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Drug resistance in topoisomerase-targeting therapy*

Lekooporność w terapii skierowanej na topoizomerazy

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Summary

Drug resistance is a well-known phenomenon that occurs when initially responsive to chemotherapy cancer cells become tolerant and elude further effectiveness of anticancer drugs. Based on their mechanism of action, anticancer drugs can be divided into cytotoxic-based agents and target-based agents. An important role among the therapeutics of the second group is played by drugs targeting topoisomerases, nuclear enzymes critical to DNA function and cell survival. These enzymes are cellular targets of several groups of anticancer agents which generate DNA damage in rapidly proliferating cancer cells. Drugs targeting topoisomerase I are mostly analogs of camtothecin, a natural compound isolated from the bark of a tree growing in China. Drugs targeting topoisomerase II are divided into poisons, such as anthracycline antibiotics, whose action is based on intercalation between DNA bases, and catalytic inhibitors that block topoisomerase II at different stages of the catalytic cycle. Unfortunately, chemotherapy is often limited by the induction of drug resistance. Identifying mechanisms that promote drug resistance is critical for the improvement of patient prognosis. Cancer drug resistance is a complex phenomenon that may be influenced by many factors. Here we discuss various mechanisms by which cancer cells can develop resistance to topoisomerase-directed drugs, which include enhanced drug efflux, mutations in topoisomerase genes, hypophosphorylation of topoisomerase II catalytic domain, activation of NF-κB transcription factor and drug inactivation. All these events may lead to the ineffective induction of cancer cell death. Attempts at circumventing drug resistance through the inhibition of cellular efflux pumps, use of silencing RNAs or inhibition of some important mechanisms, which can allow cancer cells to survive therapy, are also presented.

Keywords: **drug efflux • gene mutations • doxorubicin • camptothecin • siRNA**

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INTRODUCTION

One of the major problems in cancer therapy is multidrug resistance (MDR), which is the ability of cancer cells to elude the effect of chemotherapeutics [38].

Resistance to chemotherapy can be either innate, due to genetic conditions or, more often, acquired from treatment. Innate resistance is characteristic of tumors of secretory organs, such as the liver, colon and adrenal glands [30]. Acquired drug resistance can arise due to several host or tumor-related factors and develop by numerous mechanisms, including increased drug efflux, metabolic changes that promote drug inactivation and degradation, alterations of drug target, activation of DNA repair mechanisms, cell death inhibition, and the epithelial-mesenchymal transition [39, 58].

Drug efflux is linked to the activity of the ATP-binding cassette (ABC) transmembrane transporters. These proteins are efflux pumps that transport various anticancer drugs out of the cells, reducing their accumulation and causing drug resistance [21].

Many anti-cancer drugs must undergo metabolic activation in order to acquire clinical efficacy and cancer cells may inhibit drug activation. Down-regulation or mutation in some proteins, including P450 system, glutathione-S-transferase family and uridine diphospho-glucuronosyltransferase superfamily, can produce a decrease in the activation of drugs and lead to drug resistance [67].

The effectiveness of drugs in many types of cancer is associated with molecular target and alterations of this target, such as modifications or mutations [63]. Such target alterations can lead to drug resistance. For example, apoptosis-related protein p53 is mutated in 50% of cancers, resulting in inactivation of p53 regulators and co-factors such as caspase-9 and apoptotic protease activating factor 1 (Apaf-1). These pro-apoptotic proteins become non-functional and non-responsive to anticancer drugs [35, 84].

The repair of damaged DNA often results in anticancer drug resistance. DNA damage response mechanisms in cancer cells can reverse the drug-induced damage. For example, platinum-containing drugs, such as cisplatin, can evoke apoptosis in cancer cells by causing DNA crosslinks. However, cisplatin damage can be reversed by DNA repair mechanisms, including nucleotide excision and homologues recombination [7, 60].

Inhibition of cell death is a process antagonistic to apoptosis. Many types of cancers show a high expression of anti-apototic proteins (BCL-2 family or Akt) and up-regulation of transcription modulators (NF-κB and STAT). Some drugs that are protein inhibitors effective in inducing apoptosis in cancer cells can produce resistance after prolonged use [62, 79].

The epithelial-mesenchymal transition (EMT) plays a critical role in metastasis, angiogenesis, and invasion of cancer cells. During EMT, cancer cells can reduce the expression of integrins and cadherins (cell adhesion receptors) that help in cell-cell attachment, while increase the expression of growth factors [44]. As a consequence of these mechanisms, the initially sensitive to the treatment cancer cells take on a drug-resistant phenotype.

Based on their mechanism of action, anticancer drugs can be divided into two major groups: cytotoxic-based agents and target-based agents [85]. The cytotoxic drugs quickly kill dividing cancer cells by influencing the components of their mitotic pathway or DNA replication. The target-based drugs block the growth of cancer cells by affecting the molecular targets involved in cancer growth, progression and spread [92]. Among the agents of the second group, drugs targeting topoisomerases play an important role in cancer chemotherapy.

Human topoisomerases (type I and II) are nuclear enzymes critical for DNA function and cell survival. They play an important role in DNA replication and transcription [98]. During these processes DNA becomes overwound ahead of a replication fork and that would eventually stop the ability of DNA or RNA polymerases to continue down the DNA strand. There are three main types of topology, supercoiling, knotting and catenation, which keep DNA as compact as possible when it is not in the process of replication or transcription. However, these topological states seriously hinder replication and transcription. Additionally, during the replication process, the newly replicated and the original DNA become interwound and must be completely separated in order to ensure genomic integrity when a cell divides. Topoisomerase I and II correct the topological problems, as they bind to the double-stranded DNA, and create transient breaks in one or both DNA strands, which results in relaxing and untangling of the intertwined DNA chains, but they control DNA topology by very different mechanisms [80].

Type I topoisomerase cuts one strand of a DNA double helix, passes another unbroken DNA strand through it, and then reanneals the cut strand. Type II topoisomerase simultaneously cuts both DNA strands, which allows for their untangling. Type II topoisomerase, unlike type I enzyme, needs energy in the form of ATP to do its job. ATP hydrolysis is essential for strand passage activity of this enzyme, although DNA cleavage may occur in the absence of ATP. Topoisomerase II also plays an important role in DNA replication and is required for the condensation and segregation of chromosomes. The expression of this enzyme is cell cycle dependent and its protein level and catalytic activity is the highest in the G2/M phase [4, 9]. Topoisomerases I and II are both abundant nuclear proteins and can substitute for each other in most situations [52].

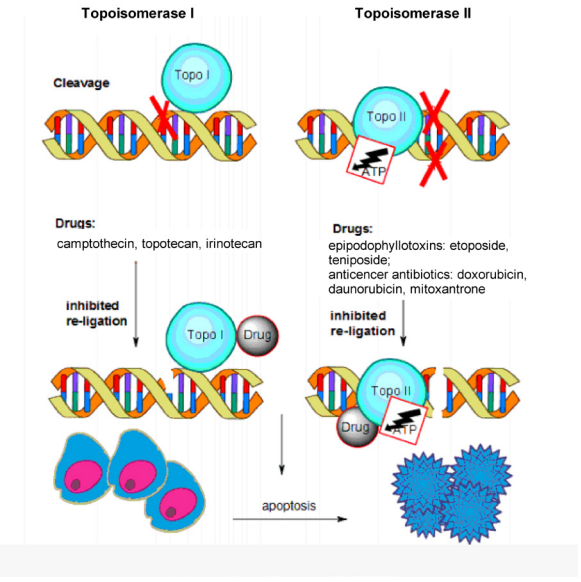


Fig. 1. The mechanism of anticancer activity of topoisomerase-directed drugs. Topoisomerases I and II (Topo I and Topo II) bind to the double-stranded DNA and create transient breaks in one (Topo I) or both (Topo II) DNA strands, which results in relaxating and untangling of the intertwined DNA chains. Anticancer drugs inhibit the re-ligation of DNA chains, which results in stabilization of the DNA-enzyme cleavable complex. This leads to the inhibition of replication and transcription, causing cancer cells death

Topoisomerase protein levels or mRNA expression of several human neoplasms are higher than those of normal tissues and are well correlated to unfavorable prognosis in most types of solid tumors. For example, in small cell lung cancer, the level of topoisomerase I plays a key prognostic and predictive role [82]. This enzyme is also a reliable marker for ovarian cancer prognosis [51]. Topoisomerase II is up-regulated in breast [23, 46, 94] and esophageal cancer [34]. The levels of both topoisomerases were shown to be enhanced in colorectal cancer [77, 91]. Cancer cells, which divide rapidly, rely on topoisomerases more than healthy cells. Therefore, these enzymes became cellular targets for several clinically active anticancer drugs, which are usually selective against either type I or type II topoisomerase.

TOPOISOMERASE-DIRECTED DRUGS

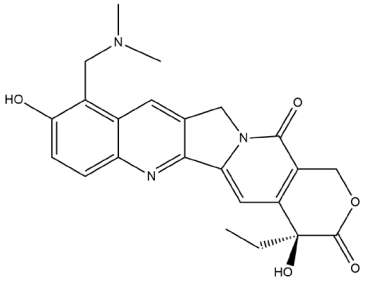
Drugs targeting topoisomerase I

The mechanism of topoisomerase I anticancer drugs is based on inhibition of the re-ligation function of this enzyme, resulting in the stabilization of the DNA--enzyme cleavable complex. This leads to the stalling of replication fork and impairs replication and transcription in rapidly proliferating cancer cells (Fig. 1).

Topoisomerase I is not a cell cycle-dependent enzyme and, therefore, it is a desirable cellular target for the development of anticancer drugs. The best known example of topoisomerase I targeting drug is camptothecin, a quinoline alkaloid isolated from the bark and stem of Camptotheca acuminata, a tree native to China, used for cancer treatment in traditional Chinese medicine [61]. Camptothecin and its analogs inhibit the rejoining step of the breakage/rejoining reaction, which traps topoisomerase I in a covalent linkage with DNA (the cleavable complex).

Camptothecin showed significant activity against a broad range of tumors but because of its low water solubility and severe side-effects was not a good drug candidate. Numerous synthetic analogs of camptothecin were obtained and two of them, topotecan and irinotecan (whose active metabolite is designated SN-38) (Fig. 2), with better therapeutic profile have been approved as anticancer drugs [96]. Camptothecin-based drugs are highly selective as topoisomerase I inhibitors which is their exclusive target [24].

In addition to camptothecin analogs, there are three classes of non-camptothecin-like topoisomerase I inhibitors that have been in clinical development. The first class, indolocarbazoles, has poor selectivity and is no longer considered as drug candidates [88, 93]. The phenanthridine derivatives (such as topovale also designated ARC-11) entered the phase I study of clinical trials [25]. The third class consists of indenoisoquinoline derivatives, which are chemically stable and show equal or greater antiproliferative activity than camptothecins [1, 2].



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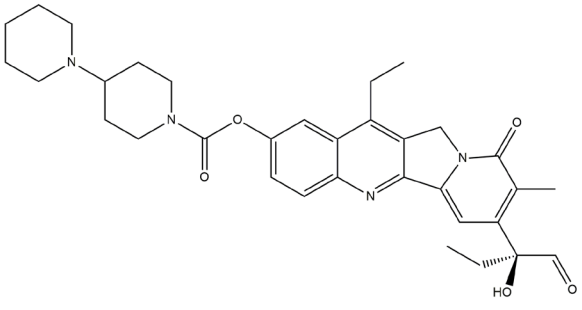

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Fig. 2. The structure of topotecan (1) and irinotecan (2)

They trap topoisomerase I cleavable complex at different sites than camptothecin-based drugs, but are also highly selective to this enzyme [1, 2, 66], and, what is very important, are not the substrates for ABC transporters [1].

Drugs targeting topoisomerase II

Drugs targeting topoisomerase II fall into two categories, poisons and catalytic inhibitors [74].

The poisoning mechanism of topoisomerase II is based on intercalation of drugs between DNA bases at the site of strand cleavage, which stabilizes the cleaved complex and prevents re-ligation of the double-strand breaks (Fig. 1). Thus, topoisomerase II poisons convert this enzyme to a nuclease that irreversibly cleaves DNA double-stranded molecule [102].

The best known poisons among anticancer drugs targeting topoisomerase II are epipodophyllotoxins, such as etoposide and teniposide, and antitumor antibiotics, such as doxorubicin, daunorubicin and mitoxantrone (Fig. 3).

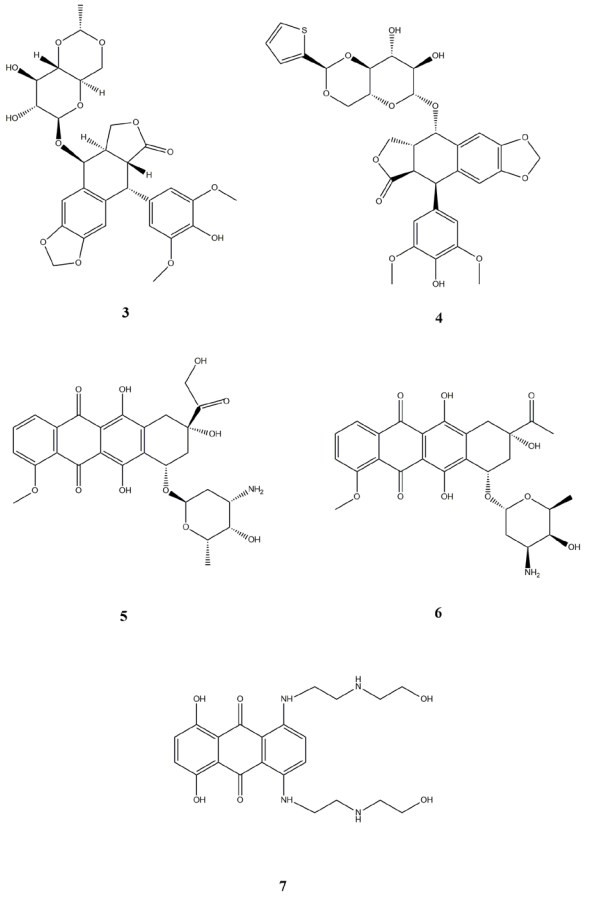

Fig. 3. The structure of etoposide (3), teniposide (4), doxorubicin (5), daunrubicin (6) and mitoxantrone (7)

Etoposide and teniposide are semi-synthetic, less toxic derivatives of podophyllotoxin, a compound isolated from a mayapple plant (Podophyllum peltatum) *[32]*. These drugs form ternary complexes with the topoisomerase II and DNA, preventing re-ligation of the DNA breaks which results in irreversible DNA damage and apoptosis of rapidly proliferating cancer cells [68, 74].

Dawnorubicin and doxorubicin are tetracycline antibiotics produced by *Streptomyces peucetiu.* They cause the formation of irreversible covalent cross-links between the topoisomerase II and DNA, leading to DNA breakage and consequently, to cell death. Additionally, tetracyclines are planar compounds that intercalate into DNA, blocking transcription and replication.

Topoisomerase II general catalytic inhibitors reduce enzyme activity without generating DNA damage directly. They have more varied mechanisms of action, and can impact enzyme activity by affecting substrate binding, DNA cleavage, or enzyme turnover. Several classes of catalytic inhibitors have been described, including bisdioxopiperazines (ICRF-159, ICRF-187, MST-16), novobiocin and suramin. These agents block topoisomerase II in different stages of the catalytic cycle. ICRF-187 (commonly known as dexrazoxane) is used to mitigate the cardiotoxicity of anthracycline-based treatments [87, 95]. Novobiocin inhibits topoisomerase II by blocking the ATP-binding site. Suramin modulates the activity of cellular enzymes, affecting topoisomerase II growth factor receptors [50, 70] (Fig. 4).

Topoisomerase II-targeting drugs are active against a broad range of cancers, from practically all solid tumors to numerous leukemic cell types. Among them, only mitoxantrone, a synthetic antibiotic, has a narrow spectrum of activity, restricted to breast, prostate, acute leukemia, and lymphoma.

RESISTANCE TO TOPOISOMERASE-TARGETING DRUGS

Cancer cells frequently develop resistance to topoisomerase-directed drugs, which greatly limits the success of the therapy. Resistance to drugs targeting topoisomerases may arise from several factors, the best known of which are high rate of drug efflux from cancer cells, mutations in topoisomerase genes, reduced cellular accumulation of drugs, increased NF-κB level, drug inactivation.

Enhanced drug efflux

The best-known mechanism of resistance to topoisomerase-targeting drugs is, as in the case of many other chemotherapeutics, their high efflux rate. Efflux is an energy-dependent outward transport of various potentially dangerous substances out of the cells, caused by the members of a big family of proteins, the ATP binding cassette (ABC) family (Fig. 5) [21]. All ABC transporters posses two types of domains, ATP-binding domains

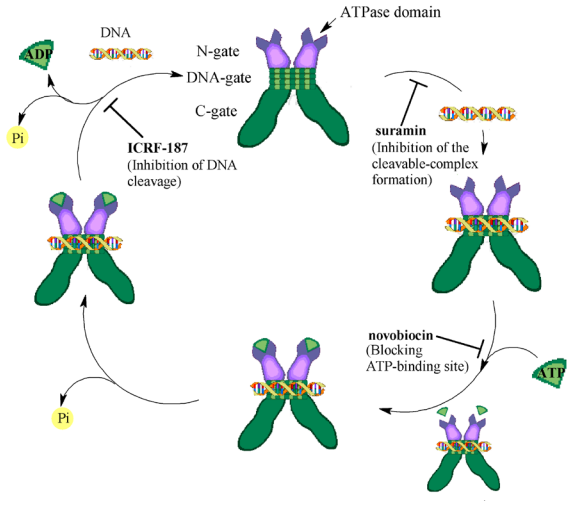

Fig. 4. Sites of action of topoisomerase II catalytic inhibitors.

that bind and hydrolyze ATP, providing the driving force for transport, and transmembrane domains that form a pore-like structure across the membrane, through which a range of different substrates can be transported. The conformational changes within the transmembrane domains are responsible for the opened or closed states of these structures and participate in substrate recognition and translocation across the lipid membrane [56, 89].

The ABC transporters have evolved as a complex cellular defense system for the recognition and removal of toxic agents entering the cells from their environment. Five out of seven subfamilies of the ABC(A-G) transporters are related to chemoresistance in cancer therapy, as the rapidly dividing malignant cells use them to protect themselves from medical interventions [13, 20].

ABCB1 protein, also known as P-glycoprotein 1 (P-gp) or multidrug resistance protein 1 (MDR1), was the first transporter pump that was linked to drug resistance [45]. ABCB1 is often overexpressed in various types of cancers, rendering these cancers multidrug resistant [54]. It was shown that the expression of ABCB1 gene in liver, kidney, brain and colon is often increased when cancer develops in these tissues [36, 49].

This transporter has a broad substrate specificity and is able to efflux from the cells many xenobiotics, including antracyclines. The overexpression of ABCB1 is often observed in malignant cells resistant to doxorubicin [42].

The ABCC1 (MRP1) protein was found to be responsible for the resistance against anthracyclines and irinotecan [97, 105, 106]. ABCB1- and ABCC1-mediated drug resistance was reported in malignant cells treated with mitoxantrone [69]. Simultaneous resistance to doxorubicin, etoposide and mitoxantrone observed in several cancer cell lines was caused by ABCG2 (also known as the breast cancer resistance protein, BCRP) [22]. The recently published results indicate that resistance to topotecan in ovarian cancer cell lines can be linked mostly to the over-expression of ABCG2 gene, while the level of ABCB1 seems to play only a complementary role [47]. ABCG2 (also referred to as BCRP) and ABCC4 (MRP4) were shown to confer cellular resistance to irinotecan and etoposide [33, 71, 76, 81].

Generally, the over-expression of several ABC family transporters was found in a large number of leukemias and solid tumors, indicating that these pumps play an important role in multidrug resistance of multiple malignancies [14, 78].

To overcome resistance mediated by a transport system, the concomitant administration of anticancer drugs with ABC transporter inhibitors, also known as chemosensitizers, was proposed [72]. Chemosensitizers may improve drug transport in several ways. They can interact with ABC transporter proteins, change the level of intracellular ATP, which is a source of energy for the ABC pumps, or they can influence membrane phospholipids, increasing membrane permeability for ions that decrease the activity of these transporters [6]. The well-known inhibitor of ABC transporters is cyclosporin A which effectively increases the cellular concentration and, subsequently, the cytotoxicity of a broad spectrum of antitumor drugs. For example, cyclosporin A was shown to enhance the retention of mitoxantrone in cells overexpressing ABCB1 and several inhibitors of ABCC4 that can increase the effectiveness of topoisomerase-directed drugs, such as topotecan, are now available [11, 75].

An innovative approach to overcoming multidrug resistance is the use of small interfering RNAs (siRNAs) for the regulation of ABC transporter gene expression [104]. siRNAs, also known as silencing RNAs, are a class of short (20-25 base pairs in length) double-stranded RNA molecules that interfere with the expression of specific genes with complementary nucleotide sequences by degrading mRNA after transcription, preventing translation.

A co-delivery of an appropriate anticancer drug and siRNA that is able to silence the expression of an efflux transporter responsible for the removal of that drug from resistant cancer cells can greatly improve a drug's sensitivity. It was shown that the co-administration of doxorubicin and ABCB1 siRNA to a drug-resistant cancer cell line (KB-V1) resulted in a markedly increased intracellular concentration of the drug [64].

Similarly, a reduction of ABCB1 level using appropriate siRNA, followed by doxorubicin delivery, increased the cytotoxic effect of this drug in MCF-7 breast cancer cells and in osteosarcoma cell lines [65, 86]. All these reports indicate that silencing ABC transporters by siRNAs can be achieved and may result in the satisfactory improvement of cancer treatment efficiency.

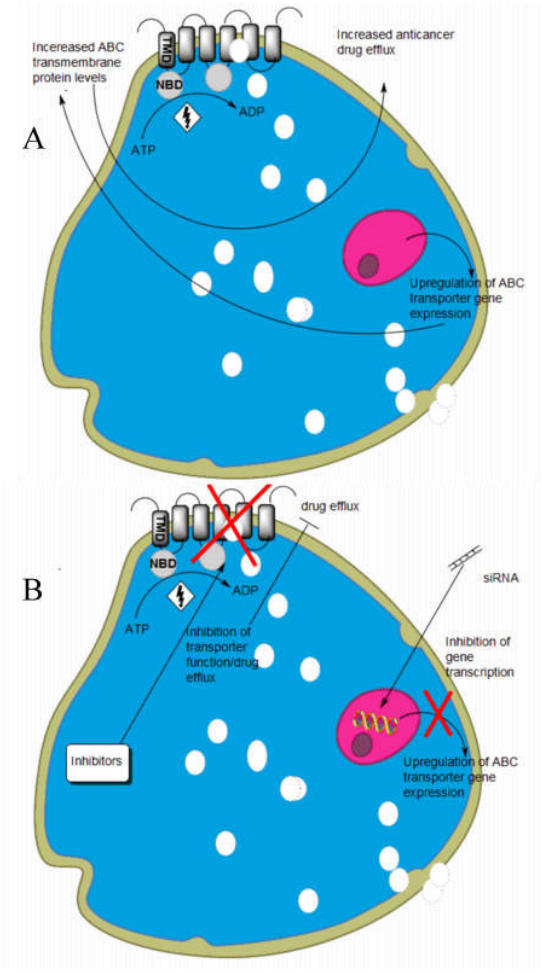

Fig. 5. The mechanism of drug efflux mediated by ABC transporters in cancer cells (A); schematic representation of selected methods used to overcome multidrug resistance mediated by ABC transporters (B)

Mutations in topoisomerase genes

The emergence of mutations in topoisomerase genes is another reason of resistance to topoisomerase-directed agents and a big challenge for the development of effective therapy with these drugs.

Several point mutations in topoisomerase I gene (*TOPO1)* were observed in the cells resistant to camptothecin derivatives and these mutations were identified in different regions of this gene. Resistance to topotecan was caused by the replacement of Phe-361 or Asn-722 by Ser in the binding pocket of the enzyme [15]. A mutant, in which Ala-653 in the linker domain of topoisomerase I was replaced by Pro, turned out to be resistant to camptothecin-based drugs and, in the absence of the drug, displayed a cleavage-religation equilibrium strongly shifted towards religation. It indicated that the unchanged linker slowed the rate of religation, permitting topoisomerase I to be longer associated with DNA, which rendered the enzyme sensitive to camptothecin drugs. On the other hand, a mutated linker was responsible for a decreased enzyme binding affinity, which led to drug resistance. Thus, it was demonstrated that not only the active site of the enzyme but also the linker is an essential domain in topoisomerase I sequence [26]. In another study, it was hypothesized that in the topoisomerase I polypeptide chain Leu-617, Arg-621 and Glu-710 residues are important for the linker functionality and that a mutation of one of these residues could influence irinotecan (SN-38) binding to the ternary complex by reducing the enzyme affinity for the drug [31].

In SN-38 resistant colon cancer cell line, a mutation of topoisomerase I gene in which Gly-365 was replaced by Ser was also observed. This mutation disturbed the catalytic activity of topoisomerase I and decreased the stability of the ternary complex between topoisomerase I, DNA and SN-38 [3].

The X-ray crystal structure studies of topoisomerase I joined covalently to DNA and bound to topotecan made it possible to distinguish between three groups of mutations producing resistance to this drug. In the first group, changes in residues directly interacting with the drug were observed. In the second group, mutations altered the interactions of the enzyme with the DNA, destabilizing the drug binding site. Mutations of the third group were in the regions that do not directly interact with the DNA or the drug.

The example of the third group mutations is the replacement of Thr-729 for Ala in a hydrophobic pocket of the enzyme C-terminal domain. To understand the contribution of this residue in drug resistance, several substitutions of Thr-729 were introduced into the topoisomerase I chain. The obtained results indicated that the integrity of hydrophobic pocket, where Thr-729 is positioned, is essential for drug sensitivity and DNA binding [57]. Resistance to topoisomerase II-targeting drugs can also arise from mutations affecting the way the drug interacts with the enzyme [29]. However, in some drug resistant mutations, such as replacement of Arg-450 for Gln, ATP hydrolysis was affected, implying that the resistance mechanism is based on the inhibition of the enzyme function, as opposed to the inhibition of specific enzyme-drug interactions [8].

Recently, it was reported that not only mutations in topoisomerase genes but also the level of other genes can play an important, so far unknown, role in drug resistance [41, 43]. For example, the expression of HERC5 (encoding an ubiquitin ligase) was identified as a predictor of poor survival in lung cancer patients [101]. The expression level of the IFI16 (interferon, gamma-inducible protein 16) gene was increased in the doxorubicin-resistant cell lines. SPP1 (secreted phosphoprotein 1), also known as osteopontin (OPN), which normally plays a role in the

mineralization of bone tissue, was found to be up-regulated in many cancers and appears to be involved in drug resistance [5]. Treatment of cancer cells with exogenous OPN induced the expression of ABCB1 and ABCG2 transporters and increased the levels of resistance to topotecan and doxorubicin [19]. The overexpression of OPN was observed in all topotecan-resistant breast cancer cell lines and these cell lines also expressed ABCB1 and ABCG2 at a very high level. Thus, OPN appears to be involved in drug resistance mainly through stimulating ABC-transporter expression [42].

The data obtained so far points also to the status of p53, which is the most frequently altered gene in human cancers. The protein encoded by this gene acts as a tumor suppressor, regulating cell division and keeping cells from growing and dividing too fast or in an uncontrolled way. The p53 protein is localized in the nucleus of all cells, where it binds directly to the DNA. The influence of p53 mutations on the resistance of cancer cells to camtothecin derivatives is discussed in an elegant review by Tomicic and Kaina [90].

OTHER MECHANISMS OF RESISTANCE

Hypophosphorylation of catalytic domain of topoisomerase II

The activity of topoisomerase II is regulated by the post-translational modifications, including site-specific phosphorylation of this enzyme, which occurs in a cell cycle phase-dependent manner [99]. A correlation has been found between topoisomerase II hypophosphorylation and the resistance of cancer cells to etoposide. It was reported that hypophosphorylation of Ser-1106 in a catalytic domain of topoisomerase II results in drug resistance in the human leukemia cell line, HL-60 and is likely to be responsible for the failure of topoisomerase II-targeting drug treatment in cancer patients [12].

Activation of nuclear factor-KB

Another mechanism by which tumor cells become resistant to anticancer drugs is through the activation of the nuclear factor-κB (NF-κB) [53]. NF-κB is a protein complex that controls transcription of DNA, production of cytokines and cell survival. Strict regulation of NF-κB activation or termination is indispensable for the integrity of cellular functions and dysregulation of this pathway occurs in many diseases, including cancer [10, 37].

NF-κB regulates the expression of several genes whose products are involved in tumorigenesis. These include anti-apoptotic genes (e.g., Bcl-xL, cIAP, survivin, and cFLIP), cyclooxygenase (COX-2), matrix metalloproteinase 9 (MMP-9), genes encoding adhesion molecules, chemokines, and inflammatory cytokines and cell cycle regulatory genes.

Several anticancer drugs have been shown to activate NF-κB in various cancer cell lines and, as a result, attenuation of apoptosis occurred. Thus, methods have been sought to inhibit NF-κB activation induced by chemotherapeutic agents and enhance apoptosis.

Berberine is a plant-derived isoquinoline alkaloid used in traditional Chinese medicine that can enhance chemosensitivity to topoisomerase I- and II-targeting drugs, such as irinotecan and doxorubicin, by suppressing NFκB activation [55, 73, 107].

Another widely studied compound known to decrease NFκB constitutive activity is parthenolide, a sesquiterpene lactone isolated from feverfew (Tanacetum parthenium) [40]. For example, resistance to doxorubicin in melanoma cells, caused by enhanced NF-κB and ABCB5 transporter expression, was markedly reduced by co-treatment with parthenolide [100]. Parthenolide also enhanced the apoptotic cytotoxicity of doxorubicin in A549 lung cancer cells by suppressing ABCB1 expression, probably also through mechanisms involving attenuation of NF-κB activation [103]. Summing up, parthenolide may appear effective in combating some pro-survival effects of doxorubicin in the combined treatment.

Drug inactivation

Some chemotherapeutics require metabolic activation or inactivation, which may be decreased in cancer cells.

Glucuronidation is a major mechanism leading to the elimination of xenobiotics from the body in bile or urine. It is also an important pathway for the removal of anticancer agents. The uridine diphospho-glucuronosyltransferase (UGT) enzyme catalyses glucuronidation of various substrates, including anticancer drugs and, as a result of this process, inactive hydrophilic glucuronides are eliminated from the body. The UGT genes that code this enzyme provide metabolic defense for many tissues, including breast, prostate, gut and skin from various pathogens, but are also responsible for the removal of anticancer drugs [67]. Glucuronidation has been identified as one of the mechanisms of intrinsic drug resistance to irinotecan in human colon cancer cells [16, 17, 18]. However, genetic polymorphisms in the UGT, leading to a decreased expression of this gene, were identified and responsiveness to irinotecan due to silencing of UGT gene was observed. In addition to polymorphism, methylation of UGT was also shown to contribute to the increased sensitivity of some tumors to irinotecan, as opposed to tumors that overexpress UGT [27, 38].

CONCLUSIONS

DNA topoisomerases are enzymes that regulate DNA topology and are essential for the integrity of the genetic material during replication and transcription. Drugs that inhibit the action of these enzymes are widely used

in cancer chemotherapy. However, cancer cells have the ability to develop resistance to topoisomerase-directed drugs. Among the mechanisms that promote drug resistance, the most common are the efflux of drugs by the ABC transporters, mutations in the topoisomerase genes, enhanced NF-κB constitutive activity and drug inactivation. Understanding these mechanisms is essential for the improvement of cancer therapy. The effectiveness of topoisomerase-targeting drugs can be enhanced by their concomitant administration with ABC transporter inhibitors or by the use of silencing RNAs (siRNAs), which can regulate ABC transporter gene expression. Some naturally occurring compounds, such as berberine or parthenolide, may reverse the ABC transporter-mediated drug resistance by mechanisms involving attenuation of NF-κB activation. Further progress of anticancer therapy employing topoisomerase-targeting drugs may involve co-administration of these drugs with sensitizing agents able to inhibit drug efflux.

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