Role of ATP-binding cassette transporters in drug distribution to the heart and protection from toxic compounds

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Abstract

ATP-binding cassette (ABC) transporters consist of a family of proteins that translocate substrates against a concentration gradient from the intracellular toward the extracellular milieu. Among the members of the ABC transporter superfamily, P-glycoprotein has been studied most extensively and has been found to be expressed in tissues such as liver, kidneys, and intestines. This suggests a physiological function for this transporter in the protection and detoxification of the organism. P-glycoprotein and other ABC transporters were also found to be expressed in the myocardium. Current literature suggests that ABC transporters have a role in controlling distribution of xenobiotics to the heart, thus protecting this organ.
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Keywords: ABC transporters, cardiac drug distribution, cardiotoxicity, drug efflux, heart protection

Introduction

Accumulation of xenobiotics into tissues depends not only on their ability to enter cells, but also on their ability to leave them. The ATP-binding cassette (ABC) proteins represent a large family of transmembrane transporters of around 50 ABC members that translocate substrates against a concentration gradient from the intracellular toward the extracellular regions after hydrolysis of ATP. The member of the ABC transporter superfamily that has been studied most extensively is P-glycoprotein. It was first found to be overexpressed in tumor cells, in which it conferred resistance to several anticancer drugs [1]. Although it was at first believed to be confined to tumor cells, it was subsequently recognized to be expressed in normal tissues such as at the apical surface of liver hepatocytes, in proximal tubular cells of kidneys, and in enterocytes of the intestines. This suggested a physiological function for P-glycoprotein in the detoxification of the organism by excreting its substrates into bile, urine, and the intestinal contents [2–4]. Given the importance of these tissues in the absorption, metabolism, and excretion of drugs, the idea was rapidly conceived that P-glycoprotein had an important influence on drug disposition. ABC

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transporters were also found to be expressed in other tissues such as the heart, suggesting a role in detoxification and protection of the heart from the accumulation of xenobiotics [5]. The aim of this paper is to shed light on the involvement of ABC transporters in the distribution of xenobiotics to the heart, and to discuss their role in the protection of this organ from toxic compounds.

Expression of ABC transporters in the heart

The superfamily of ABC transporters is divided into seven different subfamilies [6], presented in *Table I*. Encoded proteins are classified on the basis of the sequence and organization of their nucleotide-binding domain(s) and similarity in gene structure. To date, eight of those recognized to have a role in the transport of xenobiotics in tissues have been found to be expressed in the heart (they are highlighted in *Table I*). These proteins are ABCB1 (P-glycoprotein or MDR1), ABCC1 (MRP1), ABCC3 (MRP3), ABCC4 (MRP4), ABCC5 (MRP5), ABCC10 (MRP7), ABCG2 (BCRP), and ABCA8. Molecular biology techniques used in human and rodents revealed these transporters to be expressed in either myocytes or vascular endothelial cells of the heart in these species [5]. Because P-glycoprotein was expressed in endothelial cells of human cardiac vasculature, it was proposed that P-glycoprotein serves as a functional barrier between blood and cardiac myocytes in a manner similar to the blood–brain barrier [7,8].

ABC transporters and evidence of their role in the protection of the heart

ABC transporter drug substrates, and cardiotoxicity associated with deficiency in ABC transporter genes

Mice genetically deficient in genes coding for ABC transporters such as P-glycoprotein or MRP1 have been useful models in which to demonstrate the role of transporters in preventing the accumulation of xenobiotics in the heart. Indeed, in mice genetically deficient in genes coding for P-glycoprotein, significantly greater concentrations of drugs such as vinblastine, loperamide, and enaminone anticonvulsants were observed in the heart compared with those observed in wild-type mice [9–11]. In addition, greater concentrations of drugs such as etoposide, grepafloxacin, and vincristine were observed in the heart of mice genetically deficient for the gene coding for MRP1 [12–14] in comparison with wild-type mice. These findings suggest that these ABC transporters contribute to the protection of the heart from xenobiotics.

Table I. Classification of human ATP-binding cassette (ABC) transporters into subfamilies. (Adapted from [5].)

ABC1 (Subfamily A)	MDR/TAP (Subfamily B)	MRP/CFTR (Subfamily C)	ALD (Subfamily D)	OABP (Subfamily E)	GCN20 (Subfamily F)	White (Subfamily G)
ABCA1	ABCB1 (MDR1 or P-GP)	ABCC1 (MRP1)	ABCD1 (ALDP)	ABCE1 (OABP)	ABCF1	ABCG1
ABCA2	ABCB2 (TAP1)	ABCC2 (MRP2 or cMOAT)	ABCD2 (ALDR)		ABCF2	ABCG2 (BCRP)
ABCA3	ABCB3 (TAP2)	ABCC3 (MRP3)	ABCD3		ABCF3	ABCG4
ABCA4	ABCB4 (MDR3)	ABCC4 (MRP4)	ABCD4			ABCG5
ABCA5	ABCB5	ABCC5 (MRP5)				ABCG8
ABCA6	ABCB6	ABCC6 (MRP6)				
ABCA7	ABCB7	ABCC7 (CFTR)				
ABCA8	ABCB8	ABCC8 (SUR1)				
ABCA9	ABCB9	ABCC9 (SUR2)				
ABCA10	ABCB10	ABCC10 (MRP7)				
ABCA12	ABCB11 (BSEP or SPGP)	ABCC11 (MRP8)				
ABCA13		ABCC12 (MRP9)				
		ABCC13				

Shaded cells represent ABC transporters expressed in the heart and having recognized activities in the transport of drugs.

Table II. Examples of commonly used drugs that are substrates of ATP-binding cassette (ABC) transporters and may be related to cardiotoxicity related to drug–drug interactions.

Transporter	Cardiac drugs			Antibiotic drugs		
	Sodium channel blockers	Calcium channel blockers	Cardiac glycosides	Fluoroquinolones	Macrolides	
	Quinidine	Verapamil	Digoxin	Grepafloxacin	Erythromycin	Clarithromycin
ABCB1 (MDR1 or P-gp)	[20,21]	[22,23]	[24,25]	[26,27]	[21,28]	[29]
ABCC1 (MRP1)				[26]		
ABCA8			[30]			

	Anticancer drugs					
	Anthracyclines		Vinca alkaloids		Epipodophyllotoxins	Other
	Daunorubicin	Doxorubicin	Vinblastine	Vincristine	Etoposide (VP-16)	Paclitaxel
ABCB1 (MDR1 or P-gp)	[31]	[1,32]	[1,32]		[32]	[33]
ABCC1 (MRP1)	[34]	[34,35]	[34]	[34,35]	[34,35]	[34]
			[35]			[35]
ABCC3 (MRP3)	[36]	[36]		[36]	[36,37]	[36]
		[37]		[37]		
ABCC5 (MRP5)	[38]			[38]	[38]	
ABCC10 (MRP7)		[39]	[39]	[39]		[39]
ABCG2 (BCRP)	[40]	[40]		[40,41]	[41]	[40,41]
ABCA8		[30]				

	HIV drugs				Immunosuppressive drugs	
	Protease inhibitor					
	Indinavir	Nelfinavir	Ritonavir	Saquinavir	Cyclosporin A	Tacrolimus (FK506)
ABCB1 (MDR1 or P-gp)	[42]	[42,43]	[43]	[42,43]	[10,44]	[44]
ABCC1 (MRP1)	[45]		[43]	[43]		
			[45]	[45]		
ABCC3 (MRP3)	[45]		[45]	[45]		
ABCC4 (MRP4)						
ABCC5 (MRP5)	[45]		[45]	[45]		
ABCG2 (BCRP)	[41,45]	[41]	[45]	[45]		

Clear cells represent evidence that the drug is a substrate (or inhibitor) of the ABC transporter.
Shaded cells represent evidence that the drug is not a substrate (or inhibitor) of the ABC transporter.

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A team of investigators generated transgenic mice that overexpressed *MDR1*, the human gene coding for P-glycoprotein, specifically in the cardiac muscle. The administration of single or repeated intravenous doses of doxorubicin led to degenerative changes in the heart of control mice that were absent in transgenic animals [15]. These findings confirmed the role of P-glycoprotein in detoxification processes in the heart.

In humans treated with anthracyclines for non Hodgkin lymphoma, the propensity for anthracycline-induced cardiotoxicity was increased in patients carrying single nucleotide polymorphisms in MRP1 and MRP2. The acute anthracycline-induced cardiotoxicity was associated with the Gly671Val variant of MRP1 and with the Val1188Glu–Cys1515Tyr haplotype of MRP2. The association of polymorphisms in the gene coding for MRP1 and MRP2 and the observed anthracycline-induced cardiotoxicity provide further proof of the importance of ABC transporters in the protection of the heart [16].

Cardiotoxicity and interactions of ABC transporter drug substrates

Many cases of cardiotoxicity have been linked to an increase in drug concentrations in the heart after co-administration of antineoplastic drugs and multidrug-resistance-reversing agents (drugs identified as P-glycoprotein inhibitors and having the capability of restoring the drug sensitivity of antineoplastic-resistant tumor cells). For instance, it was found that the co-administration of doxorubicin and the multidrug-resistance-reversing drug, verapamil, increased the peak concentration of doxorubicin in the heart of mice by 40%. The co-administration augmented the incidence and severity of degenerative changes in cardiac tissue, and decreased the survival rate compared with doxorubicin alone [17]. Other studies in rodents demonstrated that two other multidrug-resistance-reversing agents, cyclosporine A or its analog, PSC 833, could also increase doxorubicin concentrations [18,19]. This latter finding correlated with a greater incidence and severity of myocardial damage [19]. The mechanism involved is probably related to an accumulation of drugs in the heart as a result of inhibition of the normal protective function of P-glycoprotein, or other ABC transporters, by multidrug-resistance-reversing agents. These findings suggest that caution is advisable when prescribing a combination of ABC transporter substrates to patients. *Table II* lists some drugs commonly used for the treatment of cardiac diseases, cancer, infections, and human immunodeficiency virus, and immunosuppressive drugs that are substrates of ABC transporters and may be associated with cardiotoxicities related to drug–drug interactions [20–45].

ABC transporters and cellular mechanisms of cardiotoxicity such as drug-induced long QT syndrome

ABC transporter activities control intracellular access of drugs to their binding sites and modulate the efficacy or toxicity of the drugs. Drug-induced prolongation of cardiac repolarization (drug-induced long QT syndrome) is currently a major concern for patient safety and the pharmaceutical industry. The block of a specific cardiac potassium current, the rapid component of the delayed rectifier channel (I_{Kr}), encoded by the Human ether-a-go-go-related gene (*HERG*, *KCNE1*), is the underlying mechanism of prolonged repolarization observed in patients undergoing treatment with most QT-prolonging drugs. Excessive prolongation of cardiac repolarization (QT interval) increases the risk of early afterdepolarization, which, in the context of increased dispersed repolarization, could trigger a polymorphic ventricular tachycardia termed *torsades de pointes*. The I_{Kr}-binding site for currently used drugs is believed to be on the intracellular site of the channel embedded in the plasma membrane [46,47]. Consequently, factors such as ABC transporters that regulate intracellular concentrations of I_{Kr}-binding drugs could modulate the risk of the drug-induced long QT syndrome. Recently, the risk of QT prolongation after concomitant administration of two P-glycoprotein substrates, domperidone and ketoconazole, has been recognized [48]: cardiac QT-interval prolongation was observed when domperidone and ketoconazole were administered concomitantly, but not when domperidone was administered alone.

Conclusion

It is now widely accepted that transporters, along with CYP450 enzymes, contribute significantly to the bioavailability and drug disposition of xenobiotics. Cases of increased concentrations of drugs in the heart, cardiotoxicity occurring after the administration of concomitant ABC transporter substrates, and the use of knockout mice demonstrate the important role of these proteins in the efflux of drugs from the heart. We are still at an early stage in the discovery of ABC transporters in the myocardium and their involvement in the cardiac disposition of drugs. Nevertheless, there is increasing evidence that already indicates a major role of these transporters in the protection of the heart from toxic compounds. ■

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