Global Journal of Pharmacology 4 (2): 75-82, 2010
ISSN 1992-0075

ABC Membrane Transporters: Target for Drugs and Diseases

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Abstract: One of the major factors that may interfere with adequate drug response in patients of cancer and acute infections is the extracellular efflux of drugs through membrane transporters. These transporters are broadly divided into two superfamilies i.e. ATP Binding Cassette protein (ABC) transporters and Solute Carrier Protein (SLC) transporters. The important subtypes of ABC transporters are ABCA1, ABCA4, ABCB1, ABCB4, ABC1, ABCC2, ABCC7, ABCG2 and ABCD1. A potential strategy to overcome multidrug resistance to anticancer and antimicrobial drugs is to co-administer efflux pump inhibitors (Reversal Agents). Besides this role in drug resistance, membrane transporters also perform physiological functions like mediating ATP-dependent Cobalamine transport, modulation of ATP-sensitive potassium channels and insulin release. Similarly, absence of or defect in cellular transporters may underlie some genetic disorders e.g. Cystic fibrosis, Retinitis Pigmentosa, Tangiers disease, Stargardt disease etc; and also sometimes be responsible for interindividual variations in drug response, adverse drug reactions and drug interactions. Literature search included original and review articles published between 1998 and 2010.

Key words: Membrane transporters · Multidrug resistance · Genetic disorders

INTRODUCTION

A membrane transporter is a protein involved in the movement of ions, small molecules or macromolecules across a biological membrane via the processes of facilitated diffusion or active transport. Structurally, membrane transporters are integral membrane proteins; i.e they exist within and span the membrane across which they transport exogenous and endogenous substances. Membrane transporters are recognized as key players in the processes of drug absorption, distribution, metabolism and elimination. The location of uptake and efflux transporters in organs responsible for drug biotransformation and excretion, endow on transporters a unique gatekeeper function in controlling drug access to metabolizing enzymes and elimination pathways. Various genes encoding for specific transporters have now been identified and have enabled a classification of transporters, broadly, into two superfamilies, namely the ATP binding cassette proteins (ABC) transporters and Solute carrier proteins (SLC) transporters [1].

Variations may be induced in the functioning of ABC and SLC transporters by drugs, genetic polymorphism and over-expression. Such variations are thought responsible, in many cases, for treatment failures, interindividual variability in drug response and adverse drug reactions. In the following article, an attempt has been made to define the physiological and pathological role and therapeutic importance of various transporters from the ABC superfamily of transporters, based on literature published between the years 1998 and 2010.

ABC Transporters: The ATP Binding Cassete proteins i.e. the. ABC-transporter is the largest superfamily of transporters found in humans. ABC transporters utilize the energy from adenosine triphosphate (ATP) hydrolysis to carry out the function of translocation of various substrates across membranes. ABC transporters can be divided into 7 groups based on their amino acid sequence homology. ABCA, ABCB, ABCC, ABCD, ABCE, ABCF and ABCG [2].

ABCA Transporters: This subfamily is composed of 12 transporters that are split into two subgroups. The first group ABCA1–A4, A7, A12, A13 transporters encode the genes that map to six different chromosomes. The second group of ABCA transporters includes A5-A6, A8-A10

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and the genes encoding them are organized into a head-to-tail cluster on chromosome 17q24. Both the locations and functions of the ABCA1 and ABCA4 transporter have been outlined in detail. The locations of ABCA2, A3, A12 and A13 as well as those of the second group of transporters are as now known. The ABCA5 transporter is expressed in skeletal muscle, ABCA6 in the liver, ABCA8 in the ovary, ABCA9 in the heart and ABCA10 in the skeletal muscle. The functions and physiological role of these receptors are as yet uncharacterized and the same holds true of the second group of. Hence no disease process or pathological state has as yet been linked with aberrations or mutations in these above transporters.

ABCA1 Transporters: The ABCA1 transporter is highly expressed in the liver and is present on the basolateral surface of hepatocytes. The ABCA1 transporter is involved in the removal of cholesterol and phospholipids from cells onto high-density lipoproteins (HDL) particles. Thus they increase HDL levels and decrease triglyceride levels. Although the exact mechanisms how ABC transporters mediate lipid transport are not completely resolved, vesicular transport processes involving different interactive proteins like β2-syntrophin, α1-syntrophin, Lin7 and cdc42 are critically involved in cellular lipid transport. Lipid homeostasis is controlled mainly by transporter ABCA1 and, in addition, ABCG1 transporter also assists this function. Induction of ABCA1 gene in macrophages is especially beneficial for preventing atherosclerosis as it causes efflux of excess cholesterol. Efflux of excess cholesterol is also thought to mediate other beneficial properties like anti-inflammatory and antioxidant property.

Mutations in the ABCA1 transporter gene cause a well defined clinical syndrome,i.e. Tangier's disease [3]. These patients have low levels of HDLc and triglycerides are high and show increased incidence of cardiovascular diseases. Thus, in addition to hypolipidemic agents, therapies that increase expression of ABCA1 transporters could provide a new approach for the treatment of these patients.

It has been found that Liver X Receptor (LXR) family of transcription factors can supregulate the expression of the ABCA1 gene. Cholesterol lowering drugs like fibrates have been shown to induce expression of ABCA1 transporters in transgenic mice. Fenofibrate, Bezafibrate, Gemfibrozil and LY518674 were tested for HepG2 cells and primary-cultured mouse hepatocytes [4]. All the compounds examined, increased ABCA1 expression and HDL biogenesis in association with the liver X receptor á upregulation. The Statins have also been found to elevate HDL levels through ABCA1 transporters upregulations [5]. Doxazocin an alpha blocker antihypertensive drug also increases ABCA1 transporter expression through LXR [6].

ABCA4 Transporters: ABCA4 is a retina-specific ABC transporter, expressed exclusively in photoreceptors, it is also known as Rim Protein (RmP) or as ABCR. The ABCA4 transporter is postulated to be involved in the active transport of all-trans-retinal aldehyde (atRAL) across photoreceptor disk membranes. Mutations in the *ABCA4* gene have been associated with multiple ocular disorders, predominantly chorioretinal disorders. Complete loss of ABCA4 transporter function leads to retinitis pigmentosa, whereas patients with moderately severe mutations develop the so-called Stargardt disease (STGD) [7]. The primary pathologic defect in Stargardt's disease is an accumulation of elevated phosphatidylethanolamine (PE) in rod outer segments and retinal pigment epithelium (RPE). The accumulation of an adduct of atRAL, PE and N-retinylidene-N-retinylethanolamine (A2E) collectively called as lipofuscin pigment is deposited in the retinal pigment epithelial layer.

The build-up of lipofuscin causes atrophy of the macula and the underlying RPE. This accumulation appears to be responsible for the photoreceptor death and severe visual loss in these patients. The effects of isotretinoin on lipofuscin accumulation in knockout mice were tested [8]. These results suggested that treatment with isotretinoin may inhibit lipofuscin accumulation and thus delay the onset of visual loss in patients of Stargardt's disease Results also suggested that isotretinoin may be an effective treatment for other forms of retinal or macular degeneration associated with lipofuscin accumulation.

ABCB Transporters: sThis is the most variable subfamily and includes 11 subtypes of transporters. The functions of each of them have been characterised. The transporters of this family are involved in transport of iron, peptides and drug molecules across cells. The functions of all ABCB transporters are characterised, except for ABCB3, ABCB5, ABCB9 And ABCB10 transporters.

ABCB1 Transporters (MDR1/P-Glycoprotein): The ABCB1 transporter (P-glycoprotein) is glycosylated and is expressed in various tissues like intestine, liver, brain, placenta, adrenal and testes.

This transporter performs a crucial physiological function, namely, protection of cells and organs against toxic compounds and metabolites. This transporter is an ATP-dependent drug efflux pump for xenobiotic compounds, which shows broad substrate specificity [9]. The ABCB1 transporter, in addition, can be inhibited and is inducible by many drugs, leading sometimes to various clinically important drug interactions. Due to its high transport capacity, substrate recognition, susceptibility to inhibitors and inducers, this is the transporter that is predominantly involved in multidrug resiststance (MDR) and drug interactions.

Under normal conditions, ABCB1 protects patients from Digoxin toxicity by facilitating its extracellular efflux. When ABCB1 is inhibited by drugs such as Clarithromycin or Itraconazole, patients are at higher risk for Digoxin toxicity, particularly those relating to the Central Nervous System. On the other hand, when Rifampin is used in combination with Digoxin it leads to decreased serum Digoxin levels because Rifampin being an inducer increases the intestinal ABCB1, which decreases Digoxin levels and decreases its oral bioavailability.

The ABCB1 transporter along with the ABCC1 and ABCG2 transporters, play an important role in the development of Multidrug Resistance. One of the underlying mechanisms of MDR is cellular overproduction of the ABCB1 transporter which acts as an efflux pump for various anticancer drugs. The gene encoding for the ABCB1 transporter is overexpressed in drug-resistant cells and therefore, drugs that attenuate this overexpression have the therapeutic potential of circumventing multidrug resistance [10].

A potential strategy to overcome multidrug resistance to anticancer drugs is to co-administer efflux pump inhibitors (reversal agents) [11]. First generation reversal agents include drugs already in current clinical use for other indications (e.g. Verapamil, Cyclosporine A, Quinine, Erythromycin). First-generation reversal drugs were not specifically developed for inhibiting ABCB1 efflux functions. Besides possessing primarily other pharmacological activities, as well as a relatively low affinity for ABCB1 transporters, their clinical applications were very limited.

Second-generation reversal drugs were developed on the lines of the first generation agents drugs, but were specifically synthesized or designed to minimize certain unwanted and toxic effects of the latter by eliminating those pharmacological actions which did not serve to minimize multidrug resistance. Most of the second generation drugs were analogues of the first generation drugs. e.g. dexverapamil, valspodar, cinchonine etc. but did not show adequate effects as an MDR reversal agents in clinical studies, most probably owing to lesser affinity towards P-Glycoprotein.

Clinical trials with third generation modulators (e.g. Biricodar, Zosuquidar and Laniquidar) specifically developed for MDR reversal are ongoing. A potential use of these agents may be to enhance intestinal drug absorption and increase drug penetration across biologically important protective barriers, such as the blood-brain, blood-cerebrospinal fluid and the maternal-fetal barriers. Limitations to the use of these modulators include multiple cellular mechanisms of resistance, alterations in pharmacokinetics of cytotoxic agents and clinical toxicities [12].

Other approaches to overcome multidrug resistance reversal have also been considered i.e. the use of ABCB1 transporters targeting antibodies such as UIC2 or the use of antisense strategies targeting the ABCB1 messenger RNA. More recently, the development of transcriptional regulators appears promising. In addition, development of anticancer drugs that are not substrates of this drug transporter may act as potent inhibitors of MDR tumors (e.g. Epothilones, second generation taxanes) [13].

Recently, a number of single-nucleotide polymorphisms (SNPs) in ABCB genes have been identified which can result in problems including altered drug levels, host susceptibility to diseases such as Parkinson's disease, inflammatory bowel disease, refractory seizures and delayed CD4 cell recovery during antiretroviral therapy. However, in many such cases, the reported effects of these SNPs have been inconsistent and, in some cases, conflicting [14,15].

ABCB2 / TAP1 and ABC B3 / TAP 2 Transporters (Transporters Associated with Antigen Processsing): These transporters are localized in the membrane of endoplasmic reticulum and serve to pump degraded cytosolic peptides into membrane bound compartment where MHC CLASS I molecular complexes assemble. The ABCB3 transporter also functions as a peptide transporter and is involved in antigen presentation. It forms a heterodimer with TAP1/ ABCB2 in order to transport peptides from the cytoplasm to endoplasmic reticulum. Variations or Abnormalities in ABCB2 and ABCB3 transporters can thus produce a deficient immune response which could possibly cause immunosuppresion.

Several DNA viruses such as the herpes simplex virus express molecules that interfere with antigen expression by disrupting the function of the ABCB2 –B3 complex. In addition, tumor cell lines have been described that are mutated and deficient in ABCB2 –B3 activity. Patients with inherited immunodeficiency because of ABCB2 mutations have also been described [16].

ABCB4 / MDR3 Transporters: The ABCB4 transporter is principally expressed in the bile canalicular membrane of the liver, but is also found in the heart, muscle and in B lymphocytes. In the liver, they are involved in transport of phosphatidylcholine. Mutations of ABCB4 are responsible for progressive familial intrahepatic cholestasis type 3, which is characterised by a defect in fatty acid secretion into bile. Mutations of ABCB4 transporter are also responsible for intrahepatic cholestasis of pregnancy (ICP), a liver disorder associated with increased risk of intrauterine fetal death and prematurity.

ABCB4 (MDR3) is also involved in multidrug resistance to certain anticancer drugs. Paclitaxel-resistant cell lines overexpressed both ABCB1 and ABCB4. Treatment of these lines with either chemically synthesized siRNAs (small interfering RNA) or transfection with specific vectors that express targeted siRNAs demonstrated decreased mRNA and protein levels of ABCB1 or ABCB4. ABCB4 transporter siRNA-treated cell lines showed a minor reduction in Paclitaxel resistance [17].

ABCB6-8 Transporters: These proteins are not well characterized but are most probably localized in the mitochondrial inner membrane. ABCB6, ABCB7 and ABCB8 transporters are involved in mitochondrial iron homeostasis. They transport heme from mitochondria to the cytosol. They are also thought to contribute some inherited metabolic disorders such as ABCB6 for lethal metabolic syndrome characterized by development of atherosclerotic risk factors including dyslipidemia, insulin resistance, obesity and hypertension, while ABCB7 for X linked Sideroblastic anemia with ataxia [18].

ABCB11 / BSEP Transporters (Bile Salt Export Pump): ABCB11 transporters are located in the liver and are involved in the secretion of bile. Mutations in ABCB11 can cause progressive familial intrahepatic cholestasis type 2 in which there is a defect in bile acid excretion i.e. a defect in the bile salt export pump (BSEP).

ABCC Transporters: The ABCC subfamily consists of 12 transporters with a diverse spectrum of functions that includes ion transport, cell surface receptor and toxin secretion activities. All of them are involved in MDR except C7, C8 and C9. The ABCC10-ABCC12 (MRP7 - MRP9) transporters show low tissue expression and therefore are not much involved in the transport function.

ABCC1 (MRP1) / ABCC2 (MRP2)/ ABCC3 (MRP3) Transporters (Multidrug Resistance –associated Protein 3): ABCC1, ABCC2 and ABCC3 transporters each have a distinctive pattern of tissue expression and substrate specificity. Together, these transporters play important roles in the disposition and elimination of drugs and other organic anions and in maintenance of blood-tissue barriers.

The ABCC1 transporter is commonly known as Multidrug Resistance-associated protein 1 (MRP1), while an alternative name for it is Leukotriene C(4) transporter (LTC4 transporter). The ABCC1 transporter is present in the basolateral membrane of intestinal epithelium and in other cells. It mediates ATP-dependent transport of glutathione and glutathione conjugates, leukotriene C4, estradiol-17-beta-o-glucuronide, methotrexate, antiviral drugs and other xenobiotics. It confers resistance to anticancer drugs by exporting anti-cancer agents through the cell membrane. It also mediates ATP-dependent Cobalamine transport [19] and also iron efflux with the help of NO [20].

ABCC2 Transporters: The ABCC2 transporter is located in the canalicular membrane of hepatocytes. This transporter was originally known as the canalicular multispecific organic anion transporter (cMOAT). Mutations in the ABCC2 transporter in the canalicular membrane of hepatocytes were found in patients with Dubin-Johnson syndrome [21]. These mutations particularly affect the transport of bilirubin into bile. As a result, bilirubin accumulates in the body causing severe conjugated hyperbilirubinemia. In transfected cells, overexpression of the ABCC2 transporter resulted in resistance to Methotrexate, Cisplatin, Etoposide, Doxorubicin, Epirubicin, Cisplatin and Mitoxantrone [22].

Recent work has shown that ABCC3 is also an organic anion transporter located in the basolateral membrane of the hepatocytes. However, unlike ABCC1 and ABCC2 transporters, it prefers shows substrate preference for glucuronate conjugates over GSH conjugates.

The physiological function of the ABCC3 transporter remains to be established. A massive increase in the expression of ABCC3 transporters has been seen in the liver of cholestatic rats and humans. Thus it may allow efflux of organic anions from the liver into the blood when secretion into bile is blocked. A role for the ABCC3 transporter in the normal uptake of bile salts from the gut has also been postulated.

The potential involvement of these transporters in clinical drug resistance has led to a search for compounds that can be used to inhibit these transporters. Attempts to find inhibitors for ABCC have concentrated mainly on ABCC1 and ABCC2 transporters. Compounds that efficiently block ABCB1 transporters, only have a low affinity for ABCC1 or ABCC2 transporters and thus can not be considered as potent inhibitors. Subsequent potent competitive inhibitors developed were the leukotriene D_4 antagonist MK571 and organic acids that were originally developed to inhibit transport of uric acid, like Sulfinpyrazone, Benzbromarone and Probenecid. Although ABCC1 and ABCC2 transporters have a similar substrate specificity but the inhibitors for ABCC1 transporters are not necessarily potent inhibitors of ABCC2 transporters. Sulfinpyrazone, for instance, does not inhibit transport of the model substrate dinitrophenyl *S*-glutathione by ABCC2 [22].

Similarly, the glutathione conjugate of ethacrynic acid (GS-EA) is a good inhibitor of ABCC1. A transporter series of novel GS-EA analogues were synthesized in which peptide bonds of the GSH backbone were replaced by isosteric groups. These compounds also partially reversed the resistance of these cells to methotrexate [23]. Tricyclic isoxazoles also were identified from a screen as a novel class of selective multidrug ABCC1 inhibitors [24].

An experimental drug, LY402913 inhibited ABCC1 transporter and reversed drug resistance to MRP1 substrates, such as Doxorubicin, in HeLa-T5 cells while showing no inherent cytotoxicity. It is suggested that 2' 7'-bis-(carboxypropyl)-5(6)-carboxyfluorescein (BCPCF) efflux from human erythrocytes is mainly due to ABCC1 activity. The most efficient flavanones, euchrestaflavanone A and sophoraflavanone H, induce upto almost 50% inhibition of BCPCF efflux from human erythrocytes and provide a promising base for development of potent ABCC1 inhibitors [25] Targeting ABCC1 transporters may also help to overcome cobalamine deficiency associated with certain hematological and neurological disorders.

ABCC4 (MRP4) / ABCC5 (MRP5) / ABCC6 (MRP6) Transporters: sThe human ABCC4, ABCC5 and ABCC6 transporters have been recently characterised as primary active transporters. ABCC4 can mediate the transport of several nucleoside analogues including anti HIV drugs, such as 9-(2-phosphonylmethoxyethyl)adenine (PMEA) and Azidothymidine Monophosphate (AZTMP). High levels of ABCC4 transporters severely impaired the antiviral efficacy of several nucleoside analogues. ABCC4 transporters can also confer resistance to anticancer base analogues (e.g., 6-mercaptopurine and Thioguanine), however the physiological function of ABCC4 and ABCC5 transporters is not yet clearly known.

The ABCC6 transporter is highly expressed in the liver and kidneys and to a low extent in a few other tissues. Both the physiologic functions and the potential involvement of ABCC6 in drug resistance are still unclear. Mutations affecting the human ABCC6 gene were described in patients with Pseudoxanthoma elasticum, a rare heritable disorder resulting in the calcification of elastic fibres [18].

ABCC7 Transporters

ABCC7 Transporter: The ABCC7 transporter also called as CFTR (cystic fibrosis transmembrane conductance regulator) is located mainly in the exocrine tissues and fuctions mainly as chloride ion channel allowing anions to diffuse through the membrane in either direction (absorptive or secretory) depending on the electrochemical gradients. The absence or dysfunction of CFTR results in aberrant ion movements at epithelial surfaces of the respiratory, intestinal and reproductive tracts as well as other secretory and reabsorptive epithelia.

Hence mutations in ABCC7 gene deficiency results in cystic fibrosis, congenital bilateral absence of the vas deferens, disseminated bronchiectasis, allergic bronchopulmonary aspergillosis and chronic pancreatitis.

Cystic Fibrosis (CF) is caused by mutations of the ABCC7 transporter gene i.e. deletion of a phenylalanine at position 508 (delta F508) which results in abnormal chloride transport. Activators of the ABCC7 channel may be useful for therapy of cystic fibrosis. Flavonoids (Genistein, Apigenin, Kaempferol and Quercetin) and bromotetramisole (Br-t) strongly activate ABCC7 chloride channels on Chinese hamster ovary cells and human airway epithelial cells and can form the basis for pharmacotherapy targets for cystic fibrosis [26].

The ABCC7 transporter is specifically found in Leishmania major and no orthologues were found in the genome of related organisms like Trypanosoma cruzi, Trypanosoma brucei. ABCC7 also called as PRP1 i.e. Pentamidine resistant protein 1 are intracellular proteins and are probably part of tubulovescicular elements which are involved in endocytosis and exocytosis in leishmania. ABCC7 transporters can confer resistance to Pentamidine and Antimony in Leishmania sp. parasites in the intracellular stage [27].

ABCC8 Transporters: This transporter functions as a modulator of ATP-sensitive potassium channels (K(ATP) channels) and insulin release. Common polymorphisms in these genes ABCC8 have been associated with type 2 diabetes. This transporter provides a high affinity binding site for antidiabetic drugs sulfonylurea (SUR1) and thiazolidinediones (Repaglinide, Nateglinide) which are widely used to treat patients with NIDDM. These drugs lower blood glucose levels by blocking ATP-dependent potassium channels in pancreatic beta cells to stimulate insulin secretion. Mutations have also been shown in the genes for these subunits, namely for the plasma membrane sulfonylurea receptor (SUR1), ABCC8 transporter and its associated inwardly rectifying potassium channel. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) can occur as a result of mutations in the K_+^{ATP} channels in pancreatic β-cells which play a major role in modulating insulin secretion from the β-cells. Thus knowing the exact locus of the abnormality in the β-cell, preventive measures can be implemented by applying genotyping [28,29].

ABCC8 Ser1369Ala polymorphism was recently reported to influence progression to diabetes as well as response to antidiabetic agent Gliclazide. The patients with Ala/Ala genotype appeared to respond significantly better to Gliclazide than did patients with Ser/Ser genotype. One study in China had shown that genetic variation can be a significant determinant of response to oral hypoglycemic drugs [30].

Recently few studies have shown that SUR1 is upregulated in CNS ischemia and injury and this is in association with different pore-forming subunits. Preclinical and clinical studies demonstrating the potential importance of blockade of SUR1 by sulfonylureas such as Glibenclamide (Glyburide) in diverse conditions as stroke and spinal cord injury are ongoing [31].

ABCD Transporters: s This subfamily contains 4 genes that encode transporters expressed exclusively in the human peroxisome membrane where they function in the regulation of very long chain fatty acid transport. ABCD genes are under complex regulation at the transcriptional level and are linked to cell lipid metabolism and hence they share with the ABCA and ABCG subclasses the sensitivity to the peroxisome proliferator-activated receptor and retinoid X receptor family of nuclear receptors. Mutation of the gene encoding for the ABCD1 transporter is responsible for the X-linked form of Adrenoleukodystrophy(ALD), a disorder characterized by neurodegeneration and adrenal deficiency, typically initiating in late childhood. Cells from ALD patients are characterized by an accumulation of unbranched saturated fatty acids, but the exact role of ABCD1 in this process has yet to be elucidated [2,18].

ABCE [Oligoadenylate Binding Protein (OABP)] AND ABCF Transporters: ABCE and ABCF transporter subfamilies have ATP binding domain and thus are closely related to other ABC transporters but they do not have transmembrane i.e. TM domain. As yet they are not involved in any membrane transport functions. ABCE has been found to block the activity of Ribonuclease L. Activation of enzyme Ribonuclease L leads to inhibition of protein synthesis primarily interferons; hence, ABCE functions to promote interferon activity. The ABCF transporter may be regulated by tumor necrosis factor-alpha and play a role in enhancement of protein synthesis and the inflammatory process [2,18].

ABCG Subfamily of Transporters: ABCG subfamily has five member transporters: ABCG1, ABCG2, ABCG4, ABCG5 and ABCG8. Except for ABCG2, the members of the ABCG family play an important role in the efflux transport of cholesterol and in foam cell formation of human macrophages. In atherosclerotic arteries, ABCG1 is highly expressed in foamy macrophages and in bundles of nerves present in the outermost layer of the artery. In contrast ABCG2 (BCRP-Breast cancer resistance protein) is involved in multidrug resistance; and it confers resistance to anticancer drugs and plays a critical role in the pharmacokinetics of drugs in the clearance organs and tissue barriers [32]. Phytoestrogens and flavonoids reverse breast cancer resistance protein/ ABCG2 mediated multidrug resistance. To circumvent ABCG2 mediated MDR, a common approach is the use of potent and specific inhibitors of BCRP transport such as fumitremorgin C, Novobiocin and GF120918 [33].

GF120918 is an acridine carboxamide derivative and was first identified as a third generation ABCB1 inhibitor. In patients GF120918 increased apparent bioavailability of oral Topotecan and also reversed the Doxorubicin and Topotecan resistance of ABCG2 overexpressing cell lines [34]. Low concentrations of the Tyrosine Kinase inhibitors like Gefitinib selectively modulated ABCG2-ATPase activity, inhibited ABCG2-dependent active drug extrusion and significantly affected drug resistance patterns in cells expressing ABCG2 [35]. Very recent studies showed that mutations in two members of the subfamily G of human ABC transporters (ABCG5 and ABCG8) cause a condition called sitosterolemia in which plant sterols accumulate in the body and may be responsible for influencing total body sterol homeostasis [36].

CONCLUSION

It is important to apply the available knowledge of various human ABC transporters to clinical practice and to development of new therapeutic modalities. Genetic polymorphisms and mutations of human ABC transporter genes are seen to be linked both to certain disease states and patients' responses to medication especially anticancer agents. Though the study of human ABC transporters is still in its infancy, recent and significant insights in this area have helped in the elucidation of the cause of several inheritable human disease conditions and may create important inroads in the improved understanding of drug pharmacokinetics and effective therapy of cancerous states by circumventing the hurdle of resistance to agents used in the treatment of such conditions.

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