of cancers[[87](#_ENREF_87)].

***Evasion of apoptosis in cancer cells***

Evasion of apoptosis, one of the hallmarks of human cancers, contributes to carcinogenesis, tumor progression as well as drug resistance in cancer[[73](#_ENREF_73)]. Indeed, suppression of apoptosis has been observed in drug resistant cancer cells, leading to drug resistance to chemotherapeutic agents especially to apoptosis inducers[[88](#_ENREF_88),[89](#_ENREF_89)]. Resistance to apoptosis in cancer cells is often associated with increased expression of anti-apoptotic genes and proteins as well as decreased expression of pro-apoptotic genes and proteins (Figure 2)[[90](#_ENREF_90)]. For instance, Bcl-2, Bcl-XL, Mcl-1 and X-linked inhibitor of apoptosis protein (XIAP) have been found to be overexpressed in various cancers, whereas p53, Bax, Bim, p53 upregulated modulator of apoptosis (PUMA), apoptotic protease activating factor 1 (APAF1) are mutated or suppressed[[90](#_ENREF_90)]. Indeed, in colon cancer SW620 Ad300 cells overexpressing P-gp, which were selected by doxorubicin and resistant to apoptosis, Bcl-2 protein level was significantly up-regulated when compared with the parental SW620 cells, whereas Bax and p53 levels were down-regulated[[91](#_ENREF_91)]. Loss of Bax expression was found to reduce the sensitivity of colon cancer cells HCT116 to apoptosis induced by 5-FU and oxaliplatin[[92](#_ENREF_92)]. Besides, epidermal growth factor receptor (EGFR), a protein tyrosine kinase, was also overexpressed in colorectal tumors[[93](#_ENREF_93)]. Through its regulation on anti-apoptotic signaling pathways including PI3K/Akt and STATs (signal transducers and activators of transcription), overexpression of EGFR also contributes to the resistance of cancer cells to apoptosis (Figure 2)[[94](#_ENREF_94),[95](#_ENREF_95)]. Nevertheless, these altered genes and proteins are potential targets for the development of novel anticancer drugs and successful chemotherapy for cancers resistant to apoptosis.

As the most frequently mutant gene in cancer, tumor suppressor p53 plays a pivotal role in the regulation of apoptosis and in the protection of the body against cancer. The p53 protein is a transcriptional factor activated and stabilized by post-translational modifications following DNA damage (Figure 2)[[96](#_ENREF_96)]. Usually, p53 executes its function through the transactivation of target genes that are mainly involved in the regulation of cell cycle arrest and apoptosis[[97](#_ENREF_97),[98](#_ENREF_98)]. When DNA is slightly damaged, activation of p53 results in G1 phase cell cycle arrest by targeting p21 and the subsequent inhibition of cyclin-dependent kinases, to allow DNA repair to proceed. However, if DNA damage is severe and cannot be repaired successfully, p53 triggers apoptosis through targeting Bax, which is essential for the mitochondrial outer membrane permeabilization, cytochrome c release and caspase activation[[99](#_ENREF_99)]. In addition, anti-apoptotic protein Bcl-2 is also suppressed by wild-type p53, its down-regulation by p53 also promotes apoptosis[[100](#_ENREF_100)].

The mutation of p53 has been found in more than 50% of all types of human cancers[[101](#_ENREF_101)]. In fact, loss of p53 function was found in approximately 80% of colorectal cancers[[102](#_ENREF_102)]. The majority (> 75% in colorectal carcinomas) of the mutations are missense mutations consisting of single amino acid substitutions, which affect the responses of cancer cells to chemotherapeutic agents[[103](#_ENREF_103)]. In contrast to wild-type p53, mutant p53 attenuates its pro-apoptotic function and inhibits wild-type p53 function. As a result, the suppression or loss of wild-type p53 function could decrease the sensitivity of cancer cells to DNA-damaging agents and facilitate the evasion of p53-mediated apoptosis (Figure 2)[[104](#_ENREF_104)]. Although the apoptotic signaling pathways are not totally inactivated in p53 mutant cancer cells, the cells become insensitive to DNA damage, thereby increasing the threshold required for DNA damage to activate apoptosis and finally giving rise to drug resistance to apoptosis inducers[[105](#_ENREF_105)].

Accumulating evidence has demonstrated that p53 mutant or null cancer cells tend to be more resistant to a range of cytotoxic drugs including DNA crosslinking agents, antimitotic agents, antimetabolites and topoisomerase I/II inhibitors, as compared with their respective p53 wild-type cells[[106](#_ENREF_106),[107](#_ENREF_107)]. It has been reported that apoptosis induced by 5-FU and oxaliplatin was significantly reduced in p53 mutant HCT116 cells, when compared with the p53 wild-type cells[[108](#_ENREF_108)]. Disruption of p53 function also led to the resistance of human colon cancer cells to 5-FU both *in vitro* and in xenograft tumors in nude mice[[109](#_ENREF_109)]. Besides, clinical study showed that colorectal tumors with mutant p53 had a weak or no response to 5-FU treatment, and patients with wild-type p53 colorectal tumors had longer survival than those with mutant p53 tumors[[110](#_ENREF_110)]. Of note, the extent of resistance for different agents is different, partly depending on the cancer cell lines, the *p53* gene status and the mechanisms of action of the agents[[107](#_ENREF_107)]. For instance, the sensitivity of colon cancer cells to irinotecan is independent of p53 status in xeno-transplanted colorectal tumors[[111](#_ENREF_111)].

***Strategies to overcome resistance to apoptosis***

Since apoptosis is suppressed in drug resistant cancer cells, restoration of apoptotic signals and inhibition of cancer cell growth by alternative cell death pathways are supposed to be effective means to treat such resistant cancers.

To restore the impaired apoptotic signals in cancer cells, BH3 mimetics, small molecules that mimic the BH3-only proteins by inserting their BH3 domain into the hydrophobic groove of the Bcl-2 proteins, were developed to inhibit the function of Bcl-2 proteins and induce apoptosis[[112](#_ENREF_112)]. A number of BH3 mimetics were reported to induce apoptosis and sensitize the apoptosis-resistant colon cancer cells to anticancer drugs. For example, combination treatment of carfilzomib and ABT-263, a BH3 mimetic, synergistically enhanced apoptosis in colon cancer cells with mutant *KRAS*-mediated apoptosis resistance[[113](#_ENREF_113)]. Another BH3 mimetic obatoclax was shown to reduce HIF-1α level in colon cancer cells HT29, HCT8 and HCT116 and sensitize the hypoxic cells to apoptosis induced by 5-FU[[114](#_ENREF_114)]. BH3 mimetic ABT-737 could overcome resistance to immunotoxin-mediated apoptosis in colon cancer DLD1 cells. It also increased the level of apoptosis in suspended SW480 cells and sensitized the metastatic SW620 cells to anoikis[[115](#_ENREF_115),[116](#_ENREF_116)]. In addition to BH3 mimetics, EGFR tyrosine kinase inhibitors are also used to restore the apoptosis function in cancer cells. Some inhibitors including cetuximab and panitumumab have already been approved by FDA for the treatment of advanced colon cancer as monotherapy or adjuvant therapy. Combination treatment of irinotecan with cetuximab could overcome resistance to irinotecan through abrogating drug efflux, restoring apoptosis and impairing DNA-repair activity[[117](#_ENREF_117)]. This combination of treatment was also used to treat patients with metastatic colorectal cancer resistant to fluoropyrimidine and oxaliplatin[[118](#_ENREF_118)]. A list of BH3 mimetics and EGFR inhibitors with the activity to restore apoptotic signals is presented in Table 2.

In terms of alternative cell death pathways, despite that autophagy can protect cancer cells against apoptosis in response to chemotherapy, it can also lead to cell death in cancer cells especially in the apoptosis-resistant cancer cells[[119](#_ENREF_119)]. The pro-cell death function of autophagy suggests that treatment of autophagy inducers may be a novel therapeutic approach to overcome resistance to apoptosis in cancer cells. As reported, DNA-alkylating agent temozolomide and rapamycin, an inhibitor of the mammalian target of rapamycin, induced autophagy but not apoptosis in malignant glioma cells that highly express Bcl-2[[120](#_ENREF_120),[121](#_ENREF_121)]. Histone deacetylase inhibitors sodium butyrate and suberoylanilide hydroxamic acid induced autophagy in HeLa cervical cancer cells overexpressing Bcl-XL, but induced apoptosis in parental HeLa cells[[122](#_ENREF_122),[123](#_ENREF_123)]. Cryptotanshinone and dihydrotanshinone also induced more autophagic cell death in apoptosis-resistant colon cancer cells than that in the parental cancer cells[[91](#_ENREF_91)]. In addition, a number of structurally different natural products such as curcumin, resveratrol, paclitaxel and quercetin have been shown to activate autophagic signaling pathways and cause cell death in various cancer cell lines including colon cancer cells (Table 2)[[124-127](#_ENREF_124)]. Thus, through the induction of type II programmed cell death, autophagy inducers may be further developed for sensitizing the apoptosis-resistant cancer cells to chemotherapy.

As cancer cells with mutant p53 generally have greater resistance to chemotherapy than those with wild-type p53, cytotoxic agents that kill cancer cells p53-independently should be promising candidates to overcome drug resistance caused by p53 mutations. It has been reported that natural products such as triptolide, resveratrol and dihydrotanshinone could inhibit cell proliferation and induce p53-independent apoptosis in different cancer cell lines especially in p53-deficient cancer cells (Table 2)[[127-129](#_ENREF_127)]. Hence, the apoptosis-resistant cancer cells with mutant p53 should be relatively sensitive to this kind of cytotoxic agents in terms of cell death.

Taken together, agents including BH3 mimetics and EGFR inhibitors can restore the apoptotic signaling pathways in colon cancer cells. They are effective drugs to sensitize apoptosis-resistant cancers to apoptosis induced by anticancer drugs. Moreover, pharmacological compounds that can induce autophagic cell death or p53-independent cytotoxicity are also promising candidates to overcome resistance of colon cancer cells to apoptosis.

**Conclusion**

Combination treatments of conventional anticancer drugs with inhibitors of ABC transporters, BH3 mimetics, EGFR inhibitors or autophagy inducers were proved to be the effective approaches for the circumvention of drug resistance in colon cancer in pre-clinical studies. A few agents such as cetuximab and panitumumab have been successfully approved as drugs for colon cancer therapy in clinics. However, most of the combination of treatments failed to reverse drug resistance in clinical studies, suggesting that targeting a single mechanism is not sufficient to reverse drug resistance in patients with cancer.

Of note, polymorphisms in genes related to drug resistance including *ABCB1*, *ABCC1*, *ABCG2* and *TP53* have been recognized[[130](#_ENREF_130),[131](#_ENREF_131)], leading to the interindividual differences in tumorigenesis, drug resistance mechanisms and outcome of treatments. Besides, as the defense mechanism of cancer cells, drug resistance keeps developing during tumorigenesis and drug treatments. Thus, the mechanisms of drug resistance may vary at different cancer stages as well as at different phases of therapies. Given that the mechanisms of drug resistance are different among cancer patients and may change even in a single patient during the progression of cancer, personalized and specific combination therapy should be more effective and safer for the reversal of drug resistance in clinics.

In summary, drug resistance in colon cancer is still an obstacle to successful chemotherapy and novel therapeutic strategies are urgently needed. Hence, investigation on the underlying mechanisms conferring drug resistance as well as development of safe and effective reversing agents by targeting these mechanisms play a pivotal role in the successful chemotherapy for colon cancer.

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**Figure 1 Schematic model of ATP-binding cassette transporters P-gp, MRP1 and BCRP.** The functional unit of P-gp consists of two NBDs and two TMDs containing 12 (2 × 6) membrane-spanning alpha helices. MRP1 also has a core structure containing two NBDs and two TMDs. Besides, it still has a third TMD (TMD0) with 5 predicted transmembrane segments and an extra N-terminus. BCRP is a "half transporter" consisting of only one NBD and one TMD. TMD: transmembrane domain; NBD: nucleotide-binding domain; P-gp: P-glycoprotein; MRP1: multidrug resistance-associated protein 1; BCRP: breast cancer resistant protein; TMDs: transmembrane domains.



**Figure 2 Overexpression of ATP-binding cassette transporters and evasion of apoptosis confer drug resistance in cancer.** Overexpression of ABC transporters on the plasma membrane, a transport based cellular mechanism of drug resistance, can mediate the efflux of their substrate anticancer drugs out of cancer cells, and decrease their intracellular accumulation and therapeutic efficacies. On the other hand, evasion of apoptosis, a non-transport based cellular mechanism of drug resistance, also leads to the resistance of cancer cells to therapeutic agents in particular apoptosis inducers. Generally, DNA damage caused by anticancer drugs activates p53, which triggers apoptosis through targeting Bax. p53 also suppresses anti-apoptotic protein Bcl-2 and promotes apoptosis. However, anti-apoptotic proteins such as Bcl-2 and Mcl-1 are overexpressed in various cancers, whereas pro-apoptotic proteins including p53, Bax and Bim are mutated or suppressed. The alterations of these proteins decrease the sensitivity of cancer cells to DNA-damaging agents and lead to their resistance to apoptosis. Besides, protein tyrosine kinase EGFR is also overexpressed in tumors, through its regulation on anti-apoptotic signaling pathways, including PI3K/Akt and STATs, overexpression of EGFR also contributes to the resistance of cancer cells to apoptosis. EGFR: epidermal growth factor receptor; STAT: signal transducers and activators of transcription; ABC: ATP-binding cassette.

**Table 1 Selective anticancer drug substrates and inhibitors of ATP-binding cassette transporters P-gp, MRP1 and BCRP**

|  |  |  |  |
| --- | --- | --- | --- |
| **Transporters** | **Anticancer drug substrates** | **Inhibitors** | **Ref.** |
| P-gp(*ABCB1*) | Actinomycin D, bisantrene, colchicine, daunorubicin, dasatinib, docetaxel, doxorubicin, epirubicin, etoposide, imatinib, irinotecan, mitoxantrone, nilotinib, paclitaxel, saquinivir, teniposide, topotecan, vinblastine, vincristine, vindesine, vinorelbine | Biricodar, chloroquine, cryptotanshinone, curcumin, cyclosporin A, dexverapamil, dihydrotanshinone, dofequidar, laniquidar, nifedipine, quinidine, sipholenol A, tamoxifen, tariquidar, valspodar, verapamil, zosuquidar | [[12](#_ENREF_12),[66-68](#_ENREF_66),[132](#_ENREF_132),[133](#_ENREF_133)] |
| MRP1(*ABCC1*) | Colchicine, doxorubicin, etoposide, imatinib, irinotecan, methotrexate, mitoxantrone, saquinivir, topotecan, vinblastine, vincristine | Biricodar, [celecoxib](http://www.ncbi.nlm.nih.gov/pubmed/25916699), curcumin, [dinaciclib](http://www.ncbi.nlm.nih.gov/pubmed/26300056), dofequidar, flavonoids, ibrutinib, myricetin, sulindac, tariquidar | [[133-141](#_ENREF_133)] |
| BCRP(*ABCG2*) | Bisantrene, daunorubicin, doxorubicin, etoposide, gefitinib, imatinib, irinotecan, methotrexate, mitoxantrone, SN-38, teniposide, topotecan, vincristine | Biricodar, corticosterone, curcumin, cyclosporin A, elacridar, gefitinib, imatinib, ketoconazole, lopinacir, nifedipine, quercetin, rotenoids, stilbenoids, tariquidar, tectochrysin | [[12](#_ENREF_12),[142-146](#_ENREF_142)] |

P-gp: P-glycoprotein; MRP1: multidrug resistance-associated protein 1; BCRP: breast cancer resistant protein.

**Table 2 Potential agents to overcome resistance of cancer cells to apoptosis (non-exhaustive list)**

|  |  |  |
| --- | --- | --- |
| **Restoration of apoptotic signals** | **Alternative cell death** | **Ref.** |
| **BH3 mimetics** | **EGFR inhibitors** | **Autophagy inducers** | **Agents with 53-independent toxicity** |
| ABT-199 (venetoclax), ABT-263 (navitoclax)，ABT-737, apogossypol, apogossypolone, gossypol, maritoclax, obatoclax, sabutoclax | Afatinib, cetuximab, dacomitinib, [erlotinib](https://en.wikipedia.org/wiki/Erlotinib), [gefitinib](https://en.wikipedia.org/wiki/Gefitinib), [lapatinib](https://en.wikipedia.org/wiki/Lapatinib), [matuzumab](https://en.wikipedia.org/wiki/Matuzumab), neratinib, [nimotuzumab](https://en.wikipedia.org/wiki/Nimotuzumab), panitumumab, [zalutumumab](https://en.wikipedia.org/wiki/Zalutumumab) | Clonidine, cryptotanshinone, curcumin, dihydrotanshinone, evodiamine, genistein, helenalin, monascuspiloin, oridonin, paclitaxel, quercetin, rapamycin, resveratrol, sodium valproate, verapamil | Betulinic acid, crocetin, cryptotanshinone, dihydrotanshinone, epigallocatechic-3-gallate, genistein, α-iso-cubebenol, resveratrol, triptolide, thymoquinone, ursolic acid | [[91](#_ENREF_91),[112-115](#_ENREF_112),[117](#_ENREF_117),[120](#_ENREF_120),[121](#_ENREF_121), [124](#_ENREF_124),[127-129](#_ENREF_127),[147-156](#_ENREF_147)] |

EGFR: epidermal growth factor receptor.