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The ATP-Binding Cassette Transporters and Their Implication in Drug Disposition: A Special Look at the Heart

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***Abstract*——The passage of drugs across cell membranes dictates their absorption, distribution, metabolism, and excretion. This process is determined by several factors including the molecular weight of the compounds, their shape, degree of ionization, and binding to proteins. Accumulation of xenobiotics into tissues does not depend only on their ability to enter cells, but also on their ability to leave them. For instance, the role of efflux transporters such as ATP-binding cassette (ABC) proteins in the disposition of drugs is now well recognized. Actually, ABC transporters act in synergy with drug-metabolizing enzymes to protect the organism from toxic compounds. The most studied transporter from the ABC transporter superfamily, P-glycoprotein, was found to be overexpressed in tumor cells and associated with an acquired resistance to several anticancer drugs. P-glycoprotein, thought at first to be confined to tumor cells, was subsequently recognized to be expressed in normal tissues such as the liver, kidney, intestine, and heart. Even though information remains rather limited on the functional role of ABC transporters in the myocardium, it is hypothesized that they may modulate efficacy and toxicity of cardioactive agents. This review addresses recent progress on knowledge about the ABC transporters in drug disposition and more precisely their role in drug distribution to the heart.**

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I. Introduction

It was first demonstrated in 1973 that accumulation of xenobiotics into tissues does not depend only on their ability to enter cells but also on their ability to leave them. Indeed, Dano (1973) demonstrated using Ehrlich ascites tumor cells that intracellular concentrations of daunorubicin could be lowered by an active drug extrusion mechanism. A few years later, Juliano and Ling (1976) isolated a large glycoprotein in the plasma membrane of colchicine-resistant Chinese hamster ovary cells: they named this protein the P-glycoprotein (P-gp[1]). The gene coding for P-gp (*MDR1*) was then identified due to its overexpression in tumor cells associated with an acquired resistance to several anticancer drugs (Ueda et al., 1987). P-gp, thought at first to be confined to tumor cells, was subsequently recognized to be expressed in normal tissues, suggesting a physiological function for this transporter.

There have been ~50 ABC transporters discovered so far in the human. Among them, 14 have at least one published report of evidence of activity in the transport of xenobiotics. It is now evident that these transporters exhibit a protective role of the organism in the gut, the liver, the brain, the testis, or the placenta. On the other hand, there is relatively limited information on the functional role of P-gp and other ABC transporters in the heart.

Expression of ABC transporters in the heart is probably associated with regulation of normal physiological functions of this organ. ABC transporters may control access to essential nutrients as well as protect against potential toxic substances. It can be conceived that pathological conditions may trigger changes in the overall expression of these transporters. It can also be hypothesized that polymorphisms in ABC transporters may predispose patients to various cardiac diseases. In addition, ABC transporter activities may control intracellular access of drugs to their binding sites and then modulate drug efficacy or toxicity.

Therefore, the aim of this article is to review literature evidence for the expression of ABC transporters in the heart and to shed light on the involvement of ABC transporters in the distribution of drugs to this organ. Modulation of cardiac ABC transporter activities, regulation of their expression, and genetic polymorphisms will be discussed as potential mechanisms of drug activities or toxicities to the heart.

II. ATP-Binding Cassette Transporters

The ATP-binding cassette proteins represent the largest family of transmembrane transporters. These proteins are expressed in a large variety of organisms and ~50 ABC transporters have been identified so far in the human (Tirona and Kim, 2002). The superfamily of ABC transporters is divided into seven different subfamilies [Dean et al., 2001; see also M. Müller's website at http://www.nutrigene.4t.com/humanabc.htm (last updated March 2005)]. Because the transporters are ATP-dependent efflux proteins, ATP hydrolysis is required to translocate substrates against a concentration gradient from the intracellular toward the extracellular regions. A large range of endogene and exogene substrates are transported by ABC superfamily proteins, which include amino acids, sugars, ions, glycans, peptides, proteins, and phospholipids (Tirona and Kim, 2002).

A. Classification

Encoded proteins from the ABC transporter superfamily are classified on the basis of the sequence and organization of their nucleotide-binding domain(s) and similarity in gene structure (for an inventory of all ABC transporters, see http://www.nutrigene.4t.com/humanabc.htm). The members of the seven human ABC transporter subfamilies are listed in Table 1 in which proteins with a known activity in the transport of xenobiotics are presented in boldface type. Two subfamily proteins are particularly involved in the transport of xenobiotics. These are the multidrug resistance (MDR)/TAP (subfamily B) and the multidrug resistance-associated proteins (MRP)/CFTR (subfamily C). Table 2 summarizes some properties of ABC transporters having a recognized role in the transport of xenobiotics.

Some ABC transporters with no evidence of function in the transport of drugs were found to be expressed in the heart. These will not be discussed extensively in this manuscript but are discussed elsewhere (Solbach et al., 2006).

B. Structure and Mechanisms of Action

ABC proteins typically contain 12 hydrophobic transmembrane regions that span the cell membrane. These regions are split into two halves forming two distinct transmembrane domains (TMDs), each with a nucleotide-binding domain (NBD) (Fig. 1A). P-gp, BSEP, MRP4, MRP5, MRP8, and MRP9 are transporters having this structure. However, other MRP transporters (MRP1, MRP2, MRP3 and MRP6, MRP7) have an extra TMD toward the N terminus comprising five extra transmembrane regions (Fig. 1B). Finally, other ABC proteins such as BCRP are half-transporters and contain only six transmembrane regions and one NBD (Hyde et al., 1990) (Fig. 1C). ABC family members share 30 to 50% (200–250 amino acids) sequence homologies among them. The regions of high homology include the two NBDs that are located toward the cytoplasmic side of the membrane (Higgins et al., 1986; Hyde et al., 1990).

TMDs are thought to contain the substrate-binding site, and it is suggested that differences in substrate

[1] Abbreviations: P-gp, P-glycoprotein; ABC, ATP-binding cassette; MDR, multidrug resistance; MRP, multidrug resistance-associated protein; BCRP, breast cancer resistance protein; TMD, transmembrane domain; NBD, nucleotide-binding domain; RT, real-time; PCR, polymerase chain reaction; PSC 833, valspodar.

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TABLE 1
Classification of human ABC transporters into subfamilies
Cells in boldface type represent ABC transporters having recognized activities in the transport of drugs.

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				

cMOAT, canalicular multispecific organic anion transporter; ALD, adrenoleukodystrophy; ALDR, adrenoleukodystrophy-related; ALDP, adrenoleukodystrophy protein; OABP, organic anion-binding transporter; SPGP, sister of P-glycoprotein.

specificities are a consequence of structurally divergent TMDs (Locher et al., 2002; Chang, 2003). NBDs are the sites of binding and hydrolysis of cytoplasmic ATP. Hydrolysis of ATP ensures availability of the energy required for the uphill transport of substrates (Schneider and Hunke, 1998). All ABC transporters contain within each NBD at least three highly conserved sequence motifs; the signature sequence, the Walker A, and the Walker B (Fig. 1). The signature sequence has been suggested to be involved in the transduction of ATP hydrolysis energy to the conformational changes in the TMD responsible for the translocation of substrates (Hyde et al., 1990). Specific amino acids are important in Walker A and Walker B motifs. Indeed, an amino acid change of the lysine and aspartate residues in the Walker A and the Walker B motif, respectively, in either NBD, resulted in a loss of the ATP hydrolysis activity of the P-gp (Takada et al., 1998; Urbatsch et al., 1998; Hrycyna et al., 1999).

Visualization of the structure is necessary to understand how ABC transporters translocate their substrates across cell membranes. The crystal structure of the *Escherichia coli* vitamin B_{12} transporter BtuCD and the X-ray structure of the MsbA, both bacterial ABC transporters, contributed to additional information (Locher et al., 2002; Reyes and Chang, 2005). For instance, it is now believed that nucleotide binding and hydrolysis are properties of the dimeric NBD and not of an individual domain. The BtuCD structure demonstrated that no continuous channel is present through the membrane. It has been suggested that a set of at least two gates is required in ABC transporters to alternatively block access to one side of the membrane or the other (Locher and Borths, 2004).

Crystal structures at higher resolution are required to elucidate additional fundamental questions such as the signal routes by which TMDs control ATPase activity in the NBD in response to substrate binding. In addition, further information is required to understand how NBDs use ATP hydrolysis energy to lead to conformational changes in the TMDs that are responsible for substrate translocation.

III. ATP-Binding Cassette Transporters and the Disposition of Drugs in Cardiac Tissues

A. Evidence for the Presence of ATP-Binding Cassette Transporters in the Heart

1. Use of Different Molecular Biology Techniques. As mentioned earlier, ABC transporters first identified in tumor cells were later recognized to be expressed in normal tissues such as the heart. Table 3 summarizes evidence of the expression of ABC transporters in the heart using different molecular biology techniques.

It was demonstrated that P-gp is encoded by the *ABCB1* (also called *MDR1*) gene in humans and by the *mdr1a* (also called *mdr3*) and *mdr1b* (also called *mdr1*) genes in rodents (Schinkel, 1997) (Table 4). The two P-gp isoforms in mice seemed to fulfill the same function as the single MDR1 in humans (Schinkel et al., 1997). At the end of the 1980s and in the 1990s, the expression of P-gp in tissues was extensively studied. Studies using human heart tissues showed P-gp (MDR1) to be expressed in the heart, although generally at relatively low levels. The first study with such evidence was performed by Fojo et al. (1987) by slot blot hybridization. Afterward, in the early 1990s, the immunohistochemistry technique was used to measure P-gp expression in human tissues including the heart. In 1990, van der Valk et al. obtained strong staining in human cardiac muscle with C-219 antibody (that can also recognize MDR3/P-gp), weak staining with a second antibody JSB-1, and an absence of staining with a third antibody MRK-16. Two years later, strong staining was obtained in fetal heart specimens with the antibody C-219 but not with the MDR1-specific antibodies, MRK-16 and JSB-1.

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TABLE 2
Properties of ABC transporters involved in transport of drugs

ABC Transporter	No. of Transmembrane Domains	Main Tissue Expression	Apical or Basolateral Membrane Localization	Substrates[a]	References
ABCB1 (MDR1 or P-gp)	2	Liver, kidney, intestine, brain, testis, adrenal gland, uterus, ovary	Apical	Quinidine, verapamil, celiprolol, talinolol, digoxin, daunorubicin, doxorubicin, vinblastine, etoposide, methotrexate, mitoxantrone, paclitaxel, topotecan, indinavir, nelfinavir, ritonavir, saquinavir	Kartner et al. (1983), Ueda et al. (1987), Pastan et al. (1988), de Lannoy and Silverman (1992), Hendricks et al. (1992), Peters and Roelofs (1992), Karlsson et al. (1993), de Graaf et al. (1996), Sparreboom et al. (1997), Kim et al. (1998), Gramatte and Oertel (1999), Verschraagen et al. (1999), Jones et al. (2001)
ABCB4 (MDR3)	2	Liver	Apical	Vinblastine, paclitaxel, digoxin	Smith et al. (2000)
ABCB11 (BSEP or SPGP)	2	Liver, intestine	Apical	Vinblastine, cyclosporin, rifampicin	Török et al. (1999), Lecureur et al. (2000), Stieger et al. (2000)
ABCC1 (MRP1)	3	Intestine, brain, kidney, lung, testis	Basolateral	Doxorubicin, daunorubicin, vinblastine, vincristine, etoposide, methotrexate, paclitaxel, grepafloxacin	Cole et al. (1992, 1994), Flens et al. (1996), Sharp et al. (1998), Hooijerb et al. (1999), Evers et al. (2000), Tamai et al. (2000), Cherrington et al. (2002)
ABCC2 (MRP2 or cMOAT)	3	Liver, intestine, kidney	Apical	Cisplatin, doxorubicin, etoposide, vincristine, methotrexate, indinavir, ritonavir, saquinavir, adefovir, cidofovir	Schaub et al. (1997), Cui et al. (1999), Hooijberg et al. (1999), Kawabe et al. (1999), Fromm et al. (2000), Miller (2001), Huisman et al. (2002)
ABCC3 (MRP3)	3	Intestine, kidney, liver, pancreas, placenta, colon	Basolateral	Daunorubicin, doxorubicin, vincristine, etoposide, teniposide, methotrexate	Kool et al. (1997), Belinsky et al. (1998), Kool et al. (1999), Zeng et al. (1999), St-Pierre et al. (2000), Zelcer et al. (2001)
ABCC4 (MRP4)	2	Prostate, lung, adrenal gland, ovary, testis	Basolateral and apical (depending on cell type)	Methotrexate, adefovir	Lee et al. (1998), Schuetz et al. (1999), Lee et al. (2000), Chen et al. (2002
ABCC5 (MRP5)	2	Skeletal muscle, heart, brain	Basolateral	Adefovir	Kool et al. (1997), Belinsky et al. (1998), Wijnholds et al. (2000), Haimeur et al. (2004)
ABCC6 (MRP6)	3	Kidney, liver	Basolateral	Cisplatin, doxorubicin, etoposide, daunorubicin,	Belinsky and Kruh (1999), Bergen et al. (2000), Belinsky et al. (2002)
ABCC10 (MRP7)	3	Heart, skeletal, muscle, spleen, liver	Not determined	Doxorubicin, vinblastine, vincristine, paclitaxel, docetaxel	Kao et al. (2002), Orr et al. (2003), Hopper-Borge et al. (2004)
ABCC11 (MRP8)	2	Breast, testis	Not determined	Purine and pyrimidine nucleotide analogs	Bera et al. (2001)
ABCC12 (MRP9)	2	Breast, testis, brain, ovary, skeletal muscle	Not determined	Not determined	Bera et al. (2002)
ABCG2 (BCRP)	1	Placenta, brain	Apical	Daunorubicin, doxorubicin, etoposide, teniposide, methotrexate, mitoxantrone, topotecan	Doyle et al. (1998), Maliepaard et al. (1999, 2001), Volk et al. (2002), Allen et al. (2003), Volk and Schneider (2003), Wang et al. (2003), Aronica et al. (2005)
ABCA8	Not determined	Heart, skeletal muscle, liver	Not determined	Doxorubicin, digoxin	Tsuruoka et al. (2002)

cMOAT, canalicular multispecific organic anion transporter; BSEP, bile salt export pump; TAP, transporter associated with antigen processing; CFTR, cystic fibrosis transmembrane conductance regulator.
[a] Not an exhaustive list.

Therefore, van Kalken et al. (1992) concluded that *MDR1* expression in the fetal heart was unlikely considering the lack of staining with MDR1-specific antibodies and the absence of mRNA expression by RNase protection assay. A similar study used four antibodies directed against MDR1 in endocardium, mid-myocardium and epicardium (Pavelic et al., 1993). Only mid-myocardium revealed weak immunostaining for three of the antibod-

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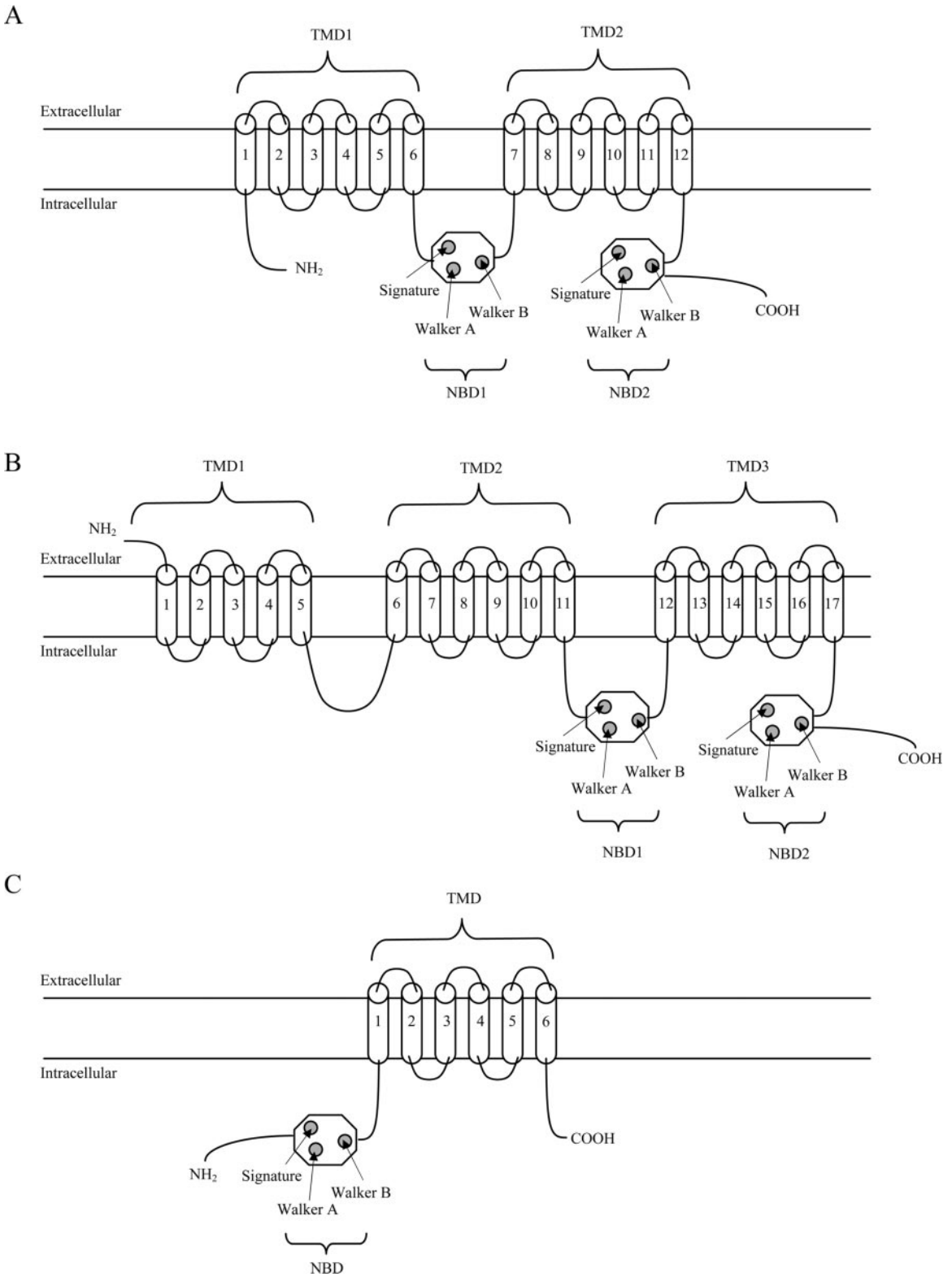

FIG. 1. General representation of the ABC transporter protein arrangements. A, P-gp, BSEP, MRP4, MRP5, MRP8, and MRP9 proteins contain 12 transmembrane regions, split into two halves forming transmembrane domains (TMD), each with a nucleotide-binding domain (NBD). B, MRP1, MRP2, MRP3, MRP6, and MRP7 have 5 extra transmembrane regions toward the N terminus. C, BCRP is a half-transporter and contains only 6 transmembrane regions and 1 NBD.

ies, suggesting nevertheless the presence of P-gp in heart muscle. A few years later, positive staining was also obtained with JSB-1 in human heart tissue, indicating one more time the presence of P-gp in heart muscle (Sugawara et al., 1997). More recently, P-gp was detected by immunohistochemistry, using the antibody

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TABLE 3
Presence of ABC transporters in the heart detected by different molecular biology techniques

ABC Transporter	Heart Species	Technique	Expression Level[a]	Reference
ABCB1 (MDR1 or P-gp)	Human	Slot blot hybridization	Low	Fojo et al. (1987)
	Human	Immunohistochemistry	Very low	van der Valk et al. (1990)
	Human fetus	Immunohistochemistry and RNase protection	Unlikely or very low	van Kalken et al. (1992)
	Human	Immunohistochemistry	Low	Pavelic et al. (1993)
	Human	Immunohistochemistry	Intermediate	Sugawara et al. (1997)
	Human	RT-PCR and immunohistochemistry	Present[b]	Meissner et al. (2002)
	Human	RT-PCR and immunohistochemistry	Present[b]	Meissner et al. (2004)
	Human	RT-PCR	Very low[c]	Nishimura et al. (2004)
ABCB1 (MDR1 or P-gp)	Chinese hamster	RNase protection	Very low	Baas and Borst (1988)
	C57Bl/6J mouse	Hydridization/Northern blot	Intermediate	Croop et al. (1989)
	BALB/c mouse	RNase protection	Low	Teeter et al. (1990)
	Wistar newborn and adult rat	RT-PCR	Low/intermediate	Cayre et al. (1996)
	Wistar newborn rat cultured ventricular myocytes	RT-PCR	High	Cayre et al. (1996)
	Sprague-Dawley rat	Western blot and immunodetection	Intermediate	Beaulieu et al. (1997)
	Wistar rat	Immunohistochemistry	Present[b]	Estevez et al. (2000)
	Wistar rat	RT-PCR	Present[b]	Rosati et al. (2003)
	FVB mouse	RT-PCR	High[c]	Muramatsu et al. (2004)
ABCB4 (MDR3)	Human	RNase protection	Low	Smit et al. (1994)
	Human	Immunohistochemistry	Not detected probably due to a too low level	Smit et al. (1994)
ABCB4 (MDR2)	C57Bl/6J mouse	Hydridization/Northern blot	Intermediate	Croop et al. (1989)
	BALB/c mouse	RNase protection	Intermediate	Teeter et al. (1990)
	Fisher rat	RNase protection	High	Brown et al. (1993)
	Sprague-Dawley rat	Northern blot and PCR	Low	Furuya et al. (1994)
ABCC1 (MRP1)	Human	Immunohistochemistry	High	Flens et al. (1996)[d]
	CD1 mouse	Northern blot	High	Stride et al. (1996)[d]
	Human	Immunohistochemistry	Not detected	Sugawara et al. (1997)[d]
	FVB mouse	Western blot	Present[b]	Wijnholds et al. (1997)
	Chicken	Northern blot	High	Hagen et al. (2000)
	Wistar rat	RT-PCR	Present[b]	Rosati et al. (2003)
	Wistar rat	PCR	Present[b]	Ghosh et al. (2004)
	FVB mouse	RT-PCR	High[c]	Muramatsu et al. (2004)
	Human	RT-PCR	Intermediate[c]	Nishimura et al. (2004)
ABCC2 (MRP2 or cMOAT)	Wistar rat	RT-PCR	Not detected	Rosati et al. (2003)
	FVB mouse	RT-PCR	Low[c]	Muramatsu et al. (2004)
	Human	RT-PCR	Very low[c]	Nishimura et al. (2004)
ABCC3 (MRP3)	FVB mouse	RT-PCR	Intermediate[c]	Muramatsu et al. (2004)
	Human	RT-PCR	Low[c]	Nishimura et al. (2004)
ABCC4 (MRP4)	FVB mouse	RT-PCR	Intermediate[c]	Muramatsu et al. (2004)
ABCC5 (MRP5)	Human	RT-PCR and immunohistochemistry	Present[b]	Dazert et al. (2003)
	FVB mouse	RT-PCR	Intermediate[c]	Muramatsu et al. (2004)
ABCC6 (MRP6)	FVB mouse	RT-PCR	Very low[c]	Muramatsu et al. (2004)
ABCC10 (MRP7)	Mouse	RT-PCR and Northern blot	Present[b]	Kao et al. (2002)
	FVB mouse	RT-PCR	Intermediate[c]	Muramatsu et al. (2004)
ABCG2 (BCRP)	C57BL/6 mouse	RT-PCR and immunohistochemistry	Present[b]	Martin et al. (2004)
	Human	RT-PCR and immunohistochemistry	Present[b]	Meissner et al. (2006)
ABCA1[e]	Human	RT-PCR	High[c]	Nishimura et al. (2004)
ABCA5[e]	Mouse	Immunohistochemistry	Present[b]	Kubo et al. (2005)
ABCA6[e]	Human	RT-PCR and dot blot analysis	High	Kaminski et al. (2001)
ABCA9[e]	Human	RT-PCR and dot blot analysis	High	Piehler et al. (2002)
ABCA8	Human	Northern blot	High	Tsuruoka et al. (2002)
ABCA10[e]	Human	RT-PCR and dot blot analysis	High	Wenzel et al. (2003)
ABCD2 (ALDR)[e]	Human	Northern blot	High	Holzinger et al. (1997)

cMOAT, canalicular multispecific organic anion transporter; ALDR, adrenoleukodystrophy-related.
[a] Relative because assessed by different authors.
[b] Present means that the level cannot be compared with that in other tissues because only heart was studied or very few tissues, including the heart.
[c] Assessed by the authors of this article on the basis of comparisons with other tissues analyzed.
[d] Not specified in the publication but probably corresponds to MRP1.
[e] No evidence in the literature of the role of this ABC transporter in drug disposition.

JSB-1, in 15 human left ventricular and 51 excised auricular heart samples. Confirmation was obtained by real-time (RT) polymerase chain reaction (PCR), which detected the expression of MDR1-specific mRNA in all heart samples studied. Immunohistochemistry and in situ hybridization techniques subsequently localized P-gp predominantly in endothelial cells of capillaries and arterioles. Because the expression of P-gp in cells of human heart vessels is similar to that of P-gp in brain, it was proposed that P-gp serves as a functional barrier

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TABLE 4
Classification of mammalian P-glycoprotein isoforms

Adapted from Smit et al. (1994) by permission from Macmillan Publishers Ltd: *Laboratory Investigation* **71:**638–649, copyright © 1994 (http://www.nature.com/labinvest/).

P-gp Class	I	II	III[a]
Human	MDR1[b]		MDR3[c] (MDR2)[d]
Mouse	mdr3[e] (mdr1a)[f]	mdr1[g] (mdr1b)[f]	mdr2[h]
Hamster	P-gp1[i]	P-gp2[i]	P-gp3[i]

[a] Involved in phospholipid transport (Smit et al., 1993).
The nomenclature of the human, mouse, and hamster P-gp genes is according to [b] Chen et al. (1986), [c] Van der Bliek et al. (1987), [e] Devault and Gros (1990), [g] Gros et al. (1986), [h] Gros et al. (1988), and [i] Ng et al. (1989). Alternative designations are given in parentheses: [d] Roninson et al. (1986) and [f] Hsu et al. (1989).

between blood and cardiac myocytes (Meissner et al., 2002, 2004). Another recent study revealed the presence of P-gp mRNA, although at very low levels, in the heart of an Asian male by RT-PCR (Nishimura et al., 2004).

Studies using an RNase protection assay in rodents provided evidence of P-gp expression in the heart. Indeed, P-gp mRNA was detected, although at very low levels, in the heart of Chinese hamsters (Baas and Borst, 1988). Significant levels of both mdr1a and mdr1b mRNA were also found in BALB/c and C57BL/6J mice using two different techniques (Croop et al., 1989; Teeter et al., 1990). In Wistar rats, *mdr1a* gene expression was observed using RT-PCR; the signal seemed stronger in cultured myocytes than in cardiac tissue from adult and newborn rats suggesting an *mdr1a* cardiac expression more specifically localized into myocytes (Cayre et al., 1996). This was confirmed a few years later by the study of Estevez et al. (2000), who demonstrated for the first time by immunohistochemistry (JSB-1 antibody) the expression of the P-gp protein in cardiomyocytes. The P-gp transporter was also found to be present in endothelial luminal membranes in rat heart although not restricted to this site (Beaulieu et al., 1997). These results were in agreement with the results of Meissner et al. (2002), who demonstrated P-gp in endothelial cells of human heart small vessels.

The presence of the second isoform of P-gp, MDR3 in human and mdr2 in rodents was also studied. In human, RNase protection results demonstrated low levels of MDR3 mRNA in several tissues including the heart (Smit et al., 1994). In mice and rats, low to high levels of mdr2 mRNA were obtained by different molecular biology techniques (Croop et al., 1989; Teeter et al., 1990; Brown et al., 1993; Furuya et al., 1994).

The expression of MRPs has been studied extensively since the mid-1990s. MRP1 was detected at high levels in the heart of several species including humans (Flens et al., 1996; Wijnholds et al., 1997). Only one report did not detect MRP in human heart (Sugawara et al., 1997). MRP1 mRNA was found to be abundant in the heart of CD1 mice and chickens by Northern blot analysis, and in rats by RT-PCR (Stride et al., 1996; Hagen et al., 2000; Rosati et al., 2003). Moreover, Ghosh et al. (2004) observed cardiac *MRP1* gene expression by PCR in heart of Wistar rats, which was increased in diabetic cardiomyocytes. Recently, the presence of MRP1, MRP3, and MRP2 mRNA at intermediate, low, and very low levels, respectively, was demonstrated in human heart (Nishimura et al., 2004).

Immunohistochemistry revealed localization of another multidrug resistance protein, MRP5, in human heart. MRP5 mRNA was detectable by RT-PCR in 21 auricular and 15 left ventricular human heart samples with auricular samples showing less MRP5 mRNA than ventricular samples (Dazert et al., 2003). MRP5 was found to be present in three different cell types in the heart: in vascular smooth muscle cells, in myocytes, and in vascular endothelial cells (Dazert et al., 2003). Kao et al. (2002) reported that another member of the MRP subfamily, mrp7, was also present in the mouse heart. Using immunohistochemistry and Northern blot analysis, they demonstrated that the mouse mrp7 has two spliced transcripts, mrp7A and mrp7B, which both seemed to be expressed at similar levels.

Muramatsu et al. (2004) studied by RT-PCR mRNA expression of mdr1a and mrp1 to mrp7 in wild-type and combined *mdr1a/1b*$^{-/-}$, *mrp1*$^{-/-}$ weanling and adult mice in several tissues. Notably, both mdr1a and mrp1 were highly expressed in the heart and lung of wild-type weanling and adult mice. Moreover, mrp3, mrp4, and mrp5 showed relatively high levels of expression in the heart of both wild-type and knockout mice. For most transporters, levels of expression were more important in adult than in weanling mice.

The ABC transporter ABCG2 (also named BCRP) plays a major role in multidrug resistance. A recent study demonstrated the expression of ABCG2 in the developing and adult mouse heart. This finding supports the presence of an ABCG2-expressing side population of cells in the heart that are probably responsible for the development, maintenance, and repair of this organ (Martin et al., 2004). Moreover, Meissner et al. (2006) recently showed the presence of ABCG2 in endothelial cells in human heart.

One transporter from the ABCD subfamily, ABCD2, and some transporters from the ABCA subfamily were observed to be highly expressed in the human heart. The *ABCA1, ABCA6, ABCA9,* and *ABCA10* genes were revealed to be ubiquitously expressed with the highest mRNA levels in a few tissues including the heart (Kaminski et al., 2001; Piehler et al., 2002; Wenzel et al., 2003, Nishimura et al., 2004). ABCA5 was also found to be expressed in cardiomyocytes (Kubo et al., 2005). Moreover, the use of *abca5*$^{-/-}$ mice revealed an important physiological role of this transporter for the heart. ABCA8 mRNA expression was demonstrated to be widely distributed in various organs and especially well expressed in some tissues such as the heart (Tsuruoka et al., 2002). The ABCA8 protein is the only one from the ABCA subfamily that showed an activity in the transport of drugs. Moreover, the presence of ABCD2 (ALDR) mRNA in a variety of human tissues was revealed, pre-

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dominantly in heart and brain (Holzinger et al., 1997). Further work is required to elucidate the precise biological functions of ABCD2 and ABCA transporters.

Rosati et al., (2003) studied the physiological modulation of mdr1a, mdr1b, mrp1 and mrp2 in some tissues including the heart during rat ontogeny. In this research in which hearts were collected at different developmental stages, both mdr1a and mdr1b levels of transcript were detected by RT-PCR and increased during rat ontogeny to obtain the highest levels at 30 and/or 60 days of age. These results suggest that ABC transporters play an important physiological role in the protection of the cardiac organ against xenobiotics and toxins, when, for example, the rat becomes independent from breast feeding (Rosati et al., 2003). In contrast, no variation with age was observed for mrp1, and the presence of mrp2 was not detected in these hearts (Rosati et al., 2003).

Some contradictory results are still obtained relative to the presence of ABC transporters in the heart (Table 3). This may be due, at least in part, to the use of different techniques. For instance, with the immunohistochemistry technique, it is recommended for P-gp identification that C-219 antibody be used with caution because of its cross-reactivity with unrelated proteins. More than one antibody should be used to assess P-gp and ABC transporter expression in tissues (Pavelic et al., 1993; Jetté et al., 1995). Controversial results on expression levels may be due not only to a lack of correlation between mRNA and protein expression but also to cardiac cell type-specific expression of the protein (i.e., myocytes, endothelial cells, or smooth muscle).

2. Use of Knockout Mice. The generation of mice genetically disrupted for ABC transporter genes has been very useful in the investigation of the assessment of the role of these transporters in the metabolism of specific drugs. The use of these knockout mice is especially relevant to assess the safety of an anticancer drug when it is expected to be coadministered with a multidrug resistance-reversing agent that blocks P-gp or to predict drug-drug interaction toxicities. For instance, toxicities observed following the administration of a compound in *mdr1a*$^{-/-}$ or *mdr1a/1b*$^{-/-}$ mice, compared with wild-type animals, would predict toxicities following the coadministration of this compound and P-gp substrates, as these mice are deficient in P-gp. We review in Table 5 literature evidence of increased cardiac concentrations of drugs in mice deficient in ABC transporters. These findings indirectly suggest the presence and role of ABC transporter proteins in the heart.

Schinkel et al. (1994) demonstrated the importance of P-gp using *mdr1a*$^{-/-}$ in the metabolism of vinblastine in several tissues including the heart. The absence of the *mdr1a* gene had a clear effect on vinblastine concentrations. The most striking effect was observed in heart, which had 7- to 14-fold higher concentrations of vinblastine in *mdr1a*$^{-/-}$ mice between 8 and 24 h after injection of 6 mg/kg. This finding indicated that the absence of mdr1a P-gp had an important effect on the pharmacokinetics and tissue distribution of vinblastine (Schinkel et al., 1994; van Asperen et al., 1996). Another study showed that following a 96-h infusion, vinblastine levels in the heart of *mdr1a*$^{-/-}$ mice were 1.7-fold higher than in control animals, suggesting again the likelihood of an important role for P-gp in the protection of the heart (van Asperen et al., 1999).

TABLE 5
In vivo evidence of the presence of ABC transporters in the heart by the use of knockout mice

ABC Transporter Studied	Mice Type	Reference
mdr1a/1b (P-gp or ABCB1)		
Vinblastine levels were about 3-fold higher in hearts of *mdr1a*$^{-/-}$ mice, which had a longer elimination vs. wild-type mice	*mdr1a*$^{-/-}$ and wild-type	Schinkel et al. (1994)
In *mdr1a*$^{-/-}$ mice, heart accumulated increased amounts of vinblastine vs. wild-type mice	*mdr1a*$^{-/-}$ and wild-type	van Asperen et al. (1996)
Tissue levels of radioactivity in some tissues, including the heart of *mdr1a*$^{-/-}$ mice, are 2-fold higher following administration of [^{3}H]loperamide vs. wild-type mice	*mdr1a*$^{-/-}$ and wild-type	Schinkel et al. (1996)
A 1.7-fold increase in the accumulation of vinblastine was observed in the heart of *mdr1a*$^{-/-}$ mice vs. wild-type mice	*mdr1a*$^{-/-}$ and wild-type	van Asperen et al. (1999)
Tissues such as the heart displayed at least 2-fold higher tissue levels in *mdr1a/1b*$^{-/-}$ following administration of enaminone anticonvulsants vs. wild-type mice	*mdr1a/1b*$^{-/-}$ and wild-type	Cox et al. (2002)
mrp1 (ABCC1)		
There was increased toxicity in the TKO mice that accumulated etoposide in some tissues such as the heart vs. DKO mice	DKO, TKO, and wild-type	Wijnholds et al. (2000)
A higher tissue/plasma ratio was observed in some tissues such as the heart in *mrp1*$^{-/-}$ following administration of grepafloxacin vs. wild-type mice	*mdr1a/1b*$^{-/-}$, *mdr1a*$^{-/-}$, *mrp1*$^{-/-}$, and wild-type	Sasabe et al. (2004)
mdr1a/1b (P-gp or ABCB1) and mrp1 (ABCC1)		
Vincristine tissue/plasma ratio comparisons showed higher values in the heart of both weanling and adult combined *mdr1a/1b*$^{-/-}$, *mrp1*$^{-/-}$ mice than in wild-type mice	TKO and wild-type	Muramatsu et al. (2004)

DKO, *mdr1a* and *mdr1b* double-knockout mice (or *mdr1a/1b*$^{-/-}$); TKO, *mrp1*, *mdr1a* and *mdr1b* triple-knockout mice (or *mrp1*$^{-/-}$/*mdr1a/1b*$^{-/-}$).

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RNase protection assays demonstrated increased expression of mdr1b in kidney and liver in *mdr1a*$^{-/-}$ or *mdr1a*$^{+/-}$ mice compared with wild-type mice. This overexpression was attributed to a possible compensatory response of the organs to the decrease of functional mdr1a P-gp, intended to limit effects of mdr1a absence in drug disposition (Schinkel et al., 1994). This compensatory mechanism of mdr1b does not seem to be present in the heart because as mentioned above, the elimination of vinblastine was much longer in *mdr1a*$^{-/-}$ mice than in wild-type, although it is known that the heart contains significant and similar levels of both mdr1a and mdr1b mRNA (Croop et al., 1989; Teeter et al., 1990; Schinkel et al., 1994). Another study suggested an absence of a compensatory response in the heart from the mrp2 to mrp7 transporters in combined *mdr1a*/*1b*$^{-/-}$, *mrp1*$^{-/-}$ weanling and adult mice. Indeed, RT-PCR analysis showed that expression of mrp2 to mrp7 was not higher in combined *mdr1a*/*1b*$^{-/-}$, *mrp1*$^{-/-}$ mice compared with wild-type mice (Muramatsu et al., 2004).

Experiments have been performed with drugs that are not anticancer agents to determine the affinity of drugs for ABC transporters. Higher levels, approximately 2-fold, of [^{3}H]loperamide (Schinkel et al., 1996) and enaminone anticonvulsants (Cox et al., 2002) were found in some tissues such as the heart following administration of the drugs in *mdr1a*$^{-/-}$ or *mdr1a*/*1b*$^{-/-}$ mice compared with wild-type mice.

The role of the ABC transporter mrp1 in the pharmacokinetics and drug distribution of etoposide, an anticancer drug, was studied using triple-knockout (*mrp1*$^{-/-}$/*mdr1a*/*1b*$^{-/-}$) and double-knockout (*mdr1a*/*1b*$^{-/-}$) mice. In the triple-knockout mice lacking mrp1 protein, an increase in etoposide accumulation in some tissues including the heart (1.3-fold at 4 h postadministration) was observed compared with double-knockout mice. This observation indicated that the ABC transporter mrp1 contributes to the protection of the heart against drugs like etoposide (Wijnholds et al., 2000).

The transporter mrp1 has been studied recently using a fluoroquinolone antibiotic, grepafloxacin. The latter drug was administered intravenously to *mrp1*$^{-/-}$, *mdr1a*$^{-/-}$, *mdr1a*/*1b*$^{-/-}$, and wild-type mice. The tissue/plasma concentration ratio was significantly higher in several tissues of mrp1$^{-/-}$ mice such as the heart compared with wild-type animals, which was not the case for *mdr1a*$^{-/-}$ and *mdr1a*/*1b*$^{-/-}$ mice. This latter finding is surprising considering that grepafloxacin is a well-recognized substrate of P-gp (Tamai et al., 2000; Naruhashi et al., 2001; Lowes and Simmons, 2002). This interesting observation suggested that mrp1 makes a significant contribution to the distribution of its substrates in several tissues including the heart (Sasabe et al., 2004).

Another study confirmed the importance of P-gp and/or mrp1 in the tissue distribution of vincristine by the use of combined *mdr1a*/*1b*$^{-/-}$, *mrp1*$^{-/-}$ mice, and wild-type mice. Indeed, the knockout mice showed a significantly higher tissue/plasma concentration ratio compared with wild-type mice in several tissues, especially in cardiopulmonary structures (Muramatsu et al., 2004).

B. Cardiotoxicity Related to ATP-Binding Cassette Transporters

A wide range of drugs has been identified as highly effective modulators of P-gp and able to restore drug sensitivity of resistant tumor cells. These are called multidrug resistance-reversing agents. Blockade of ABC transporters in vivo by multidrug resistance-reversing agents inevitably changes drug distribution and metabolism of anticancer agents because of the inhibition of the normal protective function of P-gp in normal tissues. As a result, plasma and tissue concentrations of drugs increase and may result in toxicity.

Cardiotoxicities linked to increased heart drug concentrations following coadministration of antineoplasic agents and agents that reverse multidrug resistance have been reported. Table 6 summarizes this evidence. For instance, it was found that calcium channel blockers such as nifedipine, flunarizine, verapamil, or other agents that reverse MDR increased intracellular concentrations of anthracycline drugs such as doxorubicin, daunorubicin, and idarubicin in cardiomyocytes (Santostasi et al., 1991; Cayre et al., 1996) and ex vivo (Kang and Weiss, 2001), potentiating cardiotoxicities. A study performed approximately in the same period showed that the coadministration of verapamil and doxorubicin in mice increased the peak concentration of doxorubicin in the heart by 40%, augmented the incidence and severity of degenerative changes in cardiac tissue, and decreased the survival rate compared with doxorubicin alone (Sridhar et al., 1992). Other studies in rodents demonstrated that cyclosporin A or its analog PSC 833 could increase doxorubicin (Colombo et al., 1994; Bellamy et al., 1995; Gonzalez et al., 1995; Colombo et al., 1996a) and etoposide concentrations (Cárcel-Trullols et al., 2004) in several tissues including the heart. This increase may be correlated with a higher incidence and severity of myocardial damage when cyclosporin A and doxorubicin were administered in combination (Bellamy et al., 1995). The mechanism responsible for the enhanced cardiotoxicities is probably related to an accumulation of drugs in the heart due to the inhibition of P-gp or other ABC transporters by agents such as verapamil, cyclosporin A, or PSC 833. These findings suggest that caution is advisable when one is prescribing a combination of these drugs to reverse the multidrug resistance for cancer patients.

It was shown that heart distribution of the anthracycline drug, epidoxorubicin, was significantly increased by a 30-min pretreatment with paclitaxel or Cremophor in CDF1 mice. Indeed, heart epidoxorubicin levels were two times higher in mice pretreated with paclitaxel and

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TABLE 6
Drug-drug interactions and increased concentrations in the heart

Drugs and Effects	Study Type	Species	Reference
Calcium channel blockers that reverse MDR increased levels of anthracyclines and potentiated cardiotoxicity	In vitro	Sprague-Dawley rat	Santostasi et al. (1991)
Mice treated with verapamil and doxorubicin had a lower survival rate, higher incidence and severity of degenerative changes in cardiac tissue, and a higher peak concentration of doxorubicin in the heart compared with mice treated with doxorubicin alone	In vivo	(BALB/c × DBA/2)F1 mouse	Sridhar et al. (1992)
Cyclosporin A increased doxorubicin concentration in heart	In vivo	Crl/CD BR rat and CD_2F_1/Crl BR mouse	Colombo et al. (1994)
Increase in cardiac levels of doxorubicin when cyclosporin A administered and higher incidence and severity of myocardial damage	In vivo	SCID mouse	Bellamy et al. (1995)
Greater area under the curve of doxorubicin in the heart when combined with PSC 833 (cyclosporin A analog)	In vivo	CDF1 mouse	Gonzalez et al. (1995)
When myocardial cells incubated with daunorubicin and MDR-reversing agent (verapamil, PSC 833, or S9788), a moderate, but significant, intracellular increase of [^{3}H]daunorubicin was obtained	In vitro	Wistar newborn rat ventricular myocytes	Cayre et al. (1996)
Doxorubicin concentration increased in heart of mice pretreated with PSC 833	In vivo	BDF1 mouse	Colombo et al. (1996a)
Increased cardiotoxicity of doxorubicin in the presence of amiodarone	In vitro	Neonatal Wistar rat	Estevez et al. (2000)
Myocardial uptake of idarubicin (anticancer) was increased by verapamil	Ex vivo	Sprague-Dawley rat	Kang and Weiss (2001)
Higher tissue concentration of etoposide in heart following cyclosporin A administration	In vivo	Wistar rat	Cárcel-Trullols et al. (2004)
Pretreatment with paclitaxel induced a significant increase in epidoxorubicin in the heart	In vivo	CDF1 mouse	Colombo et al. (1996b)
Reduction of heart contractility and development of congestive heart failure were obtained with doxorubicin and paclitaxel combination	In vivo	Human	Gianni et al. (1995)
Patient received verapamil and clarithromycin and developed bradycardia and hypotension; withdrawal of verapamil resulted in resolution of symptoms	In vivo	Human	Kaeser et al. (1998)
Patient was taking verapamil and developed bradycardia while receiving erythromycin and clarithromycin	In vivo	Human	Steenbergen and Stauffer (1998)
Following coadministration of erythromycin and verapamil, the patient had atrioventricular block and QT interval prolongation	In vivo	Human	Goldschmidt et al. (2001)

S9788, 6-[4-[2,2-di(4-fluorophenyl)-ethylamino]-1-piperidinyl]-*N*,*N*′-di-2-propenyl-1,3,5-triazine-2,4-diamine.

markedly higher in mice pretreated with Cremophor compared with those treated with epidoxorubicin alone. This result suggested that the cardiotoxicity induced by anthracycline drugs could be increased when they are coadministered with paclitaxel (Colombo et al., 1996b). In line with this previous finding, a reduction in heart contractility and the development of congestive heart failure was obtained with coadministration of doxorubicin and paclitaxel in human (Gianni et al., 1995). Again, ABC transporters are thought to influence the distribution of epidoxorubicin to the heart and toxicities induced by paclitaxel.

Cardiotoxicities in patients were also observed with the concomitant administration of verapamil and erythromycin or clarithromycin. The bradycardia and hypotension symptoms developed following verapamil and clarithromycin intake disappeared with the withdrawal of verapamil (Kaeser et al., 1998; Steenbergen and Stauffer, 1998). Likewise, Goldschmidt et al. (2001) reported a case of a patient who had an atrioventricular block and QT interval prolongation following coadministration of erythromycin and verapamil. Although it was not possible in these human studies to know whether an increase in the heart concentration of the drug is responsible for cardiotoxicities, it is likely that ABC transporters, such as P-gp, would be involved in these observed cardiotoxities. Indeed, verapamil (Kim, 2002), clarithromycin (Wakasugi et al., 1998), and erythromycin (Schuetz et al., 1998; Takano et al., 1998; Kim et al., 1999) are well known substrates of P-gp. Therefore a possible mechanism of action would be the increase of drug concentrations in cardiac tissues producing cardiotoxicities due to an inhibition of heart P-gp.

Investigation of the effects of the antihistamine agent ketotifen on multidrug resistance in human breast cancer cells and doxorubicin toxicity in mice demonstrated that ketotifen increased accumulation of doxorubicin in cardiac tissues, probably due to a block of P-gp. However, ketotifen pretreatment did not enhance doxorubicin cardiotoxicities, but in fact provided protection both at the level of cardiac tissue damage and in terms of survival (Zhang and Berger, 2003).

Moreover, because of the toxic irreversible cardiac toxicity produced by doxorubicin therapy, which includes mitochondrial damage, myofibril degeneration, and vacuolar changes, a team of investigators generated transgenic mice that overexpressed the human multidrug resistance cDNA (MDR1) specifically in the cardiac

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muscle. The administration of a single or repeated doses of doxorubicin intravenously led to degenerative changes in the hearts of control mice that were absent in transgenic animals (Dell'Acqua et al., 1999). This interesting experiment provided strong evidence that *MDR1* gene therapy in the heart could provide protection against doxorubicin heart toxicity, which confirms again the important role of P-gp in detoxification processes of the heart.

C. ATP-Binding Cassette Transporters and Drug-Induced Long QT Syndrome

Drug-induced prolongation of cardiac repolarization (drug-induced Long QT syndrome) is currently a major concern for drug industry and regulatory agencies, but more importantly, it remains a major concern for patients' safety. It is now well accepted that a block of the 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 the prolonged repolarization observed in patients undergoing treatment with some QT-prolonging drugs.

Excessive prolongation of cardiac repolarization (QT) increases the risk of early afterdepolarization that could trigger, in the context of increased dispersed repolarization, 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 (Zou et al., 1997; Zhang et al., 1999). Consequently, factors such as ABC transporters that regulate intracellular concentrations of I_{Kr} binding drugs could modulate risk of cardiac toxicity.

IV. Expression of ATP-Binding Cassette Transporters

A. Regulation of Expression of ATP-Binding Cassette Transporters

1. Regulation by Drugs. Drugs have been shown to contribute to an increase in the expression of ABC transporters in tissues. Jetté et al. (1996) showed that following daily administration for 5 days of cyclosporin A (10 mg/kg) to rats, an increase in P-gp expression of 82% in the heart, compared with control groups, was obtained. After the interruption of cyclosporin A administration, values returned to control levels after 9 days. Therefore, cyclosporin A seemed to modulate the expression of P-gp in normal tissues in vivo in a reversible way. However, these results should be taken with caution as only C-219 antibody was used (Thiebaut et al., 1989; Liu et al., 1997).

More recently, a study demonstrated that a 10-day treatment in Ehrlich ascites carcinoma cell-inoculated mice with rifampicin or verapamil increased levels of P-gp proteins. On the other hand, no increase in the transcripts of mdr1a was detected (Granzotto et al., 2004). The increase in protein expression without an increase in mRNA was observed by other investigators who attributed this observation to an increased half-life of the ABC transporter protein or a post-translational effect of drugs (Hill et al., 1990; Westphal et al., 2000). However, another recent study demonstrated that in a tubular renal cell line, a 15-day treatment with rifampicin significantly increased the mRNA levels of P-gp, MRP1, MRP2, LRP, and CYP3A4 but an increase in protein was observed only for P-gp and MRP2 transporters (Magnarin et al., 2004).

Little attention has been paid to the possibility that the expression of ABC transporters may be affected by administration of compounds given to cancer patients for other pathological conditions. For example, it is not rare that cardiovascular diseases affect cancer patients. Many drugs commonly administered in patients with heart failure are P-gp substrates such as amiodarone, losartan, and digoxin (Schinkel et., 1995; Soldner et al., 2000). Chronic treatment with ABC transporter substrates could therefore potentially increase the expression level of these proteins, thereby conferring drug resistance to cancer cells in these situations and promoting therapeutic failure.

Greiner et al. (1999) have suggested that P-gp induction may be restricted to some cell types; however, few data exist about the induction of P-gp in tissues. Therefore, further studies are required to assess the implication of ABC transporter induction in tissues such as the heart, which could lead to important consequences in therapeutic effects and cardiotoxicities.

2. Regulation by Pathological Conditions. Quantitative analysis of MRP5 in ventricular heart samples from patients suffering from ischemic cardiomyopathy compared with patients having dilated cardiomyopathy or a normal heart suggested an up-regulation of MRP5 under ischemic conditions (Dazert et al., 2003). Another investigation pointed to reduced expression of P-gp in patients with dilated cardiomyopathy compared with patients with ischemic cardiomyopathy or healthy heart. This latter result was consistent both at the protein and mRNA levels (Meissner et al., 2002). Recently, the same team of investigators demonstrated that cardiac expression of BCRP was up-regulated in patients with both dilative and ischemic cardiomyopathy (Meissner et al., 2006). Sims et al. (2004) could not demonstrate a change in myocardial expression of P-gp associated with heart failure. Further observations on the effect of pathological conditions on ABC transporter expression remain to be demonstrated.

B. Polymorphisms

Therapeutic effects following the administration of a drug show a wide interindividual variability, which may be explained in part by expression of drug transporters

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in human tissues. This variability can also be partly explained by polymorphisms of ABC transporter genes.

The silent mutation at position 3435 in exon 26 (C3435T) is the only polymorphism identified so far that affects P-glycoprotein expression in human tissues (Hoffmeyer et al., 2000). For instance, in the human kidney, subjects with the TT genotype had 1.5-fold lower P-glycoprotein expression than those with the CC genotype (Siegsmund et al., 2002). Likewise, in the small intestine 2-fold lower intestinal MDR1 expression or P-gp levels were observed in the carriers homozygous for the T-allele compared with the CC genotype (Hoffmeyer et al., 2000; Schwab et al., 2003). In line with the latter finding, higher digoxin plasma concentrations were found in patients with the 3435TT genotype than in individuals with the 3435CC genotype (Hoffmeyer et al., 2000). This relationship between *MDR1* polymorphism/P-gp expression and drug disposition was not observed for other drugs such as cyclosporine, talinolol, and loperamide (von Ahsen et al., 2001; Siegmund et al., 2002; Pauli-Magnus et al., 2003). Moreover, the opposite trend was observed in some investigations. For instance, Fellay et al. (2002) obtained higher plasma concentrations of nelfinavir with the CC genotype than with the TT and CT genotypes. Several studies were performed in an attempt to correlate *MDR1* polymorphisms, particularly C3435T, to changes in P-gp expression and function, which led to contradictions. A possible explanation for these discrepancies is that most studies have focused on an individual polymorphism, such as C3435T alone, instead of accounting for combinations of single nucleotide polymorphisms potentially linked, called haplotypes (Woodahl and Ho, 2004). Environmental factors and interethnic differences could have been influencing factors.

Up until recently, there was no evidence in the literature discussing the impact of ABC transporter polymorphisms at the cardiac level. It could be predicted that low or high cardiac expression of P-gp would increase or reduce, respectively, uptake of P-gp substrate drugs, leading to important therapeutic or toxic implications. Meissner et al. (2004) investigated the significance of the *MDR1* gene polymorphism for cardiac P-gp expression levels. They observed no significant influence of the exon 26 C3435T genotype on MDR1 mRNA expression in human heart samples from the auricles. Further studies are required to assess the clinical relevance of MDR1 as well as other ABC transporter gene polymorphisms, especially at the ventricular level.

V. Summary and Future Perspectives

Approximately 50 ABC transporters have been discovered so far in the human and, among them, we reported that 14 transporters have at least one published evidence of activity in the transport of xenobiotics. In this review, we summarized the literature evidence for the presence of these ABC transporters in cardiac tissues by the use of molecular biology techniques. Indirect evidence of the expression of these transporters in the heart was also obtained by the use of knockout mice devoid of ABC transporter genes. Indeed, an increase in the cardiac uptake of ABC transporter substrates in these animals led to convincing proof of the involvement of these proteins in the distribution of drugs to cardiac tissues. Moreover, cases of increased concentrations of drugs in the heart and cardiotoxicities occurring following the administration of concomitant ABC transporter substrates seem to confirm the important role of these proteins in the transport of drugs to the heart.

The underlying mechanisms of cardiac toxicities following administration of ABC transporters substrates are probably complex. Ion channels involved in the generation of cardiac action potentials are probably one of the key factors indirectly affected by the modulation of ABC transporters in the production of cardiac adverse effects, just as the inhibition of the I_{Kr} channel in the etiology of the drug-induced Long QT syndrome.

Regulation of expression of ABC transporters remains an obscure subject, considering the contradictions reported in the literature in regard to drug induction. Interestingly, it was reported that the expression of ABC transporters in the heart could be modulated by cardiac pathological conditions. Polymorphisms in ABC transporter genes have been shown to modulate drug disposition although their impact on cardiac drug levels remains to be demonstrated. In addition, there is some evidence for the involvement of polymorphisms in drug disposition although none so far for an impact at the cardiac level.

Although P-gp remains the most studied ABC transporter, the expression of MRP transporters in the heart and in vivo observations with knockout mice strongly demonstrated the high involvement of MRPs in the distribution of drugs to cardiac tissues. Over the next few years, observations promoting the involvement of MRPs in the distribution of drugs to the heart might increase.

In brief, we are still at an early stage in the discovery of ABC transporters and their involvement in the distribution of drugs to the heart. Nevertheless, several pieces of information already indicate a major role of ABC transporters for drug efficacy or toxicity in the heart.

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