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Review

Multidrug resistance-associated ABC transporters – too much of one thing, good for nothing

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Abstract

Overexpression of ATP-binding cassette (ABC) transporters in cancer cells results in multidrug resistance (MDR) which leads to unsuccessful chemotherapy. The most important MDR-associated members of ABC superfamily are ABC B1/P-glycoprotein/MDR1, ABC C1/multidrug resistance associated protein 1 (MRP1), and ABC G2/BCRP. This study is not only focused on function, substrates, and localization of these popular proteins but also on other ABC C family members such as ABC C2–6/MRP2-6 and ABC C7/CFTR. Current research is mainly oriented on the cancer-promoting role of these proteins, but important lessons could also be learned from the physiological roles of these proteins or from polymorphisms affecting their function. Thorough knowledge of structure and detailed mechanism of efflux can aid in the discovery of new chemotherapy targets in the future. Although the best way on how to deal with MDR would be to prevent its development, we describe some new promising strategies on how to conquer both inherited and induced MDRs.

Keywords: ABC transporters; barrier; multidrug resistance; polymorphism; substrate.

Introduction

Active mechanisms that allow distribution of ions against their gradient were well studied mainly in marine physiology in the 1950s (1). In the 1960s, membrane-bound ATP-driven ion pumps were described (2, 3). ATP-utilizing proteins allowing active transport of larger molecules in bacteria and yeast were found later (e.g., maltose-binding proteins) (4). Those ubiquitous transporters were named ABC transporters to connote their specific ATP-binding cassette (5, 6). This field gained importance when the harmful role of these overexpressed transporters was recognized in cancer cells. The ability of P-glycoprotein (later named ABC B1) to efflux multiple chemotherapeutic drugs caused the so-called multidrug resistance (MDR) of cancer cells and, consequently, the relapse of illness (7) [reviewed in (8)]. Now after more than 20 years, the research has involved the description of almost 50 various mammalian ABC transporters – their structure, mechanism of function, and main regulatory pathways [reviewed in (9)]. The whole ABC superfamily, however, includes more than 100 different transport proteins found from bacteria to humans; the mammalian ABC transporters are exquisitely exporters (with the only exception of ABC C7), but the bacterial ones are also able to import [reviewed in (10)]. This review is focused on the nine 'double-edged' ABC transporters [ABC B1/P-glycoprotein/MDR1, ABC C1–6/MRP1–6, ABC C7/cystic fibrosis transmembrane regulator (CFTR), and ABC G2/breast cancer resistance protein (BCRP)] which are localized on barrier-like types of tissues where they play the 'sentinel' role; however, they are connected to the phenomenon of MDR and thus could be extremely deleterious.

Structure and evolution

ABC transporters consist mainly of transmembrane domains (TMDs) that form the 'pore' and have affinity for particular substrates, and cytosolic domains binding the ATP nucleotide [nucleotide-binding domain (NBD)]. The domains are connected by cytosolic and extracellular loops; the latter being often glycosylated. The cytosolic regions of the TMDs are thought to coordinate ATP coupling with substrate binding and translocation. The NBDs contain the characteristic Walker A, B motifs and the 'signature motif,' participating to create the 'pocket' for ATP binding. All those sequences are either involved directly in ATP binding and hydrolysis or they facilitate interfaces in the assembled transporter. All the conserved domains together form a hydrophilic pore closed on the internal cytosolic side, thus creating an aqueous compartment inside the hydrophobic membrane bilayer [for more details, see (9)]. Generally, we can classify ABC transporters either according to their sequence homology to the families (ABC A–G) or structurally to half- and full-transporters. The full-transporters (typical example is ABC B1 protein) have two TMDs and NBDs. As the name indicates, the half-transporters (represented by ABC G2) consist of only one TMD and NBD [reviewed in (11)].

For the proper assembly of transporting 'pores,' the typical number of involved TMDs is 12. The half-transporters

therefore have to homo- or heterodimerize. ABC G2 with only one TMD was evidenced to exquisitely create homodimers. Structural studies revealed that this TMD is not an analog of any of the two domains of ABC B1 as the helices are longer and thus resemble more the *Staphylococcus aureus* transporter Sav1866. The classical full transporters have a typical pattern of domain arrangement N-terminus – TMD1 – NBD1 – TMD2 – NBD2 – C-terminus, e.g., ABC B1, ABC C4, and ABC C5 (12–14), respectively (see Figure 1). However, ABC G2 has an NBD on the N-terminal side of the domain, and the linker sequence between NBD and TMD of ABC G2 is highly homologous to the linker sequence between NBD1 and TMD2 of ABC B1, which may illustrate the complicated process of evolution (15) (Figure 1). ABC C1–3 and ABC C6 have an additional N-terminal TMD consisting of five helices, which seems to be associated with their ability to efflux bulky conjugates, as the members of ABC C family that transport relatively smaller nucleosides (ABC C4 and ABC C5) do not contain this extra domain (16–19). ABC C7, composed of 12 transmembrane helices, has also one special domain, but it is located in the cytosol and probably has a regulatory function (20).

Evolutionists suppose that originally, the half-transporters emerged first and the full-transporters evolved by multiplication. The comparison of multiple variants of ABC B5 gene, however, revealed that those full-transporters could later lose some sequences, and in the end, they remind more the structure of half-transporters (21). The study in bacteria also showed that the typical structure of ABC transporters was probably formed when ATPase non-covalently associated with some membrane proteins became involved in transport – usually import of nutrients (5, 22). The ABC transporters are one of the most conserved proteins even though their genes are extremely flexible as they adapted to an extensive number of substrates during evolution and till now are able to efflux even the man-made compounds. It is supposed that MDR-related members evolved from a physiologically important member thanks to the higher occurrence of a toxic substrate and simultaneously occurring polymorphism or multiplication of a particular gene. Moreover, when a transporter is lost by mutation, this loss is at least partially compensated by a related transporter with an overlapping function. As a result, the knockout of a particular ABC transporter is rarely lethal even though the ABC transporters are one of the oldest and highly expressed of all the proteins (23, 24). So far, 32 murine knockouts of ABC transporters were made and only five of them resulted in embryonic (*ABC B7* and *ABC E5*) or early postnatal (*ABC A3*, *ABC A12*, and *ABC C9*) lethality. *ABC B7* knockout embryos die due to collapse of mitochondrial respiration process (25). Embryonic lethality was also described in *ABC E5*$^{-/-}$ mice, which is understandable as this transporter plays an important role in ribosome binding and recycling. *ABC A3* newborn knockout mice die due to lack of surfactant in lungs and following respiratory failure (26). *ABC A12* knockouts are also lethal because of severe lung and skin defects (27). Mice lacking *ABC C9*/Sur2 regulating sulfonylurea metabolism die of cardiac failure soon after birth (28). The current status of scientific progress in knockouts could be monitored at the Mouse Genome Informatics (http://www.informatics.jax.org).

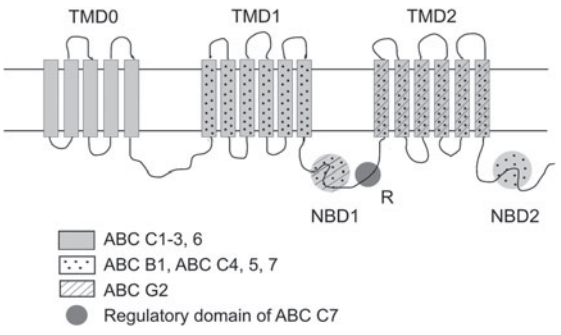

Figure 1 Schematic overlay of structural features of MDR-associated ABC transporters.

Mechanism of drug efflux

The Mechanism of drug efflux is best examined in ABC B1 protein; however, the detailed mechanism has not yet been revealed. The most significant difference between the two currently acknowledged models is the source of the power that drives the drug from a high-affinity site to a low-affinity site. In one model, the formation of the ATP-containing NBD dimer results in conformational changes that decrease the affinity of the substrate in the drug binding site and thus release the substrate. Two sequential ATP hydrolysis events then reset the ATP molecule. The second model also requires two ATP hydrolysis events, but one powers the efflux of the drug and the other resets the protein to its ground state (29). Both of these models refer to the 'alternating catalytic sites' scheme. The main point is that only one of the two NBDs hydrolyzes ATP at any given time and the two NBDs alternate during the catalytic cycle [for details, see (30)].

One of the most intriguing issues in ABC transporter field is what affects the specificity of transporter-substrate affinity as one protein could have a plethora of non-relative substrates. Drugs that are able to bind into a hydrophobic pocket on the transporter can interact through a few polar residues strongly enough to trigger catalysis or a productive transport ATPase cycle without a precise fit. The affinity is increased many hundred-folds when hydrophobic compounds concentrate on the surface of the membrane compared to the solvent concentration. Affinity of a drug for, e.g., *ABC B1* could be predicted from the number of suitably spaced pairs or triplets of electron-donor groups on its hydrophobic backbone. The concentration and orientation of substrate in the membrane and isolation from competing solvent molecules afforded by the membrane thus allow interactions with a relatively high K_m to occur with significant frequency and specificity (31). The correlation between a specific property of the substrate and the TMD size was found in bacteria. The general principle claiming 'the larger the substrate, the longer is the TMD sequence' seems to be reasonable because larger substrates would require a larger diameter of transmembrane channel (32).

Regulation of expression

Expression of ABC transporters is regulated at multiple levels – transcriptional level is influenced both by genetic and epigenetic means, post-transcriptional level is represented by changes in mRNA stabilization and translation initiation (33), and post-translational level involves cytoplasm-membrane trafficking and consecutive glycosylation. Constitutive, basal transcription of MDR proteins could be extensively potentiated by stressors as are hypoxia, inflammation, or activation of glucocorticoid or cytokine receptors [reviewed in (34)]. Those agents usually trigger stress or receptor-associated kinase cascades, which in turn activate transcription factors Sp1, HSP, MEF1, TCF/LEF, NFκB, and AP1 that have their response elements in proximal promoter (33, 35). Transcription of ABC transporters could also be upregulated by a distal element – enhanceosome. This area, which spans –10 000 bp upstream, is the target for other transcription factors activated by chemotherapeutics, differentiation agents, and DNA-damaging drugs and thus represents one of the mechanisms of induced MDR (36–38).

The phosphoinositide 3-kinase (PI3K) pathway is extremely important for the expression of ABC transporters and not only on a transcriptional level as the stability of mRNA could be influenced by the availability of components of translational machinery, e.g., eukaryotic initiation factor 4E-binding protein (eIF4E) that requires active PI3K to stay active. In a case of eIF4E shortage, the 5′ end of *ABC B1* mRNA becomes extensively folded, which reduces its competitive ability for the translational machinery (39, 40). Moreover, PI3K also affects the post-translational level of control as inhibition of PI3K/Akt results in translocation of ABC transporters from membrane to cytosol and thus in decreased function of the transporter (41, 42). Besides, phosporylation and glycosylation occurs in the endoplasmic reticulum. N-glycosylation at Asn596 was described to affect the folding process and thus the stability of the protein. This process is monitored by quality control machinery with the involvement of Derlin-1 protein, a homolog of *Drosophila* Der1 (43, 44). Properly folded proteins are multiglycosylated in Golgi apparatus and then exported to cytoplasmic membrane [reviewed in (45)]. The post-translational modification is best described in ABC G2, but similar N-glycosylation was observed also in ABC B1 and ABC C2 proteins, and thus we can suppose the common validity of these mechanisms (46).

Physiological features of MDR-associated ABC transporters

ABC B1

ABC B1 substrates are usually hydrophobic, lipid-soluble positively charged, or neutral natural products, including some chemotherapeutic agents (e.g., taxanes, anthracyclines, and vinca-alkaloids) and steroids. Substrates can bind to at least two sites in the TMDs that interact in a positively cooperative manner (12). Interactions between cholesterol of cytoplasmic membrane and ABC B1 are remarkable. Cholesterol affects both drug efflux ability and phospholipid flippase functions of ABC B1. Increase in cholesterol content greatly alters the partitioning of hydrophobic drug substrates into the membrane and thus MDRs (47).

Mutational analysis revealed over 50 polymorphisms in *ABC B1* gene; the research focused on two most abundant polymorphisms G2677T in 21st exon and C3435T in 26th exon. Both polymorphisms are synonymous and localized in extracellular loops between TMDs (48). In the site 2677, the missense polymorphism G2677A can also be found. However, even the silent polymorphism results in a different conformation of the protein and thus changes the substrate affinity (49, 50). Interestingly, the polymorphisms in 3435 and 2677 sites very often occur simultaneously (51, 52). Those two polymorphisms are scrutinized to correlate with different diseases or reaction to treatment. Positive correlation is usually found when it concerns the steroid metabolism (52, 53). Tens of studies were performed to assess the correlation of polymorphisms and outcomes or recurrence of different tumors but generally with inconsistent results. So far, the only positive study was performed on ovarian cancer treated with paclitaxel/carboplatin and demonstrated that compared to normal homozygote 2677GG, women with the minor T/A alleles were significantly less likely to relapse following treatment (54).

Polymorphism of *ABC B1* may also be involved in Alzheimer's disease as it was shown to efflux amyloid-β. Experimental models showed that inhibition of ABC B1 results in increased accumulation of amyloid-β in the brain. Nevertheless, polymorphisms G2677T/A and C3435T were not in correlation with the occurrence of Alzheimer's disease in patients. Still, a possible effect of rare deleterious variants is worthy of further investigation (55). Involvement of ABC B1 in Parkinson's disease is also possible as patients with the earliest onset have the lowest function of ABC B1 (56).

ABC C family

The majority of the ABC C family proteins are associated with MDR (ABC C1–6, 10–12), but this family also includes ABC C7, which is a cystic fibrosis transmembrane conductance regulator. Furthermore, ABC C8 and ABC C9 are the sulfonylurea receptors, which constitute the ATP-sensing subunits of a complex potassium channel. The novel ABC C13 is a pseudo-gene, which product lacks a transporting activity. In this review, we describe the features of well-studied members of ABC C family ABC C1–7. This family specializes in the transport of organic anions, such as drugs conjugated to glutathione, sulfate or glucuronate, and several glucuronosyl-, or sulfatidyl steroids [reviewed in (57)]. ABC C proteins are effective also in plants where they work as vacuolar pumps of glutathione-*S* conjugates. There is evidence showing their involvement in the processes of detoxification and heavy metal sequestration, or chlorophyll catabolite transport and ion channel regulation [for details, see (58)].

ABC C1 ABC C1 is known to efflux an important immunomodulator leukotriene C(4) from its source (i.e., mast cells). ABC C1 thus plays an important role in the development

of inflammation, e.g., allergic airway inflammation and dendritic cell mobilization (59, 60). Moreover, ABC C1-deficient mice have also impaired differentiation of dendritic cells, which appears to be independent of the leukotriene pathway. The relevant ABC C1 substrate, which is required for dendritic cell differentiation, however, remains to be identified (61).

ABC C2, and C3 Highly homologous ABC C2 and C3 are able to efflux amphiphilic anionic conjugates, e.g., bilirubin glucuronides. Insufficient expression of ABC C2 in apical membrane of hepatocytes results in Dubin-Johnson syndrome, which is characterized by deficiency in the secretion of conjugates into the bile and its excess in blood as ABC C3 in basolateral membrane tries to compensate this defect (62) (Table 1). The ability of ABC C2 and C3 to cause MDR when overexpressed has probably influenced the less favorable prognosis of breast cancer (63, 64).

ABC C4 One of the most interesting members of the ABC C family is ABC C4, whose function was initially defined by its ability to confer resistance to nucleoside analogs used as antineoplastic drugs when overexpressed. Physiologically, ABC C4 transports cyclic nucleotides (cGMP and cAMP); thus, it is part of a biological regulatory loop that occurs when intracellular cAMP levels increase (65). Furthermore, export of cyclic monophosphates may have a paracrine signaling function, as vast biological effects of extracellular cAMP and cGMP have been reported (66, 67). Interestingly, ABC C4 forms a macromolecular complex metabolizing cAMP with the help of scaffolding PDZ domain containing protein PDZK1, and what is even more striking, the involvement of ABC C7 protein (described below) was evidenced to be part of this complex (68). ABC C4 has an ubiquitous pattern of expression, compared to other members of ABC C family, which are either apically or basolaterally localized (see Table 1). For example, the dual localization of ABC C4 at the basolateral membrane of the choroid plexus epithelium and in the apical membrane of the endothelial cells of the brain capillaries efficiently defends the brain from the potentially toxic substances but in turn complicates the treatment of brain malignancies.

Activity of ABC C4 could be correlated also on the level of splicing of primary transcripts. Intron 1 contains two additional exons bearing evolutionarily conserved premature termination codons. The splicing variants with those codons are, at least partially, targets of non-sense-mediated mRNA decay, which then represents a means on how to downregulate expression of ABC C4 (69). ABC C4 expression increases when hematopoietic precursors differentiate in megakaryocytes but decreases during maturation of monocytes and granulocytes (70). The ABC C4 transporter is thus highly expressed both in human platelet δ-granules and cytoplasmic membrane and it is involved in ADP release, which is necessary for activation of platelets. Defective expression of platelet ABC C4 thus results in lack of functional δ-granules, insufficient release of ADP, and thus mild hemophilia (71).

Table 1 Intracellular localization of ABC transporters.

Tissue	Apical (luminal) side of membrane						Basolateral (abluminal) side of membrane			
	ABC B1	ABC C2	ABC C4	ABC C5	ABC C7	ABC G2	ABC C1	ABC C3	ABC C4	ABC C6
Blood-brain barrier	(128)	(129)	(130)	(130)	NA	(128)	(131)	ND	(130)	(132)
Endothelia	(133)	ND	(134)	(135)	(136)	(91, 137)	NA	(138, 139)	(134)	(140)
Lung	(133, 141)	(142)	ND	NA	(133, 141)	ND	(133, 141)	ND	ND	(140)
Liver	(100)	(143, 144)	ND	NA	(145)	(146, 147)	(148)	(143, 144)	(149, 150)	(140, 151)
Kidney	(24)	(152)	(152)	NA	(153)	(154)	(155)	(143)	ND	(140, 143)
Choroid plexus	(156)	(157)	ND	ND	(158)	(159)	(156)	(157)	(160)	(132)
Intestine	(99)	(101, 102)	(68)	(101)	(68)	(101, 102)	(101)	(101)	(68)	(140)
Syncytiotrophoblast	(147, 161, 162)	(163)	ND	(103, 109)	(164, 165)	(147, 161, 162)	(147, 161, 162)	ND	(166)	ND
Testis	(167, 168)	(168)	(167)	(169)	(170)	(168)	(167, 168)	ND	(167)	ND

The table summarizes evidences for specific distribution of studied ABC transporters. NA, not analyzed; ND, not detected.

The *ABC C4* gene and promoter are highly polymorphic. The TC genotype of the regulatory T-1393C polymorphism is associated with better event-free survival in pediatric acute lymphoblastic leukemia accompanied by lower plasma levels of methotrexate and 6-mercaptopurine, which are ABC C4 substrates used for the treatment of this disease. In contrast, the CA genotype of A934C (Lys304Asn) substitution correlated with lower event-free survival and higher frequency of high-grade thrombocytopenia (72). Explanation is probably rather complex as these polymorphisms do not affect the level of transcription or translation. ABC C4 is also important in antiretroviral therapy, as its substrates include nucleotide analogs efficiently used as therapeutics, e.g., 2′,3′-dideoxy-3′-thiacytidine (lamivudine) (73). A polymorphism T4131G in 3′ UTR was associated with a desirable 20% elevated concentration of anti-HIV drug lamivudine in lymphocytes and probably caused by altered splicing and in turn reduced function or expression of this protein (74).

ABC C5 ABC C5 is both genetically and functionally relative to ABC C4, but it differs functionally as it does not confer resistance to natural anticancer agents or methotrexate. It participates on the efflux of cyclic nucleosides and their analogs. High expression of ABC C5 was described in blood-tissue barriers, in muscle, blood, and neural cells, which points to its physiological function in signaling processes [reviewed in (75)]. The increased expression of ABC C5 was observed in ischemic cardiomyopathy, which may correlate with the ischemia-induced elevated cGMP level (76). ABC C5 together with ABC C4 was also observed in striated muscles, and its ability to efflux statins (used to decrease hypercholesterolemia) may help to protect cells from statin-induced myopathies (77). Although the gene is highly polymorphic, no correlation with any disease has as yet been described.

ABC C6 ABC C6 protein is involved in the transport of glutathione conjugates and leukotriene E4. Mutations in the *ABC C6* gene cause hereditary ectopic mineralization of connective tissues called pseudoxanthoma elasticum, which is inherited in an autosomal recessive manner. It is clinically manifested usually in the skin, the eyes, and the cardiovascular system, i.e., in tissues with only minimal expression of ABC C6 [reviewed in (78)]. Similar manifestations were also seen in dystrophic cardiac calcification, another autosomal recessive disease caused by mutation of *ABC C6*, characterized by calcium phosphate deposits in myocardial tissue and thus affecting the arterial system in patients with atherosclerosis, diabetes mellitus, and chronic renal failure. The screening of the *ABC C6* gene found that the mutation often leads to the premature termination of transcription that in turn results in protein deficiency. Interestingly, both diseases were reported to develop spontaneously in aging mice and humans, and tissues with the highest expression of ABC C6, i.e., kidney and liver, are never affected by this illness, but it is thought that the primary molecular defect occurs in liver metabolism. Thus, the preventive mechanism of ABC C6 on extensive calcification seems to be mediated by systemic rather than tissue-specific factors (79).

ABC C7 ABC C7 is an atypical, evolutionarily young ABC protein, which is the mediator of passive bidirectional diffusion of small inorganic anions and its mutations cause cystic fibrosis [its original name is cystic fibrosis transmembrane regulator (CFTR)] [for review, see (80)]. The malfunction caused by the prevalent deletion of Phe508 in NBD1 prevents conformational maturation of the whole CFTR protein, possibly by disrupting the interaction between NBD1 and NBD2 (81). Its nature makes it a unique intersection of the ion channel and ABC transporter fields; moreover, it has some special features, e.g., only one of the two NBDs is hydrolytic or its function is regulated by phosphorylation (82, 83).

What is extremely interesting from the MDR point of view is that ABC C7 is able to efflux glutathione conjugates besides its role in transport of salts. Thus, it is able to maintain the basal level of glutathione in lung epithelial lining fluid or increasing this level in reaction to oxidative stress and inflammation, caused by, e.g., cigarette smoke (84). Unexpectedly, elevation in ABC C7 expression was observed in patients with breast cancer who had no pathologic evidence of any residual invasive cancer cells in the breast and axillary lymph nodes after paclitaxel/5-fluorouracil, epirubicin, and cyclophosphamide therapy (85). Whether it is a consequence of the treatment or an inherited feature remains to be elucidated.

ABC G2 ABC G2 was initially discovered in multidrug resistant breast cancer cell lines where it conferred resistance to chemotherapeutic agents (BCRP). ABC G2 is highly expressed in normal human tissues exposed to potentially toxic metabolites or environmental substances. Therefore, ABC G2 has been increasingly recognized for its important role in absorption, elimination, and tissue distribution of drugs and xenobiotics. It is able to efflux hydrophobic substrates such as porphyrins, riboflavin, mitoxantrone, estrogens, methotrexate, topotecan, and imatinib, but also hydrophilic conjugated organic anions, particularly the sulfated conjugates. A unique feature is that ABC G2 expression in the mammary gland of mice, cows, and humans was found to be strongly induced during lactation, which exposes suckling infants and dairy consumers to xenotoxins (86). At first glance, this seems to be evolutionally disadvantageous, but originally, this could be the way to transfer riboflavin and possibly other essential vitamins (biotin, vitamin K) to infants.

In terms of cancer biology, current research is focusing on the expression and function of ABC G2 in immature stem cells as they contain it in a high abundance (87). During differentiation, the ABC G2 expression in consecutive progenitors decreases, but in the end, its expression becomes very high again in barrier tissues (e.g., intestine). *ABC G2* promoter contains HIF response elements, and thus hypoxia seems to be a potential common feature of stem cells and terminally differentiated cells. However, the high expression of ABC G2 in endothelia disproves this hypothesis. The research is focused mainly on hematopoietic precursors; immature CD34+CD38- cells have the highest expression, which declines during

differentiation to myeloid and lymphoid cells with the exception of erythrocytes and natural killers (88). The importance of ABC G2 in hematopoietic cells might be explained by its ability to confer a strong survival advantage under hypoxic conditions due to efflux of toxic porphyrins that would otherwise accumulate during heme synthesis (89). ABC G2 is also able to inhibit hematopoiesis – a mechanism could be the efflux of differentiation-inducing substrate; its nature has been, however, as yet unknown. This idea is inspired by observation of differentiation of *Dictyostelium discoideum* amoeba stalk cells by chlorinated polyketide DIF-1, which is inhibited by efflux of DIF-1 by an ABC B1-related transporter (90). Moreover, ABC G2 inhibition also impaired migration and tube formation of endothelial cells (91).

ABC G2 was also described as a uric acid transporter; increased level of uric acid in the blood is the main cause of gout and dysfunctional ABC G2, thus increasing the gout risk. The most extensively studied case is the C421A polymorphism (encoding Q141K), which is associated with enhanced protein degradation (92). This polymorphism causes dysfunction of ABC G2, which correlated to different pharmacokinetics of statins or taxanes resulting in different disease progress after therapy with these agents (93, 94). However, the lower function of polymorphic ABC G2 does not predispose to increased cancer risk (95).

Tissues with abundant expression of MDR-associated ABC transporters

The ABC transporters are extensively expressed in the barrier-like cells where they can function as sentinels but concurrently also control the distribution of nutrients; the most important of them are blood-brain and blood-testis barriers, placenta, intestine, liver, kidney, and lung. This dual role is facilitated by polarization of cell membranes via expressing different sets of ABC transporters on the membrane parts facing the lumen of vessel (luminal/apical part) and surrounding tissue (abluminal/basolateral part), respectively. Summarization of known areas of expression of the above-described ABC transporters revealed a uniform pattern in their distribution in cytoplasmic membrane. With the only exception of ABC C4 that has a tissue-specific localization, proteins ABC B1, C2, C5, C7, and ABC G2 are found in apical/luminal part of cell membranes and ABC C1, C3, and C6 in basolateral/abluminal part (Table 1). Description of particular barriers and their specific features follows.

The function of blood-brain barrier epithelial cells is modulated after birth by formation of a sheath of glial cells (mainly astrocytes), which induces a rapid increase of expression of ABC transporters in epithelial cells (96). The second brain barrier, i.e., blood-cerebrospinal fluid barrier is formed by the epithelium of the choroid plexus. Besides the transporters described above and in Table 1, ABC A1 is highly studied as it plays an important role in the prevention of cholesterol uptake in the brain and also in the accumulation of amyloid-β (97). However, the mechanism becomes more complex as it was described that amyloid-β may serve as a signaling molecule, which inhibits the expression of the ABC A1 in cultured astrocytes (98).

The defense barrier of the intestine consists mainly of cubic cells of resorbing epithelia, which are rich for many of ABC transporters that are expressed in specific gradients. ABC B1 expression gradually increases from the stomach to the colon (99). Its expression is the lowest at birth but then it increases (100). Other two apically expressed proteins ABC G2 and ABC C2 are the most abundant in the duodenum and less toward the rectum (101, 102). Specific expression pattern exhibits the basolateral ABC C3 protein as it is the highest in the duodenum and colon and decreases in the small intestine.

Hepatocytes are at a high-risk because of the exposure to the bile acid and metabolites in the blood; therefore, apical transporters excrete metabolites to bile and defend the cells from the bile acids, and basolateral ones efflux back to blood. Besides proteins in Table 1, ABC B4 floppase is important for the proper function of hepatocytes. It translocates phosphatidylcholine to the bile. Mutations in *ABC B4* thus cause a spectrum of cholestatic diseases (103). Further important lipid transporter is heterodimeric ABC G5/G8 that effluxes both plant and animal sterols into the bile and its deficiency results in abnormal level of those sterols in plasma (104).

Kidney cells also handle the distribution of a wide spectrum of metabolites and xenobiotics and are dependent on efficient glomerular filtration barrier and distribution of metabolites by the proximal tubules. ABC transporters expressed in apical membrane pump out substrates destined for terminal excretion from blood into urine and the ones on the basolateral part are returning nutrition to circulation (105).

Lung ABC transporters could either defend the ciliated epithelial cells of the surface epithelium or ciliated collecting ducts and serous cells of bronchial glands. Besides the MDR-associated ABC proteins (Table 1), the ABC A3 is specifically important for development and function of lung tissue as its mutations or polymorphisms are associated with respiratory distress, especially in prematurely born children (106).

The blood-testis barrier is formed by endothelial cells, myoid cells, and Sertoli cells. The barrier is responsible for protecting developing germ cells from xenobiotic exposure and divides the seminiferous epithelium into the basal and the apical compartments. Meiosis I and II, spermiogenesis, and spermiation all take place in a specialized microenvironment in the apical compartment, but spermatogonial renewal and differentiation and cell cycle progression up to the preleptotene spermatocyte stage take place in the basal compartment of the epithelium (107).

The human placenta consists of syncytiotrophoblast and cytotrophoblast layers. The syncytiotrophoblast is a multinucleated polarized epithelial layer which functions not only as a transport barrier, but is also responsible for hormone production. The apical membrane of the syncytiotrophoblast is directly bathed in maternal blood, while the basolateral surface is in contact with either the discontinuous cytotrophoblast layer, with stromal tissue or with fetal blood vessels. ABC C1 and ABC C5 proteins play an important role in the organ functional development considering increase in their expression during trophoblast maturation (108, 109). Another highly abundant

transporter is ABC A1 and its expression even increases during pregnancy (110). Interestingly, expression of ABC A1 also increases in hypoxic conditions both experimentally and in early-onset pre-eclamptic placentas, and thus implies that cholesterol metabolism may affect this dangerous disorder (111).

Multidrug resistance

Resistance of cancer cells to chemotherapy could be either inherited or induced by the treatment. It might be caused by increased activity of detoxifying enzymes or DNA-repair mechanisms, by changes of the drug-binding site or by evading the programed cell death. Nevertheless, the major cause is usually the increased expression of ABC transporters (112). The inherited mechanisms that lead to overexpressed ABC transporters involve karyotype rearrangements that either duplicate the genes or put them under the influence of strong promoter or enhancer (113). Some gene or promoter mutations can even create the isoform with increased function [reviewed in (114)]. The high ability to efflux drugs could also be inherited from the tumor stem cells as the less-differentiated cells are usually rich for ABC transports (especially ABC G2) (115). The increased level of ABC transporter transcription can be further induced by deregulated kinome via the stress- or hypoxia-related pathways (116). The stress signals are usually triggered by the chemotherapeutics themselves; the hypoxia is caused by insufficient supply of oxygen in the tumor niche [reviewed in (117)].

Strategies to overcome the ABC-associated MDR were first based on pharmacologic inhibitors. The inhibitors of ABC transporters are often non-metabolizable substrates but their side effects are often as much deleterious than the beneficial effect on down-regulation of ABC transporters expression (for details see [118]). This way of therapy, however, still leads to the designing of new, more specific generations of drugs.

The more advanced therapeutic strategies are based on knowledge of the molecular basis of the MDR. RNA interference experiments showed that ABC B1-associated MDR could be overcome by transient siRNA-mediated silencing or stable shRNA transfection (119). DNA targeted phosphorothioate oligonucleotides are the first generation of antisense molecules. They are resistant to nucleases, but the clinical use is limited as they could exhibit pharmacological effects unrelated to the antisense effects. They are delivered by lipofectamin, or their uptake could be enhanced by cholesterol conjugation (120). Experimentally, ribozymes were also tested; they are RNAs that have intrinsic endoribonucleolytic cleavage capacity and thus can target specific mRNA. The so-called hammerhead ribozymes were designed to target ABC B1, C2, and G2, and even the multitarget multiribozyme was designed to cleave all three mRNAs simultaneously (121).

Nanocarriers (liposomes, micelles, nanoemulsions, polymers, quantum dots, gold, iron oxide, and dendrimers), which are a promising new tool of therapy, allow the transport of drug or above-described interfering agents into the cell without recognition by ABC transporters as they are internalized via non-specific endocytosis. The versatility of those platforms allows the engineering of multifunctional nanoparticles to make the drug or RNA/DNA delivery more efficient together with active targeting, decreased clearance, and tracking of these vectors. The efficiency of this system was demonstrated in resistant leukemia cells treated with transferring-targeted liposomes loaded with doxorubicin and verapamil (122).

The nanoparticle strategy could also be combined with physical anticancer therapies. Nanoparticles could be loaded with super paramagnetic iron oxide and injected into tumor; the local hyperthermia is thus induced in magnetic field. Temperatures between 40°C and 45°C then initiate the programed cell death via multiple signals (e.g., deregulation of cell cycle and DNA repair) (123). Another combination is drug-loaded nanoparticles and ultrasound focusing to control drug release, which in *in vitro* experiments resulted in overcoming MDR (124). When nanoparticles contain photosensitizers (e.g., derivative of hematoporphyrin Photofrin 2), they could also increase the efficiency of photodynamic therapy. The most tumor-specific targeting could be achieved by additional binding of monoclonal antibodies or specific tumor-seeking molecules (125).

Expert opinion

The attention of researchers in the field of transmembrane transport shifted through the last century from the proteins that allow the survival of cells in a hypertonic environment to the transporters that support the survival of cancer cells making it resistant to the therapy. The ability to confer MDR brought the ABC transporters under the spotlight. The majority of information regarding principles of efflux, regulation of expression of ABC transporters, and its correlation with disease progression thus comes from studies performed on MDR-associated ABC transporters. Recently, the previously marginal issues of physiological role of ABC transporters come to the focus to teach us lessons given by particular MDR-associated protein in healthy homeostatic organisms. The pathways controlling the balanced, beneficial level of potentially deleterious proteins are of common interest as they represent the prospective target of anticancer therapies.

Outlook

One of the major steps was accomplished by resolving the crystallographic structure of classical mammalian ABC protein. This breakthrough was supposed to be followed by revealing the precise molecular mechanism that drives the efflux of particular substrates. However, difficulties in obtaining the structures of protein in different stages of the transport cycle still hinder the progress even though bacterial models are of much use. The most critical question stays: how is the communication maintained between NBDs and TMDs and what are the mechanisms of spreading and synchronization of signals? The knowledge of the precise mechanism could then help to find the means on how to prevent the onset of MDR in cancer cells. The most efficient way on how to deal with MDR would be the prevention of the overexpression of ABC

transporters induced by chemotherapeutics in the beginning of therapy as the strategies based on pharmacologic inhibition of already overexpressed ABC transporters are not much successful (126, 127). However, until we find the way how to precede the MDR, nanocarriers are the most promising tool that offers a platform for drug delivery. Nanocarriers can be optimized to overcome biological barriers and customized to achieve diverse treatment strategies that address the complexities of MDR cancer cells (117).

Highlights

- Functional ABC transporters consist of two TMDs and two ATP-binding domains that contain specific motifs Walker A, B and signature motif.
- A substrate having an appropriate number of electron-donor groups on its hydrophobic backbone binds to the high-affinity pocket in TMDs and the energy from hydrolyzed ATP shifts it to the low-affinity state and thus allows its efflux.
- Expression of ABC transporters is regulated on multiple levels – by proximal promoter and distal enhancing sequences, epigenetically, by stabilization of mRNA, glycosylation, and trafficking of translated product toward the membrane.
- ABC transporters are highly expressed on barrier-like tissues where they have both secretory and sentinel functions and their membrane localization has the common pattern.
- ABC genes are highly polymorphic and isoforms could have different pharmacokinetics, but correlations with diseases or diagnostic prognosis is found only rarely.

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