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ABCG 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

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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 transporter 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; Smith et al. 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,

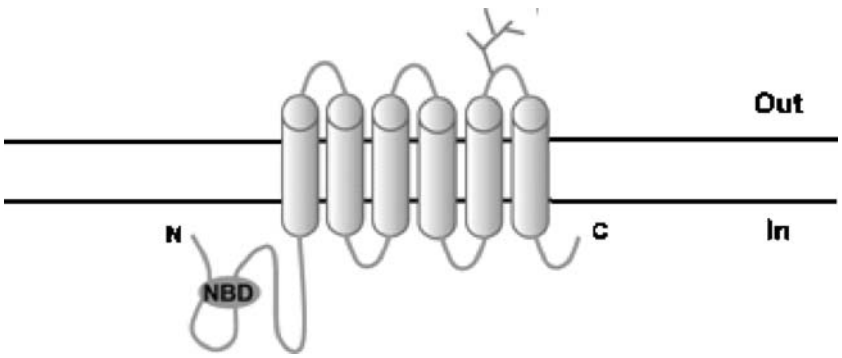

Fig. 1 Structure model of ABCG proteins. ABCG proteins are half-transporters composed of an N-terminal nucleotide-binding domain (NBD) followed by the C-terminal membrane domain containing six putative transmembrane α-helices. For review, see Tusnady et al. (2006). *In* and *Out* refer to the cytoplasm and extracellular environment, respectively

macrophages, and other cell types (see below). In these cells, ABCG1 is thought to redistribute cholesterol to a cell-surface pool that is accessible to enzymatic oxidation and to removal by high-density lipoprotein (HDL) particles. Intracellular cholesterol might serve as an intracellular signal regulating triglyceride storage and size of adipocytes. Indeed, recent studies in *Abcg1* (−/−) knockout mice showed that the gene deletion resulted in a markedly reduced size of fat cells (Buchmann et al. 2007). These results link ABCG1 function to obesity, which is a key risk factor for coronary heart disease, and which kills more than 120,000 people in the UK every year. ABCG1 has also been linked to atherosclerosis as the protein prevents excessive uptake of cholesterol in macrophages, which can lead to foam cell formation (Klucken et al. 2000; Vaughan and Oram 2005).

ABCG1 was first described by Chen et al. (1996), and independently by Savary et al. (1996) and Croop et al. (1997). Various transcripts of *ABCG1* have been detected in different cells arising from alternative splicing events or the use of different transcription initiation sites (Lorkowski et al. 2001a). Northern blot analyses showed abundant expression of ABCG1 protein in the liver, lung and spleen (Croop et al. 1997). Dot blot analysis revealed ubiquitous expression of ABCG1 (Klucken et al. 2000). The *ABCG1* gene expression is regulated by cholesterol loading and HDL_3-mediated cholesterol release in human macrophage (Klucken et al. 2000). It has also been reported that the human *ABCG1* mRNA levels from human macrophages are regulated by the liver-specific X receptor/retinoid X receptor (LXR/RXR) pathway, which has been shown to play an important role in lipid metabolism (Venkateswaran et al. 2000; Sabol et al. 2005).

ABCG1 is a 678-amino acid, 75.6-kDa integral protein. Although initial reports suggested that ABCG1 was mostly associated with the endoplasmic reticulum and the Golgi membranes of macrophages (Venkateswaran et al. 2000), subsequent studies also demonstrated the trafficking to the plasma membrane in macrophages (Klucken et al. 2000) and other cell types (Vaughan and Oram 2005; Kobayashi et al. 2006). It has been suggested that ABCG1 may heterodimerise with ABCG4, as the proteins are closely related in amino acid sequence, and have nearly identical intron locations at their structural genes (Cserepes et al. 2004).

Human ABCG4 was identified by two different groups, based on its homology to ABCG1 (Annilo et al. 2001; Oldfield et al. 2002). *ABCG4* gene expression is regulated by oxysterols and retinoids in a similar fashion to *ABCG1* (Engel et al. 2001). Wang et al. (2004) demonstrated that ABCG4 mediates the efflux of cellular cholesterol to HDL. Transfection of *ABCG4* cDNA to HEK 293 cells increased the cholesterol efflux to HDL and low-density lipoproteins (LDL) but not to apoA-I. Recently, it was shown that co-expression of the Walker A lysine mutant (K to M) of ABCG4 inhibited the ABCG1-associated ATPase activity in a negative-dominant manner, suggesting an interaction between ABCG4 and ABCG1 (Cserepes et al. 2004). Although ABCG1 has a widespread tissue distribution, the expression of ABCG4 has been shown to be restricted to nervous tissues, such as brain (Annilo et al. 2001; Oldfield et al. 2002), excluding the formation of obligate ABCG1/ABCG4 heterodimers in many tissues.

ABCG1 appears to be involved in the transport of cholesterol and phospholipids in macrophages (Klucken et al. 2000). In line with observations on sterol-dependent regulation of *ABCG1* gene expression, it has been shown that the ABCG1 protein in HEK 293 cells redistributes cholesterol to cell-surface domains where it becomes accessible for removal by HDL, thereby mediating cellular cholesterol efflux (Wang et al. 2004; Vaughan and Oram 2005). In addition to cholesterol, ABCG1 also mediates the efflux of sphingomyelin and phosphatidylcholine and it was suggested that ABCG1-mediated cholesterol efflux is sphingomyelin dependent (Kobayashi et al. 2006; Sano et al. 2007). Consistent with these observations, ABCG1 expression is found to be up-regulated in macrophage cells from patients with Tangier disease (Lorkowski et al. 2001b), a disorder which is characterized by defective efflux of lipid from macrophages and other peripheral cells, resulting in an inability to make HDL.

ABCG2

ABCG2 is a 655-amino acid, 72 kDa glycoprotein, and was initially cloned from the placenta and from highly mitoxantrone-resistant S1-M1-80 human colon carcinoma cells and doxorubicin-resistant MCF-7 AdVp human breast cancer cells. These cells showed efflux-based drug resistance without expression of ABCB1 or ABCC1 (Allikmets et al. 1998; Doyle et al. 1998). Overexpression of ABCG2 has subsequently been observed in several human cancer cell lines selected for drug resistance as well as in tumor samples of cancer patients (Doyle et al. 1998; Hardwick et al. 2007).

ABCG2 expression confers resistance on cells to (1) toxic ions such as Hoechst 33342, (2) anticancer agents including mitoxantrone and the anthracyclines daunomycin and doxorubicin, and (3) the camptothecins topotecan and SN-38 (Doyle et al. 1998; Litman et al. 2000; Ozvegy et al. 2001; Janvilisri et al. 2005). The functional expression of ABCG2 in the bacterium *Lactococcoccus lactis* raised the possibility to directly test the potential interactions of the transporter with antibiotics. In these experiments, ABCG2 expression conferred a significant resistance to macrolides, tetracyclines, fluoroquinolones and other antibiotics (Janvilisri et al. 2005). It is interesting to note that the relevance of this work was confirmed in *Abcg2* knockout mice. After oral administration of 10 mg/kg nitrofurantoin,

the area under the plasma concentration-time curve in *Abcg2* knockout mice was almost fourfold higher than in wild-type mice. In addition, nitrofurantoin was efficiently transported in the polarized canine kidney cell line MDCK-II expressing murine ABCG2 or human ABCG2 compared to the non-expressing control (Merino et al. 2005). A recent study by Ando et al. (2007) demonstrates that ABCG2 mediates the biliary excretion of fluoroquinolones, and suggests that it is also involved in the tubular secretion of ciprofloxacin and grepafloxacin.

Modulators have been identified which inhibit ABCG2 activity, including fumitremorgin C (FTC)—a mycotoxin produced by the fungus *Aspergillus fumigatus* (Rabindran et al. 2000), and gefitinib—a selective epidermal growth factor receptor tyrosine kinase inhibitor (Yanase et al. 2004; Nakamura et al. 2005). These modulators have been shown to effectively reverse drug resistance and increase cellular drug accumulation in human ABCG2-expressing cancer cell lines by inhibiting ABCG2-mediated drug efflux.

Based on (1) the formation of homodimers by ABC half-transporters such as LmrA (van Veen et al. 1998, 2000) and MsbA (Reuter et al. 2003), (2) direct biochemical data for ABCG2 using the dominant negative mutants in mammalian cells (Kage et al. 2002), and (3) functional expression of ABCG2 in non-mammalian cells such as *Spodoptera frugiperda* insect cells (Ozvegy et al. 2001), *Xenopus* oocytes (Nakanishi et al. 2003), the yeast *Pichia pastoris* (Mao et al. 2004), and *L. lactis* (Janvilisri et al. 2003), ABCG2 appears to function independent of auxiliary proteins, with the homodimer as the minimum functional unit. The functional expression of ABCG2 in *L. lactis*, which lacks glycosylation machinery, suggested that glycosylation is not essential for the function of ABCG2 (Janvilisri et al. 2003). It has been suggested that in addition to the homodimer, ABCG2 can also form higher oligomeric complexes based on experimental data from gel filtration, sucrose density gradient sedimentation, immunoprecipitation, and gel electrophoresis (Xu et al. 2004; McDevitt et al. 2006).

Various studies have demonstrated the existence of sequence variability in ABCG2 in drug-selected cell lines. The wildtype protein has an arginine at position 482 (ABCG2-R), which is located at the cytoplasmic end of TMH 3 (Allikmets et al. 1998). It has become apparent that some drug-selected mammalian cell lines expressing ABCG2 with a neutral G, T, S or M residue at position 482 display resistance to rhodamine 123, whereas cell lines expressing ABCG2-R remain sensitive to cationic rhodamine 123 and anthracyclines (Honjo et al. 2001; Ozvegy et al. 2001; Allen et al. 2002; Janvilisri et al. 2005). In addition, the mutant ABCG2 proteins mediate the efflux of anionic methotrexate at reduced rates compared to wildtype ABCG2-R (Volk et al. 2002; Mitomo et al. 2003). In line with these observations, recent work suggests that the residue at position 482 is important for substrate transport and ATPase reaction but that the nature of the residue at this position is not critical for substrate recognition and binding (Ejendal et al. 2006; Pozza et al. 2006). Hence, the identification of mutations at position 482 in ABCG2 explains some discrepancies observed in the cross-resistance profiles of human cancer cell lines.

Consistent with the notion that ABCG2 might play a role in the disposition and pharmacological activity of a broad range of compounds (Leslie et al. 2005; Hardwick et al. 2007) studies on the tissue distribution of ABCG2 revealed that the protein is expressed in the apical membrane of cells in tissues with excretory functions such as the canalicular membrane of hepatocytes, luminal membrane of villous epithelial cells in the small and large intestine, ducts and lobules of the breast (Maliepaard et al. 2001), and apical membranes of capillary vessels in the blood-brain barrier (Cooray et al. 2002). ABCG2 is also highly expressed in the apical membrane of trophoblasts (Maliepaard et al. 2001), which form the rate-limiting barrier in the placenta to the permeation of substances between maternal blood and foetal capillaries, and provides a substrate efflux mechanism that protects the developing foetus (Jonker et al. 2000).

Studies on *Abcg2*-knockout mice indicated that ABCG2 plays an important role in the transport of dietary toxins such as pheophobide A, 2-amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine and the potent human hepatocarcinogen aflatoxin B1, serving to limit the distribution of these toxins and facilitate their elimination (Jonker et al. 2002; van Herwaarden et al. 2003, 2006). Interestingly, ABCG2 is also expressed at the cell surface in immature hematopoietic stem cells and is a major determinant of the "side-population (SP) phenotype", which is defined by its low accumulation of the dye Hoechst 33342 (Zhou et al. 2001; Kim et al. 2002; Scharenberg et al. 2002). Although ABCG2 is the transporter responsible for the SP phenotype, the physiological functions of ABCG2 in this cell type are not yet elucidated.

Although members of the ABCG subfamily have been implicated in sterol transport, ABCG2 has been primarily characterized as a multidrug transporter. However, in view of its broad substrate specificity and its presence in tissues producing steroid hormones (Maliepaard et al. 2001), ABCG2 could also be involved in local lipid transport processes that may have remained undetected in ABCG2 knockout mice (Jonker et al. 2002). We have shown that both ABCG2-R and ABCG2-G mediate the transport of unconjugated steroids and primary bile acids (Janvilisri et al. 2003, 2005). The results are complementary to published data on (1) the transport of ABCG2-mediated transport of sulfated conjugates of bile acids and steroids in

mouse P388 lymphoma cells (Imai et al. 2003; Suzuki et al. 2003), and glucuronide conjugates of steroids in HEK293 cells (Chen et al. 2003), and (2) the reported interactions of ABCG2 with steroidal drugs and hormones in mammalian cells (Pavek et al. 2005; Cooray et al. 2006). In agreement with the latter findings, Huss et al. (2005) found ABCG2-mediated efflux of androgen in putative benign and malignant prostate stem cells. ABCG2 also limits the oral availability and distribution of phytoestrogens into the brain and testis, epididymis and fetus (Enokizono et al. 2007). These observations may relate in part to the recent identification of a functional estrogen response element in the human *ABCG2* promoter, which is a target for the binding of estrogen/estrogen receptor complexes (Ee et al. 2004). In addition, they may ascribe to the identification of a putative START (steroidogenic acute regulatory protein signature) lipid-binding motif in human ABCG2 and its homologue NtWBC1 in tobacco reproductive organs (Otsu et al. 2004). Recent studies have shown that cholesterol can modulate the ATPase activity of human ABCG2 in lactococcal cells, Sf9 insect cells and mammalian cells (Janvilisri et al. 2003; Pal et al. 2007; Telbisz et al. 2007). In addition, a recent report by Storch et al. (2007) suggests the localization of ABCG2 in caveolin-1 rich lipid rafts in MDCKII cells. By analogy to previous work on ABCB1 (Romsicki and Sharom 1999; Rothnie et al. 2001), cholesterol might modulate the function of ABCG2 by interaction with the MDs of the transporter and/or the NBDs. Cholesterol might also influence the binding of lipophilic substrates to ABCG2, as was suggested for ABCB1 (Romsicki and Sharom 1999). Finally, ABCG2 might directly transport lipophilic cholesterol. In this context, it is interesting that the overexpression of ABCG2 in cancer cells is also associated with the transport of phosphatidylserine in the outer membrane leaflet (Woehlecke et al. 2003).

ABCG5/ABCG8

Human ABCG5 was identified as the human homolog of the rodent isoform that was induced in the liver by treatment with LXR agonist, T0901317. *ABCG5* was found to be localized adjacent to *ABCG8* on chromosome 2p21 and to be coordinately regulated with *ABCG8* through common regulatory elements (such as the nuclear receptor LXR), resulting in similar tissue- and cell-specific expression patterns (Berge et al. 2000). The ABCG5 and ABCG8 proteins unite to form the functional heterodimeric transporter (Graf et al. 2003), and are expressed at high levels in the canalicular membrane of hepatocytes, where they play an essential role in hepatobiliary cholesterol transport. Biliary cholesterol concentrations were extremely low in *Abcg*5 *Abcg8* (−/−) knockout mice when compared with wild-type animals (Yu et al. 2002). In addition, ABCG5/ABCG8 are expressed at lower levels in the apical membrane of enterocytes in small intestine and colon, where they limit the absorption of sterols from the lumen (Berge et al. 2000; Repa et al. 2002). Mutations in either *ABCG5* or *ABCG8* cause sitosterolemia, a rare autosomal recessive disorder characterised by accumulation of both plant-derived sterols (primarily sitosterol, but also campesterol, stigmasterol, and brassicasterol) and animal-derived sterol (cholesterol) in plasma and tissues, leading to the development of xanthomas (Berge et al. 2000; Lee et al. 2001). Likewise, *Abcg*5 *Abcg8* (−/−) knockout mice had a two- to threefold increase in the fractional absorption of dietary plant sterols, which was associated with an approximately 30-fold increase in plasma sitosterol (Yu et al. 2002). Recent evidence suggests that expression of the bile salt transporter ABCB4 is required for ABCG5/ABCG8-mediated biliary sterol secretion, suggesting that cholesterol excretion into bile requires bile salt micelles as cholesterol acceptor (Langheim et al. 2005; Vrins et al. 2007).

Conclusions

There is increasing evidence, and in some cases robust data, for the contention that ABCG transporters can interact with steroids. In addition, ABCG2 also interacts with many structurally unrelated xenobiotics. This raises interesting questions regarding steroid and drug binding sites in ABCG2. Are these sites dedicated to different types of substrates, or are the sites overlapping as a result of similarities in the physicochemical properties of the transported compounds? Can steroidal compounds be used to effectively modulate drug transport by ABCG2, and can drugs modulate steroid transport by other ABCG proteins? Further biochemical analysis of the molecular properties of ABCG proteins might provide some useful answers in the near future.

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