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The role of ABC transporters in anticancer drug transport

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Abstract: The main clinical problem in cancer treatment is the development of multidrug resistance. Tumors can be intrinsically drug-resistant or develop resistance to chemotherapy. Multidrug resistance can develop by diverse mechanisms including decreased rate of drug uptake, increased drug efflux, alterations in drug metabolism, mutation of drug targets, activation of DNA repair mechanisms, and evasion of apoptosis. The use of modern genomic, proteomic, bioinformatic, and systems biology approaches has resulted in a substantial increase in our ability to identify molecular mechanisms that are involved in multidrug resistance in cancer and to find drugs that may block or reverse the development of drug resistance.

Key words: ABC transporters, cancer, neoplasm, P-glycoprotein, chemotherapy, multidrug resistance, tumor biology

1. Introduction

Initial chemotherapy of cancer may prove highly beneficial, nearly annihilating a tumor, but a few resistant cancer cells often survive and proliferate. Despite more aggressive second and third courses of chemotherapy, the remaining drug-resistant cells thrive, displaying increasing resistance to drug therapy and eventually displaying virtual invulnerability to chemotherapy. Chemotherapy may fail because the remaining tumor cells are chemotherapy-resistant. One of the main clinical issues in cancer is the development of multidrug resistance (MDR) (Fletcher et al., 2010). Malignant tumors usually consist of mixed populations of cells, some of which are drug-sensitive while others are drug-resistant. Chemotherapy leaves behind a higher proportion of drug-resistant cells (Gottesman et al., 2002; Albrecht and Viturro, 2007). MDR exists against every anticancer drug and can develop by numerous mechanisms including decreased drug uptake, increased drug efflux, activation of detoxifying systems, activation of DNA repair mechanisms, and evasion of drug-induced apoptosis (Krishna and Mayer, 2000). A well-studied mechanism of MDR involves the increased expression of members of the ATP binding cassette (ABC) transporter superfamily, many of which efflux various chemotherapeutic compounds, leading to the decrease of intracellular drug levels and consequent drug insensitivity (Ambudkar, 1999; Gottesman et al., 2002; Shepard et al., 2003).

MDR transporters include ABCB1 (also known as P-glycoprotein or MDR1), ABCC1 (also known as MRP1), and ABCG2 (also known as BCRP or MXR). The classic resistance to chemotherapy drugs has most often been linked to the overexpression of P-glycoprotein, an ATP-dependent membrane transporter that acts as a drug efflux pump (Table). The cytotoxic drugs that are most frequently associated with MDR are hydrophobic, amphipathic natural products, such as the taxanes (paclitaxel, docetaxel), vinca alkaloids (vinorelbine, vincristine, vinblastine), anthracyclines (doxorubicin, daunorubicin, epirubicin), epipodophyllotoxins (etoposide, teniposide), topotecan, dactinomycin, and mitomycin C (Ambudkar, 1999; Krishna and Mayer, 2000).

2. ABC transporters

ABC transporters are transmembrane proteins that utilize the energy of adenosine triphosphate (ATP) binding and hydrolysis to carry a wide variety of xenobiotics (including drugs), lipids, sterols, and metabolic products across the plasma and intracellular membranes (Ambudkar, 1999; Gottesman et al., 2002; Dean, 2005; Fletcher et al., 2010). The ABC transporters are the largest family of transmembrane proteins, with 7 subfamilies that are designated A to G on the basis of sequence and structural homology. Human ABC transporters are involved in several diseases that arise from polymorphisms in ABC genes. Such diseases include cystic fibrosis, adrenoleukodystrophy, Stargardt disease, Tangier disease, Mendelian diseases, progressive familial intrahepatic cholestasis, Dubin–Johnson syndrome, pseudoxanthoma elasticum, X-linked sideroblastosis

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and anemia, age-related macular degeneration, familial hypoapoproteinemia, and retinitis pigmentosum. The human ABCB (MDR/TAP) family is responsible for MDR against a variety of structurally unrelated drugs. ABCB1 or MDR1 P-glycoprotein is also involved in other biological processes for which lipid transport is the main function (Albrecht and Viturro, 2007).

3. ABC transporters in cancer

Research is under way on many fronts to better understand MDR in cancer and to find drugs that may block or reverse the development of drug resistance in cancer cells. Studies have found that P-glycoprotein, called the multidrug transporter, is expressed in increased amounts as a result of genetic alterations in cells to build their resistance to many anticancer drugs (Thomas and Coley, 2003). Genetic and molecular studies have shown that, in humans, these multidrug-resistant cells contain amplified MDR1 genes, resulting in increased gene expression. The *MDR1a* gene, which encodes P-glycoprotein, is expressed at significant levels in about half of all human cancers (Weinstein, 1991; Abolhoda et al., 1999; Zochbauer-Muller, 2001; Mochida, 2003; Yamada, 2003; Szakacs, 2004; Yoh, 2004; Konig, 2005; Oda, 2005; Haber, 2006; Oberthuer, 2006; Steinbach, 2006; Maris et al., 2007; Ohtsuki, 2007; Hanada, 2008; Oevermann, 2009; Vander Borght, 2008). The multidrug transporter is 1 of 2 major mechanisms identified in the efflux, or extraction, of drugs from animal cells. The other mechanism for drug efflux involves expression of a gene known as the multidrug resistance associated protein (*MRP*). Both the *MDR1* and the *MRP* genes are members of a superfamily of ATP-dependent transporters. There are probably other, unidentified members of this superfamily that are involved in other forms of drug resistance (Fletcher et al., 2010; Holohan et al., 2013).

The etiology of MDR may be multifactorial, but the classic resistance to the cytotoxic drugs mentioned above has most often been linked to the overexpression of P-glycoprotein, a 170-kDa ATP-dependent membrane transporter that acts as a drug efflux pump (Gottesman et al., 2002). These transporters use the energy that is released when they hydrolyze ATP to drive the transport of various molecules across the cell membrane. In addition to their physiologic expression in normal tissues, many are expressed and, importantly, overexpressed in human tumors (Thomas and Coley, 2003; Fletcher et al., 2010; Holohan et al., 2013). A number of ABC transporters and the chemotherapy drugs to which they have been shown to confer resistance are listed in the Table.

In cancerous tissue, the expression of P-glycoprotein is usually highest in tumors that are derived from tissues that normally express P-glycoprotein, such as epithelial cells of the colon, kidney, adrenal, pancreas, and liver, resulting in the potential for resistance to some cytotoxic agents before chemotherapy is initiated (Weinstein, 1991; Abolhoda et al., 1999; Zochbauer-Muller, 2001; Mochida, 2003; Yamada, 2003; Szakacs, 2004; Yoh, 2004; Konig, 2005; Oda, 2005; Haber, 2006; Oberthuer, 2006; Steinbach, 2006; Maris et al., 2007; Ohtsuki, 2007; Hanada, 2008; Oevermann, 2009; Vander Borght, 2008). In other tumors, the expression of P-glycoprotein may be low at the time of diagnosis but increases after exposure to chemotherapy agents, thereby resulting in the development of MDR in those cells. There is a growing body of literature that links the failure of certain chemotherapeutic agents to the expression of P-glycoprotein (Thomas and Coley, 2003;

Table. Human ABC transporters subfamilies and their functions in cancer.

ABC family	Function
ABCA	Responsible for the transportation of estramustine, mitoxantrone, and anthracyclines.
ABCB	Responsible for the transportation of colchicine, anthracyclines, epipodophyllotoxins, vinca alkaloids, taxanes, camptothecins, bisantrene, imatinib, mitoxantrone, saquinivir, methotrexate, camptothecins, thiopurines, and actinomycin D. Some are located in the blood–brain barrier, liver, mitochondria, transport peptides, and bile.
ABCC	Responsible for the transportation of anthracyclines, camptothecins, cisplatin, colchicine, epipodophyllotoxins, imatinib, methotrexate, mitoxantrone, taxanes, thiopurines, and vinca alkaloids.
ABCD	ABCD transporters are involved in peroxisomal import of fatty acids in the organelle.
ABCE/ABCF	These are not actually transporters but merely ATP-binding domains that were derived from the ABC family, without the transmembrane domains. These proteins mainly regulate protein synthesis.
ABCG	Transports anthracyclines, bisantrene, camptothecins, epipodophyllotoxins, lipids, flavopiridol, imatinib, methotrexate, mitoxantrone, bile, cholesterol, and other steroids.

Fletcher et al., 2010; Holohan et al., 2013). Indeed, the induction of MDR1 RNA can be rapid following exposure of tumor cells to chemotherapy. Inhibiting P-glycoprotein as a way of reversing MDR has been extensively studied. Many agents that modulate the function of P-glycoprotein have been identified, including calcium channel blockers, calmodulin antagonists, steroidal agents, protein kinase C inhibitors, immunosuppressive drugs, antibiotics, and surfactants (Ferry et al., 1996).

4. Targeting drug resistance in cancer

MDR may result from a variety of cellular adaptations including reduced drug uptake, increased energy-dependent drug efflux, altered response to drugs because of changes in programmed cell death (apoptosis), and altered cellular metabolism or sequestering of drugs within cellular compartments (summarized in the Figure). Multidrug resistance can be intrinsic (cancers do not respond to any chemotherapy) or acquired (tumors respond, sometimes dramatically, but eventually grow back and are resistant to subsequent therapy) (Krishna and Mayer, 2000; Gottesman et al., 2002; Albrecht and Viturro, 2007; Fletcher et al., 2010).

In most tissue culture studies of anticancer drug resistance, a predominant mechanism of both forms of MDR is the overexpression of an energy-dependent transporter known as P-glycoprotein, the product of the *MDR1* or *ABCB1* gene (Gottesman et al., 2002; Fletcher et al., 2010). This protein is a transmembrane transporter that resides in the plasma membrane of many cells, including cancer cells that are multidrug-resistant. P-glycoprotein recognizes a wide range of anticancer drugs, many of which are water-insoluble (lipophilic) natural products from plants such as vinca alkaloids, paclitaxel, and fungal products such as anthracyclines and actinomycin D, and keeps these drugs from accumulating at levels sufficient to kill the cell. P-glycoprotein is a member of a family of ATP-dependent transporters found in all living organisms that are called ABC (for ATP-binding cassette) transporters (Dean et al., 2001; Dean, 2005; Dean, 2009). In the human,

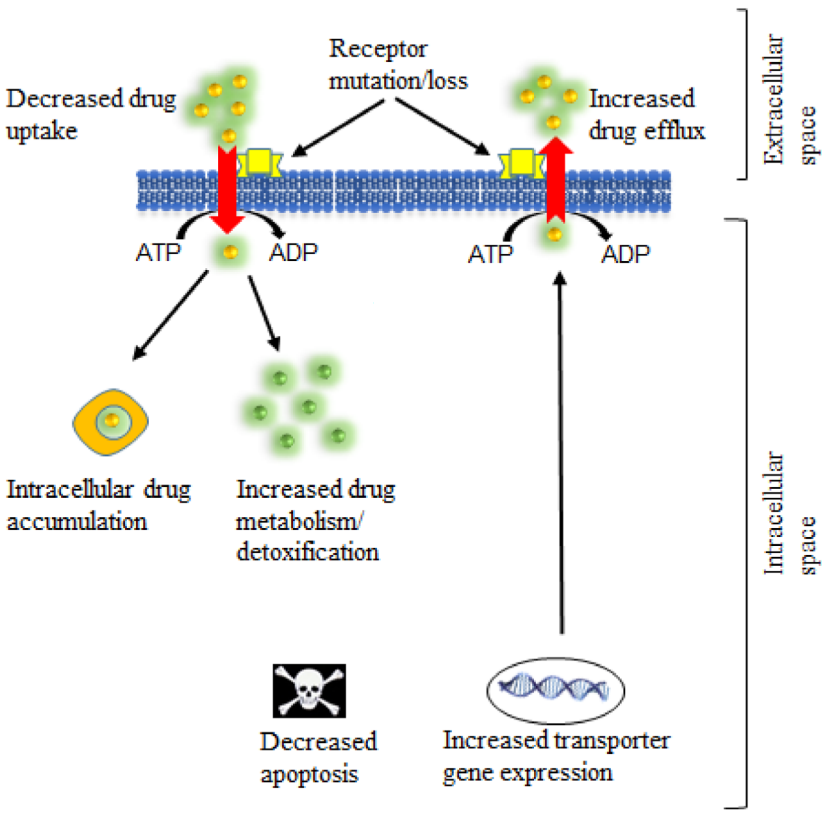

Figure. Molecular mechanisms of drug resistance. Cancer drug resistance can occur by many mechanisms, including poor drug influx, increased drug efflux, increased intracellular drug accumulation, increased drug inactivation or lack of activation; alterations such as changes in expression levels of the drug target; activation of adaptive prosurvival responses; and a lack of cell death induction due to dysfunctional apoptosis.

there are multiple transporters, and many are involved in the transport of lipophilic substances, such as cholesterol and phospholipids, into cellular organelles and out of the cell. A few of these transporters, notably ABCB1, ABCC1, and ABCG2, can pump a broad range of small molecules, many of which are used to treat cancer, and they have also been found to confer MDR to cancer cells. Several lines of evidence suggest that, among these, ABCB1 is most likely to be associated with clinical MDR in cancer, including multiple myeloma, certain types of leukemia, breast cancer, and ovarian cancer (Thomas and Coley, 2003).

Since P-glycoprotein alone can mediate resistance to a whole array of drugs through drug efflux, it is an attractive target for the improvement of anticancer therapy (Ferry et al., 1996; Krishna and Mayer, 2000). Loss of the *abcb1* genes in mice (equivalent to the human *ABCB1* gene) is compatible with life and does not result in an overt phenotype (Schinkel, 1994; Schinkel et al., 1997). These results have been interpreted to suggest that P-glycoprotein inhibitors would likely be safe for human use. Clinical trials aimed at specifically inhibiting the function of P-glycoprotein have given mixed results, but in at least some cases this inhibition has resulted in improved tumor shrinkage and increased patient survival. Unfortunately, P-glycoprotein inhibitors such as PSC-833 (valspodar) induced pharmacokinetic interactions that limited drug clearance and metabolism of the concomitantly administered chemotherapy, thereby elevating plasma concentrations beyond acceptable toxicity (Greenberg, 2004; Lhomme, 2008). The solid tumors that have proved particularly intractable, including colon, liver, kidney, and pancreatic cancers, tend to express ABCB1, but are probably also protected by many other mechanisms of drug resistance, so simple intervention by inhibition of ABCB1 has not proved beneficial in treating those particular tumors (Relling, 1996; Garraway and Chabner, 2002; Thomas and Coley, 2003; Szakacs, 2004; Fletcher et al., 2010).

The major limitation of the early agents is that they typically reverse MDR at concentrations that result in high toxicity. This, together with unfavorable pharmacokinetic interactions, prompted the development of a number of new molecules that are more potent and selective for the P-glycoprotein transporter (Thomas and Coley, 2003; Fletcher et al., 2010). These agents often produced disappointing results in vivo because their low binding affinities necessitated the use of high doses, resulting in high toxicity (Ferry et al., 1996; Krishna and Mayer, 2000; Thomas and Coley, 2003). Many of the first chemosensitizers identified were themselves substrates for P-glycoprotein and thus worked by competing with the cytotoxic compounds for efflux by the P-glycoprotein pump; therefore, high serum concentrations of the chemosensitizers were necessary to produce adequate intracellular concentrations of the cytotoxic drug (Ambudkar, 1999). In addition, many of these chemosensitizers are substrates for other transporters and enzyme systems, resulting in unpredictable pharmacokinetic interactions in the presence of chemotherapy agents. To overcome these limitations, several novel analogs of these early chemosensitizers were tested and developed, with the aim of finding P-glycoprotein modulators with less toxicity and greater potency (Krishna and Mayer, 2000). The second-generation P-glycoprotein modulators include dexverapamil, dexniguldipine, valspodar (PSC 833), and biricodar (VX-710). These agents are more potent than their predecessors and also less toxic (Krishna and Mayer, 2000; Baekelandt et al., 2001; Fracasso et al., 2001; Advani et al., 2005). The best characterized and most studied of these agents is valspodar, a nonimmunosuppressive derivative of cyclosporin D that inhibits P-glycoprotein with 10- to 20-fold greater activity than cyclosporin A (Twentyman and Bleehen, 1991; te Boekhorst et al., 1992). The third-generation P-glycoprotein inhibitors currently in development include the anthranilamide derivative tariquidar (XR9576), the cyclopropyldibenzosuberane zosuquidar (LY335979), laniquidar (R101933), and the substituted diarylimidazole ONT-093 (Dantzig et al., 1996; Starling et al., 1997; Dantzig et al., 1999; Roe et al., 1999; Newman et al., 2000; van Zuylen et al., 2000; Maliepaard et al., 2001; Mistry et al., 2002). These agents have in common a high potency and specificity for the P-glycoprotein transporter. The modulator elacridar (GF120918/GG918), while not as P-glycoprotein -specific as agents such as tariquidar, has been shown to inhibit breast cancer resistance protein BCRP (Maliepaard et al., 2001).

5. Conclusions

Much remains unknown about the fundamental biology of cancers, and although many of the molecular pathways of cancer drug resistance have now been elucidated, new effective targeted agents have yet to be introduced into clinical practice. As for mechanisms by which cancer cells become malignant, each tumor will have a unique signature of resistance mechanisms. The use of powerful high-throughput techniques such as microarray profiling, proteomics and next-generation sequencing provide data that can be used to identify potential predictive biomarkers for patient selection. Therapy will need to be personalized with respect to mechanisms of resistance. The continued development of new agents may establish the true therapeutic potential of P-glycoprotein-mediated MDR reversal.

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