

Bacterial ABC Multidrug Exporters: From Shared Proteins Motifs and Features to Diversity in Molecular Mechanisms

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Abstract Bacterial ATP-binding cassette (ABC) exporters embrace an enormous range of biological processes. They can mediate the efflux of a wide variety of substrates ranging from small inorganic ions, drugs, and antibiotics to large protein toxins and other macromolecules. They can also act as mediators and regulators in transmembrane signaling processes perhaps without mediating any direct transport reaction. This diversity in function of ABC exporters raises questions about their structure, how conformational changes are coupled to activity, and how we can use this information to inhibit, activate, or bypass physiological functions in drug-based strategies. When the first ABC transporters were discovered, now 40 years ago, it was noted by sequence comparisons that many of them shared a similar domain organization. But exactly how these domains cooperate in mediating transport activity was unknown. A wealth of biochemical studies and crystal structures of nucleotide-binding domains (NBDs), and subsequently of full-length ABC exporters, suggests that the general mechanism is based on metabolic energy-dependent alternating access of substrate-binding pocket(s) to either side of the phospholipid bilayer, but that there is diversity in the detailed molecular mechanisms that are being employed. This chapter provides an overview of the structural and mechanistic intricacies that have surfaced over the past years, and the challenges in further studies on these amazing transport proteins.

Introduction

ABC transporters have been studied since the 1970s and 1980s, when research focused on bacterial systems that mediate the import of solutes such as histidine, maltose, or peptides into the cell (Ames et al. 1977; Bavoil et al. 1980; Higgins

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et al. 1982; Gilson et al. 1982; Hiles and Higgins 1986), or the export of toxins, antimicrobial peptides, and antibiotics (Felmlee et al. 1985; Vogel et al. 1988; Gilson et al. 1990; Guilfoile and Hutchinson 1991). This coincided with the discovery of the highly conserved ATP-binding cassette in these transport proteins, and the designation of “ABC transporter” (Higgins et al. 1986). Research also focused on ABC exporters in mammals as early as 1976, when P-glycoprotein (ABCB1) was recognized as a surface glycoprotein that was overexpressed in drug-resistant Chinese hamster ovary cells (Juliano and Ling 1976). Subsequent cloning and sequencing of human ABCB1 cDNA from a multidrug-resistant cell line in 1986 allowed the assignment of ABCB1 to the same protein family as the bacterial proteins (Riordan et al. 1985; Chen et al. 1986; Ueda et al. 1987). With the discoveries and gene sequencing of many other important mammalian ABC proteins including the chloride channel CFTR (Riordan et al. 1989), multidrug resistance-associated proteins MRP1 (Cole et al. 1992) and MRP2 (Buchler et al. 1996), and transporters for antigen processing TAP1/2 (Spies et al. 1990), ABC transporters rapidly expanded into a superfamily.

Many mammalian ABC exporters show evidence of a relationship to bacterial ABC half-transporters that dimerize for function. The gene structures of proteins such as ABCB1 and CFTR point to a past internal gene duplication. Phylogenetic analyses indicate that these duplications occurred independently, while a tandem gene duplication occurred in the case of the TAP family (Hughes 1994; Dean and Allikmets 1995). ABCB1 is closely related to the hemolysin A-secreting HlyB transporter (Holland et al. 1991) and lipid A transporter MsbA (Karow and Georgopoulos 1993) in Gram-negative bacteria and multidrug transporter LmrA and orthologs in Gram-positive bacteria (van Veen et al. 1996; van Veen and Konings 1997). In accordance with the endosymbiont theory, one hypothesis to explain this observation is that eukaryotic ABCB1 and TAP genes are descended from a mitochondrial gene or genes that were subsequently translocated to the nuclear genome. Indeed, subsequent studies demonstrated that LmrA and MsbA can interact with similar substrates including lipid A, and that they exhibit a similar selectivity for cytotoxic drugs and modulators as ABCB1. Therefore, these proteins share functional and structural properties (van Veen et al. 1998; Reuter et al. 2003; Woebking et al. 2005). As this conclusion was drawn well before the entry of structural biology into the field, it is useful to emphasize that this conclusion is also supported by X-ray crystal structures of MsbA (Ward et al. 2007) and ABCB1 (Aller et al. 2009; Jin et al. 2012).

Genome sequencing and transcriptome analyses on a variety of micro-organisms allowed the expansion of the microbial branch of the ABC superfamily (Linton and Higgins 1998; Quentin et al. 1999; Moussatova et al. 2008), and underscored the importance of some of these new bacterial members in conferring antibiotic resistance on cells. In 2006, Piddock and coworkers described the overexpression of two genes encoding putative ABC half-transporters, *patA* (SP2075) and *patB* (SP2073), in multidrug resistant *Streptococcus pneumoniae* (Marrer et al. 2006a, b), which exhibited enhanced efflux of various drugs. In parallel, Robertson et al. (2005) inactivated 13 genes encoding putative efflux pumps in *S. pneumoniae*.

Inactivation of SP2075 or SP2073 gave rise to hypersusceptibility to multiple drugs including antibiotics. Subsequent work suggested that these proteins, renamed to PatA and PatB, confer innate multidrug resistance on *S. pneumoniae* by forming a heterodimeric multidrug pump PatAB (Garvey and Piddock 2008; Boncoeur et al. 2012). Other observations also suggest that overproduction of *patA* and *patB* is a clinically relevant mechanism of resistance in fluoroquinolone-resistant clinical isolates of *S. pneumonia* (Garvey et al. 2011). Orthologs of PatAB exist in other Gram-positive organisms such as LmrCD from *Lactococcus lactis* (Zaidi et al. 2008) and BmrCD from *Bacillus subtilis* (Galian et al. 2011), and similar to PatAB, endogenous expression of these transporters was found to have strong effects on the intrinsic resistance of the respective organisms to cytotoxic agents.

Thus, research over the past 40 years has identified bacterial ABC multidrug exporters as exciting proteins that can serve as accessible models for their mammalian counterparts, but that are also highly interesting in their own right because of important physiological roles of such systems in the transport of a wide variety of substrates including antibiotics, (toxic) ions, lipids, peptides, and many others in bacteria.

Domain Organization and Interactions

In the pre-crystal structure era of the 1990s, protein sequence comparisons and hydrophathy analyses suggested that bacterial ABC multidrug exporters typically consist of four domains, two membrane domains (MDs) and two nucleotide-binding domains (NBDs). The MDs are thought to contain the translocation pathway for the substrate, and as there is variety in transport substrates, there is less sequence conservation in MDs compared to NBDs. The NBDs are the engine of the transporter and contain features that allow binding and hydrolysis of ATP: Walker A and B motifs, ABC signature sequence (or C motif), conserved residues in specific areas such as the A-, D-, H-, and Q-loops, and conserved sequences in loop regions that communicate conformational changes from the NBDs to the MDs (Kerr 2002; Hanekop et al. 2006; Zaitseva et al. 2006). In many of these exporters, one MD and one NBD are fused into a half-transporter. In a variety of genetic and biochemical experiments it was demonstrated for LmrA and BmrA that these half-transporters dimerize (van Veen et al. 2000; Ravaud et al. 2006) to form the same functional unit as the monomers of mammalian ABC exporters in which the domains are fused into a single polypeptide (Loo and Clarke 1996; Taylor et al. 2001).

With the arrival of the first crystal structures of bacterial ABC half-transporters Sav1866 from *Staphylococcus aureus* (Dawson and Locher 2006, 2007) and MsbA from Gram-negative bacteria (Ward et al. 2007), many details regarding the domain organization were elucidated. The putative membrane-spanning segments in the MDs were indeed found to be α -helical, and the interactions between the two half-transporters were supported by the exchange of helical hairpins between the

two MDs. Furthermore, nucleotide binding at the NBDs was found to be associated with domain dimerization, consistent with earlier observations of fluorescence energy transfer and cysteine cross-linking between the NBDs in ABCB1 (Loo and Clarke 2000a; Urbatsch et al. 2001; Qu and Sharom 2001) and the first crystal structures of the ATP-bound sandwich dimers of isolated ABC–NBDs (Smith et al. 2002; Yuan et al. 2001). These structural insights and accompanying biochemical evidence have led to a general model in which ATP-dependent conformational changes in the NBDs drive rearrangements of the transmembrane helices (TMHs) to enforce the link between transport and ATP hydrolysis, referred to as conformational coupling, to achieve a transport mechanism often referred to as ‘alternating access’.

Alternating Access Mechanisms

Already in the early days of transporter research (Mitchell 1957; Jardetzky 1966), these proteins have been viewed as undergoing conformational changes in which a central binding site is exposed alternately to the inside or the outside of the cell, but never simultaneously to both sides. Groundbreaking studies on the proton-lactose co-transporter LacY and other secondary-active solute transporters indeed identified the substrate-binding site in a pocket at similar distance from either side of the membrane and near the molecular twofold axis of transporters. The structural change between inward- and outward-facing conformations in LacY involves rotation between the N- and C-terminal domains around the substrate-binding site, thereby allowing the binding site alternating accessibility to each side of the membrane (Abramson et al. 2003; Law et al. 2008; Gouaux 2009).

The first biochemical evidence for a change in accessibility of drug-binding sites in ABC multidrug exporters in response to nucleotide binding came from equilibrium drug-binding studies on human ABCB1 (Martin et al. 2000b) and the breast cancer resistance protein ABCG2 (McDevitt et al. 2008), which suggested that the binding of ATP, rather than its hydrolysis, causes the initial conformational shift in the drug-binding site to a low-affinity state. Studies in parallel on bacterial LmrA (van Veen et al. 2000) suggested that high- and low-affinity substrate-binding sites are accessible on the internal and external membrane surface, respectively, with occlusion of the high-affinity site in an ATP-bound state. LmrA was the first ABC extrusion system to be functionally reconstituted in proteoliposomes in a transport-active form, enabling detailed analysis of its mechanism of action and paving the way for the study of many more putative bacterial ABC transporters (Margolles et al. 1999). This work was followed by extensive pharmacological characterizations of drug-binding sites in LmrA and ABCB1 using transport and equilibrium drug-binding assays. These studies revealed the presence of communicating transport-active sites for substrates, for example for vinblastine and Hoechst 33342 in LmrA (van Veen et al. 2000) and vinblastine, Hoechst 33342, and rhodamine 123 in ABCB1 (Shapiro and Ling 1997; Martin et al. 2000a;

Lugo and Sharom 2005). In spite of these significant advances, the lack of structural information on ABC transporters limited molecular interpretations of these findings; ABC exporters remained a black box for many of the following years.

Alternating Access in a Structural Biology Context

The first structures for ABC exporters were published for Sav1866 from *S. aureus* (Dawson and Locher 2006, 2007) and MsbA from Gram-negative bacteria (Ward et al. 2007) (Table 1). These structures were named “outward-facing” (Sav1866, MsbA) and “inward-facing” (MsbA) in accordance with the accessibility to the outer membrane leaflet or inner membrane leaflet, respectively, of the central cavity that is enclosed by the two MDs of these homodimeric transporters. Related conformations were also observed in later crystal structures of ABC exporters from prokaryotic and eukaryotic organisms (Table 1). Biochemical and biophysical analyses of various MsbA conformations by EPR/DEER-based distance measurements in nitroxide spin-labeled MsbA in proteoliposomes (Zou et al. 2009; Zou and McHaourab 2009), cryo-electron microscopy of purified MsbA (Ward et al. 2009), and disulfide cross-linking of MsbA in membrane vesicles (Doshi et al. 2010, 2013) suggest that release of the hydrolysis products ADP and phosphate promotes an inward-facing conformation that binds the substrate, whereas the binding of ATP promotes the dimerization of NBDs in an outward-facing conformation from which substrate dissociates.

The Sav1866 and MsbA crystal structures revealed significant information about transmembrane helix packing and domain interactions. Firstly, in addition to NBD–NBD interactions, referred to earlier, these structures also provided invaluable insights into the communication between NBDs and MDs (Dawson and Locher 2006, 2007), and were found to be useful as templates for studies on related systems such as ABCB1 (Zolnerciks et al. 2007). Secondly, comparisons of the protein structures reveal the swapping of helical hairpins formed by TMH 1 and 2 between the MDs of the half-transporters in the outward-facing conformation, and TMH 4 and 5 in the inward-facing conformation. Hence, the conformational transitions between the inward-facing and outward-facing states require major structural rearrangements in the MDs, and a different intertwining of the half-transporters in both states. The transition between these two states might proceed via an intermediate state without this intertwining. This state was recently captured in a crystal structure for the antibacterial peptide transporter McjD from *E. coli*, which lacks intertwining and shows a well-defined binding cavity that is closed to all sides (Choudhury et al. 2014), and was also suggested for MsbA based on biochemical evidence (Doshi and van Veen 2013). When taken together, the current structures of Sav1866, MsbA, and McjD indicate that these ABC exporters adopt an inward-facing conformation in the absence of nucleotide or when bound to ADP, and that they advance via an ATP-bound occluded transition state into the ATP-bound outward-facing conformation. ATP hydrolysis finally enables dissociation of the

Table 1 Crystal structures of polyspecific ABC exporters

Protein	Organism	Conformation	Nucleotide	Inhibitor	PDB	Resolution (Å)	References
Sav1866	<i>Staphylococcus aureus</i>	Outward	ADP ^b		2HYD	3.00	Dawson and Locher (2006)
Sav1866	<i>Staphylococcus aureus</i>	Outward	AMP-PNP		2ONJ	3.40	Dawson and Locher (2007)
MsbA	<i>Escherichia coli</i>	Inward			3B5W	5.30	Ward et al. (2007)
MsbA	<i>Vibrio cholerae</i>	Inward			3B5X	5.50	Ward et al. (2007)
MsbA	<i>Salmonella typhimurium</i>	Outward	ADP-PNP		3B5Y	4.50	Ward et al. (2007)
MsbA	<i>Salmonella typhimurium</i>	Outward	AMP-OV		3B5Z	4.20	Ward et al. (2007)
MsbA	<i>Salmonella typhimurium</i>	Outward	AMP-PNP		3B60	3.70	Ward et al. (2007)
McjD	<i>Escherichia coli</i>	Occluded	AMP-PNP		4PL0	2.70	Choudhury et al. (2014)
ABCB1a	Mouse	Inward			3G5U	3.80	Aller et al. (2009)
ABCB1a	Mouse	Inward		QZ59-RRR	3G60	4.40	Aller et al. (2009)
ABCB1a	Mouse	Inward		2 × QZ59-SSS	3G61	4.35	Aller et al. (2009)
CeABCB1	<i>Caenorhabditis elegans</i>	Inward			4F4C	3.40	Jin et al. (2012)
CmABCB1	<i>Cyanidioschyzon merolae</i>	Inward			3WMF	2.60	Kodan et al. (2014)
CmABCB1	<i>Cyanidioschyzon merolae</i>	Inward		aCAP	3WVG	2.40	Kodan et al. (2014)
ABCB10	Human mitochondria	Inward	AMP-PCP		4AYX	2.90	Shintre et al. (2013)
Atm1	Yeast mitochondria	Inward			4MYC	3.06	Srinivasan et al. (2014)
NaAtm1	<i>Novosplingobium aromaticivorans</i> mitochondria	Inward			4MRN	2.50	Lee et al. (2014)
TM287/288	<i>Thermotoga maritima</i>	Inward			4Q4H	2.53	Hohl et al. (2014)
TM287/288	<i>Thermotoga maritima</i>	Inward	AMP-PNP		4Q4A	2.60	Hohl et al. (2014)

^aConformation refers to the inward- or outward-facing orientations of the cavity formed by the MDs

^bADP Adenosine-di-phosphate, AMP-PNP Adenosine 5'-(β-γ-imido)triphosphate, ADP-OV Adenosine-di-phosphate-orthovanadate, QZ59-RRR cyclic-tris-(R)-valineselenazole, QZ59-SSS cyclic-tris-(S)-valineselenazole, aCAP anti-CmABCB1 peptide

NBD dimer and resets the transporters to the inward-facing conformation. It is not clear yet whether the ATP-induced dimerization of the NBDs alone [also referred to as ‘ATP switch’ model (Higgins and Linton 2004)] is sufficient to cause the transition from the inward-facing state to the outward-facing state. As formulated in the ‘occlusion-induced switch’ model (reviewed by Seeger and van Veen 2009) this transition might require the occlusion or tight binding of a nucleotide following NBD dimerization. Furthermore, the possibility exists that conformational transitions in ABC exporters are affected by transmembrane electrochemical ion gradients (Venter et al. 2003; Choudhury et al. 2014). Thirdly, the notion that the central cavity at the MD–MD interface can indeed act as a substrate-binding pocket during alternating access was supported by a structure of mouse ABCB1a in complex with peptide inhibitors (Aller et al. 2009), and by superimposition of known change-in-drug-specificity mutations in ABCB1 (Loo and Clarke 2000b, 2008) and MsbA (Woecking et al. 2008) on the structures of these proteins (Gutmann et al. 2010). The studies on ABCB1 suggest that structurally dissimilar substrates interact with sets of polar and aromatic side chains in a flexible binding chamber (Stockner et al. 2009) in a fashion that is analogous to substrate binding in protein crystals of multidrug-binding transcriptional regulators (Zhelezнова et al. 1999; Schumacher et al. 2001) and the resistance-nodulation-cell division (RND) transporter AcrB (Murakami et al. 2006; Seeger et al. 2006). Alternating access of this binding chamber in the MDs is achieved through small-scale tilting and rotation of several individual TMHs with respect to each other (Omote and Al-Shawi 2006; Gutmann et al. 2010; Crowley et al. 2010). More recently, alternating access of the central binding chamber in response to nucleotide binding was also shown for ABCB1 in an EPR approach (van Wonderen et al. 2014).

The notion that ATP binding drives the drug extrusion step (the reorientation of the drug-binding chamber from the cell’s interior to the external face of the plasma membrane) whereas ATP hydrolysis and release of ADP and Pi allow reorientation of the chamber back to the interior, shows parallels with the catalytic mechanism proposed for bacterial ABC importers such as the maltose importer MalFGK2 and the vitamin B12 importer BtuCD (Davidson 2002; Chen et al. 2003; Dawson et al. 2007; Korkhov et al. 2012), and is also reminiscent of the earlier mechanisms proposed for secondary-active transporters. It provided a sense of existence of a unifying theory for the transport mechanism of ABC exporters, which turned into a narrow template for some.

Diversity in Mechanisms

While bacterial ABC exporters such as LmrA, and eukaryotic ABC exporters such as ABCB1 require two functionally active ATPase sites for transport (van Veen et al. 2000; Hrycyna et al. 1998), it is interesting to note that others (referred to as heterodimeric ABC exporters) contain two asymmetric ATP sites. Bacterial LmrCD, BmrCD, and T287/288 (Zaidi et al. 2008; Galian et al. 2011; Hohl et al. 2012;

Mishra et al. 2014), yeast Pdr5 (Ernst et al. 2010), mammalian ABCB2/3 (also referred to as TAP1/2) (Vos et al. 2000; Seyffer and Tampe 2014), and many mammalian ABCC proteins (including the multidrug resistance-associated proteins MRP1 and MRP2) (Hipfner et al. 1999; Borst and Elferink 2002; Gottesman et al. 2002) are examples of the latter. One of these ATP sites is formed exclusively by consensus residues and operates as an ATPase unit, while the other site contains non-consensus substitutions in one or more motifs, and is referred to as the degenerate site. The non-consensus substitutions in the Walker B, H-loop, and signature motif within the degenerate ATP site inhibit ATPase activity and affect NBD dimer stability (Hou et al. 2002; Perria et al. 2006; Procko et al. 2006). The latter is also affected in the D-loop region of the degenerate site in TM287/288 (Hohl et al. 2014). The functional role of ATP binding and closed dimer formation in heterodimeric ABC proteins was first illustrated by studies on CFTR, where instead of mediating transport, the ATP-binding-dependent NBD dimerization opens a chloride channel, whereas hydrolysis of ATP at the consensus site closes the channel (Vergani et al. 2005). Although the basic reaction steps at the NBDs (ATP binding, ATP hydrolysis, ADP/Pi release) are shared between conventional ABC exporters and heterodimeric ABC exporters, the number, order, and kinetics of these steps most likely differ, thus giving rise to a diversity of mechanisms.

Mechanisms of transport might even be diverse within classes of ABC exporters. Although many conventional ABC export systems possess two functional ATPase sites, diversity might arise depending on whether two ATP molecules are hydrolyzed simultaneously or sequentially within one transport cycle, or hydrolyzed in an alternating fashion (van Veen et al. 2000; Jones and George 2013). The latter mechanism could be similar to that of heterodimeric ABC exporters within one transport cycle, but different from this class, the role of the ATP sites in ATP hydrolysis or exclusive ATP binding would swap in sequential transport cycles, thus making the requirement for two functional ATPase sites compulsory. Most of these mechanisms will involve an asymmetric stage or stages in terms nucleotide binding at some point of catalysis, for example with ADP binding to one site and ATP binding to the other, which adds to the complexity of analyses and correct assignment of mechanisms with current experimental techniques.

The degree of proximity of the two NBDs in structures of intact ABC exporters (Table 1) suggests that the structural differences between the open and closed dimers might vary from more subtle to complete dimer dissociation. Catalytic mechanisms might differ between transporters depending on the extent of cooperativity between the nucleotide-binding pockets, on the oligomeric assembly of which the ABC half-transporter is part [e.g., in stand-alone MsbA dimer versus multicomponent transporters such as MacA-MacB-TolC (Zgurskaya 2009; Hinchliffe et al. 2013)], and on signals arising from substrate binding in the binding pocket. As different ABC exporters translocate substrates with different physico-chemical properties, ranging from small inorganic ions, medium-sized antimicrobial agents and polysulfides, large lipids and polysaccharides, to very large polypeptides (see Table 1 and Higgins (1992) for overview), and combinations thereof (Velamakanni et al. 2009), whereas others such bacterial FtsEX

(de Leeuw et al. 1999) and mammalian SUR (Burke et al. 2008) act as mediators in transmembrane signaling processes perhaps without mediating any direct transport reaction, diversity in mechanisms will arise from this enormous diversity in substrates and physiological roles.

Summary

The past years of research on ABC exporters in bacteria and other organisms have provided important insights into their clinical relevance, and have revealed many details about the biochemistry, pharmacology, and structural biology of these proteins. These advancements now raise the appreciation that although ABC exporters share typical protein motifs and features, they have evolved in different directions, giving rise to a diversity in mechanisms that underlies the variety in physiological functions. It is expected that the increased knowledge will facilitate our ability to inhibit, activate, or bypass ABC exporter activities in drug-based strategies. The opportunities for further research are therefore truly dazzling.

Acknowledgments Work in the author's laboratory is funded by the Biotechnology and Biological Sciences Research Council, Medical Research Council, and Human Frontier Science Program. He is also grateful for support from the British Society for Antimicrobial Chemotherapy.

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ABC Transporters - 40 Years on

George, A. (Ed.)

2016, XIV, 376 p. 50 illus., 6 illus. in color., Hardcover

ISBN: 978-3-319-23475-5