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MINI-REVIEW ARTICLE

The Emerging Role of the SLCO1B3 Protein in Cancer Resistance

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Abstract: Currently, chemotherapy is one of the mainstays of oncologic therapies. But the efficacy of chemotherapy is often limited by drug resistance and severe side effects. Consequently, it is becoming increasingly important to investigate the underlying mechanism and overcome the problem of anticancer chemotherapy resistance. The solute carrier organic anion transporter family member 1B3 (SLCO1B3), a functional transporter normally expressed in the liver, transports a variety of endogenous and exogenous compounds, including hormones and their conjugates as well as some anticancer drugs. The extrahepatic expression of SLCO1B3 has been detected in different cancer cell lines and cancer tissues. Recently, accumulating data indicates that the abnormal expression and function of SLCO1B3 are involved in resistance to anticancer drugs, such as taxanes, camptothecin and its analogs, SN-38, and Androgen Deprivation Therapy (ADT) in breast, prostate, lung, hepatic, and colorectal cancer, respectively. Thus, more investigations have been implemented to identify the potential SLCO1B3-related mechanisms of cancer drug resistance. In this review, we focus on the emerging roles of SLCO1B3 protein in the development of cancer chemotherapy resistance and briefly discuss the mechanisms of resistance. Elucidating the function of SLCO1B3 in chemoresistance may bring out novel therapeutic strategies for cancer treatment.

Keywords: Cancer, chemotherapy, SLCO1B3, drug resistance, anticancer drugs, androgen deprivation therapy.

1. INTRODUCTION

Cancer chemotherapy was first introduced to patients with Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders in 1964 [1]. In past decades, chemotherapy has become an important mainstream anticancer therapy. A variety of advanced chemotherapeutic agents have been developed [2]. However, chemotherapy resistance, including intrinsic and acquired resistance, has become a major obstacle to the successful treatment of many cancers [3, 4]. Moreover, tumor cells could gain a cross-resistance to a large number of chemotherapeutic drugs of different structures and mechanisms, called Multiple Drug Resistance (MDR) [5]. Once chemoresistance occurs, few therapeutic options exist. Moreover, studies reported that chemotherapy resistance is associated with poor prognosis [6] and tumor relapse [7, 8]. Understanding the mechanisms of chemoresistance is crucial for finding new strategies and better cancer therapy.

Various molecular mechanisms contribute to chemotherapy resistance (Figure **1**), such as alterations in drug targets [9], increased drug efflux [10], reduced drug intake [11], increased drug inactivation [12, 13], aberrant gene regulation [14-16], and deregulated apoptosis [17]. Furthermore, molecules in tumor environment [18], such as integrins [19, 20], cytokines and growth factors [21], can also play roles in resistance to chemotherapy [5]. Furthermore, hypoxia and cancer stem cells regulation also have been shown to induce chemoresistance in cancer cells [22, 23].

The achievable therapeutic drug concentration is determined by drug absorption, disposition, metabolism, and elimination. Solute Carriers (SLCs), a major transporter family involved in drug uptake, are important in determining the chemotherapy efficacy (sensitivity and resistance) and/or toxicity [24]. The SLCs superfamily includes approximately

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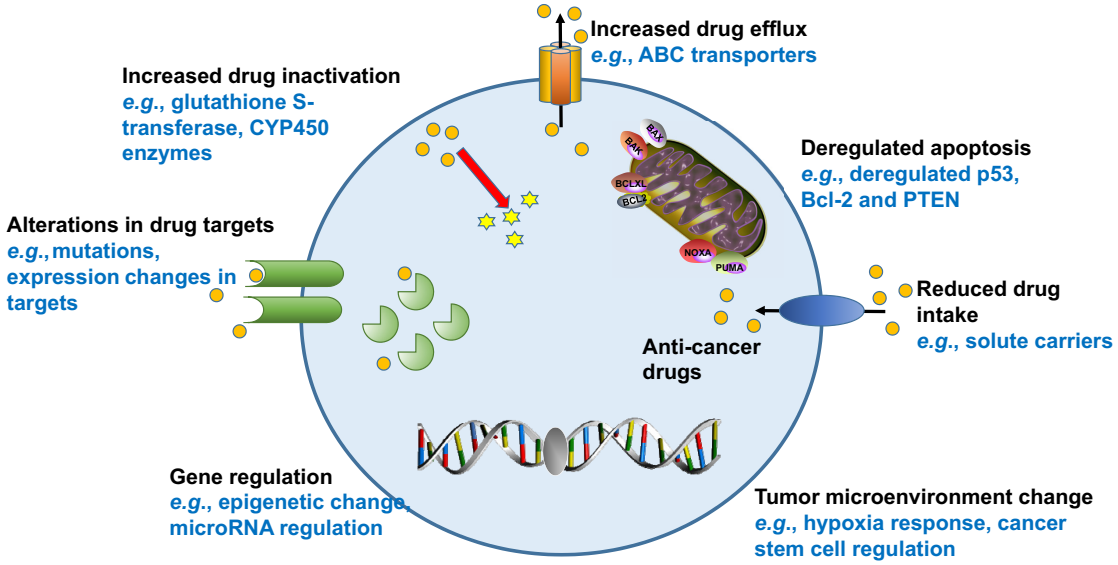

Figure 1. Mechanisms of drug resistance in cancer cells: increased drug efflux, reduced drug intake, increased drug inactivation, altered drug targets, deregulated apoptosis, aberrant gene regulation, and tumor microenvironment changes. ABC and CYP450 denote ATP-binding cassette and cytochrome 450, respectively.

400 proteins that are classified in 52 distinct families. Two proteins, the solute carrier organic anion transporter family members 1B3 (SLCO1B3) and 1B1 (SLCO1B1), which are highly expressed in hepatocytes, are the most widely studied solute carriers.

SLCO1B3, also named organic anion transporting polypeptide (OATP) 1B3 [25], LST-2 [26] and OATP8 [27], plays crucial roles in transporting some clinically important drugs and endogenous compounds into cells [28-30]. Normally, SLCO1B3 is expressed in the basolateral hepatocytes [29]. Recent reports revealed a truncated SLCO1B3 form that is also expressed in human tumors and some cancer cell lines [31-33]. This type of SLCO1B3 mainly remains in the cytosol and is considered as a potential prognostic biomarker of colorectal [32, 34, 35] and pancreatic cancers [32, 36]. Many anticancer agents are substrates of SLCO1B3, such as methotrexate [26], paclitaxel [37], docetaxel [38], cisplatin [39], carboplatin [39], irinotecan metabolite SN-38 [40] and certain tyrosine kinase inhibitors [41, 42]. These drugs are widely used for the treatment of colon, prostate, breast, and lung cancer. Recent evidence shows that the abnormal expression and genetic variant of SLCO1B3 can trigger resistance to camptothecin, SN-38, taxanes, and androgen deprivation therapy in colorectal and prostate cancer. The loss of SLCO1B3 decreases taxane uptake and triggers drug resistance [43] in prostate cancer. Aberrant overexpression of SLCO1B3 in the cytoplasm contributes to the camptothecin resistance in colon tumor [44]. Moreover, different polymorphic variants of SLCO1B3 have distinct transport characteristics, which may be related to the resistance of androgen deprivation therapy [45, 46].

In this review, we briefly summarize the structure, properties, substrates and function of SLCO1B3, and mainly focus on exploiting the relationships between SLCO1B3 and cancer chemotherapy resistance. Importantly, we summarize the possible SLCO1B3-related mechanisms of anticancer drug resistance. This review will provide supportive information on the potential role of SLCO1B3 in cancer therapy.

2. STRUCTURE AND PROPERTIES OF SLCO1B3

2.1. Structure of SLCO1B3

The *SLCO1B3* gene located on human chromosome 12p12-31.7 to 12p12-37.2 encodes a transmembrane protein consisting of of 702 residues [29]. SLCO1B3 is heavily glycosylated [29] and consists of 12 predicted transmembrane domains with intracellular N- and C-termini based on a hydrophobicity analysis [26]. The N-terminal region is important for the membrane trafficking of SLCO1B3. The molecular weight of the glycosylated protein is about 120 kDa [29]. Meier-Abt *et al.*, suggested a positively charged central hydrophilic pore in SLCO1B3 consisting of conserved basic residues directed towards the pore to translocate substrates, which fits to the typically anionic substrates of SLCO1B3. However, the substrate-binding sites or the transport mechanism involved were not identified [47]. Recently, it was revealed that some positively charged amino acid residues are pivotal for optimal membrane expression and the transport activities of certain substrates [48-50]. Additionally, transmembrane domain 10 might play a critical role in the substrate selectivity and functions of SLCO1B3 [50, 51].

2.2. Substrates of SLCO1B3

SLCO1B3 is a key transporter for a wide spectrum of xenobiotics and many endogenous substrates including bile salts [52], bilirubin [28, 53], steroid conjugates [54], Bromosulfophthalein (BSP) [29], Taurocholate (TCA) [55], leukotriene C4 [29], and some hormones as well as their conjugates [28] (Table **1**). Some substrates are transported by SLCO1B1 and SLCO1B3, such as bilirubin and its

Table 1. Selected substrates of SLCO1B3.

Substrate	-	References
Endogenous compounds:	Bilirubin	[28]
	Bromosulfophthalein (BSP)	[29]
	Leukotriene C4	[29]
	Dehydroepiandrosterone sulfate (DHEAS)	[29]
	Testosterone	[45]
	Thyroxine (T4)	[62]
	Triiodothyronine (T3)	[62]
	Cholecystokinin 8 (CCK-8)	[62]
	Estradiol-17 glucuronide	[62]
	Estrone-3-sulfate	[63]
	Taurocholate (TCA)	[55]
Exogenous compounds:	Methotrexate	[26]
Anticancer drugs:	Paclitaxel	[37]
	Docetaxel	[37]
	Cisplatin	[39]
	Carboplatin	[39]
	Oxaliplatin	[39]
	SN-38	[40]
	Imatinib	[41]
	Lapatinib	[42]
	Rapamycin	[55]
	Demethylphalloin	[64]
	Dihydromicrocystin-LR	[65]
	Sorafenib	[66]
	Doxorubicin	[67]
	AR-67	[68]

glucuronide conjugates, bile acids, peptides, hormones and their conjugates, toxins and clinically important drugs [56]. However, the intestinal peptide Cholecystokinin Octapeptide (CCK-8) [55], digoxin [57], telmisartan [58], paclitaxel [37] and docetaxel [37] are transported into hepatocytes specifically by SLCO1B3 and not by SLCO1B1. As for endogenous substrates, SLCO1B1 and SLCO1B3 are generally responsible for the hepatocellular uptake of unconjugated bilirubin for glucuronidation and the subsequent reuptake of conjugated bilirubin by downstream hepatocytes after the bilirubin secretion by sinusoidal transporters Multidrug Resistance Protein 3 (MRP3) [59]. The deficiency in these transporters leads to increased plasma concentrations of unconjugated and of conjugated bilirubin, resulted in the Rotor syndrome, a hereditary hyperbilirubinemia [60]. For exogenous substrates, SLCO1B3 is involved in hepatic drug elimination and drug pharmacokinetics [56]. Both Drug-Drug Interactions (DDIs) mediated by SLCO1B3 in co-administration therapies and polymorphisms of SLCO1B3 are important for the pharmacokinetics of some substrate drugs [61].

2.3. SLCO1B3 Expression in Normal and Tumor Cells

Generally, SLCO1B3 is a liver-specific transporter that transports endogenous and exogenous compounds in normal hepatic cells. Northern blot analysis showed high SLCO1B3 mRNA levels in human liver [29]. Additionally, SLCO1B3 glycoprotein was detected in the basolateral hepatocyte membrane of the human liver by a specific antibody raised against the C-terminus of SLCO1B3, which is identical to the membrane domain of SLCO1B1 [29, 69]. Hepatocytes show a stronger expression of SLCO1B3 in the pericentral region than in the periportal region [29]. However, in Hepatocellular Carcinoma (HCC), the SLCO1B3 mRNA expression and protein level was decreased or not detected [70, 71]. SLCO1B3 is less expressed in HCC with higher intensity lesion and preoperatively undetectable HCCs [72, 73]. Recently, it was suggested that the SLCO1B3 gene is also transcribed in extrahepatic tissues [74, 75]. For instance, SLCO1B3 mRNA is present in testis [76], but there is no evidence of protein expression [77]. In normal colon tissues, minimal mRNA expression was detected [44]. Low or absent

SLCO1B3 expression in the normal pancreas was also detected by immunofluorescence staining [36].

Interestingly, a unique SLCO1B3 variant mRNA was identified in cancer tissues [75], first in 2012 by Miki Nagai *et al*. [31]. Similarly, a predominant cancer-specific variant of SLCO1B3 (csSLCO1B3) was discovered in the colon [44] and pancreatic cancers [32]. Furthermore, SLCO1B3 mRNA is upregulated in non-small-cell lung cancer tumors [78] and prostate tumors as well as testicular tumors [79], and the protein expression and distinct localization of SLCO1B3 in cancerous prostate, colon, and bladder tissues were demonstrated [79]. This tumor-specific SLCO1B3 was termed cancer type SLCO1B3 (Ct-SLCO1B3) whereas SLCO1B3 exclusively expressed in hepatocytes is known as liver-type SLCO1B3 (Lt-SLCO1B3) [75]. The Ct-SLCO1B3 has an identical transcription start site to Lt- SLCO1B3 but it is located within the second intron of the SLCO1B3 gene (Figure **2**). Ct-SLCO1B3 lacks the N-terminal region of the liver-specific SLCO1B3 (Figure **2**). Up to date, two tumor-specific SLCO1B3 mRNA have been identified, [75] *i.e.*, Ct-SLCO1B3-C and Ct-SLCO1B3-V1. Ct-SLCO1B3-V1 was first found by Thakkar *et al*., in colon and pancreatic cancers and observed as predominantly expressed in the cytosol [32]. The transporter potential of tumor-specific SLCO1B3 remains unclear, although a minimal or negligible transport activity was suggested [32].

It was postulated that cancer-type SLCO1B3 is the primary mRNA isoform expressed in cancer tissues [33]. Most recently, both Lt- and Ct-SLCO1B3 mRNA were detected in ovarian, prostate, bladder, and breast cancers [75]. Interestingly, the Lt-SLCO1B3 mRNA levels were significantly higher in prostate cancer tissues than the Ct-SLCO1B3 mRNA levels [75].

3. CANCER DRUG RESISTANCE RELATED TO SLCO1B3

SLCO1B3 is responsible for the transport of a variety of antitumor drugs (Table **1**), such as paclitaxel, docetaxel, and methotrexate [67]. Recent evidence suggests that functional changes and expression rates of SLCO1B3 may be associated with chemotherapy resistance.

3.1. Resistance to Camptothecin and its Analogs

Camptothecin (CPT), discovered in the wood bark of *Camptotheca acuminata*, specifically inhibits topoisomerase I [80], mediated by passive diffusion [81, 82]. CPT and its analogs, alone or in combination with other anticancer drugs, show great efficacy against CRC [80, 83, 84]. In a study of apoptotic resistance in colon cancer [44], overexpressed SLCO1B3 triggered a significant cell survival advantage in colon cancer cell lines, such as RKO and HCT-8 cells, following CPT treatment but also enhanced cell survival in HCT-116 $p53^{+/+}$ cells upon CPT or oxaliplatin treatment. Thus, the drug transporter SLCO1B3 might be responsible for the apoptotic resistance to chemotherapy in colorectal cancer.

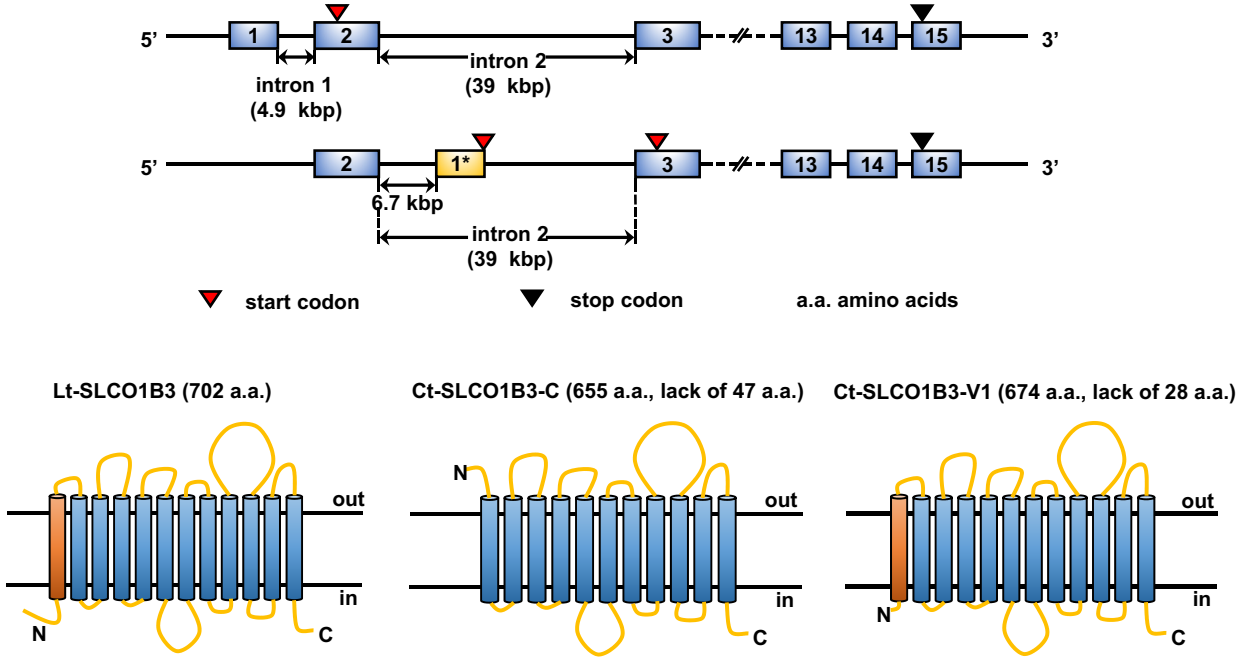

Figure 2. Structure and Characteristics of SLCO1B3. Normally, SLCO1B3 consists of fifteen exons (upper panel) and is mainly expressed in basolateral hepatocyte membrane. Cancer-specific SLCO1B3 lacks exon 2 and has thus fourteen exons. Its transcription start site is located in intron 2. The exon numbers are shown in each box. The white-blue boxes indicate exon region identical in Ct- and Lt-SLCO1B3. The yellow box indicates the specific exon (exon 1*) of Ct-SLCO1B3, which is located in intron 2. The translation start codons (red triangles) and stop codons (black triangles) are marked. The lower panel shows the translocation product of Lt-SLCO1B3 and the predicted translocation products of cancer-specific SLCO1B3 (Ct-SLCO1B3-C and Ct-SLCO1B3-V1). The orange box indicates the transmembrane domain 1 of Lt-SLCO1B3. The letters N and C represent the amino-terminal and carboxyl-terminal, respectively. The words out and in indicate the intracellular and extracellular, respectively.

Irinotecan (CPT-11), a semisynthetic camptothecin analog, is widely used in chemotherapies to treat colorectal, ovarian, and lung cancer [84]. SN-38, a novel substrate of SLCO1B3 [40], is the primary active pharmacodynamically metabolite of CPT-11. SLCO1B3 is associated with the disposition of CPT-11 and SN-38 [85, 86]. A recent study suggests that the uptake of SN-38 depends on the expression of SLCO1B3. In Lt-SLCO1B3 overexpressed 293 cells, the SN-38 uptake was higher than in mock cells, which explains why these cells were more sensitive to SN-38 [40]. However, in colorectal cancer, high intracellular cancer-type SLCO1B3 expression significantly decreased progression-free survival compared with patients with low SLCO1B3 expression. This indicates that Ct-SLCO1B3 expression may be associated with a poorer clinical response to irinotecan therapy [85].

AR-67 (7-t-butyldimethylsilyl-10-hydroxycamptothecin) is a lipophilic camptothecin analog that exists pH-dependent as lactone or carboxylate forms [87, 88]. The lactone form shows high lipophilicity and improved human blood stability [89], whereas the negatively charged AR-67 carboxylate is transported by SLCO1B3. However, SLCO1B3-expressing HeLa cells were not more sensitive to AR-67 carboxylate than mock cells, even after exposure to the anionic AR-67 carboxylate [90].

3.2. Resistance to Taxane Anticancer Agents

Taxanes, isolated from *Taxus brevifolia*, can bind to specific sites on tubulin and promote the formation of microtubules blocking cell division [91]. It has been successfully used in chemotherapy for a variety of cancer types, such as breast, prostate, and lung cancer [92]. Docetaxel, a semisynthetic analog of paclitaxel (taxel) used for the treatment of many cancer types, acts as standard first-line chemotherapy in mCRPC [92, 93]. Both paclitaxel and docetaxel are substrates of the SLCO1B3 transporter. Cabazitaxel is the most recently FDA-approved taxane anticancer agent, with great efficacy in docetaxel-resistant patients with mCRPC [94].

The expression level of SLCO1B3 may also affect the sensitivity of taxanes. In breast cancer, paclitaxel resistant cell lines expressed SLCO1B3 at lower quantities than paclitaxel sensitive cell lines [95]. A series of studies confirmed that SLCO1B3 expression predicts the response to paclitaxel in breast cancer [95, 96]. In HepG2 cells, reduced expression of SLCO1B3 may result in lower intracellular paclitaxel concentration and resistance [97]. In prostate cancer [43], a significant downregulation of SLCO1B3 expression was observed in docetaxel-resistant cells as well as in enzalutamide- and abiraterone-resistant cells that are cross-resistant to docetaxel, suggesting that the expression of SLCO1B3 in prostate tumor cells influences both the efficacy of taxanes treatment and the androgen responsiveness. Thus, the drug transporter SLCO1B3 appears to play a crucial role in taxanes resistance and even cross-resistance in prostate cancer. SLCO1B3 expression may also serve as a possible prognostic factor for endometrial cancer treated with paclitaxel and carboplatin [98]. Higher expression levels of SLCO1B3 indicated a longer disease-free and overall survival time.

3.3. Resistance to Hormone Therapy in Cancer

As a transporter of steroid hormones, the expression and function of SLCO1B3 is considered to be important for hormone therapies in cancer. Androgen Deprivation Therapy (ADT) is the first-line therapy for men with advanced prostate cancer and is achieved with medical castration (hormonal therapy) or through surgical orchiectomy [99]. However, continuous androgen deprivation may be related to ADT resistance [100] and progress to mCRPC [101]. Testosterone is one of the endogenous substrates of SLCO1B3 [45], which is overexpressed in prostate cancer [102]. However, higher SLCO1B3 expression results in more uptake of androgen causing resistance to ADT [103]. The SLCO1B3 genetic variants are also associated with the resistance of ADT [104]. Moreover, the polymorphism of SLCO1B3 may determine the effect of ADT [102, 104]. Patients with the T allelic variant, which increases testosterone uptake efficiency, have a shorter time to androgen independence than those with other variants, leading to a poorer response to ADT [102]. Besides, patients carrying *SLCO1B3* genetic variation importing for androgens more efficiently exhibited a shorter time to progression on ADT; therefore, genetic variants of SLCO1B3 may be the pharmacogenomic determinants of ADT resistance in prostate cancer [104]. Hamada *et al.,* [45] identified that patients with the 334GG/699AA SLCO1B3 haplotype correlated with impaired testosterone transport, longer median survival, and improved survival probability after 10 years, whereas patients with the GG/AA or TG/GA genotypes had shorter survival times. Sissung *et al.,* [46] demonstrated that SLCO1B3 expression in prostate cancer affects the uptake of testosterone. They also found that polymorphic variations in SLCO1B3 are associated with progression-free survival in patients with ADT treatment. They concluded that the *de novo* expression of SLCO1B3 in prostate cancer may drive resistance to ADT.

Estrogens play a key role in the development and growth of hormone-dependent breast cancer. Estradiol-17 glucuronide and Estrone-3-sulfate (E3S) are the most common estrone conjugates and also substrates of SLCO1B3 [63]. For example, SLCO1B3 mediates E3S transport and contributes to the growth of estrogen-dependent breast cancer [105]. In Estrogen Receptor-positive (ER-positive) patients, expression of SLCO1B3 correlated to decreased recurrence and improved prognosis [27]. The tamoxifen therapy, which blocks ER, was more effecient in SLCO1B3-positive patients [27] indicating that SLCO1B3 is a potential prognostic factor and maybe a therapeutic target for hormone-dependent breast cancer.

4. THE POSSIBLE SLCO1B3-RELATED MECHANISMS OF CANCER DRUG RESISTANCE

Despite much research it remains unclear how SLCO1B3 interferes with chemoresistance. This section discusses investigations of possible mechanisms where SLCO1B3 interferes with the efficacy of chemotherapy by driving drug resistance in tumor cells.

4.1. Decreased Drug Intake: Loss of SLCO1B3 Function

Lt-SLCO1B3 is a transmembrane protein that mediates uptake of various drugs including anticancer drugs. The transport activity of SLCO1B3 correlates to the cytotoxic sensitivity of chemotherapeutic drugs [86]. Downregulated influx transporters may reduce the cellular uptake and decrease the chemotherapeutic efficacy. While SLCO1B3 was initially considered as a transporter of taxane, *e.g*., paclitaxel, docetaxel, and cabazitaxel, studies revealed that decreased expression of Lt-SLCO1B3 is a resistance mechanism for taxane in breast cancer, prostate cancer, and HepG2 cells (Figure **3**). Studying mCRPC, Morree *et al*., [43] found that a loss of SLCO1B3 contributes to taxane resistance in prostate cancer utilizing bioinformatics, drug uptake assays of docetaxel and cabazitaxel *in vitro*, and cytotoxicity assays of two docetaxel-resistant patient-derived xenografts of CRPC. They also found that SLCO1B3 expression is downregulated leading to decreased intratumoral concentrations of docetaxel and cabazitaxel indicating a decreased response to taxane therapy. Downregulation of SLCO1B3 has also been found in breast cancers and HepG2 cells. Moreover, SLCO1B3 expression predicts the breast cell line response to paclitaxel with 82% accuracy.

Recently, a specific cancer type of SLCO1B3 providing a minimal transport function was identified with high expression levels in several cancers, such as colon, lung, prostate, and pancreas cancer [75]. However, highly expressed Ct-SLCO1B3 does not mean more sensitive to chemotherapy. In colorectal cancer, high intracellular cancer-type SLCO1B3 expression provides a poorer clinical response to irinotecan therapy due to its minimal transport function [85].

Cumulative evidence suggests that changes in the expression and function of SLCO1B3 may corelate with its transcriptional regulation. In hepatocellular carcinoma, the mechanism of reduced SLCO1B3 expression is associated with the inactivation of SLCO1B3 transcription by the Hepatocyte Nuclear Factor (HNF) 3β [71]. A most recent study identified a new genetic variation of the *SLCO1B3* gene (5035G>A) that consistently reduced the expression of SLCO1B3. Notably, Ct-SLCO1B3 is transcriptionally regulated in response to hypoxia in colon and pancreatic cancer [106]. A functional Hypoxia Response Elements (HRE) site in the Ct-SLCO1B3 promoter physically interacts with HIF-1α. Therefore, HIF-1α was suggested to play a critical role in the regulation of Ct-SLCO1B3 in colon and pancreatic cancer cells. In addition, an association between the mRNA expression and DNA methylation status of SLCO1B3 in cancer cell lines and the involvement of DNA-methylation based gene-silencing in the regulation of SLCO1B3 expression was revealed [107]. It was further suggested that DNA methylation plays crucial roles in the regulation of Ct-SLCO1B3 expression, which can determine the distinct usage of tissue- and cell-type-specific Transcriptional Start Sites (TSSs), leading to the predominant of the corresponding SLCO1B3 variant [108].

4.2. Deregulated Apoptosis: Alterations in the p53 Signaling Pathway

Dysfunctional apoptotic pathways in cells are a hallmark of cancer [109], which can drive cancer drug resistance due to deregulations in the network of genes and proteins, such as p53 [110], Bcl-2 [111], and PTEN [112]. Abnormalities in these genes lead to abnormal apoptosis even uncontrolled cell proliferation and the development of anticancer drug resistance [113].

Lee *et al*., [44] confirmed overexpressed SLCO1B3 mRNA and protein levels in colorectal adenocarcinomas and that the overexpression of SLCO1B3 conferred apoptotic resistance in colon cancer to tumor cells against camptothecin and oxaliplatin treatment by altering p53-dependent pathways. Their results indicate that the activation/cleavage of caspase-3 and poly (ADP-ribose) polymerase (PARP), a crucial marker of apoptosis [114], is substantially decreased in CPT-treated colon cancer cells with wild-type p53 overexpressing SLCO1B3. They also examined the effects of SLCO1B3 overexpression on the transcriptional activities of endogenous p53 and its downstream signaling molecules by p53-responsive reporter assays and immunoblot analysis in CRC cell line models *in vitro*. Overexpressed SLCO1B3 inhibited endogenous p53 transcriptional activity, as demonstrated by the substantial reduction in or undetectable protein levels of p53 downstream targets, P21WAF1, and PUMA. Previous studies showed that P21WAF1 and PUMA are transcriptionally regulated by p53 and play critical roles in apoptosis [115, 116]. Overexpression of SLCO1B3 may be a potential underlying mechanism of chemoresistance in tumors harboring wild-type p53. A point mutation (G583E) variant of SLCO1B3, which lacks transport activity, indicates that the antiapoptotic effect of SLCO1B3 may be correlated with its transporter function [44]. Additionally, knockdown of SLCO1B3 in colorectal cancer cell lines decreased both the cell size and the spheroid volume, which relates with reduced activation of the mammalian Target Of Rapamycin (mTOR) pathway [117].

4.3. Resistance due to SLCO1B3 Genetic Variation

The *SLCO1B3* gene is highly polymorphic. Some genetic variants may alter the expression, localization, and the transport function of SLCO1B3, thereby impacting the disposition and efficacy of the chemotherapeutic agents and hormonal therapy [118] (Figure **3**).

In chronic myeloid leukemia patients [119], the SLCO1B3 699GG/344TT genotypes are more frequent SNPs in the responder group, but the 699GG and 344TT SNPs were related to a failed clinical response of Imatinib (IM). In contrast, SLCO1B3 334TT/699GG carriers might be related to a higher intracellular concentration of IM. Several *SLCO1B3* genetic variants affect the transport and response of taxane. In a subgroup analysis of Non-Small-Cell Lung Cancer (NSCLC) patients treated with docetaxel [120] showed a significant association between tumor response and G2677T/A in SLCO1B3. For paclitaxel, a reduced uptake

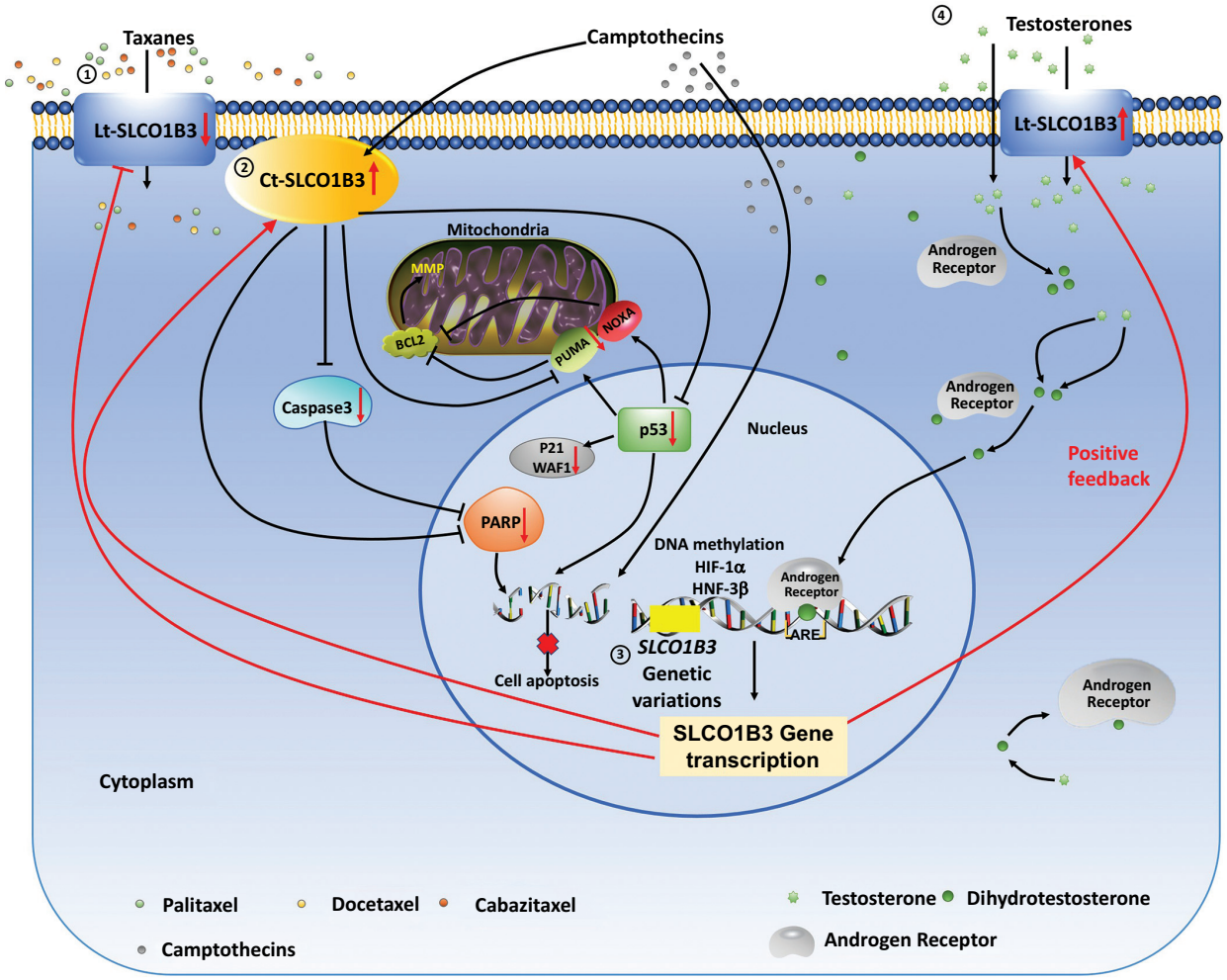

Figure 3. Proposed SLCO1B3-related mechanisms of anticancer drug resistance. ① Loss of Lt-SLCO1B3 contributes to taxane resistance. Taxane anticancer agents, which suppress microtubule dynamics and result in cell death by apoptosis, are the substrates of SLCO1B3. Downregulated SLCO1B3 may cause less disposition of taxane, leading to subsequent resistance. ② Overexpression of Ct-SLCO1B3. Overexpressed Ct-SLCO1B3 alters the p53-dependent signaling pathway which cause reduced p53, P21WAF1, and PUMA expression. Additionally, Ct-SLCO1B3 has minimal transport function and leads to decreased disposition of anticancer drugs. ③ Overexpression of Lt-SLCO1B3 works against ADT therapy in prostate cancer. Intraprostatic testosterone concentration is decreased during androgen deprivation therapy due to the inhibited production of testosterone by testes. In the testosterone scavenging mechanism, testosterone enters into prostate tumor cells not only through SLCO1B3 transporters but also through simple diffusion. A positive feedback mechanism may induce the expression of SLCO1B3 to increase the testosterone intake of prostate tumor cells. In SLCO1B3-overexpressed prostate cells, more testosterone is influxed into cells. ④ Genetic variations of SLCO1B3 affect its transportation function. The expression of SLCO1B3 may be regulated by Hepatocyte Nuclear Factor (HNF) 3β, DNA methylation, and HIF-1α that varies depending on tissues types. The red down arrow represents the reduction of these molecules. The red up arrow represents the increase of these molecules. The black down arrow represents the reduction of these drugs. The black up arrow represents the increase of these drugs.

has been observed in the oocyte overexpressing the c.699 G > A variant. In addition, patients with the c.334 T > G and c.699 G > A homozygous variants in SLCO1B3 showed a higher incidence of grade 3 or 4 anemia in NSCLC patients treated with paclitaxel and carboplatin [121].

4.4. The Possible Mechanism of SLCO1B Related to ADT Resistance

SLCO1B3 appears to play a key role in the development of ADT resistance. For years, it has been postulated that two mechanisms, SLCO1B3 overexpression [103] and genetic variations [102, 118] are attributed to the development of ADT resistance (Figure **3**). Overexpressed SLCO1B3 in castration prostate cancer may drive resistance to ADT through the increased uptake of testosterone in prostate tumor cells starved of androgens [46, 103]. Testosterone is one of the substrates of the SLCO1B3 transporter and overexpressed SLCO1B3 could affect the uptake of testosterone in prostate tumor cells [45]. Sissung, T. M. *et al*., [103] observed that prostate cancer was the only cancer type that remarkably expressed the liver-type SLCO1B3 *de novo*. Furthermore, expression of Lt-SLCO1B3 was > 325-fold higher than Ct-SLCO1B3 in prostate cancer tissues [103]. This was confirmed in a recent

study, as the expression frequency of Lt- SLCO1B3 mRNA was significantly higher than for Ct-SLCO1B3 mRNA in prostate cancer tissues [75]. Sissung *et al*., demonstrated that only Lt-SLCO1B3 appeared to take responsibility for the increase of testosterone uptake [103]. The mechanism of increasing Lt-SLCO1B3 in prostate cancer remains unclear, although some mechanisms of castration resistance in prostate tumors were suggested [46]. A positive feedback mechanism may induce the expression of Lt-SLCO1B3 to increase the testosterone intake of prostate tumor cells. Testosterone enters prostate tumor cells besides the SLCO1B3 transporter mediated uptake also by diffusion [45]. Testosterone is first converted to dihydrotestosterone in prostate tumor cells, which targets and activates Androgen Receptor (AR) [45]. After AR is translocated into the cell nucleus, AR binds to the TGTTCT consensus sequence of the androgen-responsive element and regulates gene transcription. Seven identical sequences in the SLCO1B3 promoter have been discovered. Upregulation of SLCO1B3 might be related to anoxic conditions in tumors due to the HREs (hypoxia response elements) in the SLCO1B3 promoter [26]. HIF-1α can also bind to certain HREs in SLCO1B3 [103]. Moreover, recent data suggest that the SLCO1B3 gene clusters with hypoxia-associated genes [122]. Similarly, expression of SLCO1B3 was upregulated by hypoxia in some cancer cell lines and two functional HIF response elements within intron 1 of SLCO1B3 [117]. These investigations suggest that hypoxia might be a driver of resistance to ADT through changes in the tumor microenvironment.

Recent studies indicate that the *SLCO1B3* genetic variations are also related to the resistance of ADT therapy in prostate cancers [102]. SLCO1B3 variants c.334T>G and c.699G>A significantly impair the testosterone transport [102, 118]. Additionally, SLCO1B3 variation 699G>A exhibits a decreased transport activity for testosterone [118], but not for estradiol-17-glucuronide or methotrexate. These findings indicate that the SLCO1B3 functional transport alteration of genetic variants may be substrate-specific.

CONCLUSION

Chemoresistance challenges the effective treatment of cancer with the undelying mechanisms being very complex. SLCO1B3, an influx transporter, plays a vital role in the uptake of the various anticancer drugs into the tumor cell, thereby determining the efficacy of chemotherapies. Recent evidence clearly shows that SLCO1B3 is associated with resistance to anticancer therapy, such as resistances to taxanes, camptothecin and its analogs, and androgen deprivation therapy. However, the resistance mechanisms differ among various anticancer chemotherapies. Down-regulation of Lt-SLCO1B3 contributes to taxane resistance, while overexpression of Lt-SLCO1B3 and Ct-SLCO1B3 may trigger resistances to ADT and camptothecin, respectively. To date, the resistance factors of different chemotherapeutics remain unclear. One reason is the distinct types of SLCO1B3, *i.e*., Lt- and Ct-SLCO1B3, and the remarkably higher transport activity of Lt-SLCO1B3. Loss of it may cause decreased disposition of anticancer drugs in the cell. In contrast, the tumor-specific SLCO1B3, which is a *bona fide* cancer-associated, has minimal or negligible transport potential. Another reason is that *SLCO1B3* is a highly polymorphic gene, and its variants have different transport activities. Current studies remain superficial, most still focus on investigating the link between SLCO1B3 and resistance. Little is known about the regulatory mechanisms of SLCO1B3 in different cancers, although these findings may have important clinical relevance to predict the response to chemotherapies and hormonal therapies. Further research on exploring the particular changes and regulation of SLCO1B3 in chemo-resistance will be an important direction and will provide new treatments to overcome chemotherapy resistance.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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