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Review Article

A Review on ATP Binding Cassette (ABC) Transporters

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ABSTRACT

ATP binding cassette (ABC) transporters form a special famil of membrane proteins, characterized by homologous ATP-binding, and large, multispanningtransmembrane domains. Several members of this family are primary active transporters, which significantly modulate the absorption, metabolism, cellular effectivity and toxicity of pharmacological agents. ABC transporters can transport a wide variety of substrates across biological membranes in an energy-dependent manner. Many ABC transporters such as P-glycoprotein (P-gp), multidrug resistance-associated protein 1 (MRP1) and breast cancer resistance protein (BCRP) are highly expressed in bronchial epithelium. This review provides a general overview of the human ABC transporters, their expression, localization and basic mechanism of action in a brief manner.

Keywords: ABC transporters; localization; structure; multidrug resistance

1. INTRODUCTION

Lipid membranes play an import role in cell survival and homeostasis by providing a barrier between the interior of the cell and its exterior environment. An essential function in every cell is the ability to import nutrients as well as export waste products and signaling molecules. ATP-binding cassette (ABC) transporters play significant physiological and toxicological roles in these export and import processes [1]. ABC transporters utilize the hydrolysis of ATP to drive transport of substrates against their concentration gradient. Generally, in eukaryotic cells these transporters are exporters while in prokaryotic cells they are both importers and exporters [1].

ABC transporters were first discovered in prokaryotic cells of Escherichia coli (E. coli). The first eukaryotic transporter

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to be discovered was P-glycoprotein (MDR1), by it involvement in cancer multidrug resistance(MDR) [2].Today, 50 ABC transporters have been identified in humans. Mutations in these transporters can lead to a variety of genetic diseases, including bleeding, many liver and eye disorders, all of which are caused by the failure to export a specific ligand across a lipid bilayer [2].

1.1. The ABC Transporter Family

The ATP binding cassette (ABC) proteins represent a highly diversify superfamily in all living kingdoms, with 50 human proteins, 14 of which are associated with various diseases. They are found in all organisms from prokaryotes to eukaryotes and carry a wide variety of xenobiotics (including drugs), lipids, sugars, amino acids, sterols, and metabolic products across the plasma and intracellular membranes [1]. Although differences are observed in their functions, substrate specificities, molecular mechanisms, and in vivo localizations, they share a high degree of sequence and structural homology. They are classified into 7 subfamilies that are designated A to G based on the similarity in the gene structure, order of the domains, and sequence homology in the NBDs and TMDs**[Table1]** [3].These members of the ABC superfamily are associated with abroad spectrum of physiological functions, includingdetoxification (ABCB1/MDR1, ABCC1/MRP1), defenseagainst xenobiotics and oxidative stress (ABCCs/MRPs),absorption and secretion processes (MDRs, MRPs), lipidmetabolism (ABCA1, MDR3, ABCGs), antigen presentation(ABCB2/TAP1 and ABCB3/TAP2), etc [4-6].

Even though most of the human ABC transporters play a role in the export of physiological substrates and xenobiotics(amino acids, peptides, lipids, inorganic ions…), three of them play critical clinical roles in chemotherapeutic drug resistance [7] .These are the P-glycoprotein (ABCB1, P-gp), the Multidrug Resistance associated Proteins or MRPs (MRP), and the Breast Cancer Resistance Protein (BCRP, ABCG2).They are highly expressed in the gut, liver and kidneys where they restrict the bioavailability of administered drugs [7-8] .

1.1.1. Multidrug resistance ABC transporters ABCB1/MDR1

P-Glycoprotein (Pgp) was one of the first members of the ABC superfamily to be studied extensively and is among proteins whose structure and function is well perceived [2]. Overexpression of P-glycoprotein was linked to multidrug resistance (MDR) in mammalian cell lines and human cancers and also known to be linked to poor absorption of some pharmaceutical products.P-glycoprotein in higher mammals including human being forms a small gene family. In humans MDR1 protein (where the gene encoding this protein is ABCB1) is drug transporter, whereas MDR2/3 protein (ABCB4) exports phosphatidylcholine (PC) into the bile [2]. Tissue distribution of Pgp is diverse and almost all epithelial cells with excretory roles. Among these cells the apical surface of epithelial cells lining the colon, small intestine, pancreatic ductules, bile ductless and kidney proximal tubules, and the adrenal gland are good examples. Beside these the endothelial cells of the blood–brain barrier, the blood–testis barrier, and the blood–mammary tissue barrier also have this transporter.P-glycoprotein is expressed at high levels at the luminal surface of cells in the pregnant endometrium, as well as the placenta which may explain the protective role of the protein for the fetus [9-10].

Table.1Human ABC transporters and their basic features

Family	Member	Alias	Expression	Function
ABCA	ABCA1	ABC1	Ubiquitous	Removal of cholesterol and PLs
	ABCA2	ABC2	Brain	onto HDL particles
	ABCA3	ABC3,	Lung	Drug resistance
	ABCA4	ABCC	Rod	Surfactant protection
	ABCA5	ABCR	photoreceptors	N-retinydilester-PE efflux
	ABCA6		Muscle, heart, testes	
	ABCA7		Liver	
	ABCA8		Spleen, thymus	
	ABCA9		Ovary	
	ABCA10		Heart	
	ABCA11		Muscle, heart	
	ABCA12		Stomach	
			Low in all tissues	
ABCB	ABCB1	MDR1, PGP	Adrenal, kidney, brain	Multidrug resistance
	ABCB2	TAP1	Ubiquitous, ER	Peptide transport into the ER
	ABCB3	TAP2	Ubiquitous, ER	Peptide transport into the ER
	ABCB4	PGP3,	Liver	Phosphatidylcholine transport
	ABCB5	MDR3	Ubiquitous	
	ABCB6		Mitochondria	
	ABCB7	MTABC3	Mitochondria	
	ABCB8	ABC7	Mitochondria	Iron transport
	ABCB9	MABC1	Heart, brain	Heme transport
	ABCB10		Mitochondria	Heme transport
	ABCB11	MTABC2	Liver	Bile salt transport
		SPGP, BSEP		
ABCC	ABCC1	MRP1	Ubiquitous	Drug resistance
	ABCC2	MRP2, cMOAT	Liver	Organic anion transport
	ABCC3	MRP3, cMOAT-2	Lung, intestine, liver	Drug resistance
	ABCC4	MRP4, MOAT-B	Prostate	Nucleoside transport
	ABCC5	MRP5, MOAT-C	Ubiquitous	Nucleoside transport
	ABCC6	MRP6	Kidney, liver	
	ABCC7	CFTR	Exocrine tissues	Chloride ion transport
	ABCC8	SUR	Pancreas	Sulfonylurea receptor
	ABCC9	SUR2	Heart, muscle	
	ABCC10	MRP7	Low in all tissues	
	ABCC11	MRP8	Low in all tissues	
	ABCC12	MRP9	Low in all tissues	
ABCD	ABCD1	ALD	Peroxisomes	VLCFA transport regulation
	ABCD2	ALD1,ALDR	Peroxisomes	
	ABCD3	PMP70, PXMP1	Peroxisomes	
	ABCD4	PMP69, P70R	Peroxisomes	
ABCE	ABCE1	OABP	Ovary, testes, spleen	Oligoadenylate-binding protein
ABCF	ABCF1	ABC50	Ubiquitous	
	ABCF2		Ubiquitous	

	ABCF3		Ubiquitous	
ABCG	ABCG1 ABCG2 ABCG4 ABCG5 ABCG8	ABC8, Human white ABCP, MXR, BCRP White2 Steroline 1 Steroline 2	Ubiquitous Placenta, intestine Liver Liver, intestine Liver, intestine	Cholesterol transport Drug resistance Sterol transport Sterol transp

Physiological role of this protein is to protect susceptible organs and tissues such as the brain, testis, fetus, and inner ear from toxic xenobiotics as can be seen from their direction of substrate transport and tissue distribution. These concepts have been strongly supported by studies on transgenic knockout mice lacking one or both of the genes encoding the drug-transporting Pgps Abcb1a and Abcb1b. These mice are sterile and alive but they are highly susceptible to toxins compared to the wild mice. In the same manner certain dogs having naturally occurring lack of Pgp due to a frameshift mutation in the MDR1 showed hypersensitivity to ivermectin (neurotoxin) supporting the experimental finding in mice. P-glycoprotein in the intestinal epithelium plays an important role in the extrusion of many drugs. It reduces the absorption and oral bioavailability of those drugs that are transport substrates [11].

P-glycoprotein has the ability to interact with literally hundreds of structurally diverse substrates which include non-polar and weakly amphipathic compounds. Some compounds interact with Pgp and are called modulators (also known as MDR chemosensitizers, reversers, or inhibitors. Modulators are able to reverse MDR in intact cells in vitro, by interfering with the ability of Pgp to efflux drug e.g. verapamil, cyclosporin A [11].

MRP1/ABCC1

Multidrug resistance-associated protein 1 (MRP1, ABCC1) was first discovered in a small cell lung cancer cell line, H69AR. These cells had developed drug resistance to Doxorubicin (DOX) without the increase in expression of P-gp, leading to the discovery of another ABC transporter involved in drug resistance, MRP1 [12]. In humans, there have been 12 ABCC family members discovered, ABCC1-ABCC12. MRP1 is a 190 kDa heavily glycosylated ABC transporter that contains three MSDs and two NBDs. MRP1 is highly conserved between humans and rodents with 88% sequence homology. However, rodent MRP1cannot transport anthracyclines like Doxorubicin [13]. MRP1 is ubiquitously expressed especially in heart, skin, lung, brain capillaryendothelial cells, and the small intestine. Substrates forMrp1 are usuallyamphiphilic anionic compounds. Hydrophobic metabolic by products can also be substrates through conjugation with glutathione (GSH), sulfate, or glucuronic acid. So, it can transport hydrophobic compounds in the presence of GSH. Transport specificity of MRP1 overlaps with some MDR1 substrates, and includes epipodophyllotoxins, vinca alkaloids, anthracyclines(doxorubicin and danorubicin) [14].

ABCG2/BCRP

In the late 1990's, a breast cancer cell line highly resistant to Doxorubicin was found to be lack expression of MDR1 and MRP1. A new ABC transporter was found in the cells and named Breast Cancer Resistance Protein (BCRP), or ABCG2 (54). ABCG2 is a half transporter, where the gene encodes one MSD with six TM helices and one NBD.

Homodimerization of two ABCG2 half transporters creates a fully functional transporter. Over expression of ABCG2 alone in insect cells yields a functional transporter so it is not thought to heterodimerize with any other partners [15].

ABCG2 is primarily expressed in the apical membrane of the small intestine, liver, mammary gland, testis, BBB, and placenta. It effluxes several chemotherapeutic drugs including mitoxantrone, doxorubicin, irinotecan, imatinib, and methotrexate (MTX), as well as some food carcinogens and vitamins such as riboflavin and folic acid [16]. Like Mrp1, ABCG2 can also transport sulfate and glucuronide conjugates. ABCG2 transcriptional regulation is similar to MDR1 and Mrp1, with Sp1 and AP-1 binding sites [12]. Expression can also be enhanced by estrogens by the estrogen response element(ERE), which has been shown in estrogen receptor (ER)-positive cells [16]. The primary role of ABCG2 appears to overlap with the functions of MDR1 and Mrp1 as discussed above. The main role of ABCG2 is thought to involve prevention of drug accumulation and to increase clearance of xenobiotics, which can be emphasized by its expression in tissues like the intestine, BBB, and placenta. On the other hand, ABCG2 may play a negative role in the mammary gland, where although it effluxes vitamins like riboflavin, other ABCG2 substrates like chemotherapeutic drugs and carcinogens canbecome concentrated in milk[16]. Excretion of drugs into milk can be beneficial to themother by preventing build-up of xenobiotics, however, it can result in a detrimentalaccumulation of xenobiotics in the suckling newborn.

1.2. Localization and expression of ABC transporters

ABC transporters with multidrug transporter function (ABCB1/MDR1, ABCC1/MRP1,ABCG2) show a widespread expression profile, providing a cellular defense mechanism throughout the organism**[table1].** But they are expressed more in tissues important for absorption and metabolism and elimination, such as lung, gut, liver and kidney. The tissue distribution of these three major multidrug resistance proteins is overlapping but different. MDR1 is more restricted to tissues involved in the absorption and secretion, such as the canalicular surface of hepatocytes in the liver, in the epithelial cells of the proximal convoluted tubule in the kidney, the apical surface of gastrointestinal epithelial cells, the cortex and medulla of the adrenal glands, myoepithelium and in cells of the

immune system [1-4]. ABCC1/MRP1 expression is high in all tissues; it is elevated at blood–normal tissue barriers, including testicular tubules, the choroid plexus, where it contributes to the blood–CSF (cerebrospinal fluid) barrier, and in bone marrow precursor cells and reduced in the liver.Recent reports have demonstrated that ABCG2 is highly expressed in the hepatocytes of the liver, zonareticularis layer of the adrenal glands, alveolar pneumocytes of the lung, prostate epithelium, uterine endocervical cells, cortical tubules of the kidney, islet and acinar cells in the pancreas, epithelial cells of the gastrointestinal tract and ducts and lobules of the mammary glands [17-18] **.** In tissues where different multidrug transporters are present, the sub-cellular localization of these proteins can be a discriminating feature.

In addition to their role in normal physiology, ABC transporters are highly expressed in multiple tumour types,such as breast cancer, sarcoma and certain leukaemias.

1.3. Structure of ABC transporters

Typical ABC transporter consists of two membrane-spanning domains (MSDs), and two cytosolic nucleotide binding domains (NBDs). ABC transporter domains can be encoded into separate polypeptides like the vitamin B12 importer BtuCD in E. Coli [19], they can be half transporters (one MSD and one NBD) that dimerize to form a functional transporter like ABCG5 and ABCG8, or full-length and contain all four domains encoded into one peptide, as in P-glycoprotein. Some also have an extended transmembrane (TM) domain and consist of three MSDs such as MRP1 [1]**.**

Membrane-spanning domains consist of several TM helices (most commonly six) involved in substrate binding, specificity, and movement across the cell membrane.MSDs also have intracellular loops (ICLs) that interact with the NBDs and may assist in conformational alterations to facilitate substrate transport [20]**.** Hydrolysis of ATP in NBDs confers a structural change in the MSD domain, allowing transport across the lipid bilayer. Nucleotide binding domainsconsist of 200-300 amino acids and are highly conserved across genes [21]. They contain a Walker A and B motif [20-21] separated by 90-120 amino acids and a signature C-loop or LSGGQ motif upstream of the Walker Bmotif. The NBD also contains signature ABC motifs D-, H-, A-, and Q-Loops. Crystal structures of three ABC transporters have been described: Vitamin B12 importer BtuCD from E. Coli [22], metal-chelate importer HI1470/1 from Haemophilus influenza [23], and the drug exporter Sav1866 from Staphlococcusaureus [24]. In the two bacterial importers, the MSDs do not intertwine, whereas Sav1866 shows interaction of the two MSDs. One transmembrane domain (TMD) is formed by helices 4 and 5, and the other TMD is composed of helices, 1, 2, 3, and 6 [24]. This has also been proven through cross-linking studies of human P-gp [8] and by the crystal structure of mouse P-gp showing intertwining of the TMs [5].

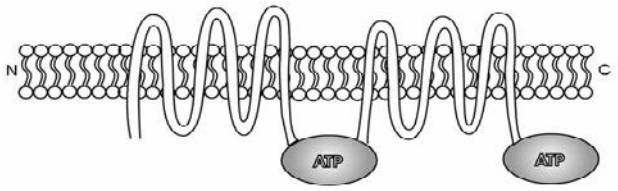

Fig 1: Full ABC transporter consists of two transmembrane domains and two nucleotide binding domains encoded by a single polypeptide

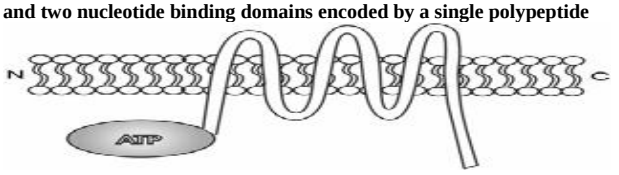

Fig 2: Half ABC transporter consists of one transmembrane domain and one nucleotide binding domain.

1.4. Molecular Mechanism of action

Based on the structure of the above mentioned transporters and extensive studies of P-gp drug affinity, a model has been derived for the mechanism of transport, called the ATP-switch model [12]**.** The model uses the switch between low and high affinity states of substrate binding, coupled with the ATP catalytic cycle, to explain the mechanism of transport. The whole process can be explained in four steps: substrate binding, ATP binding and substrate translocation, ATP hydrolysis, and return to the substrate binding conformation.

When ATP is not bound in the NBD, the transporter has an open conformation and a high affinity for substrate. In this configuration, the two MSDs are opened towards the cytosol with the NBD in an open conformation. The crystal structure of the inward facing conformation that substrates could access the binding pocket from the inner leaflet of the plasma membrane or the cytosol [5]**.** This provides a hydrophilic pocket inside the transporter for substrate to bind. Substrate promiscuity results from the upper half of the binding pocket containing hydrophobic and aromatic residues while the lower half contains more polar residues [5]**.**

Substrate binding induces a conformational change in the NBD which is propagated from the MSDs through interactions with the ICLs [25]. At this point, the NBDs have a greater affinity for ATP. Binding of ATP causes the NBDs to form a closed dimer. This is sufficient to cause a large enough conformational change in the MSDs to put them in an outward-facing arrangement, causing translocation and export of the substrate from the cell due to decreased affinity for the substrate. The hydrolysis of two ATP molecules releases sufficient energy to be harnessed for conformational change in the MSDs [1]**,** returning them to the open conformation. The closed formation of the NBD is a transient state. Hydrolysis of ATP is an unavoidable consequence of the closed conformation. The mechanism has been proposed to be through base catalysisor substrate assisted catalysis. Either way, the hydrolysis leads to destabilization of the closed NBD conformation and the subsequent release of adenosine

diphosphate (ADP) and a phosphate (Pi), returning the transporter to the open conformation, and once again making it accessible for substrate binding [26].

1.5. Substrate and Inhibitor of ABC Transporters

ABC transporters proteins are capable of transporting a vast and chemically diverse array of compounds, which are structurally unrelatedacross the plasma membrane as well as intracellular membranes. They are bulky lipophilic cationic, anionic, and neutrally charged drugs and toxinsas well as conjugated organic anions that encompass dietary and environmental carcinogens, pesticides, metals, metalloids, and lipid peroxidation products [1-2].The three major proteins involved in cancer multidrug resistance are MDR1 (P-glycoprotein, ABCB1), MRP1 (multidrug resistance protein 1, ABCC1) and the ABCG2 multidrug transporter (BCRP/ MXR). MDR1 and MRP1 can recognize and transport a large variety ofhydrophobicdrugs,andMRP1 can also extrude anionic drugs or drug conjugates [15]. The substrate specificity of ABCG2 partially overlaps with that of MDR1 and MRP1 that is the compounds transported by ABCG2 are also large, hydrophobic molecules, including mitoxantrone, topotecan, flavopiridol, and methotrexate.

2. PHARMACOKINETICS PROPERTIES OF ABC TRANSPORTERS

There is an increasing appreciation of the role that transport proteins play in the absorption, distribution, and elimination of a wide variety of drugs in clinical use. These transporters can be divided into efflux transporters belonging to the ATP-binding cassette (ABC) family and solute carrier (SLC) family members that mediate the influx or bidirectional movement of drugs across the cell membrane [27]. Their coordinated expression and activities at the basolateral and apical side of transporting epithelia are significant determinants of drug disposition, drug–druginteractions, and variability in drug response and toxicity. This review focuses on ABC transporters that are involved in drug transport. They can be found in the *ABCB*, *ABCC*, and *ABCG* families, because of their expression in transporting epithelia, including the intestine, liver, and kidney, they play an important role in the absorption, distribution, and removal of drugs [4]. Many of them are also associated with multidrug resistance (MDR) of tumor cells causing treatment failure in cancer.

1.6. Drug Absorption

Oral bioavailability of drugs was initially thought to be affected by drug absorption. By now it has been well established that active efflux by ABC transporters in the small intestine is a major contributor to poor absorption and low bioavailability [28]. Enterocytes of the small intestine are equipped with an array of influx transporters at the luminal membrane for the absorption of food components and drugs. Three major ABC transporters have been shown to localize to the apical/luminal membrane of enterocytes, and, thus, are thought to form a barrier to intestinal absorption of substrate drugs: ABCB1/P-gp/, MRP1 and BCRP [1-4]. Their expression level varies between different segments of the intestine. In general, these are expressed at high level in the brush border membrane of the intestine that can effectively pump drugs back into the intestinal lumen, thereby limiting the extent of substrate drug absorption. Regarding the role in limitingintestinal absorption, MRP1 is the most thoroughlycharacterized ABC transporter [14]. The most direct evidence hascome from the numerous in vivo studies utilizing MRP1knock-out mice. Although the expression levels of both the BCRP and P-glycoprotein are higher in the small intestine than the expression MRP1, there are much fewer data available on their role in drug absorption [12-13].

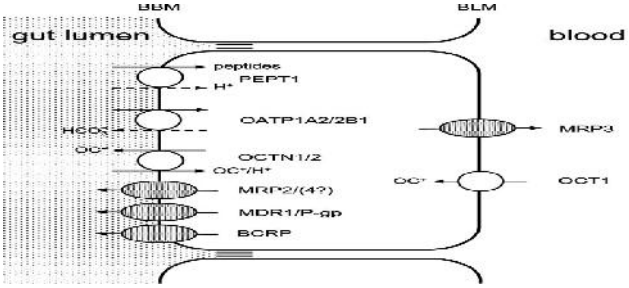

Fig 3: Schematic model of the major drug transporters in enterocytes of human small intestine.

2.2 Drug Distribution

To be effective, absorbed drugs must be transported from the site of administration to the site of action [29]. The CNS is the tissue most frequently targeted by drugs. The blood– CNS interface is composed of the blood microvascular endothelial cells (blood-brain-barrier, BBB) and the choroid plexus (blood–cerebrospinal fluid (CSF)–barrier). It has been long known that lipophilicity is required for BBB penetration. However, many lipophilic drugs exhibit poor BBB penetration. Now it is known that the poor BBB permeability of these compounds is due to the efflux functions of ABC transporters [29].

It is well established that the MDR1 protein localized in the apical/luminal membrane of the brain capillary endothelial cells is a major barrier of CNS penetration of drugs. Multiple studies have shown the pivotal importance of MDR1 in protecting the brain from xenobiotics. The most convincing studies were carried out by utilizing mdr1 knock-out animals. Each of the studies showed a dramatic increase in the brain levels and/or brain/blood ratio of drugs when MDR1 substrates were administered to Mdr1a knock-out mice.It is also generally accepted that MRP1 is localized in the basolateral membrane of the choroid epithelial cells, preventing CSF penetration of drugs and toxicants [30]. More recently, other ABC transporters, such as MRP2 and BCRP have also been implicated in protecting the brain tissue against xenobiotics [29].

2.3 Drug Elimination

The liver and Kidney have a remarkable ability to efficiently extract drugs with high protein binding from the blood circulation [31-32].

The hepatic uptake of drugs is frequently followed by Phase I and Phase II biotransformation and efflux of the

metabolite(s) into bile and contributes to the hepatic first-pass effect. Influx and efflux transporters expressed at the sinusoidal (basolateral) and canalicular (apical) membrane of hepatocytes have been recognized as critical determinants in drug elimination [15]. Efflux transporters expressed in the canalicular membrane represent the final step in the vectorial transport of drugs and drug metabolites from blood into bile. Excretion of cationic drugs across the canalicular membrane is mainly mediatedby MDR1/P-gp. MRP2 and BCRP are primarily responsible for the canalicular efflux of unconjugated and conjugated anionic drugs, including glucuronide, sulfo, and glutathione conjugates [33]. The localization of MRP3 and MRP4 at the sinusoidal membrane indicates that these conjugates are also transported back into the circulation so that they can undergo renal elimination.

At the proximal tubular brush border membrane, a team of four ABC transporters mediate the primary active efflux of drugs, viz., MDR1/P-gp, MRP2, MRP4, and BCRP. P-glycoprotein likely provides the efflux pathway for digoxin and a number of hydrophobic cationic drugs [34]. MRP2 and MRP4 are involved in the efflux of anionic drugs and drug conjugates that have been either formed in the proximal tubular cell or released from the liver and taken up from the circulation [16]. MRP4 appears to have a higher affinity for organic anions. BCRP has recently been localized to the proximal tubule brush border membrane, suggesting its potential involvement in renal drug excretion.

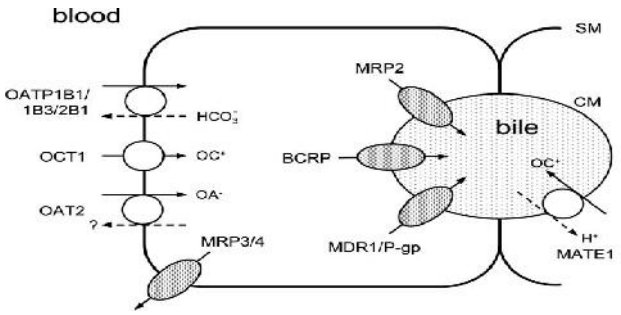

Fig 4: Schematic model of the major drug transporters in human hepatocytes

3. THE ROLE OF ABC TRANSPORTERS IN TOXICITY

ABC transporters have a pivotal role in host detoxification and protection of the body against xenobiotics. This role is revealed by their the tissue distribution, which are highly expressed in important pharmacological barriers, such as the brush border membrane of intestinal cells, the biliary canalicular membrane of hepatocytes, the lumenal membrane in proximal tubules of the kidney and the epithelium that contributes to the blood–brain barrier [4-6].

The efflux pumps are determinants for the absorption, distribution and excretion of drugs, xenobiotics and their metabolites **[table 1]** [28-30]. Entrance in the systemic circulation is prevented by the apical expression of ABC transporters in the intestine, like P-gp and BCRP, and the action of these transporters leads to a decreased drug concentration in the liver [33]. The liver is the major site of xenobiotic metabolism in the body, in which enzymes, like the cytochrome P-450 (CYP) family members catalyze the oxidative metabolism of many drugs, eventually affecting both drug efficacy and drug toxicity [33]. P-glycoprotein is able to mediate cellular efflux of CYP modulators, like rifampicine. Rifampicine induces CYP3A activity in a dose-dependent manner, thus a lower intracellular concentration results in a decreased CYP3A activity [16]. Drug distribution to the brain is hampered by ABC transporters like P-gp, multidrug resistance proteins 1 and 2 (MRP1/2; ABCC1/2), MRP4 (ABCC4) and BCRP in the blood-brain. Although these transporters protect the central nervous system, effective drug treatment of brain tumors, epilepsy and several mental disorders is limited [29-30]. The importance of transporters in the blood-brain barrier was emphasized inMRP1a(-/-) mice,which died from the neurotoxic action of ivermectin, a known P-gp substrate, after treatmentfor mite infestation.ABC transporters affect, besides drug absorption and drug distribution, also theexcretion of drugs into the bile or urine. In the liver, ABC transporters are responsible for the elimination of xenobiotics and their metabolites into bile (P-gp, Bile Salt Export Pump (BSEP;ABCB6), and MRP2) or in the systemic circulation (MRP1/3). More water-soluble drugs can beexcreted into urine by the kidney, where ABC transporters are localized along the apical membrane (P-gp, MRP2/4 and BCRP) of proximal tubule cells [34].

The defense mechanism formed by ABC transporters under physiological circumstances is directed against accumulation of potentially harmful compounds. Interestingly, in a situation of organ damage or disease, changes in the expression levels of ABC transporters have been observed, likely to compensate for the increased load of harmful products of oxidative stress formed during an insult or to compensate for the loss of efflux pumps in damaged tissues. In severe human liver disease (primary biliary cirrhosis, cell necrosis or chronic hepatitis), MRP2 is down-regulated, but P-gp, BCRP, MRP1 and MRP3 (ABCC3) were up-regulated, suggesting protection against the accumulation of toxic bile constituents and prevention of further liver damage [38].

4. THE ROLE OF ABC TRANSPORTERS IN METABOLISM

Transporters not only maintain the connectivity of metabolites across different cell types but also determine the uptake and secretion profile of individual cells. The metabolite exchangesof individual cell types with the corresponding extracellular compartment are inevitably connected to their internal biochemical pathways and cell functions. Defective metabolite transport processes have been associated with various pathological conditions, including inborn errors of metabolism [40]. Hence, knowledge of the cellular transport systems is fundamental to understanding human metabolism.Major cellular transport system is carried out by the largest transporter gene family called ATP-binding cassette (ABC) transporter superfamily.

These proteins translocate a wide variety of substrates including lipids, sugars, amino acids, metal ions, peptides, and proteins, and a large number of hydrophobic compounds and metabolites across extra- and intracellular membranes [1]. They have been mainly documented to play a major role in lipid transport and lipid-related disorders. The association between cholesterol and atherosclerosis is thought to involve the cellular uptake and deposition of cholesterol. By removing cholesterol from the cells, the reverse cholesterol pathway provides protection for the artery wall against unwanted lipid deposition. It has been suggested that ABCA1 is the key protein in controlling the cellular apolipoprotein-mediated lipid removal pathway [41-42]. Mutations in the ABCA1 gene result in Tangier disease, a genetic disorder characterized by an abnormal lipoprotein profile and the accumulation of cholesterol esters in various tissues [42]. Cholesterol efflux from Tangier-fibroblasts to lipid- poor apolipoproteins is defective, suggesting that ABCA1 has a key role in the modulation of the reverse cholesterol transport **[43-44].** Several other ABC transporters have also been implicated in lipid and/or cholesterol transport. The expression level of ABCG1 in human macrophages is greatly increased by cholesterol loading and by lipoproteins, suggesting that this protein is involved in the metabolism of these lipids **[45].** There are no published functional and localization data available as yet regarding this ABC transporter in various cell types. However, it has been documented in detail, that close relatives of ABCG1, that is ABCG5 and ABCG8, play a key role in lipid metabolism, as mutations of either of these genes was found to cause a heritable disorder altering the absorption and excretion of plant- and fish-derived steroid molecules [38]. In these patients high levels of blood sitosterols, and an altered cholesterol metabolism leads to atherosclerosis and cardiac diseases. ABCG5 and ABCG8 were documented to work as obligate heretodimers, and both their function and correct cellular localization depends on this dimerization process **[46]**. ABCB4 (MDR3) is a specific phosphatidyl choline transporter residing in the bile canalicular membrane in the liver, and has an essential function in the proper bile formation **[46].** Modulation of the expression and function of these lipid transporter proteins may soon become an important pharmacological target.

5. CONCLUSION

Thus this review focuses on the structure, localization, types, and mechanism of action, multidrug resistance of ABC transporters and their role in toxicity and metabolism. Hence on the basis of this review, the plausible role of ABC transporters in different diseases including cancer can be elucidated, which will pave way for exploring its functions in a detailed manner in near future.

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