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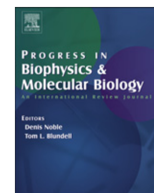

Review

Perspectives on the structure–function of ABC transporters: The Switch and Constant Contact Models

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A B S T R A C T

ABC transporters constitute one of the largest protein families across the kingdoms of archaea, eubacteria and eukarya. They couple ATP hydrolysis to vectorial translocation of diverse substrates across membranes. The ABC transporter architecture comprises two transmembrane domains and two cytosolic ATP-binding cassettes. During 2002–2012, nine prokaryotic ABC transporter structures and two eukaryotic structures have been solved to medium resolution. Despite a wealth of biochemical, biophysical, and structural data, fundamental questions remain regarding the coupling of ATP hydrolysis to unidirectional substrate translocation, and the mechanistic suite of steps involved. The mechanics of the ATP cassette dimer is defined most popularly by the 'Switch Model', which proposes that hydrolysis in each protomer is sequential, and that as the sites are freed of nucleotide, the protomers lose contact across a large solvent-filled gap of 20–30 Å; as captured in several X-ray solved structures. Our 'Constant Contact' model for the operational mechanics of ATP binding and hydrolysis in the ATP-binding cassettes is derived from the 'alternating sites' model, proposed in 1995, and which requires an intrinsic asymmetry in the ATP sites, but does not require the partner protomers to lose contact. Thus one of the most debated issues regarding the function of ABC transporters is whether the cooperative mechanics of ATP hydrolysis requires the ATP cassettes to separate or remain in constant contact and this dilemma is discussed at length in this review.

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Contents

1. Introduction 95
1.1. ABC transporters: a brief phylogenetic and structural journey 95
1.2. The nucleotide-binding domains and ATP catalysis: the two-cylinder engine 98
1.3. The Switch Model 99
1.4. The Constant Contact Model 102
1.5. East is East and... 104
References 104

1. Introduction

1.1. ABC transporters: a brief phylogenetic and structural journey

The ATP-Binding Cassette (ABC) superfamily (Holland and Blight, 1999; Hyde et al., 1990) comprises two subfamilies: The larger of these contains primary active transporters that utilize the energy of ATP hydrolysis to translocate substrates across cellular membranes. One of these is atypically a chloride ion channel, the cystic fibrosis transmembrane conductance regulator (CFTR), and

Abbreviations: TMD, transmembrane domain; NBD, nucleotide-binding domain; ICL, intracytosolic loop; MD, molecular dynamics; MDR, multidrug resistance; CH, coupling helix; HSD, helical subdomain; CSD, core subdomain.

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when dysfunctional is responsible for the inherited genetic disorder cystic fibrosis in Caucasians (Gadsby et al., 2006; Riordan et al., 1989). The second subfamily comprises ABC proteins – non-transporters – that are localised to the cytosol or nucleus and are employed for maintenance and repair of DNA and for gene regulation. The two subfamilies are known collectively as the ABC-ATPase superfamily ((Holland and Blight, 1999). ABC transporters have been conserved across the three kingdoms of archaea, eubacteria and eukarya (Dean et al., 2001; Higgins, 1992; Higgins et al., 1986; Jones and George, 1999). Their primordial origin and ubiquitous distribution reflect fundamental import and export requirements, for example, to accumulate essential nutrients such as amino acids, sugars, ions, and vitamins in prokaryotes, or to expel variously in prokaryotes or eukaryotes, drugs, toxins, polysaccharides, lipids, hormones, peptides, and proteases. ABC transporters are integral membrane proteins that were first described in the 1970s and 1980s with the identification of human P-glycoprotein as the cause of cytotoxic drug resistance (Juliano and Ling, 1976) and characterization of the maltose and histidine bacterial permease systems (Ferenci et al., 1977; Gilson et al., 1982; Higgins et al., 1986). ABC transporters are also involved in diverse cellular processes including, maintenance of osmotic homeostasis, drug resistance, antigen processing, cell division, bacterial immunity, pathogenesis and sporulation, cholesterol and lipid trafficking, and developmental stem cell biology (Davidson et al., 2008; Eckford and Sharom, 2009; Ernst et al., 2010; Fath and Kolter, 1993; Higgins, 1992; Hollenstein et al., 2007a; Jones and George, 2004; Jones et al., 2009; Juranka et al., 1989; Kerr et al., 2010; Kos and Ford, 2009; Saurin et al., 1999; Schneider and Hunke, 1998; van Veen and Konings, 1998).

Perhaps the greatest focus in ABC transporter research has been centered around the multidrug resistance problem and, in particular, that of human P-glycoprotein (P-gp; MDR1; ABCB1). P-gp is an efflux pump that elaborates resistance to cytotoxic drugs in about 50% of human cancers (Gottesman and Ling, 2006). Of most concern is the means by which P-gp effuxes hundreds of different drugs and yet how similar it is to the 47 other known members of the human ABC transporter family that have nothing like its diversity of substrate recognition, though MRP1, BCRP, and TAP also have broad substrate spectra. Victor Ling's group discovered and named P-gp in 1976 (Juliano and Ling, 1976) and ten years later expanded on its role in multidrug resistance in cancer cells, by determining that: it was a near perfect tandem duplication of the haemolysin transporter from *Escherichia coli*; ABC transporters arose from a common ancestor; transport was coupled to energy production; P-gp could bind and export structurally diverse drugs; its chief physiological role might be to protect cells from lipophilic toxins; and that its multidrug resistance property simply reflects gene amplification or overexpression (Gerlach et al., 1986).

The canonical architecture of ABC transporters comprises two transmembrane domains (TMDs) and two cytosolic nucleotide-binding domains (NBDs), also known as ATP-binding cassettes (Fig. 1). The structural organisation of the four domains is a dimer of dimers, which can deploy as single polypeptides, homo- or heterodimers, or multisubunit protomers, reflecting ancient gene duplication events and fusions of the cytosolic catalytic domains to the integral membrane-spanning domains (Higgins, 1992; Hyde et al., 1990; Jones and George, 2004). The TMDs contain poorly defined substrate-binding sites and translocation pathways for unidirectional import or export. Three distinct folds have been observed in structures of ABC transporter TMDs (Jones et al., 2009). Despite a plethora of published information, several controversial areas remain to be resolved and these are primarily related to identifying substrate-binding sites and the translocation pathway through the transmembrane domains; and the mechanistic suite of steps that drive ATP binding and hydrolysis in the nucleotide-binding domains. Though the TMDs and their cognate substrate binding-sites are beyond the scope of this review, the sites remain elusive and continue to befuddle researchers, in contrast to substantial progress on site recognition in the TMDs of several secondary active transporters (Boudker and Verdon, 2010).

The TMDs extend beyond the bilayer as intracytosolic loops (ICLs) that form the interface between the NBDs and TMDs. The ICLs are not really loops but helical bundles, with each containing an α-helix at right angles to the bundle and which fits into a groove between the core and helical subdomains of the NBD. The ICL 'coupling helices' (CH1, CH2) (Dawson and Locher, 2006) are proposed to propagate the energy of ATP binding and hydrolysis to substrate transport. In ABC exporters, the coupling helix that is common to both ABC importers and exporters, namely CH2, in contrast to importers, engages the TMD of the opposite half of the transporter (Fig. 2). The contacts between the NBDs and the TMDs are significantly more extensive in exporters than importers, with no equivalent in the importers to CH1. In exporters, CH1 interacts directly with regions contacting the nucleotide adenine ring, acting to sequester the nucleotide and the active site from the bulk solvent in the ATP-bound state. Interestingly, it has been shown for ABC importers and exporters that vanadate trapping, which mimics the pentacoordinate transition state of ATP hydrolysis, results in an occluded state of the nucleotide in the active site (Senior et al., 1995; Sharma and Davidson, 2000). In exporters, CH1 occludes the nucleotide and is positioned alongside CH2, which binds in the groove between the two lobes of the NBD, as does the single CH2 in importers (Jones et al., 2009).

Though there are now eleven complete ABC structures (nine prokaryote; two eukaryote), with several variations of some of the same transporter, solved at medium to low resolution (2.2–5.5 Å) (Aller et al., 2009; Dawson and Locher, 2006, 2007; Gerber et al., 2008; Hohl et al., 2012; Hollenstein et al., 2007b; Hvorup et al., 2007; Kadaba et al., 2008; Khare et al., 2009; Locher et al., 2002; Oldham and Chen, 2011; Oldham et al., 2007; Pinkett et al., 2007; Ward et al., 2007), only two have been resolved with either bound substrate (the maltose permease; Oldham et al., 2007, Fig. 1A) or inhibitor (murine ABCB1a; Aller et al., 2009, Fig. 1B). Maltose is bound to MalF by hydrogen bond and aromatic ring stacking contacts to 10 residues, but no contacts to its partner TMD, MalG. Genetic studies indicate that mutations in 6 of the 10 residues bound to maltose severely decrease or eliminate maltose transport, an important finding, but as an interesting contrast, some ABC permeases might lack substrate-binding sites, with substrate specificity governed solely by which binding protein attaches (Moussatova et al., 2008; Oldham et al., 2008). Putting these two observations together tempts one to speculate there aren't substrate sites *per se* in the TMDs of ABC importers. Substrates are delivered by their cognate PBPs to the TMDs and then translocated along a 'slippery slide' of interacting resides that line the pathway to the interior of the cell. The most recent report is of four crystal structures of the full-length wild-type maltose transporter, stabilized by a non-hydrolyzable ATP analogue or ADP in conjunction with phosphate analogues BeF_3^-, VO_4^{3-}, or AlF_4^- determined to 2.2–2.4 Å resolution (Oldham and Chen, 2011). The data from these four structures produced the conclusions that ABC transporters catalyze ATP hydrolysis via a general base mechanism; and that the ground-state and transition-state complexes are in the same outward-facing conformation, and thus represent only a chemical, rather than mechanical, step in the process.

The first eukaryotic ABC transporter structure, murine ABCB1a (Aller et al., 2009) deploys a large cavity between the TMDs that is partly filled by either of two dendroamide cyclic peptide stereoisomers that are related to MDR reversing agents (Ogino et al.,

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