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Invited Review

Current Advances in Modulation of ABC Transporter-mediated Multidrug Resistance in Cancer

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ABSTRACT
In the last few decades, cancer chemotherapy has seen major medical advances. However, multidrug resistance (MDR), due to overexpression of ATP-binding cassette (ABC) transporters is a major impediment in the process of cancer treatment. ABC transporters lead to MDR by actively effluxing various amphipathic compounds, causing decreased intracellular drug accumulation in a patient's tumor cells. Conventionally, pharmacological development of synthetic molecules or identification of natural products that block ABC transporter-mediated efflux have been sought to combat MDR. Although, the strategy is attractive due to its simplicity, clinical success with these chemosensitizers has been marginal. Therefore, newer approaches to identify or synthesize one or more ABC transporters, such as selective resensitizers with limited nonspecific toxicity, have been undertaken. This review briefs the current advances in modulators and strategies being applied to resensitize chemotherapeutics in ABC transporters-mediated MDR tumors.

Keywords: ABC transporter, multidrug resistance, chemosensitizers, modulators, tyrosine kinase inhibitor

INTRODUCTION

Chemotherapy has been the mainstay of cancer treatment for several decades. An anticancer drug depletes the growth of cancer cells and precludes them from multiplying further. However, as with chemotherapy, resistance seems to be a major impediment in the course of cancer treatment. Chronic treatment of cancer with a chemotherapeutic agents produces resistance or a state of insensitivity to the particular agents and decreases the effectiveness of anticancer agents (Gottesman MM, 2002). Patients with multidrug resistance (MDR) tumors become insensitive to chemotherapeutic agents through different mechanisms, thus increasing the likelihood of "cancer recurrence" (Borst and Elferink, 2002).

MDR in Cancer

MDR is a phenomenon where cancer cells become resistant to a diverse, wide spectrum of drugs of different classes, structures, and cellular targets, leading to decreased cytotoxic efficacy of anticancer drugs (Deeley et al., 2006). Cancer chemotherapy MDR is analogous to antibiotic resistance, which leads to poor absorption, increased metabolism, environmental changes, and poor penetration to specific sites, thereby limiting drug delivery. Generally, MDR may be the result of overexpression of certain transporters involved in
effluxing the drug from the cell, after exposure to chemotherapeutic drugs over a period of time (Gottesman MM, 2002).
The mechanisms of drug resistance are complicated; resistance can either be due to host factors (acquired) or genetic changes in cancer cells (Gottesman MM, 2002; Jemal et al., 2005). This includes alterations in the permeability of the lipid bilayer membrane, inhibition of apoptosis, increased DNA repair of cancer cells, decreased activation or detoxification of drugs, or changes in the number of cell surface receptors or transporters necessary to accumulate or efflux a drug outside the cell (Mao and Unadkat, 2005; Ambudkar et al., 1999). One of the major reasons underlying acquired resistance or MDR is overexpression of efflux proteins belonging to the ATP binding cassette (ABC) family of transporters. ABC transporters are the largest transmembrane protein family encoded in the human genome (Dean and Allikmets, 2001).

ABC Transporters

ABC transporters are the most diverse and largest superfamily ubiquitously present in both prokaryotes and eukaryotes. The term ABC transporter, is based on the fact that almost all of the members of ABC superfamily, from yeast to bacteria to man, share a conserved consensus

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sequence of 90-110 amino acids (Higgins CF, 1992), where ATP binds and is hydrolyzed via ATPase enzyme. This consensus has Walker A and B motifs a little further downstream than that of another C region (also called a signature, linker, or docapeptide region). So far, there are 49 genes that are included in the ABC superfamily (although most literature recognizes only 48 genes, being that the ABCC13/MRP10 gene seems to be nonfunctional). These genes are classified on the basis of identical sequences in their nucleotide binding domains (NBDs), also known as ATP-binding domains (ABDs) (Deeley et al., 2006). The ABC family of transporters is divided into seven subfamilies ABC- A to G, which are further divided into sub-subfamilies (except the ABCE/OABP family), depending on their structural similarities or differences in their transmembrane domains (TMDs) (Schinkel and Jonker, 2003; Dean and Anillo, 2005). Mainly, three members of the ABC transporter family, ABCB1 (MDR1, P glycoprotein or Pgp), ABCC1 (MRP1) and ABCG2 (BCRP, MXR, ABCP), appear to play important roles in the development of MDR in cancer cells. Essentially, overexpression of these ABC drug transporters in cancer cells confers cross-resistance to a multitude of drugs belonging to various chemical classes even without structural similarity. Thus ABC transporters lead to MDR by actively effluxing chemotherapeutic drugs and reducing the accumulated amount of drug below the effective cytotoxic level (Gottesman et al., 2002; Wu et al., 2008).

Clinical Significance of ABC Transporters

It has become evident from previous studies that ABC transporters are involved in pumping of not only toxic metabolites or xenobiotics out of the cell, but also transporting a multitude of biologically important substrates across extracellular and intracellular membranes. These include, but are not limited to: amino acids, cholesterol and its derivatives, sugars, vitamins, peptides, lipids, some important proteins, hydrophobic drugs and antibiotics (Dean and Anillo, 2005; Shi et al., 2007a; Shi et al., 2007b). ABCB1 is expressed in blood capillaries of brain and subserves as an important part of the blood brain barrier (Gottesman et al., 2002). The ABCC subfamily, also known as the multiple resistance protein (MRP) family, was recently discovered to play a role in MDR in different cancers such as lung cancer (both small and non-small cell lung cancers), bladder cancer, and breast cancer (Leonard et al., 2003). ABCG2 is not only expressed in relatively high levels in the placental syncytiotrophoblasts, but also in the apical membrane of the epithelium of the small intestine, the liver canalicular membrane, and the luminal surface of the endothelial cells of human brain microvessels. Overexpression of ABCG2 in various cell lines and tissues makes it an important MDR factor in solid tumors, such as breast cancer, colon cancer, gastric carcinomas, hepatocellular carcinoma, endometrial carcinoma, small cell lung cancer, melanoma, and ovarian, gastric, and intestinal cancers as described before (Mao and Unadkat, 2005). High levels of ABCG2 expression were also found in acute lymphoblastic leukemia and acute myelogenous leukemia (Krishnamurthy and Schuetz, 2006). This strategic and systematic tissue localization pattern indicates that ABCG2 plays an important role in protecting the body and the fetus against toxins and xenobiotics (Allen and Schinkel, 2002). For example, concentrations of fluoroqinolones in the breast milk were altered by expression of ABCG2 (Merino et al., 2006). Additionally, under hypoxic conditions, ABCG2 expression was seen to be upregulated in stem cells, preventing accumulation of heme, which would otherwise cause mitochondrial death (Mao and Unadkat, 2005). Furthermore, ABCG2 plays an important pharmacokinetic role in absorption, distribution, metabolism, and elimination of drugs that are ABCG2 substrates, leading to alteration in drug bioavailability (Ambudkar et al., 1999; Schinkel and Jonker, 2003; Mao and Unadkt, 2005).

ABCB1 has been implicated as a major factor in MDR to chemotherapeutic regimen and has a wide substrate profile ranging from cytotoxic drugs such as anthracyclines (doxorubicin, daunorubicin), vinca alkaloids (vinblastine, vincristine), taxanes, epipodophyllotoxins (etoposide, teniposide), imatinib mesylate (also known as STI-571 and Gleevec) (Gottesman et al., 2002; Dean and Anillo, 2005), antibiotics (dactinomycin, actinomycin D) (Sauna et al., 2001). Some other drugs, including HMG-CoA reductase inhibitors (statins), antihistamines, antiarrhythmics, steroid hormones, calcium channel blockers and HIV protease inhibitors (Sarkadi et al., 2006), are also substrates of ABCB1. Interestingly, all of the substrates of ABCB1 are hydrophobic compounds with molecular weights ranging from 0.3-2 KDa (Sauna et al., 2001). The wide spectrum of chemotherapeutic agents transported by ABCG2 varies from organic anion conjugates, nucleoside analogues, organic dyes, and tyrosine kinase inhibitors (TKIs) to anthracyclines (such as DOX, MX), camptothecin-derived indolocarbazole topoisomerase I inhibitors, methotrexate (MTX), and flavopiridols (Mao and Unadkat, 2005). The ABCC family transporters' substrate profile overlaps that of the ABCB1/Pgp substrate list, but with few exceptions such as taxanes (example: paclitaxel, and docetaxel), which are poor substrates of most of the ABCC family members excluding ABCC10. Also, ABCC has a high affinity for negatively charged lipophilic compounds, unlike ABCB1, which transports neutral to positively charged lipophilic compounds (Kruh and Belinsky, 2003). Since ABCC family members are involved in the translocation of compounds after phase II glutathione-S-conjugation, sulfate or glucuronide conjugation, and other organic anions such as MTX, many are called multispecific organic anion transporters or MOAT (Norris et al., 2005). Again, the presence of the ABC transporter might play an important role in effluxing toxicants or important chemotherapeutic chemicals, leading to MDR. Nonetheless, their absences or mutations can lead to other diseases, as exemplified by ABCC2/MRP2 gene mutation, which caused mild liver disease associated with conjugated hyperbilirubinamia, also called Dubin-Johnson Syndrome (Toh et al., 1999). Another notable example includes a mutation of the ABCC6/MRP6 gene, resulting in Pseudoxanthoma Elasticum Disorder, which is characterized by calcification of elastic fibers of the skin, retina and arteries, forming lesions (Ringpfeil et al., 2000). In the following section, we summarize the strategies and current modulators used to combat MDR.

Strategies to Overcome MDR

Successful cytotoxicity by cancer chemotherapeutics can only be attained if optimal pharmacokinetics, tumor penetration, and intracellular concentration are maintained

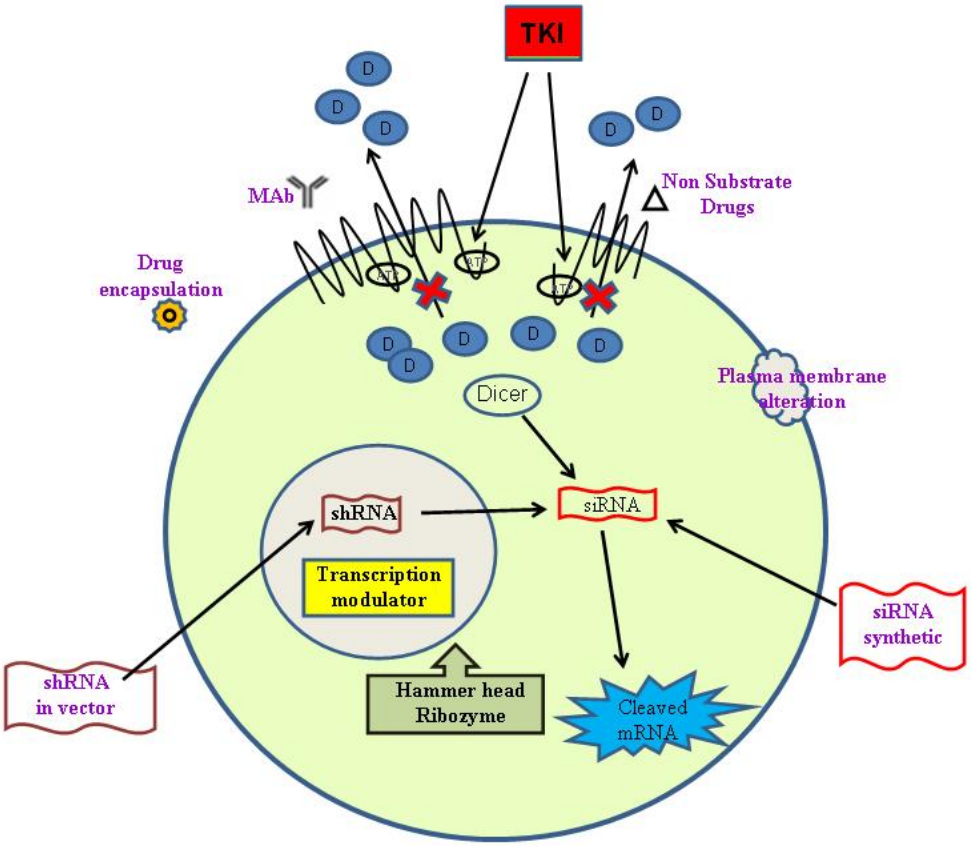

FIGURE : Schematic representation of different approaches to avoid MDR mediated by ABC transporters
The major techniques previously sought to modulate ABC transporters mediated MDR includes "synthetic siRNA"; "shRNA in a vector"; "Hammer head ribozyme"; "negative modulator/transcriptional regulator"; "Plasma membrane alteration"; "Monoclonal antibodies"; "non substrate drugs"; and "drug encapsulation" besides few other discussed in this review. Recently, "Tyrosine kinase inhibitors" have shown to inhibit drug efflux function of ABC transporters, sensitizing MDR cancer cells effectively compared to conventional chemotherapy.

in the malignant cancerous cell. Unfortunately, as stated earlier, overexpression of ABC transporters results in MDR, which consequently impedes effective cancer chemotherapy development and treatment by ejecting drugs outside the cell through the ABC engine. Therefore, it becomes pertinent to reverse MDR that is mediated by ABC transporters in order to achieve better clinical outcome.

Several strategies to overcome ABC transporter mediated MDR have been proposed since ABCB1 was shown to cause MDR, its role in drug disposition and metabolism was *also* confirmed in studies on knockout mouse models (Schinkel et al., 1995). In fact, ABCB1 is a marker in numerous cancer types; hence it was studied in more detail. Efforts to reverse clinical resistance to cytotoxic chemotherapeutic drugs met limited success with co-administration of "first generation" (since they were the first in their class to enter clinical trials) ABCB1 inhibitors, such as quinine, verapamil, and cyclosporine A, which were otherwise clinically approved for other indications (Leonard et al., 2003; Szakacs et al., 2006). However, "second generation" inhibitors, such as valspodar (PSC833) and biricodar (VX-710), showed more positive outcomes with less toxicity, more bioavailability at the tumor site, and resensitization of MDR cells when re-treated with initial chemotherapy in resistant cancer (Goldman B, 2003). But once again, "second generation" inhibitors failed in clinical trials due to both severe pharmacokinetic interaction with other chemotherapeutic agents and inhibition of cytochrome P450 3A, which probably reduced drug clearance significantly (Szakacs et al., 2006; Leonard et al., 2003). This led to the search for "third generation" inhibitors, including laniquidar (R101933), elacridar (GF120918), tariquidar (XR9576), and zosuquidar (LY335979) (Szackas et al., 2006), which were found effective not only in inhibiting ABCB1, but also ABCC1/MRP1 and ABCG2. In fact, preliminary analysis in Phase III trials with zosuquidar (LY335979) in AML patients has shown that it can be given safely without dose reduction of the adjuvant chemotherapeutic drug (Szakacs et al., 2006).

Reversal agents for other ABC transporters involved in MDR, such as the ABCC/MRP family or ABCG2 are still in "first generation" phase. Until now, agosterol-A (AG-A), cyclosporine A, VX-710 (biricodar), MK571 (a leukotriene D4-receptor antagonist), flavonoids, raloxifene analogs, isoxazole-based molecules, leukotriene C4, and PAK-104P (Chen et al., 1999a; Chen et al., 1999b; Qadir et al., 2005) have shown to inhibit ABCC1/MRP1- and ABCC2/MRP2-mediated MDR, whereas probenecid, sulfinpyrazone, and

indomethacin have shown to reverse ABCC3/MRP3-mediated accumulation of etoposide (Zelcer et al., 2001). However, inhibitors for ABCC4, ABCC5, ABCC6, ABCC10, ABCC11 and ABCC12 have not been explored in detail (Kruh et al., 2007). Recently, we found that cepharanthine, which was isolated from *Stephania erecta*, a biscoclaurine alkaloid, can reverse ABCC10/MRP7-mediated MDR (Zhou et al., 2009). As of now, known ABCG2 reversal agents include: rauwolfia serpentine alkaloids, estrogen agonists (Doyle and Ross, 2003), and some nonspecific inhibitors like GF120918 and biricodar (VX-710), which also inhibits ABCB1/Pgp and ABCC1/MRP1. Some specific ABCG2 inhibitors, such as Fumitremorgin C (FTC), could specifically and completely block ABCG2 transporter; however they cannot be used because their neurotoxic behaviour (Rabindran et al., 2000). Furthermore, certain phytochemicals such as curcumin, some polyphenols, ginsenosides and antimalarials have shown promising chemosensitivity towards more than one ABC transporters with low intrinsic toxicity (Shukla et al., 2008a). Again, *in vivo* trials with all of these inhibitors suffered from unpredictable pharmacokinetic interaction, low bioavailability, poor delivery or stability issues, and variability in drug transporter expression levels among individuals as well as simultaneous involvement of several drug transporters in tumor tissues, and hence never progressed to clinical trials.

Targeted Approach to Overcome MDR

Investigators have sought alternative approaches to circumvent ABC transporters upon failure of conventional MDR inhibitors. One strategy includes drug nano-encapsulation for effective delivery of drugs in a MDR tumor site-directed manner. For instance, investigators co-administered paclitaxel and ceramide, an apoptosis modulator with nanoparticle beads made from poly(ethylene oxide)-modified poly(epsiloncaprolactone) to increase bioavailibility (van Vlerken et al., 2007). Another strategy involves use of biological antibodies against ABCB1/Pgp i.e.MRK16, and some highly specific peptide analogues of TMDs, which could interfere with the function or proper assembly of target ABC transporter proteins (Sharom et al., 1999). A particularly interesting approach of targeting mRNA at molecular level via use of hammerhead ribozymes against ABCG2 (Kowalski et al., 2002), antisense oligonucleotides and small interference RNA (siRNA) (Shi et al., 2006; Xu et al., 2004) has also been proposed.

Another approach sought to prevent ABCB1 overexpression by modifying the plasma membrane via the use of fatty acid-polyethylene glycol fatty acid diesters that work on the cell membrane surface and thus circumvents both MDR phenotype and short-term ABCB1 expression in Ara C-treated cells (Komarov et al., 1996). Additionally, alteration in plasma membranes through transcriptional modulators such as 8-CL-c-AMP, a type I cAMP-dependent protein kinase (PKA) inhibitor was shown to downregulate ABCB1 expression in a concentration dependent manner (Xu et al., 2002). Other transcriptional regulators implicated in ABCB1 transporter mediated MDR are Protein Kinase C (PKC), NF-κB (Jin et al., 2000) among others. Other transcriptional modulators such as p53, and transcription factor complex AP-1 regulate ABCC1 (Wang et al., 1998; Kurz et al., 2001). Furthermore, newer highly lipophilic agents are designed such that they are not substrates of either ABCB1 or ABCG2 but solute carriers, a superfamily of membrane transport proteins (SLCs) efficiates the uptake of cytotoxic agents and avoids MDR (Huang and Sadee, 2006). Although experimental results indicate that these strategies are effective in vitro, their clinical utility is limited due to difficulties in delivery, stability, and potency. More recently, while attempting to establish a profile of substrates and inhibitors for ABC transporters involved in MDR, some inhibitors have shown positive correlation i.e. potentiated toxicity of other chemotherapeutic drugs in the presence of ABC transporters. For example, thiosemicarbazone (NSC73306) increased toxicity where more ABCB1/Pgp was expressed compared to drug-sensitive cells (Ludwig et al., 2006). Similarly, KP772 a lanthanum compound potentiates cytotoxicity by having preferential selectivity towards tumor cells overexpressing either ABCB1 (Pgp), ABCC1 (MRP1) or ABCG2 (Heffeter et al., 2007). Nicholsan et al. had a similar observation with phosphatidylinositol-3-kinase inhibitor (LY294002), which hypersensitized ABCB1-overexpressing cells, probably through apoptosis induction (Nicholsan et al., 2003). If so, then overexpression of ABC transporter can also be exploited to combat MDR. Presently, selective inhibitors with more limited nonspecific toxicity are sought for specific ABC transporters. Current research interests are directed toward the screening of novel compounds, with specific attention towards tyrosine kinase inhibitors (TKIs).

TKIs' Role in ABC Transporter Modulation

Recently, cancer-specific targeted therapies in the form of TKIs have been approved for the treatment of various cancers. Modulation of growth factor signaling through inhibition of tyrosine kinases is an interesting and successful strategy. Several TKIs compete with several oncogenic tyrosine kinases at the ATP binding site of the catalytic domain. TKIs are mostly small molecules, which are given orally and confer a favorable safety profile alone or in combination with other chemotherapeutic agents or radiotherapy. Since hydrophobic TKIs target intracellular protein tyrosine kinase domain, it was hypothesized that some transmembrane transporters, such as ABC transporters, might modulate TKI activity (Ozvegy-Laczka et al., 2005). Interestingly**,** submicromolar concentrations of the TKIs examined selectively modulated MDR protein-ATPase activity, inhibited MDR-dependent active drug extrusion, and significantly affected drug resistance patterns in cells expressing MDR (Shi et al., 2007a, Dai et al., 2008). Initially, canertinib (CI-1033), a human epidermal receptor type (HER) TKI, was found to moderately reverse ABCG2 mediated drug resistance (Erlichman et al., 2001). It was followed by imatinib mesylate (STI-571, Gleevec) and gefitinib (ZD1839, Iressa), which were also shown to modulate ABCB1 and ABCG2 transporter activity (Shukla et al., 2008b; Ozvegy-Laczka et al., 2005). Gefitinib, an inhibitor of the tyrosine kinase activity of EGFR/Her-1, has been reported to interact with ABCG2 and ABCB1 and to reverse ABCB1- and/or ABCG2-mediated MDR by directly inhibiting their drug pump function in cancer cells (Elkind et al., 2005). Furthermore, ABCG2-transduced cells were found to be resistant to gefitinib (Ozvegy-Laczka et al., 2005), and expression of ABCG2, except its nonfunctional mutant, protects EGFR signaling-dependent tumor cells

from death on exposure to gefitinib. This protection, however, can be reversed by the ABCG2-specific inhibitor Ko143 (Elkind et al., 2005). These reports strongly suggested that ABCG2 could actively pump gefitinib out of the cells. Previously, we found that other EGFR TKI inhibitors such as AG1478, erlotinib and lapatinib were also able to antagonize ABCB1- and ABCG2-mediated MDR, suggesting that these TKIs might be substrates of these two transporters (Shi et al., 2007a, Dai et al., 2008). In addition, Bcr-abl TKIs, such as imatinib and nilotinib, were also found to reverse ABCB1- and ABCG2-mediated resistance (Shukla et al., 2008b, Tiwari et al., 2009). An *in vivo* study involving gefitinib and camptothecin derivative combination has shown improved pharmacokinetic and anti-tumor activity of camptothecin derivatives (Ozvegy-Laczka et al., 2005). We also saw that the response to paclitaxel is augmented by lapatinib in ABCB1-overexpressing KBv200 cell xenografts in nude mice (Dai et al., 2008). Additionally, we found that erlotinib, lapatinib, imatinib, and nilotinib can reverse another ABC transporter called MRP7 mediated drug resistance (Unpublished data). Certain multikinase TKIs, such as sunitinib, were also shown to interact with both ABCG2 and ABCB1, respectively (Shukla et al., 2008c, Dai et al., 2009). These *in vitro* and *in vivo* studies suggest combination therapy with TKIs and conventional anticancer drugs may sensitize MDR overexpressing cancer cells. Further studies are required to ascertain use of TKIs as ABC transporter modulators in clinics.

SUMMARY

ABC transporters not only provide protection against xenobiotics but are also involved in pharmacokinetic alteration of certain chemotherapeutic agents. Nonetheless, ABC transporter overexpression is implicated in MDR, and is one of the major factors in chemotherapeutic failure. Currently, no drug has been clinically approved for the reversal of MDR due to detrimental pharmacokinetic interactions, including toxicity issues. However, due to clinical benefits foreseen in improvising chemotherapeutic treatment through MDR reversal, researchers continue to search for a novel, safe yet effective inhibitor of these transporters. Recent advances in ABC transporters modulation and MDR reversal are aimed towards targeting signaling pathways at the molecular level. Tyrosine kinase inhibitors possess significant collateral sensitivity towards MDR cells. However, further understanding of modulation by TKIs at the molecular level will be required for them to serve as frontiers for treatment of MDR in cancer chemotherapy.

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