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*Review Article*

# Human ABCG2: structure, function, and its role in multidrug resistance

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**Abstract:** Human ABCG2 is a member of the ATP-binding cassette (ABC) transporter superfamily and is known to contribute to multidrug resistance (MDR) in cancer chemotherapy. Among ABC transporters that are known to cause MDR, ABCG2 is particularly interesting for its potential role in protecting cancer stem cells and its complex oligomeric structure. Recent studies have also revealed that the biogenesis of ABCG2 could be modulated by small molecule compounds. These modulators, upon binding to ABCG2, accelerate the endocytosis and trafficking to lysosome for degradation and effectively reduce the half-life of ABCG2. Hence, targeting ABCG2 stability could be a new venue for therapeutic discovery to sensitize drug resistant human cancers. In this report, we review recent progress on understanding the structure, function, biogenesis, as well as physiological and pathophysiological functions of ABCG2.

**Keywords:** Human ABCG2, structure, function, multidrug resistance, ATP-binding cassette, cancer, chemotherapy

## Introduction

Chemotherapy has been a major form of treatment for various cancers since 1940s. However, ineffectiveness and failure of chemotherapy with single agent was soon observed. This is probably due to the ability of cancer cells to mutate spontaneously at a rate of approximately $10^{-7}$ cells per generation and acquire resistance to the single agent in response to the pressures imposed by the drug treatment via a selection process [1]. In order to resolve this issue, the break-through concept of combinational therapy was introduced in the 1960s, which was based on the premise that the emergence of resistant cancers could be prevented with an alternating combination of drugs that have different targets. Nevertheless, multidrug resistance (MDR), which refers to the ability of organisms and cells to display resistance to a wide range of drugs that are structurally and functionally unrelated, has become a pervasive clinical problem in a majority of cancers ever since the introduction of combinational therapy.

Cellular and molecular mechanisms of MDR have been extensively studied. Studies with drug-selected model cell lines have repeatedly demonstrated that over-expression of some members of the ATP-binding cassette (ABC) transporter superfamily including breast cancer resistance protein (BCRP or ABCG2), P-glycoprotein (Pgp or ABCB1), and multidrug resistance associated protein 1 (MRP1 or ABCC1) is one of the major mechanisms responsible for MDR. The increased expressions of these ABC transporters on plasma membranes cause increased efflux and decreased intracellular accumulation of many unrelated anti-cancer drugs, leading to MDR.

ABC transporters represent one of the largest families of transporter proteins. In human alone, there are 48 ABC transporters and they have been divided into seven distinct subfamilies from ABCA through ABCG, based on their gene structure similarities and sequence homology [2]. Human ABC transporters are exclusively exporters. They use energy from ATP hydrolysis and are predominantly involved in the efflux of endogenous materials such as metabolic products, vitamins, lipids and sterols, as well as ex-

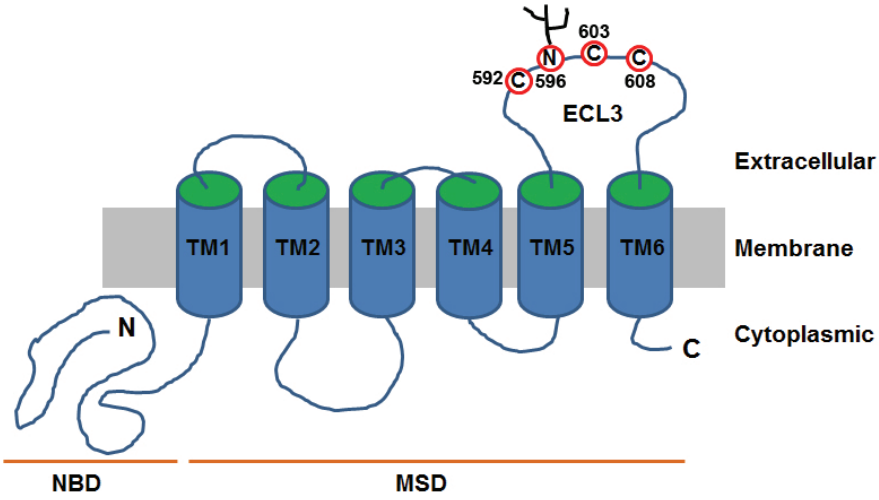


**Figure 1.** Membrane topology model of ABCG2. The schematic topological model was constructed on the basis of sequence analysis and the available experimental data. Nucleotide-binding domain (NBD), membrane-spanning domain (MSD), transmembrane (TM) segments, and extracellular loop 3 (ECL3) are indicated. The cysteine residues and N-linked glycosylation sites in ECL3 are also shown.

ogenous drugs and toxins from cytoplasm into extracellular space or intracellular compartments such as endoplasmic reticulum and peroxisomes. Therefore, human ABC transporters play essential roles in a majority of physiological, pathological, and pharmacological processes.

ABCG2 is one of the human ABC transporters that have been implicated in MDR in cancer chemotherapy [3, 4]. ABCG2 gene was cloned independently from both drug-selected model cell lines and human cDNA library in 1998. ABCG2 cloned by Ross's group from a drug-selected human breast cancer cell line MCF-7/AdVp3000 was termed as BCRP [5]. Simultaneously, Dean's group cloned a nearly identical transporter as an expressed sequence tag and named it ABCP for its high expression in placenta [6]. Shortly after, the cDNA of ABCG2 was cloned independently from a mitoxantrone-selected human colon carcinoma cell line, S1-M1-80, and was designated MXR for mitoxantrone resistance [7]. Human ABCG2 is an important molecule in both innate and acquired MDR, in regulation of drug bioavailability, in prognosis prediction of both hematopoietic and solid malignancies, and in protecting cancer stem cells. In this article, we will review recent progresses on the study of human ABCG2 regarding its structure, function, role in MDR, and its substrates as well as modulators and biogenesis.

## Structure of ABCG2

All human ABC transporters have a distinctive modular architecture, consisting of at least one hydrophilic nucleotide binding domain (NBD) located in cytoplasm and one hydrophobic membrane-spanning domain (MSD). Based on the structure and arrangement of NBD and MSD, they can be grouped into 'full transporters', 'half transporters' and non-transporter type ABC proteins [8]. Typically, full transporters, such as ABCB1, comprise two homologous halves and are characterized by two MSDs and two NBDs with an arrangement of $MSD_1$-$NBD_1$-$MSD_2$-$NBD_2$. Other types of full transporters, such as ABCC1, have an extra MSD ($MSD_0$) at the amino terminus with a domain structure of $MSD_0$-$MSD_1$-$NBD_1$-$MSD_2$-$NBD_2$. Half transporters contain only one MSD and one NBD, which are about half the size of a full transporter. These half transporters include members of the ABCD subfamily and some of the ABCB subfamily with a domain structure of MSD-NBD, and members of the ABCG subfamily with a reversed NBD-MSD configuration. The non-transporter ABC proteins include members of the ABCE and ABCF subfamilies that do not have MSDs.

Human ABCG2 is a half transporter with a domain structure of NBD-MSD and the MSD consists of 6 putative transmembrane (TM) segments (**Figure 1**). This topological folding of ABCG2 with 6 TM segments has been demonstrated using epitope tagging although the exact location of the TM segments is slightly different from the original prediction [9]. The previously predicted TM2 and TM5 are shifted to the extracellular and intracellular loops in the new model, respectively. Further studies are needed

to verify the exact location of these two TM segments and the new sequences that now function as TM2 and TM5. Nevertheless, future studies of the MSD of ABCG2 need to take into consideration of the possible alteration in the TM segment assignments.

Because of its half size nature, ABCG2 has been thought to exist and work as a homo-dimer. This hypothesis is supported by a study showing that co-expression of an ATPase-dead ABCG2 with the wild-type ABCG2 resulted in reduction of the ABCG2 transport activity and that ABCG2 migrated as monomers on SDS-PAGE under reducing conditions but as a dimer complex in the absence of reducing agents [10]. It was also found that human ABCG2 expressed in insect or bacterial cells retains its function, which argues against the necessity of other mammalian protein partners for ABCG2 function [11].

However, emerging evidence suggest that ABCG2 may exist as a higher order of homo-oligomer on plasma membranes. Using chemical crosslinking and non-reducing SDS-PAGE, Litman et al. first detected higher forms of oligomers in addition to dimeric proteins [12]. Using various biochemical methods such as non-denaturing PAGE, perfluoro-octanoic acid-PAGE (PFO-PAGE), gel filtration chromatography, sucrose gradient sedimentation, chemical crosslinking as well as co-immunoprecipitation, we unambiguously demonstrated that the major oligomeric unit of human ABCG2 in plasma membranes is a homo-dodecamer with a minimum stable unit of homo-tetramer [13] (**Figure 2**). No monomeric or dimeric ABCG2 was found under non-denaturing conditions using all methods mentioned above, suggesting that the major form of ABCG2 is likely bigger than a homo-dimer, possibly a dodecamer. Using chemical cross-linking, Bhatia et al. also showed the existence of higher order oligomers of ABCG2 in both isolated cell membranes and whole cell preparations [14]. Furthermore, using fluorescence resonance energy transfer (FRET) analysis of CFP/YFP tagged ABCG2 in whole cells, Wang et al. also showed the existence of oligomeric ABCG2 although the exact size of the complex could not be assessed with this method [15].

Later, examining purified human ABCG2 using cryo-electron microscopy revealed that purified human ABCG2 may exist as a homo-octamer

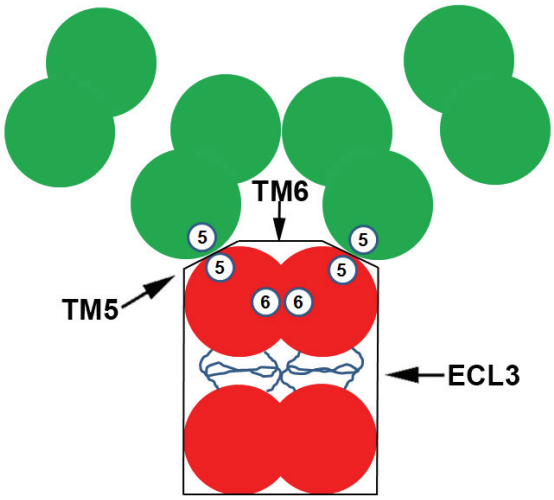


**Figure 2.** Schematic model of the dodecameric ABCG2. Three different possible interaction sites contributed by TM5 (5), TM6 (6), and ECL3 are shown.

consisting of four homo-dimeric ABCG2 complexes [16]. Yet, in another study using improved purification method preserving lipid environment, it was found that the purified ABCG2 in the presence of all solubilized membrane components may be a tetrameric complex when expressed in Sf9 cells [17]. In a third study of purified ABCG2 using electron microscopy, it was also found that the major oligomeric complex of ABCG2 is a tetramer [18]. Although the causes for the discrepancy between the later three studies of purified ABCG2 are unknown, it is clear that all these studies have demonstrated the existence of an oligomeric ABCG2 complex bigger than a dimer. However, use of different detergents and methods of purification in these studies may affect the outcome considering that the minimal stable ABCG2 complex is a tetramer and manipulation with various chemical or physical forces will break down the higher forms of oligomers to tetramers [13]. The observation of tetramers in two of the three studies of purified ABCG2 is consistent with this conclusion.

Using deletion mapping and co-immunoprecipitation of differentially tagged ABCG2 constructs, Xu et al. [19] mapped the oligomerization domain of human ABCG2 to its MSD consisting of extracellular loop 3 (ECL3) with its flanking TM segments (TM5 and TM6). The polypeptide consisting of TM5-ECL3-TM6 not only forms a homo-dodecameric complex by

itself but also exerts a dominant negative effect on the drug transport function of wild-type ABCG2, possibly by forming hetero-complexes with the wild-type molecule. We recently found that ECL3, TM5, and TM6 all contain oligomerization activities [20], suggesting that each of these three segments may be responsible for three different inter-molecular contacts responsible for the formation of a homododecamer [13, 19] (see also **Figure 2**). However, each segment plays a different role in ABCG2 drug transport function [20]. While TM5 is essential for ABCG2 function in drug transport, TM6 and ECL3 are replaceable.

ECL3 is an interesting loop containing three cysteine residues that may involve in formation of intra- and inter-molecular disulfide bonds. While $Cys^{603}$ was identified to form the inter-molecular disulfide bond [21] and it may potentially contribute to dimer formation as shown using non-reducing PAGE [10, 21], formation of the oligomeric ABCG2 does not depend on the inter-molecular disulfide bonds [13]. Furthermore, it appears that $Cys^{603}$ is not required for the expression or localization of ABCG2, nor is it essential for the ATPase or transport activity of ABCG2 [14, 21, 22]. Considering the possibility that the inter-molecular disulfide bonds may be due to oxidation during sample preparation [13], the above studies suggest that the functional ABCG2 does not necessarily need an intermolecular disulfide bridge for its function and/or oligomerization.

## Regulation of ABCG2 expression

In normal human tissues, ABCG2 is prominently expressed in placental syncytiotrophoblasts, epithelium of small intestine and colon, liver canalicular membranes, and ducts and lobules of mammary tissue [23]. ABCG2 expression has also been detected in the luminal membrane of epithelial cells in normal gallbladder [24], alveolar pneumocytes, sebaceous glands, interstitial cells of testes, prostate epithelium, endocervical cells of uterus, squamous epithelium of cervix, islet and acinar cells of pancreas, zona reticularis layer of adrenal gland, kidney cortical tubules and hepatocytes [25, 26]. ABCG2 is also present in veinous and capillary endothelium. Furthermore, ABCG2 is predominantly localized to the plasma membranes of cells in the above mentioned tissues [27], many of which harbor secretory or barrier function. This specific distribution profile of ABCG2 is closely related to the physiological role of human ABCG2 (see below). Increased expression of ABCG2 is frequently seen in both drug resistant cancer cell lines and clinical tumor tissues. The expression of ABCG2 in normal and cancer cells appears to be regulated at different levels including gene amplification, epigenetic modifications, transcriptional and posttranscriptional regulation.

### *Gene amplification*

Gene amplification has long been recognized as a major contributor to the increased expression of ABCB1 [28]. It was, thus, thought that the increased expression of ABCG2 in drug resistant cancer cells might also be due to gene amplification. The first report on ABCG2 gene amplification was a study of a few mitoxantrone-selected derivative cell lines of MCF-7 using Southern blot analysis [29]. This finding was later verified using comparative genomic hybridization (CGH) and Southern blot in MCF-7/MX cells as well as in Adriamycin-selected MCF-7/AdVp3000 cells [30]. The mitoxantrone-sensitive parental cell line MCF-7, on the other hand, had no amplification or chromosome translocation of the ABCG2 gene. It has also been shown that the resistance level to SN-38 in colorectal cancer cells positively correlates with ABCG2 gene amplification [31], suggesting that gene amplification of ABCG2 is not restricted to MCF-7 breast cancer cells.

Using stepwise-selected glioblastoma cell line SF295 against mitoxantrone in combination with Southern blot and fluorescence in situ hybridization (FISH), Rao et al. [32] examined the mechanisms of ABCG2 gene amplification during drug selection. It was found that double minute chromosomes was responsible for ABCG2 gene amplification in the drug resistant SF395 derivative cell lines selected with low concentration of mitoxantrone (50 and 100nM). However, in the derivative cell lines selected with high concentration of mitoxantrone (250 and 500nM), ABCG2 gene amplification appears to be due to chromosomal reintegration of the amplicon at multiple chromosomes to generate a more stable genotype.

### *Epigenetic regulation*

In addition to gene amplification, ABCG2 gene

has also been found to be regulated epigenetically. Demethylation of the ABCG2 gene has been found to contribute to increased ABCG2 expression in human multiple myeloma cells [33]. Methylation of ABCG2 gene was also found in renal carcinoma cell lines and treatment with demethylating agents increases ABCG2 expression [34]. Chromatin immunoprecipitation assay showed that the methylated promoter of ABCG2 interacted with methyl CpG island-binding proteins MBD2 and MeCP2, which further recruited histone deacetylase 1 and a co-repressor, resulting in interruption of ABCG2 transcription. Moreover, inhibition of DNA methylation in PC-6 lung cancer cells greatly increased both mRNA and protein levels of ABCG2 and the promoter methylation of ABCG2 is inversely correlated with ABCG2 expression in both SCLC and NSCLC cells [35], indicating that promoter demethylation of ABCG2 could be a common regulatory mechanism for ABCG2 up-regulation in cancer cells.

Histone acetylation has also been shown to possibly regulate ABCG2 promoter activity [36]. Following drug selection in several cancer cell lines and subsequent overexpression of ABCG2, the authors observed an increase in acetylated histone H3 but a decrease in class I HDACs associated with the ABCG2 promoter. The increased ABCG2 expression requires three prerequisites, removal of the repressive histone marker (trimethylated histone H3 lysine), recruitment of RNA polymerase II and recruitment of a chromatin-remodeling factor to the ABCG2 promoter. These observations suggest that the regulation of ABCG2 expression is complex at both genetic and epigenetic levels.

*Transcriptional regulation of ABCG2*

In addition to the regulation at genetic and epigenetic levels, transcriptional regulation of ABCG2 expression has also been reported. The human ABCG2 gene is located on chromosome 4q22 and spans more than 66 kbp [30]. It contains 16 exons and 15 introns [37]. While the first exon contains most of the 5'-untranslated region (5'-UTR), the translation initiation site is located in exon 2. The ABCG2 gene has a TATA-less promoter with its basal promoter activity conferred by a sequence ~312 bases upstream from the transcription start site. A CCAAT box is present at about 274 bases upstream from the transcription start site and its removal reduces the transcription activity of the ABCG2 gene. There are five putative Sp1 sites downstream from a putative CpG island, a common feature of promoters lacking a TATA box. In pancreatic cancer cells, it was found that the homeobox gene MSX2 helps recruit SP1 to the Sp1 binding sites in the ABCG2 promoter and increases ABCG2 gene transcription [38].

In addition to SP1, several other transcription factors have been shown to involve in regulating ABCG2 expression. These transcription factors include but not limited to estrogen receptor alpha (ERα), hypoxia-inducible factor 1 (HIF-1), peroxisome proliferator-activated receptor gamma (PPARγ), progesterone receptor (PGR) and aryl hydrocarbon receptor (AHR).

Sequence analysis of the 5'-flanking region of the ABCG2 gene has led to the discovery of a putative estrogen response element (ERE) between positions -188 to -172 of the ABCG2 promoter [39]. Deletion and site-directed mutagenesis analysis confirmed the existence of ERE in this region. It is further demonstrated that 17β-estradiol (E2) could promote the mRNA expression of ABCG2 through activation of estrogen receptor alpha (ERα), which directly binds to the ERE located in the ABCG2 promoter.

A study by Krishnamurthy et al. [40] showed that hypoxia also increases the mRNA level of ABCG2 in three different human cell lines. Analysis of the 5'-flanking sequence of human ABCG2 gene revealed three putative hypoxia response elements (HREs), all located upstream of the transcription start site. Using site-directed mutagenesis and electrophoretic mobility shift assays (EMSA), it was found that the HIF-1 complex specifically binds to the ABCG2 promoter through the only functional HRE at -116, bases upstream of the transcription start site and promotes ABCG2 transcription. This up-regulation of ABCG2 transcription by activated HIF-1 under hypoxia condition may stand for one of the mechanisms in some tumors to facilitate drug resistance. Moreover, IL-6 or ER stress inducer could synergistically increase ABCG2 expression through the site overlapping with XBP-1 and HIF-1 binding sites on the ABCG2 promoter, indicating that HRE might be involved in the effect of ER stress on ABCG2 expression as well [41].

Another nuclear receptor transcription factor

that was thought to regulate ABCG2 expression is PPARγ. It was first observed that the mRNA level of ABCG2 was increased in human myeloid lineage monocyte-derived dendritic cells upon treatment with PPARγ agonist rosiglitazone [42]. This effect was completely abolished by PPARγ antagonist or PPARγ siRNA, indicating that PPARγ is likely involved. To elucidate the mechanisms of the above finding, the promoter sequence of the ABCG2 gene was analyzed and three potential PPAR response elements were found in a conserved region of ~150 bp in length (-3946 to -3796). EMSA analysis further demonstrated that all three putative elements were able to bind PPARγ-RXR heterodimers specifically, suggesting that this genomic region likely plays an important role in the PPARγ-dependent transcriptional regulation of ABCG2 gene.

More recently, a novel progesterone response element (PRE) has also been identified between -243 to -115 of the ABCG2 promoter region [43, 44]. Progesterone significantly increases ABCG2 mRNA level in progesterone receptor B (PGR-B)- but not PGR-A-transfected cells. Although EMSA confirmed the direct binding of PRE in the ABCG2 promoter with either PGR-B or PGR-A, mutations in PRE only decreased the progesterone-response in PGR-B-transfected but not PGR-A-transfected cells. Further deletion of the PRE nearly completely abrogated the progesterone effect on ABCG2 promoter activity. Interestingly, co-expressing PGR-A and PGR-B significantly decreased the progesterone-response compared with PGR-B alone, indicating that progesterone induces ABCG2 transcription through PGR-B, while PGR-A may inhibit the effect of PGR-B via an undefined mechanism.

Two other elements have also been found in the ABCG2 promoter and they are proximal dioxin-response element (DRE) between -194 and -190, bases upstream of the transcription start site of the human ABCG2 gene and an antioxidant response element (ARE) at -431 to -420 [45-48]. While the first one may be responsible for direct binding of AHR and the subsequent induction of ABCG2 transcription, the second one is possibly responsible for Nrf2-mediated ABCG2 expression through interaction with Nrf2. However, whether these elements work in concert or compete with each other is largely unknown and further investigation may provide valuable information for the characterization of transcriptional regulation of ABCG2.

*Posttranscriptional regulation of ABCG2*

ABCG2 is also under posttranscriptional regulation by microRNAs. In $CD34^+/CD38^-$ hematopoietic stem cells isolated from human umbilical cord blood, it was found that hsa-miR-520h inhibits ABCG2 expression and possibly promotes the differentiation of these stem cells [49]. hsa-miR-520h has also been shown to down-regulate ABCG2 expression, resulting in inhibition of migration and invasion of pancreatic cancer cells [50]. Another miRNA, miR-328, also targets ABCG2 gene and decreases ABCG2 mRNA and protein levels through mRNA cleavage [51]. The proximal miRNA response element (MRE) of ABCG2 is located in the 3'-UTR of ABCG2 mRNA in various cancer cell lines [52]. Interestingly, it was found that this putative MRE of ABCG2 was lost in drug resistant cells and, therefore, the drug resistant cancer cells can evade ABCG2 mRNA degradation and protein synthesis repression mediated by miRNAs, leading to overexpression of ABCG2 [53].

While misfolded ABCG2 proteins, such as $Cys^{592}$ and $Cys^{608}$ mutants that lack the intramolecular disulfide bond and lose proper membrane trafficking and the $Asn^{596}$ mutant that lose N-linked glycosylation, have been shown to be removed from ER by retrograde translocation to the cytosol compartment, ubiquitinated by ubiquitin ligase and degraded in proteasome, wild-type ABCG2 is degraded in lysosomes [54-57].

Endocytosis and degradation of wild type ABCG2 in lysosome can also be accelerated by ABCG2 inhibitors. Recently, it was found that a new ABCG2 inhibitor, PZ-39, not only inhibits ABCG2 function, but also causes conformational change and accelerates degradation of ABCG2 via endocytosis and trafficking to lysosomes [58]. Later, it was found that there are a group of dynamic ABCG2 inhibitors that could accelerate ABCG2 degradation in lysosomes [59] (also see below). These inhibitors may also hijack newly synthesized ABCG2 from ER and direct them to lysosome for degradation or cause ER-associated degradation (ERAD). Indeed, in a recent study it was found that Derlin-1, a protein component of a complex that mediates ERAD, promotes the degradation of wild-type ABCG2 through suppression of ER to Golgi transport [60].

## ABCG2 in MDR

Although human ABCG2 is widely expressed in normal tissues, overexpression of ABCG2 has been frequently found in various drug-selected cancer cell lines and contributes to the clinical MDR of hematopoietic malignancies and solid tumors. Increased ABCG2 expression has also been linked to cancer stem cells.

*ABCG2 in MDR of cancer cell lines*

As mentioned earlier, ABCG2 was originally cloned from an Adriamycin-selected breast cancer cell line MCF-7/AdVp3000, which exhibited resistance to a range of cytotoxic agents, including mitoxantrone, doxorubicin and daunorubicin, but had no increased expression of ABCB1 or ABCC1 [5]. Overexpression of ABCG2 has been found in and correlated to the MDR phenotypes of numerous drug-selected cancer cell lines derived from various tumor types, including topotecan-selected ovarian tumor cell line T8 [61], mitoxantrone-selected colon cancer cell lines S1-M1-80 [7] and HT29 [62], SN-38-selected human small cell lung cancer cells PC-6/SN2-5 [63], mitoxantrone-selected human gastric carcinoma cell line EPG85-257RNOV [64], gefitinib-resistant non-small cell lung cancer (NSCLC) cells [65], epirubicin-resistant human hepatocyte carcinoma cells HLE-EPI [66], as well as topotecan and doxorubicin-selected human multiple myeloma cells [33]. However, the ABCG2-mediated drug resistance profiles found in these cell lines vary, which might be attributed to different cell origin or the involvement of other resistance factors selected by different drugs. Recently, several other mechanisms of drug resistance have also be identified in the Adriamycin-selected MCF7/AdVp3000 cells. These new mechanisms of resistance in MCF7/AdVp3000 include but are not limited to increased expression of other ABC transporters [67], 14-3-3σ and HSP27 [68], as well as fatty acid synthase [69]. Likely, alteration in other factors such as DNA repair proteins [70] and apoptosis [71] also contribute to the observed differences in level of resistance in different cell lines. Therefore, ABCG2 may be only one of the multiple factors responsible for MDR and a more complex model is required for better evaluation of MDR cell lines.

*ABCG2 in hematopoietic malignancies*

Although the cellular models are powerful tools to examine the MDR phenotype mediated by ABCG2, the clinical relevance of ABCG2 was established using clinical samples. Many studies have provided evidence demonstrating overexpression of ABCG2 in many different hematopoietic malignancies and its association with patient response. Early studies by Ross et al. have indicated relatively high levels of ABCG2 expression in 33% of acute myeloid leukemia (AML) blast cells [72]. Several follow-up studies have also demonstrated that ABCG2 expression correlates with prognosis and survival of AML patients (**Table 1**). However, such an association was not found in some other studies (**Table 1**). Currently, the reason for different findings of these studies is unknown. However, it is possible that the method used for detecting ABCG2 expression, sample size, as well as patient stratification may all play some role in different interpretation of the findings in these studies. Expression of other ABC transporters in these patients may also affect the outcome. It has been shown that AML patients expressing one or none of functional ABCB1, ABCC3 or ABCG2 have better prognosis than those patients expressing two or all of the above transporters [73]. Thus, analysis of a group of ABC transporters rather than a single one may provide a better picture regarding prediction of prognosis and chemotherapy response of AML patients. These data also suggest that modulation of all susceptible ABC transporters may be necessary for better treatment of AML patients.

The role of ABCG2 expression in acute lymphocytic leukemia (ALL) has also been implicated but stays inconclusive (**Table 1**). A correlation between ABCG2 expression and prognosis in adult ALL patients was reported in two different studies [74, 75]. However, this association was not found in a third study of childhood ALL [76]. Although it is not yet clear, the discordance between these studies might be due to differences in adult or childhood ALL (**Table 1**). Thus, more studies to compare adult and childhood ALL may help address this potential issue.

*ABCG2 in solid tumors*

Correlations between ABCG2 expression and prognosis of solid tumors have also been studied (**Table 2**). Similar to the studies of hematopoietic malignancies, some studies of solid tumors showed correlation between ABCG2 expression and prognosis while others did not. For example, in one study of breast cancer patients

**Table 1.** ABCG2 expression in human hematopoietic malignancies

| Type | Correlation | Methods | N[1] | Reference |
|---|---|---|---|---|
| AML | Yes | RT-PCR | 20 | [72] |
| AML | No (mitoxantrone, topotecan or doxorubicin based therapy) | ICC (BXP34) | 20 | [162] |
| AML | Yes (daunorubicin based therapy) | ICC (BXP34) | 20 | [162] |
| AML | No | FCM (BXP34 & BXP21) | 20 | [163] |
| AML | Yes (relapse/refractory) | RT-PCR | 20 | [164] |
| AML (child) | Yes (prognosis, relapse) | RT-PCR | 59 | [165] |
| AML (adult) | No | RT-PCR | 40 | [166] |
| AML | No | RT-PCR | 51 | [167] |
| AML (adult) | Yes (prognosis on daunorubicin and mitoxantrone therapy) | RT-PCR | 149 | [168] |
| AML (adult) | Yes (complete remission, DFS, overall survival) | FCM (BXP21) | 85 | [73] |
| AML | Yes (relapse and DFS) | FCM (BXP34) | 73 | [169] |
| AML | Yes (complete response rate) | RT-PCR | 154 | [170] |
| AML | Yes (DFS, relapse, overall survival to fludarabine-basd therapy) | | 138 | [171] |
| ALL (child) | No (prognosis) | RT-PCR | 67 | [76] |
| ALL | Yes (B-lineage) | FCM (BXP34) | 46 | [75] |
| ALL (adult) | Yes (DFS) | ICC (BXP21) | 30 | [74] |

[1] Number of subjeects studied

it was found that ABCG2 expression correlates with response to anthracycline-based chemotherapy [77]. However, in another study of breast cancers, no such correlation was identified [78]. Thus, whether ABCG2 over-expression contributes to MDR in solid tumors is currently inconclusive. More studies are clearly needed to investigate the role of ABCG2 in drug resistance and chemotherapy response of solid tumors.

## Physiological functions of ABCG2

Although ABCG2 appears to play an important role in MDR of human cancer cells, its expression and distribution pattern in normal tissues (see above) implicates that it must play some important physiological functions such as protecting the organism as a first line of defense against environmental insults. Data collected from ABCG2-null mice help appreciate this first line of defense role of ABCG2 [79]. ABCG2-null mice are more susceptible to phototoxic skin lesions, which are caused by accumulation of pheophorbide a, a chlorophyll degradation product found in food and supplements [79][79].

### *GI tract*

Human ABCG2 is physiologically expressed in the apical membrane of epithelial cells in the gastrointestinal (GI) tract, with maximal expression in the duodenum and a gradual decrease along the GI tract to the rectum [80]. ABCG2 is also constitutively expressed in the liver canalicular membranes, which supports a possible protective role of ABCG2 against xenobiotic absorption and towards toxic metabolites excretion. Indeed, it has been shown that administration of GF120918, a dual inhibitor of ABCB1 and ABCG2, resulted in a significant increase in the bioavailability and systemic concentration of topotecan after oral administration [81]. It was also found that GF120918 could markedly reduce the biliary and renal excretion of topotecan after intravenous administration. Considering that topotecan has higher affinity with ABCG2 than ABCB1, inhibition of ABCG2 by GF120918 may be the major mechanism responsible for the increased intestinal absorption and decreased biliary and renal excretion of topotecan. ABCG2 also appears to be responsible for the efflux of sulfate and glucuronide conjugates of xenobiotics and hormones, which are mostly products of phase II metabolism [82], suggesting that ABCG2 has a major role in extruding toxic metabolites via the biliary pathway.

### *Blood-brain barrier*

ABCG2 is constitutively expressed at the blood-

**Table 2.** ABCG2 expression in human solid tumors

| Type | Correlation | Methods | N[1] | Reference |
|---|---|---|---|---|
| Breast carcinoma | No (doxorubicin-based treatment) | RT-PCR | 43 | [78] |
| Breast carcinoma | No (anthracycline-based therapy) | IHC (BXP21 & BXP34) | 52 | [172] |
| Breast cancer | Yes (anthracycline-based therapy) | RT-PCR | 59 | [77] |
| Digestive tract tumors | Yes | IHC (BXP21) | 32 | [173] |
| Colorectal & cervical cancer | Yes (downregulation) | IHC | 154 | [174] |
| Endometrial carcinoma | Yes | IHC (BXP21) | 5 | [173] |
| Lung tumors | Yes | IHC (BXP21) | 10 | [173] |
| NSCLC | Yes (PFS and overall survival to platinum-based therapy) | IHC (BXP21) | 72 | [175] |
| NSCLC | Yes (short survival to cisplatin-based therapy) | IHC (BXP21) | 156 | [176] |
| SCLC | Yes (response and PFS to platinum-based therapy) | IHC (BXP21) | 130 | [177] |
| Melanoma | Yes | IHC (BXP21) | 5 | [173] |
| Melanoma | No | RT-PCR | 18 | [178] |
| Retinoblastoma | Yes (invasion) | IHC (5D3) | 39 | [104] |
| Retinoblastoma | No | IHC (BXP21) | 18 | [179] |
| Esophageal carcinoma | Yes | RT-PCR | 100 | [180] |
| T/NK-cell lymphoma | Yes | IHC | 45 | [181] |
| Diffuse large B-cell lymphoma | Yes (prognosis) | IHC (BXP21) | 67 | [182] |

[1]Numer of subjects studied

brain barrier mainly at the luminal cell surface of microvessel endothelium, serving as a crucial barrier to drug access into the brain [83-85]. It is now clear that ABCG2 works with ABCB1 in the blood-brain barrier and is responsible for restricting numerous xenobiotics into the brain. The positive impact of this function is that ABCG2 protects brain from the toxicity of xenobiotics while the negative impact is that ABCG2 impedes therapeutic agents to reach their intracerebral targets for treating brain tumors.

*Placenta*

ABCG2 expression is highest on the plasma membranes of the chorionic villi in placenta [12]. This cellular localization indicates that ABCG2 may play a major role in protecting fetus against toxic materials ingested by the mother. In ABCG2-null mice, the fetal exposure to topotecan and other dietary toxins increased significantly [86], further confirming the protective role of ABCG2 in the placenta.

*Stem cells*

A fascinating property of hematopoietic stem cells is their ability to actively extrude Hoechst 33342, a fluorescent dye. The low Hoechst 33342-staining cells isolated by subsequent fluorescence-activated cell sorting (FACS) are termed as 'side population' (SP) [87], which have been shown to possess stem cell-like characteristics in a variety of tissues [88-91]. ABCG2 expression is high in SP cells than non-SP cells, and has been characterized to be the Hoechst 33342 efflux pump in SP [92, 93]. Moreover, ectopic over-expression of ABCG2 conferred a SP phenotype in HEK293 cells, indicating that ABCG2 may serve as an attractive candidate marker for stem cells [92]. On the other hand, ABCG2 is differentially expressed during hematopoiesis, with the highest levels in the primitive bone marrow stem cell populations, followed by a sharp reduction in response to stem cell differentiation, suggesting a possible dual role of ABCG2 in maintaining human pluripotent stem cells in an undifferentiated state and in protecting these stem cells from xenobiotics or other toxins *in vivo*. [88, 89, 92].

Studies with ABCG2-null mice further confirmed that ABCG2 is necessary for SP phenotype, since loss of ABCG2 expression resulted in a drastic decrease in SP cells in the bone marrow and skeletal muscle. Notably, it has also been shown that the hematopoietic cells of ABCG2-null mice became more sensitive to the cytotox-

icity of mitoxantrone, confirming the physiological protection function of ABCG2 in hematopoietic cells [94].

Based on similar concept, ABCG2 has also been proposed to play a role in protecting putative cancer stem cells. ABCG2 has been shown to be responsible for extrusion of Hoechst dye in SP cells of breast [95-97], lung [96, 98], prostate [97], GI tract [99], head and neck [100], pancreas [101], nasopharyngeal carcinoma [102] neuroblastoma and glioblastoma [96], glioma [97], leukemia [97], and retinoblastoma [103, 104]. It has been shown that the cancer SP cells with higher ABCG2 expression was capable of sustained expansion ex vivo, asymmetric division, higher rate of tumorigenesis in vivo. However, in some studies it was reported that the cancer cells with or without ABCG2 expression are equally tumorigenic [97] and, thus, raising a question whether ABCG2 plays any role in the stemness of cancer cells. Further studies are clearly needed to elucidate the expression and role of ABCG2 in putative cancer stem cells.

## Substrates of ABCG2

The substrates of ABCG2, identified directly by cellular or vesicular transport assays, or indirectly by substrate-stimulated ATPase activity or cytotoxicity assays, comprise a broad spectrum of anticancer drugs, sulfate and glucuronide conjugates of sterols and xenobiotics, natural compounds and toxins, fluorescent dyes, photosensitizers, and antibiotics (**Table 3**).

One of the major constituents of ABCG2 substrates is anticancer drugs, including topoisomerase inhibitors, anthracyclines, camptothecin (CPT) analogs, tyrosine kinase inhibitors (TKI), and antimetabolites. ABCG2 also transports many sulfate and glucuronide conjugates of steroids and xenobiotics, which are two common products of mammalian Phase II metabolism, suggesting that ABCG2 is important in drug metabolic pathways. ABCG2 also mediates the efflux of Pheophorbide a (PhA), a chlorophyll catabolite [105], and many other photosensitizers [106], implicating ABCG2 as a possible cause for photodynamic therapy resistance. Interestingly, ABCG2 may also be involved in the transport of Aβ peptides at the blood-brain barrier and up-regulation of ABCG2 correlates with Aβ deposition in cerebrovessels, leading to cerebral amyloid angiopathy in Alzheimer's disease patients [107].

Interestingly, in early studies with MCF-7/AdVp3000 or mitoxantrone-selected S1-M1-80 cell lines, transport of rhodamine 123 has been observed [108]. However, the transport ability of rhodamine 123 was not seen in several other ABCG2 over-expressing cell lines [109]. This inconsistency led to discovery of a gain of function ABCG2 mutant with $R^{482}G/T$ mutation [109, 110] Both the $R^{482}G$ and $R^{482}T$ mutants and the wild-type ABCG2 are able to efflux mitoxantrone, topotecan, SN-38, Hoechst 33342 [111] and BODIPY-prazosin [112]. However, the $R^{482}G$ and $R^{482}T$ mutants have higher affinity with anthracyclines, including doxorubicin, daunorubicin, epirubicin, as well as bisantrene, fluorescence dye rhodamine 123 and lysotracker green [112]. Only the wild type ABCG2 can effectively transport methotrexate (MTX) [113, 114], MTX diglutamate and triglutamate, as well as folic acid [115]. These data suggest that amino acid 482 may be a 'hot spot' for mutation and this mutation affects substrate specificity of ABCG2.

Nevertheless, a study using IAARh123, the photoreactive analogue of rhodamine 123, has surprisingly shown that the wild type ABCG2 along with the two $R^{482}G$ and $R^{482}T$ mutants can all bind directly to IAARh123 although the wild type ABCG2 could not transport rhodamine [116]. This observation not only shows the direct binding of substrates to ABCG2 but also suggests the inability of the wild type ABCG2 to transport rhodamine 123 may not occur at the initial binding step. In a follow-up study of nine $R^{482}$ mutations, it was found that the $R^{482}$ mutations induce major changes in both substrate specificity and transport activity of ABCG2 [117]. Although $R^{482}$ mutations have not been identified in any clinical samples [110, 118, 119], $R^{482}$ mutants provide a superior tool to explore ABCG2 functions and to assist the modification of ABCG2 substrates and the development of ABCG2 inhibitors.

## Modulation of ABCG2 function and expression for chemosensitization

Because of the possible role of ABCG2 in causing MDR, considerable efforts have been paid to identify chemosensitizing agents targeting ABCG2 to sensitize ABCG2-mediated MDR for better treatment of human cancers. Some of these ABCG2 modulators are listed in **Table 4**.

**Table 3.** Summary of ABCG2 substrates

| Substrates | Reference |
|---|---|
| Topoisomerase inhibitors | |
| Mitoxantrone (topoisomerase II inhibitor) | [183] |
| Bisantrene (topoisomerase II inhibitor) | [108] |
| Etoposide (topoisomeriase II inihibitor) | [184] |
| Becatecarin (topoisomerase II inhibitor) | [185] |
| NB-506, J-107088 (topoisomerase I inhibitors) | [186] |
| Anthracyclines (Topoisomerase II inhibitors) | |
| Daunorubicin | [11] |
| Doxobucincin | [11] |
| Epirubicin | [112] |
| Pirarubicin | [184] |
| Camptothecin analogs (Topoisomerase I inhibitors) | |
| Topotecan | [61] |
| SN-38 | [61] |
| CPT-11 | [127] |
| 9-aminocamptothecin | [127] |
| NX211 | [127] |
| DX-8951f | [187] |
| Homocamptothecins | [188] |
| BN80915 (diflomotecan) | [188] |
| Gimatecan | [189] |
| Belotecan | [190] |
| Tyrosine kinase inhibitors | |
| Gefitinib | [141] |
| Dasatinib | [191] |
| Erlotinib | [192] |
| Vandetanib | [193] |
| Nilotinib | [194] |
| Sorafenib | [195] |
| Tandutinib | [196] |
| CI1033 (Pan-HER TKI) | [133] |
| CP-724,714 (HER2 TKI) | [197] |
| Symadex (fms-like tyrosine kinase 3 inhibitor) | [198] |
| Antimetabolites | |
| MTX, MTX diglutamate, MTX triglutamate (antifolate) | [115] |
| GW1843, Tomudex (antifolates) | [199] |
| Trimetrexatte, piritrexim, metoprine, pyrimethamine (lipophilic antifolates)* | [200] |
| 5-fluorouracil (pyrimidine analog) | [184] |
| CdAMP (nucleotide), cladribine (nucleoside) | [201] |
| Other anticancer drugs | |
| Flavopiridol (cyclin-dependent kinase inhibitor) | [119] |
| JNJ-7706621 (CDK and aurora kinases inhibitor) | [202] |
| Bicalutamide (non-steroidal anti-androgen) | [203] |
| NSC73306 | [204] |
| Phenethyl isothiocyanate (PEITC) | [205] |
| TH-337 (indazole-based tubulin inhibitors) | [206] |
| Sufate and glucuronide conjugates of xenobiotics | |
| Estrone 3-sulfate (E1S) | [207] |
| 17beta-estradiol sulfate | [208] |
| DHEAS | [207] |
| 4[35S]-methylumbelliferone sulfate | [207] |
| E3040 sulfate | [207] |
| Troglitazone sulfate | [209] |
| 3-O-sulfate conjugate of 17alpha-ethinylestradiol | [210] |

| | |
|---|---|
| SN-38-glucuronide | [211] |
| [3H]17beta-estradiol-17beta-D-glucuronide | [207] |
| [14C]4-methylumbelliferone glucuronide | [207] |
| BP-3-sulfate and BP-3-glucuronide | [45] |
| Phenolic MPA glucuronide | [212] |
| **Photosensitizers** | |
| Pheophorbide a | [105] |
| Pyropheophorbide a methyl ester | [106] |
| Chlorine E6 | [106] |
| 5-aminolevulinic acid | [106] |
| Phytoporphyrin | [213] |
| HPPH | [214] |
| **Natural compounds and toxins** | |
| Folic acid | [115] |
| Urate | [215] |
| Genistein | [145] |
| Riboflavin (vitamin B2) | [216] |
| Vitamin K3, plumbagin | [217] |
| Glutathione (GSH) | [218] |
| Sphingosine 1-phosphate | [219] |
| PhIP (carcinogen) | [220] |
| PPIX (heme precursor) | [221] |
| **Fluorescent dyes** | |
| Rhodamine 123 | [108] |
| Hoechst 33342 | [111] |
| Lysotracker green | [112] |
| BODIPY-prazosin | [222] |
| D-luciferin (firefly luciferase substrate) | [223] |
| Cholyl-L-lysyl-fluorescein (fluorescent bile salt derivative) | [224] |
| BODIPY-FL-dihydropyridine | [225] |
| **Others** | |
| [(125)I]Iodoarylazidoprazosin (IAAP), [(3)H]azidopine | [225] |
| Sulfasalazine (anti-inflammatory) | [226] |
| Erythromycin (macrolide antibiotic) | [227] |
| Ciprofloxacin, ofloxacin, norfloxacin,enrofloxacin, grepafloxacin, ulifloxacin (fluoroquinolone antibiotics) | [228-230] |
| Nitrofurantoin (urinary tract antibiotic) | [231] |
| Moxidectin (parasiticide) | [232] |
| Albendazole suloxide and oxfendazole (anthelmintics) | [233] |
| Ganciclovir (antiviral drug) | [234] |
| Zidovudine (NRTI) | [235] |
| Lamivudine (NRTI) | [236] |
| Leflunomide and A771726 (antirheumatic drugs) | [237] |
| Diclofenac (analgesic and anti-inflammatory drug) | [238] |
| Cimetidine (histamine H2-receptor antagonist) | [220] |
| ME3277 (hydrophilic glycoprotein IIb/IIIa antagonist) | [239] |
| Pitavastatin (HMG-CoA reductase inhibitor) | [240] |
| Rosuvastatin (HMG-CoA reductase inhibitor) | [241] |
| Dipyridamole (thromboxane synthase inhibitor) | [242] |
| Glyburide (hypoglycemic agent) | [243] |
| Nicardipine, nifedipine, nitrendipine ($Ca^{2+}$ channel blocker) | [225] |
| Olmesartan medoxomil (angiotensin II AT1-R antagonist) | [244] |
| Befloxatone (selective monoamine oxidase inhibitor) | [245] |
| Prazosin (alpha-1-adrenergic receptor antagonist) | [108] |
| Riluzole ($Na^+$ channels blocker) | [246] |
| Amyloid-beta | [247] |
| Zoledronic acid (osteotropic compound) | [248] |
| Hesperetin conjugates (flavonoid) | [249] |
| Kaempferol (flavonoid) | [250] |

**Table 4.** ABCG2 Modulators

| Modulators | Dynamic/Static | Reference |
|---|---|---|
| ABCB1 inhibitors | | |
| Elacridar (GF120918) | | [126, 127] |
| Cyclosporin A | | [11, 129] |
| PSC0833 | | [130] |
| Pyridines derivatives | | [131] |
| Tariquidar (XR9576) | | [105] |
| Chromanone derivatives | | [132] |
| Tyrosine kinase inhibitors (TKI) | | |
| CI1033 | | [133] |
| Gefitnib (Iressa, ZD1839) | | [134, 141] |
| Imatinib mesylate (Gleevec, STI571) | | [135] |
| Nilotinib | | [137] |
| Erlotinib | | [138] |
| Lapatinib | | [139] |
| Sunitinib | | [140] |
| Other inhibitors | | |
| Flavonoids | | [143-146, 251] |
| Curcumin | Static | [148, 149] |
| PZ compounds | Dynamic | [58, 59] |
| Xanthine | Dynamic | [125] |
| FTC | Static | [120] |
| Pipecolinate derivative (VX-710) | | [252] |
| Taxane derivatives | | [253, 254] |
| Tetrahydroisoquinolin-ethyl-phenylamines | | [255, 256] |
| Novobiocin | | [150] |
| UCN-01 | | [105] |

*Modulators of ABCG2 function*

The first inhibitor of ABCG2, fumitremorgin C (FTC), was reported before ABCG2 had been discovered and was shown to sensitize the resistance in the mitoxantrone-selected S1-M1-3.2 colon cancer cell line [120]. Later, FTC was also shown to specifically inhibit ABCG2 mediated transport of chemotherapeutic agents [121]. Unfortunately, clinical development of FTC was not possible due to its neurotoxicity, which led to the development of a new tetracyclic analogue of FTC, Ko143 [122]. Ko143 appeared to be a specific and potent inhibitor of both human and murine ABCG2. Most importantly, Ko143 was nontoxic *in vitro* at therapeutic concentrations and *in vivo* in mice either through oral or intraperitoneal administration [122]. Subsequently, other FTC-type inhibitors, including the indolyl diketopiperazines [123] and tryprostatin A [124] were identified and studies on these inhibitors are ongoing.

Recently, we identified a specific ABCG2 inhibitor with dual modes of action, PZ-39, from screening of a commercial chemical compound library [58]. Unlike FTC and its derivatives, PZ-39 not only can effectively inhibit ABCG2 function, but also can bind to ABCG2 and cause its degradation by accelerating its endocytosis and trafficking to lysosomes. PZ-39 can effectively reduce the half-life of ABCG2 from ~54 hrs to ~5 hrs. Interestingly, in a follow-up study it was found that there are probably two classes of ABCG2 inhibitors with dynamic and static properties [59]. The dynamic inhibitors including PZ-39 can inhibit ABCG2 activity and induce ABCG2 degradation while the static inhibitors such as FTC only inhibit ABCG2 function. This conclusion was further confirmed by a later finding that xanthines can also cause ABCG2 degradation via lysosomes [125]. Thus, targeting ABCG2 degradation may provide a novel mechanism of ABCG2 inhibition that may become an effective way of reversing ABCG2-mediated MDR.

Numerous ABCB1 inhibitors were shown to also inhibit ABCG2. These inhibitors include elacridar (GF120918) [126, 127], reserpine [88, 128], cyclosporin A [11, 129], tariquidar (XR9576) [105], PSC-833 [130], a series of newly synthesized 1,4-dihygropyridines and pyridines, such as dihydropyridines, niguldipine, nicardipine and nitrendipine [131], and chromanone derivatives, such as piperazinobenzopyranones and phenalkylaminobenzopyranones [132].

Similarly, several tyrosine kinase inhibitors (TKIs) were shown to also inhibit ABCG2. For example, CI1033 was found to reverse ABCG2-mediated resistance to SN-38 and topotecan [133]. Gefitinib (Iressa; ZD1839) has also been shown to inhibit ABCG2-mediated drug resistance, similar as imatinib mesylate (Gleevec, STI571), EKI-785, nilotinib, erlotinib, lapatinib and sunitinib [134-140]. Since ABCG2 can directly transport or confer resistance to CI1033, gefitinib, and imatinib [141, 142], it is possible that these TKIs may act as competitive inhibitors of ABCG2.

Flavonoids, a class of polyphenolic compounds widely present in foods and herbal products, are another class of ABCG2 inhibitors. Silymarin, hesperetin, quercetin, and daidzein, as well as the stilbene resveratrol, were shown to increase intracellular accumulation of mitoxantrone and BODIPY-prazosin in ABCG2 over-expressing cells [143]. Similarly, chrysin and biochanin A have also been shown to potently inhibit ABCG2 [144]. In addition, genestein, naringenin, acacetin, kaempferol and glycosylated flavonoids reversed resistance to SN-38 and mitoxantrone in ABCG2-overexpressing K562 cells [145]. It is thought that flavonoid inhibition of ABCG2 may be via interaction with its NBD [146]. Treatment with multiple flavonoids has revealed an additive effect in ABCG2 inhibition, implying that the approach of 'flavonoid cocktails' might achieve ideal effects on reversing ABCG2-mediated MDR [147].

Curcumin represents another group of compounds that have ABCG2 inhibitory activities. Curcumin could inhibit the transport and resistance of mitoxantrone or PhA in ABCG2 overexpressing cells, without affecting ATP binding activity or expression of ABCG2 [148]. Tetrahydrocurcumin (THC), a major metabolite of curcumin, exhibited potent inhibition of ABCG2, ABCB1 and ABCC1 [149]. More importantly, THC inhibited the binding of IAAP with ABCG2, inferring that THC may inhibit ABCG2 function through direct interaction with drug binding site of ABCG2.

Several other potent ABCG2 inhibitors including novobiocin, a coumermycin antibiotic, could decrease resistance to topotecan, SN-38 and mitoxantrone at low concentrations through competitive inhibition [150]. UCN-01, a cyclin-dependent kinase inhibitor, inhibited ABCG2-mediated transport of xenobiotics [105]. Some HIV protease inhibitors including ritonavir, saquinavir, nelfinavir, and iopinavir could effectively inhibit the transport activity of wild type ABCG2 but with less effect on $R^{482}T/G$ mutants [151, 152]. However, none of the HIV inhibitors tested were ABCG2 substrates.

*Modulators of ABCG2 expression*

In addition to modulating ABCG2 function, directly inhibiting the expression of ABCG2 gene has been considered. For example, hammerhead ribozyme or antisense oligonucleotide-based treatment has been demonstrated to be a powerful therapeutic strategy to overcome drug resistance mediated by ABC transporters [153, 154]. Six hammerhead ribozymes directed against ABCG2 gene have been designed and one of them, RzB1, showed high endoribonucleolytic cleavage activity at physiological pH and temperature in a cell free system [155]. Upon introduction into cultured cells, RzB1 successfully decreased both mRNA and protein levels of ABCG2 as well as reversed the drug-resistant phenotype of a human gastric carcinoma cell line with moderate ABCG2 expression [156] and MCF-7/MX cells with high level of ABCG2 [157]. An antisense oligonucleotide targeting ABCG2 was also able to reduce ABCG2 expression and cellular resistance to topotecan [158]. Recently, RNA interference has been considered to specifically knockdown ABCG2 expression to reverse drug resistance [159-161].Thus, clearly inhibiting ABCG2 expression may serve as an alternative route to sensitize ABCG2-mediate drug resistance in cancer chemotherapy.

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