ABC transporters: structure, substrate specificities and physiological roles

A Brief Overview

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Abstract The ATP-binding cassette (ABC) transporter superfamily is one of the largest protein families with representatives in all kingdoms of life. Members of this superfamily are involved in a wide variety of transport processes with substrates ranging from small ions to relatively large polypeptides and polysaccharides. The G subfamily of ABC transporters consists of half-transporters, which oligomerise to form the functional transporter. While ABCG1, ABCG4 and ABCG5/8 are involved in the ATP-dependent translocation of steroids and, possibly, other lipids, ABCG2 (also termed the breast cancer resistance protein) has been identified as a multidrug transporter that confers resistance on tumor cells. Evidence will be summarized suggesting that ABCG2 can also mediate the binding/transport of non-drug substrates, including free and conjugated steroids. The characterization of the substrate specificities of ABCG proteins at a molecular level might provide further clues about their potential physiological role(s), and create new opportunities for the modulation of their activities in relation to human disease.

Keywords ABC transporter · ABCG family · Breast cancer resistance protein (BCRP) · Steroid transport · Multidrug resistance

Introduction

ATP-binding cassette (ABC) transporters form one of the largest families of integral membrane proteins. More than 140 representatives have been identified in species ranging from archaea to man (Gottesman 2002; Higgins 1992). These proteins are fundamental to membrane transport of a wide variety of substrates including amino acids, lipids, lipopolysaccharides, inorganic ions, peptides, sugars, metal ions, drugs and proteins (Higgins 1992). ABC transporters utilize the energy derived from ATP binding/hydrolysis to drive substrate translocation across the membrane.

To date, 49 ABC transporters have been discovered in human, which are divided into seven subfamilies (ranging from ABCA to ABCG) based on genomic organisation, order of domains and sequence conservation. Mutations in genes encoding human ABC transporters have been linked to disorders displaying mendelian inheritance (Borst and Oude 2002). These diseases include high-density lipoprotein deficiency or Tangier disease (mutation in ABCA1), progressive familial intrahepatic cholestasis type 2 (mutations in ABCB11), Dubin–Johnson syndrome (mutation in ABCC2, also termed multidrug resistance associated protein [MRP] 2) and sitosterolemia (mutations in ABCG5 and/or ABCG8). In addition, ABC transporters have been implicated in the development of resistance of tumors to anticancer drugs (ABCB1, also known as multidrug resistance P-glycoprotein MDR1) and ABCC1 (Gottesman 2002), as well as antibiotic resistance in pathogenic microorganisms. The more recently discovered human ABC half-transporter ABCG2 (also known as the breast cancer resistance protein [BCRP], mitoxantrone resistance protein [MXR], and ABC transport expressed in the placenta [ABCP]) has also been shown to confer multidrug resistance on cancer cells (Allikmets et al. 1998; Doyle et al. 1998).
ABC proteins are characterized by a highly conserved cytosolic nucleotide-binding domain (NBD), which shares approximately 30–40% identical residues between family members irrespective of the substrate specificity of these transporters. The NBDs contain three conserved sequence elements: the Walker A and Walker B motifs are separated by about 120 amino acids, and the ABC signature sequence (also termed the C motif) is situated upstream of the Walker B motif. Whereas the Walker motifs are common to many nucleotide-binding proteins, the ABC signature motif is the hallmark of ABC proteins (Higgins 1992). These three sequence elements are required for the binding and hydrolysis of ATP, which in turn provides energy for the translocation of drugs from cell membranes and cytoplasm to the exterior of the cell (Higgins et al. 1997). The membrane domain (MD) of ABC proteins consists of four to eight transmembrane helices (TMH). The MDs form the putative pathway for substrates across the lipid bilayer, and are believed to determine the substrate specificity of the transporter. There is usually little sequence similarity between the MDs of ABC transporters reflecting the structural variety of transported substrates associated with the ABC protein family.

There is physiological evidence for a role of ABC transporters in the translocation of steroids, phospholipids and long-chain fatty acids. These transporters were found either on the basis of sequence homology with known transporters or as causative genes in disease loci. For example, ABCA1 transports cellular cholesterol and phospholipids like phosphatidylcholine to cells surface-bound apolipoproteins (Oram and Yawn 2001). Mutations in ABCA1 are associated with Tangier disease. ABCA4 has been implicated in the transport of phosphatidylethanolamine in the retina, and dysfunction of the protein is linked to Stargardt’s disease. ABCB4 (also termed MDR2) mediates the transport of phosphatidylcholine across the canalicular membrane of hepatocytes during bile formation. Mutations in ABCB4 are responsible for intrahepatic cholestasis type 3 (Ruetz and Gros 1994). In a final example, peroxisomal ABC transporters such as ABCD1 are involved on the transport of long-chain fatty acids, and mutations in ABCD1 are linked to adrenoleukodystrophy (Wanders et al. 2007). The interactions of ABC transporters with steroids and phospholipids might also be relevant for multidrug transporters. ABCB1 has been reported to interact with fluorescent lipid analogues (van Helvoort et al. 1996), sphingomyelin (van Helvoort et al. 1997), progesterone (Rebbeor and Senior 1998), cholesterol (Garrigues et al. 2002) but not plant-derived sitosterols (Albrecht et al. 2002). Similar to ABCB1, the bacterial homolog LmrA can translocate fluorescent phospholipid analogues (Margolles et al. 1999). Recent work from our laboratory suggests that LmrA can also transport the lipid A anchor of lipopolysaccharides in E. coli (Reuter et al. 2003). The potential interactions between ABC transporters and lipids are particularly relevant for members of the ABCG subfamily.

The G subfamily of ABC transporters

The human ABCG subfamily contains five characterized half-transporters (ABCG1, ABCG2, ABCG4, ABCG4, ABCG5 and ABCG8), which have a domain organization characterized by an N-terminal NBD followed by C-terminal MD (as depicted in Fig. 1). These ABCG proteins are homologues of the Drosophila white protein, which forms a heterodimer with either one of two other ABCG-related proteins, brown and scarlet, to transport eye pigment precursors in Drosophila (Dressen et al. 1998). Similarly, the human ABCG proteins are likely to dimerise to form the active membrane transporter.

ABCG1/ABCG4

ABCG1 is the first member of the ABCG subfamily. The protein is expressed in the plasma membrane of adipocytes,