The ABCG2 Multidrug Transporter

Agnes Basseville, Matthew D. Hall, Cindy H. Chau, Robert W. Robey, Michael Gottesman, William D. Figg and Susan E. Bates

Abstract ABCG2 is an ATP-binding cassette (ABC) half-transporter localized to the cell membrane and important in normal physiology, in normal tissue protection including in the maternal-fetal barrier and the blood brain barrier, and potentially in multidrug resistance. Dimerization is required for function. Polymorphic variants have been described that impair trafficking to the cell surface, and one, Q141K, has been associated with a higher incidence of gout in individuals who are carriers. Working in concert with ABCB1 (P-glycoprotein), ABCG2 is expressed at high levels in the vascular endothelium of the brain and pumps xenobiotics and chemotherapeutics back into the bloodstream. ABCG2 expression is also found at high levels in some cancer types including pancreatic and liver cancers. Whether its expression in these tumor types contributes to drug resistance via drug efflux and reduction in drug accumulation is a question that remains unanswered. Studies of drug accumulation, such as through imaging solid tumors in patients, are needed to answer this question.

Introduction to ABCG2

The human ATP-binding cassette (ABC) transporters are transmembrane efflux transporters that belong to a large superfamily of 48 members including ABCG2, or human breast cancer resistance protein (BCRP), encoded by the *ABCG2* gene located on chromosome 4q22.

A. Basseville · R.W. Robey · S.E. Bates (✉)
Developmental Therapeutics Branch, National Institutes of Health, Center for Cancer Research, Bethesda, MD 20892-1906, USA
e-mail: batess@helix.nih.gov; seb2227@cumc.columbia.edu

M.D. Hall · M. Gottesman
Laboratory of Cell Biology, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD 20892-1906, USA

C.H. Chau · W.D. Figg
Genitourinary Malignancies Branch, Center for Cancer Research,
Bethesda, MD 20892-1906, USA

ABCG2 is a 655 amino acid, 72 kDa protein consisting of an N-terminal nucleotide-binding domain (NBD) containing an ABC signature motif (ALSGGQ) and a C-terminal transmembrane domain (TMD) with six hydrophobic segments and an extracellular loop between TM5 and TM6. Its structure is in reverse configuration to most other ABC transporters containing one or two NBDs that are C-terminal to the TMDs. ABCG2 is a half-transporter (one NBD and one TMD), requiring at least two NBDs to function as an efflux pump; thus, functional ABCG2 exists as either homodimers or homomultimers (Bhatia et al. 2005; Doyle and Ross 2003; Kage et al. 2002; Nakanishi et al. 2003; Xu et al. 2004). Homodimer formation involves a disulfide bridge linkage at cysteine 603 located in the extracellular loop (Henriksen et al. 2005; Wakabayashi et al. 2007). Crystallization studies reveal a tetrameric complex comprised of four homodimers (McDevitt et al. 2006) and other studies have shown that it can also form higher oligomeric states (Xie et al. 2008; Xu et al. 2007). It is speculated that ABCG2 dimerizes in the endoplasmic reticulum (ER), exits to the Golgi apparatus for posttranslational processing, and is finally then trafficked to the apical membrane of the cell (Graf et al. 2003).

This chapter is about ABCG2—its expression in normal tissues, substrate/ inhibitor specificity, role in cancer multidrug resistance, and particularly its role in the blood–brain barrier (BBB). Understanding how genetic variations affect transporter function or substrate and inhibitor specificity and drug–transporter interactions at the BBB will shed light on improving drug delivery to the brain. The contribution of ABCG2 to multidrug resistance in the tumor vasculature versus the BBB will be addressed followed by a brief discussion on prospects for transporter inhibition at the BBB.

Tissue Expression

Since ABCG2 was first discovered in drug-resistant human cancer cells, subsequent studies focused on its pattern of expression in various normal tissues, where ABCG2 was found to be involved in the absorption, distribution, metabolism, and elimination of xenobiotics and endogenous chemicals. The location and level of expression of ABCG2 highlighted major roles for ABCG2 in forming the maternal–fetal barrier, the blood–testis cell barrier, and the blood–brain barrier; controlling the absorption and efflux of xenobiotics and endogenous metabolic products within the gastrointestinal tract; and more recently its role in urate transport in the kidney.

Placenta and Mammary Gland

The highest levels of ABCG2 expression are found in placental tissue, specifically in the placental syncytiotrophoblast at the apical surface of the chorionic villi. Due to this specific localization, it is thought that ABCG2 helps form the barrier between

the maternal and fetal circulation systems, and thus protects the fetus from endogenous and exogenous toxins (Fetsch et al. 2006). It is also possible that ABCG2 transports steroid hormones produced in the placenta (Doyle and Ross 2003), since the major estrogens produced and secreted by the placenta are ABCG2 substrates (Suzuki et al. 2003).

While ABCG2 is expressed at low levels in the non-lactating adult breast, its expression is elevated in lactating mammary tissue, localized in the lobules and lactiferous ducts of the mammary gland, as well as in venous/capillary endothelium (Maliepaard et al. 2001; Faneyte et al. 2002). As opposed to the protective role ABCG2 may play in the placenta, the functional role of ABCG2 here would be to concentrate substrates such as vitamins—as has been demonstrated for riboflavin—or other essential factors into breast milk; however, enrichment of toxins in breast milk has also been demonstrated (Jonker et al. 2005; van Herwaarden et al. 2006, 2007).

Testis

High expression of ABCG2 has been reported in normal testis tissue, where it is expressed in the Sertoli–Leydig cells, in the myoid cell layer, as well as in endothelial cells (Fetsch et al. 2006; Bart et al. 2004). Due to its localization on the luminal side of the endothelium as well as the apical side of myoid cells, it probably transports substrates out of the seminiferous tubules, implying a potential role in protecting the germ cells.

Blood–Brain Barrier

ABCG2 was found to be expressed on the luminal surface of brain microvessel endothelium, suggesting a role in the blood–brain barrier (Cooray et al. 2002). Since then, numerous researchers have explored the role of ABCG2 in forming the blood–brain barrier (BBB), predominantly in murine models. ABCG2 was found to be expressed along with P-gp (ABCB1) in the microvasculature of both normal and malignant tissues from the central nervous system, but their relative functional contribution still needs to be determined. Not only do studies indicate that ABCG2 plays a role in the efflux of toxic xenobiotics in the BBB, but it also appears that it could play a role in efflux of endogenous substrates, since its activity in the transport of efflux of amyloid-β peptide was recently reported (Do et al. 2012; Tai et al. 2009).

Liver and the Gastrointestinal Tract

When Taipalensuu et al. (2001) examined jejunal mucosa from 13 normal volunteers, and compared expression levels of 10 drug efflux transporters from the ABC

family, the highest level detected was for the mRNA encoding ABCG2. Other studies indicated that ABCG2 mRNA was detected at high levels in the duodenum, decreasing along the gastrointestinal tract, and reaching lowest levels in the rectum (Gutmann et al. 2005; Hilgendorf et al. 2007). ABCG2 was localized by immunohistochemistry at the apical membrane of the small intestine, the colon, and the liver bile canaliculi. A recent quantification of intestinal ABCG2 from 14 human donors indicates that the average BCRP density in the human duodenum is 305 ± 248 fmol/cm2 and it was found at 2.6 pmol per gram in the liver (Tucker et al. 2012).

The presence of ABCG2 in the apical membrane of the small intestine and bile canniculi implies a role for the protein in xenobiotic and endogenous substrate efflux from the liver and substrate absorption in the GI tract (Adachi et al. 2005). Another role for ABCG2 in the intestine is in the secretion of endogenous uric acid, even though renal excretion is the most important factor in uric acid elimination (Hosomi et al. 2012).

Kidneys

BCRP is expressed at the apical membrane of proximal tubules, suggesting a role for BCRP in renal excretion of xenobiotics (Fetsch et al. 2006; Huls et al. 2008). In 2008, a genome-wide association study (GWAS) reported that a common single nucleotide polymorphism of ABCG2 was linked to elevated blood urate level and gout (Dehghan et al. 2008). Further studies revealed that ABCG2 was indeed involved in excretion of urate in urine, again highlighting the importance of ABCG2 in the transport of endogenous compounds (Woodward et al. 2009).

Other Sites

BCRP is expressed in a wide variety of stem cells including those of hematopoietic origin and is the molecular determinant of the side population (SP) phenotype (Zhou et al. 2001; Scharenberg et al. 2002). SP cells have been identified by their ability to effectively exclude the fluorescent vital dye Hoechst 33342 and form a distinct population, definable by flow cytometry (Goodell et al. 1996).

ABCG2 mRNA expression was reported in multiple other tissues (see Fig. 1), and various studies confirmed ABCG2 protein expression in alveolar pneumocytes, sebaceous glands, transitional epithelium of the bladder, prostate epithelium, uterine endocervical cells, cervical squamous epithelia, small and large intestinal mucosa/epithelial cells, pancreatic islet and acinar cells, zona reticularis layer of the adrenal gland, gall bladder, conjunctival epithelium, retinal pigment epithelium, spinal cord, and hepatocytes (Fetsch et al. 2006; Maliepaard et al. 2001; Aust et al. 2004; Chen et al. 2013).

Fig. 1 Log2 median-centered ABCG2 expression data obtained from analysis of 502 normal tissues, source GEO accession number GSE7307 (http://www.ncbi.nlm.nih. gov/geo/query/acc.cgi?acc= GSE7307). Selected samples were grouped by organ and median expression per organ was calculated
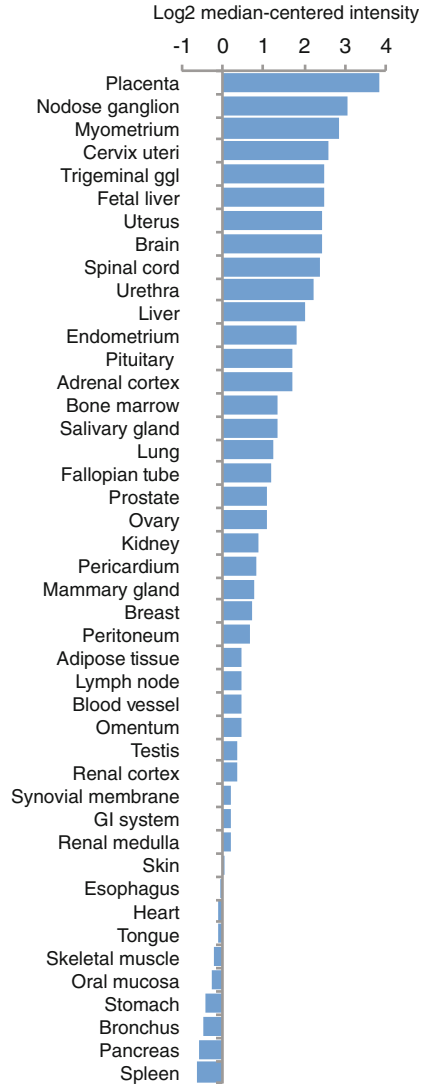
Polymorphisms and ABCG2 Null Humans

Structural and functional studies reveal that ABCG2 transporter activity is affected by both posttranslational modifications and genetic polymorphisms. During its transit through the endoplasmic reticulum–Golgi pathway to the plasma membrane, ABCG2 undergoes N-linked glycosylation at asparagine 596 (Diop and Hrycyna 2005) and formation of an intramolecular disulfide bond between C592 and C608, where mutating these cysteine residues results in impaired localization and function (Henriksen et al. 2005; Wakabayashi et al. 2007). The oligomeric glycosylated ABCG2 undergoes lysosomal degradation whereas the underglycosylated, misfolded protein lacking the intramolecular disulfide bond is degraded via the proteasome (Wakabayashi et al. 2007; Nakagawa et al. 2009; Wakabayashi-Nakao et al. 2009). Certain non-synonymous single nucleotide polymorphisms (SNPs), such as Q141 K, F208S, and S441 N, affect ABCG2 protein stability resulting in enhanced ubiquitin-mediated proteasomal degradation (Furukawa et al. 2009; Nakagawa et al. 2008). Moreover, Q141 K and F208S variants are found sequestered in the aggresome followed by subsequent degradation via autophagy (Basseville et al. 2012; Wakabayashi-Nakao et al. 2010). In addition, mutational studies of ABCG2 identified a GXXXG motif (residues 406–410), responsible for dimerization, where mutation of the glycines to leucines affected the protein's function (Polgar et al. 2004). Mutational analysis of threonine 402, three residues from the GXXXG motif, reveals a role for this residue in modulating protein folding and processing as well as dimerization (Polgar et al. 2010). Furthermore, functional variations in *ABCG2* have been shown to affect substrate binding and specificity. Mutating Arg482 and Pro485, located in the drug-binding pocket within TM3, can affect the efflux of some substrates (Ni et al. 2011).

More than 80 single nucleotide polymorphisms in the *ABCG2* gene have been identified across ethnically diverse subpopulations. Among them, Q141K (421C > A, rs2231142) and V12M (34G > A, rs2231137) occur most frequently in Asians (∼25–35 %) and with lower frequencies in Caucasians (∼10 %), and African-American populations (∼<5 %), while the remaining SNPs have allelic frequencies of less than 2 % (Backstrom et al. 2003; de Jong et al. 2004; Iida et al. 2002; Imai et al. 2002; Kobayashi et al. 2005; Kondo et al. 2004; Zamber et al. 2003). Functional studies revealed that the Q141K and D620N mutations decrease ABCG2 activity, while V12M, I206L, and N590Y do not appear to alter protein function (Morisaki et al. 2005; Vethanayagam et al. 2005). Other non-synonymous SNPs, F208S (623T > C, rs1061018) and S441 N (1321G > A), lead to reduced protein stability by enhancing proteasomal proteolysis (Furukawa et al. 2009). In fact, S441N displayed lower protein expression and impaired membrane localization (Kondo et al. 2004). Moreover, an in vitro study found 6 of the 18 ABCG2 variants to exhibit defective or impaired transport of the substrates hematoporphyrin or methotrexate: Q126stop (376C > T, rs72552713); F208S; S248P (742T > C, rs3116448); E334stop (1000G > T, rs3201997); S441 N; and F489L (1465T > C) (Tamura et al. 2006). Additional SNPs reported in the *ABCG2* promoter region,

−15622C > T and −1379A > G, may be involved in transcriptional control of the gene (Noguchi et al. 2014). The nonsense mutation Q126X (376C > T, rs72552713) introduces a stop codon resulting in a non-functional transporter (Matsuo et al. 2009).

Q141K and Drug Disposition/Clinical Outcome

Pharmacogenetics studies of ABCG2 have mainly focused on the Q141K variant. Q141K is associated with reduced protein expression (Imai et al. 2002; Morisaki et al. 2005) possibly due to increased ubiquitin-mediated proteasomal degradation (Furukawa et al. 2009), as well as reduced protein function. The SNP is located in the ATP-binding region between the Walker A and B motifs of ABCG2 and has also been associated with reduced ATPase activity, impaired membrane localization, and instability in the nucleotide-binding domain (Imai et al. 2002; Kondo et al. 2004; Mizuarai et al. 2004; Woodward et al. 2013). These findings indicate that this SNP may result in altered transporter function and have important implications for regulating drug disposition. However, studies evaluating the clinical relevance of this SNP have been inconsistent largely due to the small sample size of the study populations. Patients with the variant genotype (AA or CA) had significantly higher plasma AUC or Cmax levels for statins (Keskitalo et al. 2009a, b; Lee et al. 2013; Zhang et al. 2006; Zhou et al. 2013), TKIs (sunitinib Mizuno et al. 2012 and imatinib Takahashi et al. 2010), sulfasalazine (Urquhart et al. 2008; Yamasaki et al. 2008) as well as the camptothecin derivatives diflomotecan (Sparreboom et al. 2004) and 9-aminocamptothecin (Zamboni et al. 2006). However, no significant effects of the Q141 K variant on pharmacokinetic parameters were observed for irinotecan (de Jong et al. 2004; Han et al. 2007; Jada et al. 2007), docetaxel (Chew et al. 2011), or nitrofurantoin (Adkison et al. 2008). Furthermore, this SNP has also been linked with increased drug-induced diarrhea for Korean patients with diffuse large B-cell lymphoma receiving rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (Kim et al. 2008) or patients on gefitinib therapy (Cusatis et al. 2006). The 421AA genotype correlated with risk of grade 3 or grade 4 thrombocytopenia and neutropenia in Korean patients with metastatic renal cell carcinoma on sunitinib therapy (Kim et al. 2013).

The association of Q141 K with clinical outcome has also been mixed with a study demonstrating longer progression free survival for the variant allele in advanced ovarian cancer patients (Tian et al. 2012) and other studies showing poor outcome for patients with acute myeloid leukemia being treated with idarubicin-based therapy (Tiribelli et al. 2013) or lung cancer patients on a platinum-based regimen (Muller et al. 2009).

The other common ABCG2 SNP, 34G > A, has not been reported to significantly affect drug pharmacokinetics. The *ABCG2* (−15622C/T) polymorphism and the *ABCG2* (1143C/T, −15622C/T) haplotype were associated with gefitinib-induced moderate-to-severe diarrhea, but their functional impact is still unknown (Lemos

et al. 2011). Other genetic polymorphisms have been identified in the coding region of ABCG2 but their clinical relevance remains to be determined (Noguchi et al. 2014; Zhao et al. 2009).

ABCG2 Null Alleles

ABCG2 was identified as the genetic basis of a blood group system named Junior, Jr or Jr(a), such that null alleles of *ABCG2* cause the Jr(a−) blood type. Individuals who do not express Jr(a) antigen are rare and are mainly found in Japanese and other Asian populations. SNP analysis on genomic DNA from 6 Jr(a−) subjects led to the identification of three nonsense mutations (Q126X, Q246X, and R236X) where all three SNPs resulted in a premature stop codon in the ATP-binding domain of ABCG2 (Zelinski et al. 2012). A separate study also sequenced *ABCG2* in 18 Jr (a−) individuals and found eight mutations: three nonsense mutations described above (Q126X, R236X, and Q246X) and five frameshift mutations (I63Yfs, F182Vfs, L264Hfs, F293Lfs, and T371Lfs) (Saison et al. 2012). Individuals were either homozygous for a single *ABCG2* mutation or heterozygous for two mutations. Both studies concluded that the *ABCG2* mutations identified in the Jr(a−) individuals correspond to null alleles of *ABCG2* and are responsible for the Jr(a−) blood type. Ongoing studies have continued to identify additional new null alleles in Jr(a−) patients (Hue-Roye et al. 2013a, b; Ogasawara et al. 2014; Tanaka et al. 2014) and the functional significance is still unknown.

Substrates and Inhibitors of ABCG2

Substrates

The ABCG2 substrate spectrum has increased exponentially over the years to include physiological compounds, cancer and non-cancer therapeutics, molecularly targeted drugs, and common dietary xenobiotics. ABCG2 is involved in the physiologic efflux of multiple endogenous substrates that include conjugated organic anions (Mao and Unadkat 2015; Polgar et al. 2008); porphyrin/heme (Jonker et al. 2002; Krishnamurthy et al. 2004); folates (Chen et al. 2003); and urate (Woodward et al. 2009) as well as amyloid-β peptides across the BBB (Xiong et al. 2009).

Since it was originally discovered in drug-resistant cells, the first compounds reported as (exogenous) substrates of ABCG2 were chemotherapeutics that include mitoxantrone (Doyle et al. 1998), anthracyclines, methotrexate, camptothecin derivatives, and flavopiridol as well as tyrosine kinase inhibitors (TKIs) such as imatinib and gefitinib (Mao and Unadkat 2015; Polgar et al. 2008). Drug-selected

cell lines that express mutant forms of ABCG2 (R482G and R482T) were found to modify substrate selectivity resulting in enhanced efflux of rhodamine 123 and increased resistance to anthracyclines (Chen et al. 2003; Allen et al. 2002a; Honjo et al. 2001). Subsequent site-directed mutagenesis studies at amino acid 482 further demonstrated its importance in determining substrate recognition and transport (Miwa et al. 2003; Ozvegy-Laczka et al. 2005; Robey et al. 2003). However, it should be noted that mutations of Arg482 have never been identified in clinical samples to date.

Other substrate classes have been identified and include certain antibiotics (fluoroquinolones and erythromycin), antiretrovirals (nucleoside analogs, zidovudine and abacavir), carcinogens, flavonoids (genistein and quercetin), and HMG-CoA reductase inhibitors (Mao and Unadkat 2015; Polgar et al. 2008). Fluorescent probes have been reported to be ABCG2 substrates and include Hoechst 33342, BODIPY-prazosin, LysoTracker Green, and pheophorbide A (Litman et al. 2000; Robey et al. 2004). The transport of photosensitizers by ABCG2 further implicates this transporter as a possible cause of cellular resistance to photodynamic therapy (Robey et al. 2005). More recently, D-luciferin was identified as a specific ABCG2 substrate that can be used as a probe for (bioluminescent) imaging of ABCG2 function at the BBB in vivo (Bakhsheshian et al. 2013a).

ABCG2 has a broad substrate specificity that is distinct, but substantially overlaps, with that of P-gp and multidrug resistance protein (MRP1). Although the number of ABCG2 substrates exceeds 200, few studies have been conducted to determine structure–activity relationship (SAR) for prediction of ABCG2 substrates. One SAR study conducted with camptothecin analogs showed that ABCG2 transports compounds with high polarity at carbon positions 10 and 11 (Yoshikawa et al. 2004). A recent study by Hazai et al. (2013) developed a predictive model for wild-type ABCG2 substrates, using a support vector machine (SVM) method based on 263 known BCRP substrates and non-substrates, with an overall prediction accuracy of ∼76 % for identifying potential novel substrates.

Inhibitors

The first ABCG2 specific inhibitor identified was the diketopiperazine fumitremorgin C (FTC) isolated from the fungi *Aspergillus fumigatus* (Rabindran et al. 1998). FTC was reported to inhibit mitoxantrone resistance in drug-selected cell lines even before ABCG2 was cloned, but had no effect on resistance mediated by P-gp or MRP1 (Rabindran et al. 1998). Because of its neurotoxic effects, FTC analogs (Kol43) were soon developed with more potent inhibitory activity and high selectivity for ABCG2 and low neurotoxicity (Allen et al. 2002b; van Loevezijn et al. 2001).

Many ABCG2 inhibitors are not selective and can inhibit other ABC transporters, such as the potent dual P-gp/ABCG2 inhibitors elacridar (de Bruin et al. 1999) and tariquidar (Robey et al. 2004) as well as the growing list of TKIs

(Durmus et al. 2015). Additional classes of inhibitors include flavonoids, steroids, nucleoside analogs, and immunosuppressants (tacrolimus, cyclosporine A). Chromone derivatives and tariquidar-like structures are considered the most potent and selective inhibitors of ABCG2, inducing high inhibition of ABCG2 with low effect on ABCC1 and ABCB1 (Lecerf-Schmidt et al. 2013). Given the promiscuous nature of ABCG2, the list of inhibitors (and substrates) will continue to expand in the coming years.

The mechanism of inhibition divides ABCG2 inhibitors into two groups: "general" inhibitors that inhibit ATPase activity of the transporter such as FTC and Ko143; and "substrate-dependent" inhibitors that are ABCG2 substrates and thus act as competitive inhibitors. The latter group results in substrate-dependent inhibition where the inhibitor may interact with ABCG2 on (i) binding sites of one class of substrates but not others, or (ii) on allosteric sites to induce conformational changes in the large binding pocket that subsequently affects transport of certain substrates. For example, nelfinavir has been shown to inhibit the efflux of zidovudine and abacavir with no effect on efflux of prazosin and imatinib, suggesting that the nucleoside analogs possibly bind to ABCG2 at sites that do not overlap with those for prazosin or imatinib (Giri et al. 2009). These findings support the notion that substrates interact with ABCG2 at multiple binding regions in the protein. For this reason, predicting and screening for ABCG2 inhibitors remains a challenge in drug discovery.

Role of ABCG2 in Cancer Multidrug Resistance

The story of ABCG2 in multidrug resistance is inextricably linked with that of P-gp/ABCB1. Discovered in 1976 in drug-resistant Chinese hamster ovary cells, the therapeutic potential was quickly recognized when verapamil was found to overcome resistance by blocking drug efflux (Tsuruo et al. 1981; Juliano and Ling 1976). Other inhibitors were rapidly discovered and the idea was translated to the clinic with the first trial result reported in 1987, a trial combining verapamil with adriamycin in ovarian cancer (Ozols et al. 1987) relying on data showing that high levels of resistance due to P-gp-mediated efflux could be overcome by addition of P-gp inhibitors. For over a decade, many publications began with some variation of 'drug resistance is a major problem in the treatment of cancer', and then went on to report the detection of P-gp expression in a new tumor type or the identification of a new inhibitor to overcome resistance. Eventually it became apparent that there were drug-resistant cell lines with high levels of drug efflux but in which P-gp expression was not detectable. MRP was discovered as a mediator of drug efflux in some of those cell lines (Schneider et al. 1994), and then ABCG2 (Ross et al. 1999). However, because the discovery of P-gp preceded those of MRP and ABCG2 by two decades, it was translated to the clinic on its own.

From the first clinical trial in 1987, a series of studies testing a variety of P-gp substrates and inhibitors in patients with a variety of tumor types was carried out.

Although many trials were conducted with off-the-shelf agents developed for another purpose, a number of later P-gp inhibitors were developed specifically for that purpose. In sum, a handful of trials had a statistically significant positive outcome, but most of the studies were unconvincing and did not support a role for overcoming resistance by adding a P-gp inhibitor. In retrospect, there were mistakes in the development that may have obscured a positive signal. These included a delay in the conduct of randomized trials, failure to selectively enroll only patients whose tumors had detectable P-gp expression prior to enrollment, and utilization of inhibitors that also altered the pharmacokinetics of the anticancer drug in the combination such that lower drug doses had to be used (Amiri-Kordestani et al. 2012; Shaffer et al. 2012). A large number of trials were conducted with inconclusive results. Two randomized trials were launched in 2002—with tariquidar, a very potent P-gp inhibitor, combined with vinorelbine or paclitaxel plus carboplatin in non-small cell lung cancer. The trials were conducted at about 100 centers around the U.S., and were closed within a year for toxicity in the experimental arm, with only 304 of an expected 1000 patients enrolled (Fox and Bates 2007). The most positive signal had come from an acute leukemia study with cyclosporine A in 2001, with multiple intervening studies inconclusive (Shaffer et al. 2012). A third generation P-gp inhibitor, zosuquidar, was conclusively negative (Cripe et al. 2010). In none of the trials were patients selected because their tumors demonstrated expression of P-gp—and in the ensuing years we have learned just how important it is that the target be demonstrated in the tumor before expecting any activity from a targeted agent (Bates et al. 2012). In these studies, P-gp was the obvious target.

In this climate of disappointment, ABCG2 and ABCC1 were discovered and came of age as potential targets for cancer therapy. It was not long before inhibitors of both were discovered and with that the need to identify which tumors were ABCG2-expressing and which were P-gp-expressing. Given that the P-gp clinical trials were turning up negative, and that a clinically validated assay for P-gp had never been developed, the road to an ABCG2 inhibitor in the clinic seemed very long indeed. VX-710, biricodar, was an P-gp and ABCC1 modulator that was thought to also inhibit ABCG2 (Minderman et al. 2004). But a single arm Phase II trial of VX-710, doxorubicin, and vincristine did not meet a level of interest to be pursued (Gandhi et al. 2007). Nor were studies in ovarian, breast, or prostate cancer (Seiden et al. 2002; Toppmeyer et al. 2002; Bramwell et al. 2002; Rago et al. 2003). Notably all these studies enrolled patients with refractory or relapsed cancers and none selected patients based on transporter expression. VX-710 also required dose reduction for the anticancer agent (Toppmeyer et al. 2002; Rago et al. 2003). This is as close to an ABCG2 inhibitor trial as the field came. The disappointment with P-gp inhibitors led to a halt of almost all such clinical development, although the FDA and industry continued to be interested in the role of ABCG2 and its polymorphic variants in the disposition of substrate drugs (Mao and Unadkat 2015).

Furthermore, this impasse diverted interest in drug transporters to their role in normal tissue protection, including a focus on their role in the blood–brain barrier.

Perhaps time and improving technology will allow a reassessment of the role of drug transporters in cancer drug resistance. The sequencing methodologies employed by The Cancer Genome Atlas (TCGA) also yield gene expression quantitation. The greater sensitivity of this method has allowed detection of *ABCG2* and *ABCB1* in a large number of clinical cancer samples. As shown in Fig. 2a, the range of *ABCG2* expression is over 1000-fold among eight different tumor types shown in the dot plot: breast, pancreas, kidney, liver cancers, and glioblastomas and sarcomas. The range of expression is striking and suggests that for some tumor types the transporter expression may be higher and potentially more important than recently considered. Further, the co-expression with *ABCB1* is very striking in these tumor types, with $r = 0.659$. In Fig. 2b, colorectal cancer samples have been added. Here the correlation has fallen to 0.479 because the colon cancer samples express *ABCB1* more than *ABCG2*. In Fig. 2c, data for glioblastoma and low-grade gliomas are shown. Here a tight correlation between *ABCG2* and *ABCB1* is shown. Interestingly, relative to other tumor types, the level of expression in the glioblastomas is high, with low-grade glioma higher still, perhaps linked to normal tissue expression.

This striking analysis raises several questions. One is whether inhibition of one transporter could ever be enough in tumors that express both pumps (and see the data for murine BBB knockout models below). A second is whether the correlative studies reporting poor outcome with expression of only one transporter may have been reflecting the totality of transporter presence. Note that the question of whether drug transporters impact drug accumulation in tumor tissue has never been satisfactorily answered; studies measuring drug in tumor tissue are generally old and generally show wide interpatient variability. Clinical imaging tools are critically needed to address the question. Asking whether an P-gp/ABCG2 inhibitor could improve outcome was not the right question. Rather, the question that needs to be addressed is whether the presence of drug transporters reduces drug accumulation in tumor tissue. Certainly data shown below, gathered in murine models for normal brain penetration, imply that the P-gp/ABCG2 combination could have a tremendous impact.

The Blood–Brain Barrier

Introduction to the Blood–Brain Barrier

The blood–brain barrier (BBB) is a dynamic network of cells and proteins that regulates the molecular communication between the blood and most of the central nervous system (CNS) (Pardridge 2012). The brain and spinal cord actively adjust
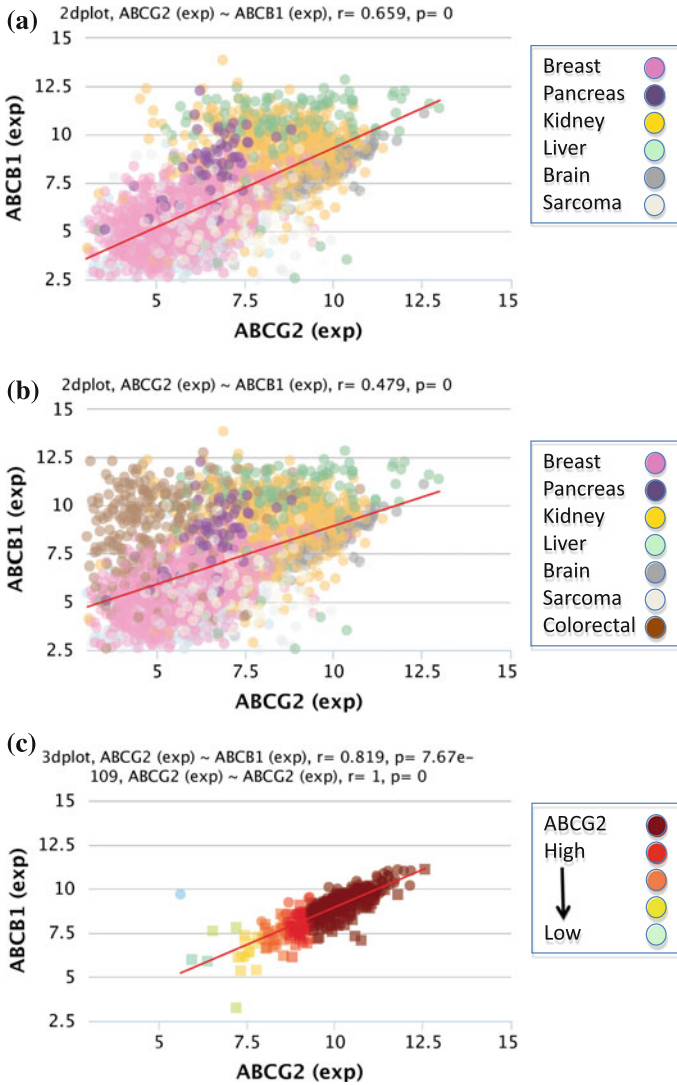
Fig. 2 Expression data for ABCB1 and ABCG2 in tumor samples in the TCGA dataset. **a** Tumor sample expression of *ABCB2* and *ABCB1* in the TCGA dataset is shown, with tissue of origin color-coded. Number of samples from TCGA depicted: breast cancer = 994; pancreatic cancer = 56; kidney cancer = 480; hepatocellular cancer = 134; glioblastoma = 169; sarcoma = 77. **b** Colorectal samples ($n = 233$) shown in addition to the samples depicted in (**a**). **c** Expression data for glioblastoma ($n = 169$, *squares*) and low-grade glioma ($n = 275$, *circles*) are shown; *darker color* represents higher transport expression with highest levels found in low-grade glioma. Data for all three graphs were acquired from CellMiner, courtesy of Rajapakse (2015)

to daily variations of nutritional and oxygen requirements while maintaining the capacity to respond to pathologic alterations in the microenvironment such as increased intracranial pressure and toxic materials in the systemic circulation (Saunders et al. 2014). The BBB presents clinical challenges in the context of vasogenic edema, neuro-imaging, and drug delivery for various pathologic conditions including tumors, epilepsy, and infection (Löscher and Potschka 2005).

A small molecule can traverse a biological barrier in several ways: by passing through the capillary cells by either passive diffusion or facilitated transport (transcellular), by passing between the endothelial cells (paracellular), or by being taken up by the cell (pinocytosis) and across the cell (transcytosis) (Pardridge 2012; Abbott 2013). The BBB protects the brain by regulating and restricting each of the described pathways. Firstly, brain capillary cells form a physical barrier preventing paracellular transport. This is achieved by capillary endothelial cells forming tight junctions via proteins such as the connexins and claudins, and are characterized by the visualization of 'kissing points' via electron microscopy (Bauer et al. 2014). An underlying basement membrane and astrocytic end-feet have also been postulated to provide an additional barrier to permeability, and the maintenance of the BBB architecture has been shown to be regulated by astrocytes and pericytes that are immediately basolateral to the basement membrane (Cabezas et al. 2014; Muoio et al. 2014). Furthermore, BBB sites have fewer pores between the endothelial cells and decreased pinocytic activity compared to peripheral endothelial cells (Georgieva et al. 2014). Therefore, in a normal physiological setting, drug delivery to the brain parenchyma relies primarily on transcytosis, and this is consistent with the observation that for many organic small molecules, brain penetrance positively correlates with the partition coefficient (logP) for those molecules (Levin 1980). However, there are outliers to this relationship. The classic example is D-glucose, whose uptake to the brain is much greater than anticipated based on logP, due to the expression of high-affinity glucose uptake transporters (such as GLUT1) at the apical surface of brain endothelial cells, and carrier-mediated transport is responsible for the uptake of amino acids and other molecules essential for metabolic function (Cornford and Hyman 2005).

The other critical role for the BBB is that of active defense, precluding entry into the brain of unwanted small molecules that are capable of passive diffusion or 'hijacking' passive transporters. This is achieved by the expression of ATP-Binding Cassette (ABC) transporters at the apical surface, primarily the drug transporters ABCG2 and ABCB1 (see next section) (Kannan et al. 2009). Here, transporters can intercept small molecules at the apical cell membrane (often referred to as the 'lipid-membrane vacuum cleaner' model), and efflux them back into the blood plasma against the concentration gradient (Gottesman et al. 2002). Drug metabolizing cytochromes are also expressed in brain endothelial cells, and ABCC1 and ABCC4 are also expressed at the apical surface—these have been associated with the transport of secondary metabolites, such as glutathione conjugates (Cole 2014). These protective processes are highly energy (ATP) dependent, and this is one of the reasons that brain endothelial cells are mitochondria-rich (Hicks et al. 1983). We present a summary of transporters expressed at the BBB in Fig. 3.
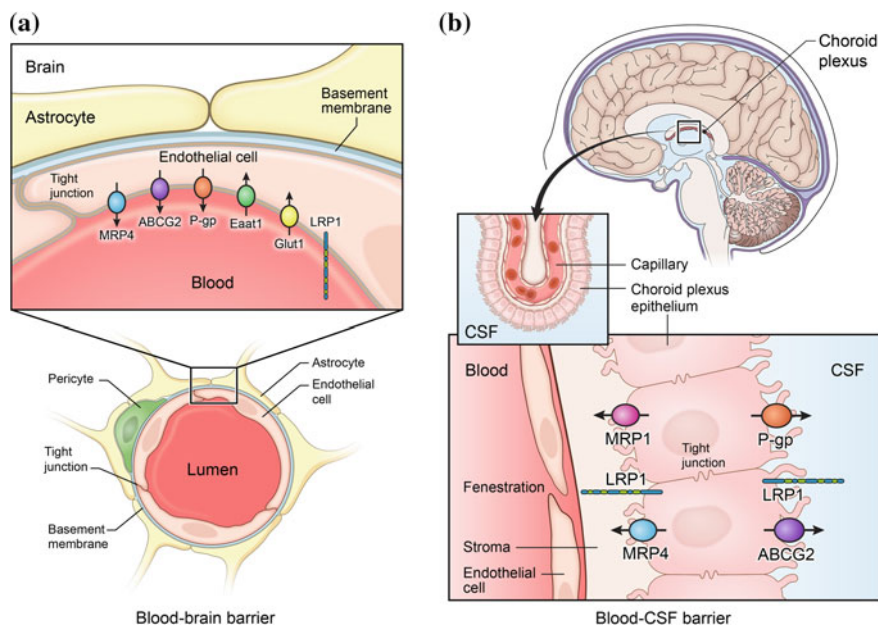
Fig. 3 Schematic representation of **a** the blood-brain barrier and **b** the blood-CSF barrier. The blood-brain barrier (**a**) is formed primarily by brain endothelial cells in capillaries, and is regulated by surrounding pericytes and astrocytes at the basolateral side of the endothelial cells. The endothelial cells form tight junctions, mediated by connexin, occludin and claudin family proteins. At the apical cell surface, ABC transporters such as P-gp (P-glycoprotein, *ABCB1*), ABCG2 (also breast cancer resistance protein) and MRP4 (multidrug resistance protein 4, *ABCC4*) transport small molecules back into the lumen. Ingress of nutrients from the blood supply is mediated by facilitative solute carrier SLC transporters, such as glutamate (excitatory amino acid transporter 1, Eaat1, *SLC1A3*) and D-glucose (glucose uptake transporter 1, Glut1, *SLC2A1*). LRP1 (low-density lipoprotein receptor-related protein 1 receptor, APOER) mediates receptor-mediated transcytosis across brain endothelial cells, and is one of several receptor targets present on the apical side of the BBB being evaluated for brain-targeted therapeutics. Lining the apical surface and projecting into the lumen is the glycocalyx (not shown), composed of glycoprotein and polysaccharide. The blood-CSF barrier (**b**) is distinct from the BBB and exists as part of the choroid plexus, responsible for producing CSF. It is comprised of epithelial cells forming tight junctions, while the endothelial capillary cells that supply nutrients for CSF production are fenestrated, allowing protein access to the choroid plexus epithelium. ABC transporter expression is a matter of some debate, but there appears to be general agreement that MRP (ABCC) transporters are oriented in the epithelium towards the blood, and that P-gp and ABCG2 are oriented towards the CSF. This has led to the hypothesis that the choroid plexus supplies drug to the CSF, and that this is a 'back door' for drug access to the brain parenchyma, and the follow-on conclusion that drug CSF levels are an acceptable surrogate indicator of drug brain concentrations. However, there is now clear evidence that there is a large divergence between brain and CSF levels for most drugs. Figure was prepared with the assistance of Alan Hoofring of NIH Medical Arts and Printing

ABC Transporter Expression at the BBB

Numerous studies have examined the expression of ABC transporters in brain capillary cells. It was recognized very early on that P-glycoprotein was expressed in brain endothelial cells, and ABCG2 expression was reported shortly after the gene itself was identified. The functional contribution of ABCG2 in protecting the BBB has been examined for a range of therapeutics. The most direct insights have been derived from gene knockout mice (see elsewhere in this chapter). For many agents the cross-recognition of substrates by P-gp and ABCG2 indicates a cooperativity in their protective role at the BBB. This is significant given the recognition that a population of humans of the Jr(a) blood group carry two missense copies of ABCG2 and do not express functional ABCG2 protein. Given the lack of reported drug-related adverse neurologic events in these patients, it is likely that redundancy with P-gp minimizes the impact of the loss of ABCG2.

The absolute levels of ABC transporter expression have been assessed, and the work of Terasaki and co-workers will be highlighted here. They have measured the expression of transporters in isolated brain capillary endothelial cells and in cell culture using quantitative liquid chromatography-tandem mass spectrometry (Kamiie et al. 2008). This method allows for measurement of protein levels, usually given as fmol/µg of cellular protein in endothelial cells isolated from brain capillaries of species including mice, monkeys, and humans. Primary findings regarding expression will be conveyed here, along with specific observations related to ABCG2. Assessment is carried out by first isolating brain capillaries from brains of the species of interest, exclusion of large vessels (that are unlikely to be capillaries), and subsequently isolating protein from the resulting capillaries (Ohtsuki et al. 2014).

A summary of expression of ABC transporters is shown in Table 1. It should be noted that ABCG2 is comprised of two functional protein units and as such two protein molecules form one functional transporter, so, for example, 14 fmol/µg ABCG2 protein results in 7 fmol/µg functional ABCG2 protein. Given that the functional capacity of ABC transporters is so high, the functional consequences could be concluded to be irrelevant (the so-called 'spare transporter' effect) (Kalvass and Pollack 2007). In mouse brain capillaries, P-gp (mdr1a, 12–15 fmol/µg protein) expression was higher than Abcg2 (4–5 fmol/µg protein), and MRP4 (ABCC4) was also detectable (Kamiie et al. 2008). The second mouse P-gp, Mdr1b, was not detectable. As a means of comparison, the highest transporter protein expression was for Glut1 (90 fmol/µg protein). Expression in adult and younger cynomolgus monkeys revealed differences from mouse, the primary difference being that ABCG2 expression (14 fmol/µg protein) was higher than P-gp (5–6 fmol/µg protein) (Ito et al. 2011). There was no difference in ABCG2 expression between adult and infant monkeys, though P-gp expression was slightly higher in infants. In Sprague-Dawley and Wistar rats, levels of P-gp (Abcb1, 19 fmol/µg protein) and Abcg2 (2–3 fmol/µg protein) were approximately equivalent between the two breeds, and Abcc4 (MRP4, 1–2 fmol/µg protein) was also detectable (Hoshi et al. 2013). In porcine brain

Table 1 Reported expression levels (fmol/µg) for various ABC efflux transporter proteins in various species

	ABCG2	ABCB1	ABCC4	ABCA2	ABCA8
	Bcrp	P-gp	MRP4		
Human (healthy)	4.1	6.1	0.2	2.9	1.2
Human (diseased)	4.0	3.1	0.3	2.1	0.7
Monkey	7.1	4.7	0.3	NR	NR
Marmoset	8.3	6.5	0.3	NR	NR
Sprague-Dawley rat	2.1	19.0	1.6	NR	NR
Wistar rat	2.9	19.2	1.5	NR	NR
Mouse	2.2	14.1	1.6	ULQ	ULQ
hCMEC/D3 cells	1.1	3.9	0.3	7.2	ULQ

ABCG2/Bcrp values are half that reported, to account for the homodimerization of protein product to form a functional unit

ULQ Under limit of quantification; *NR* Protein not reported/examined

capillaries, BCRP was more highly expressed than P-gp, but comparison with other species is complicated by an alternative analysis technique (Kubo et al. 2015). The expression of fractionated lysate was assessed to determine the localization of transporters toward the luminal (apical) or abluminal (basolateral) fraction (Kubo et al. 2015). P-gp and ABCG2 were almost exclusively located in the luminal fraction, but this does not indicate all transporters are at the cell surface, and a significant portion may be located in recycling endosomal compartments below the apical cell surface. Curiously, the cholesterol transporter ABCA1 was also detectable, but its expression was toward the abluminal surface of capillary cells. It is worth noting that in the above studies multiple other ABC transporters were assessed for expression and were not detectable, such as ABCB5, MRP1-3, ABCG5, and ABCG8 (Ito et al. 2011).

Two studies examining absolute transport protein levels in human brain microvessels have been reported; the first utilizing capillaries from brains of male patients who died of peripheral disease (Uchida et al. 2011), the second from patients with brain pathologies such as epilepsy or glioma (Shawahna et al. 2011). Major challenges in working with human brain samples are the time from death till autopsy, the tissue harvesting protocols employed, and freezer storage time, which are known to generally impact protein expression levels (Hynd et al. 2003; Harrison et al. 1995). In brains without a brain pathology, ABCG2 was more highly expressed (3–11 fmol/µg protein but with less functional protein than P-gp as explained above) than P-gp (4–9 fmol/µg protein) and MRP4 (0.1–0.3 fmol/µg protein). Of note, the lysosomal transporter ABCA2 and the proposed lipid transporter ABCA8 were also detectable (Uchida et al. 2011). Capillaries derived from brain pathologies did not deviate significantly from those of a healthy brain (Shawahna et al. 2011). An informative comparison was made between human brain microvessels and the human brain capillary endothelial cell line hCMEC/D3 (Ohtsuki et al. 2013). Strikingly, P-gp was undetectable in cells, and ABCG2

expression (1–2 fmol/µg protein) was reduced compared with fresh brain microvessels. Furthermore, ABCA2 expression (11 fmol/µg protein) was greater than brain microvessels (2–3 fmol/µg protein), and overall the correlation between primary tissue and cell culture was poor.

A controversial area of study has been that of the expression of ABC transporters in astrocytes, and whether expression occurs in the end-feet processes and is part of the BBB transport capacity. Early immunohistochemical studies of human brain reported that P-gp localized to cells also expressing glial fibrillary acidic protein (GFAP), a marker for astrocytes, but not with the brain endothelial cell marker GLUT1. This led to the hypothesis that transporters are found predominantly at the astrocyte foot processes and not in the endothelial luminal membrane (Golden and Pardridge 2000). Multiple issues arose from this model, that required drug to cross endothelial cells into the brain extracellular fluid before being pushed back across endothelial cells into the vasculature. The observations were critically discussed in the literature (Schinkel 1999), and multiple follow-up studies have demonstrated that high expression of P-gp occurs on the apical surface of capillary cells, with little to no P-gp expression in astrocytes (Loscher and Potschka 2005). Several pathologies associated with neuroinflammation, such as drug-resistant epilepsy, have led to increases in expression of P-gp in astrocytes, but this is not generally proposed to contribute to the barrier function of the neurovascular unit (Loscher and Potschka 2005).

Drug–Transporter Interactions at the BBB

Understanding the role of ABCB1 and ABCG2 at the blood–brain barrier has been aided by the study of brain penetration of various substrate drugs in murine knockout experiments. First, studies were performed in mice in which Abcb1a and Abcb1b had been deleted—the human ABCB1 equivalent. Further exploration demonstrated that when Abcg2 was deleted the effects on drug accumulation in the CNS were modest, but that when both were deleted there could be markedly greater brain penetration of substrates. Recently a study went one further step, deleting Abcc4 as well and evaluating topotecan brain accumulation (Lin et al. 2013). This was important because ABCC4 is a multidrug transporter also expressed at the blood–brain barrier. The studies demonstrated the additive effect of ABCC4 together with P-gp and ABCG2 in restricting brain penetration. The heat map in Fig. 4 depicts the results with the double knockout, *Abcb1a/b* and *Abcg2*, and shows how neither knockout alone has a major impact on the accumulation of most substrates, *but that together the impact is clinically important and statistically significant for most substrates.*
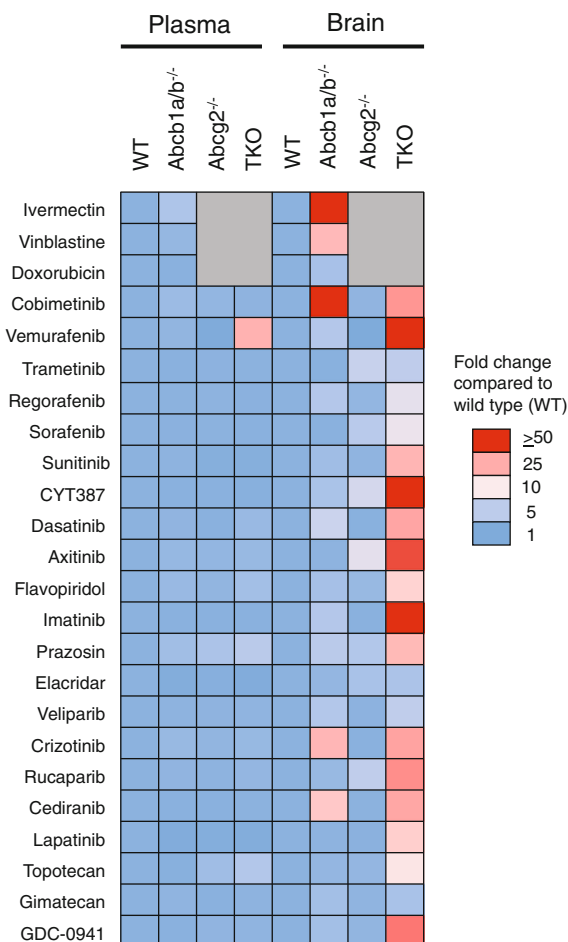
Fig. 4 Role of ABCG2 and ABCB1 in plasma or brain concentrations of chemotherapy drugs. Values shown are fold increase compared to wild-type mice, regardless of the parameter examined. Inspection of the heat map indicates that transporter knockout (in the murine model) seldom affects pharmacokinetics, and single transporter knockout seldom affects brain penetration. But double knockout has a marked effect on the brain accumulation of substrates. Data abstracted and calculated from references—using absolute concentrations where possible, to calculate fold change over wild-type (Lin et al. 2013; Schinkel et al. 1994; van Asperen et al. 1999; Choo et al. 2014; Mittapalli et al. 2012; Vaidhyanathan et al. 2014; Kort et al. 2015; Lagas et al. 2010; Oberoi et al. 2013; Durmus et al. 2013; Chen et al. 2009; Poller et al. 2011; Zhou et al. 2009; Sane et al. 2013; Lin et al. 2014; Chuan Tang et al. 2014; Durmus et al. 2015; Wang et al. 2012; Polli et al. 2009; de Vries et al. 2007; Salphati et al. 2010)

Brain Metastases and Tumor Vasculature

One area still in need of investigation is that of expression of ABCG2 and P-gp in brain tumors and brain metastases. The blood–brain barrier becomes partially disrupted in patients with both glioblastomas and brain metastases from different solid tumors. This is readily demonstrated by the MRI visualization of gadolinium contrast agent, which represents the leakage of gadolinium into the tumor. This leakage has caused some investigators to conclude there is no blood–brain barrier left in individuals with these malignancies. However, a careful observation shows that certain areas of tumors are enhanced with contrast while others are not; just as certain drugs work better than others in treating malignancies involving the CNS. The best evidence suggests that some components of the BBB remain (endothelial cells, astrocytes, basal lamina, pericytes, etc.) and contribute to the multidrug resistance seen in malignant disease in the CNS. This evidence has been gathered by studying drug concentrations in metastatic lesions in the brain in preclinical models, and reinforced by clinical studies. In brain metastases derived from MDA-MB-231 cells in nude mice, a range of paclitaxel concentrations was detected, from 22 ng/g—approximating normal brain at 14 ng/g—to 1400 ng/g, and everything in between (Lockman et al. 2010). Only 15 % of tumors had levels at the low end approximating normal brain, while 10 % of tumors had levels at the highest end, still far below the 10,000 range measured in systemic metastases. These data convincingly show that the vestiges of the BBB remain in intracranial metastases, and explain why the occasional patient shows a marked and unexpected response with an agent not thought to cross the blood–brain barrier. A recent clinical study suggested a similar range of drug penetration in metastases from patients (Morikawa et al. 2015). Levels of lapatinib varied from 1.0 to 6.5 µM and capecitabine from 0.12 to 1.97 µM. Together, these data suggest that the blood–brain barrier is leaky and aberrant in individuals with brain tumors, and the regulation of the ABC transporters in that setting not really known.

Prospects for Transporter Inhibition at the BBB

The question then becomes whether we could improve cancer therapy in the CNS by combining therapy with an efflux inhibitor. Certainly an efflux inhibitor would be most valuable when the blood–brain barrier is still intact—at a time when preventing the early development of CNS metastases would be most likely to succeed. Such a prevention strategy has been successfully explored in animal models (Palmieri et al. 2014).

Drug delivery to the CNS represents a major challenge for chemotherapeutics due to the existence of efflux transporters such as P-gp and ABCG2 at the BBB that affect drug distribution. Studies have shown that these two transporters function in concert, or even synergistically (Zhou et al. 2009). A rational approach is the

deliberate modulation of these transporters to mediate the permeability of substrates across the BBB (the "modulation of efflux" approach). However, it has also been suggested that clinical inhibition of P-gp and ABCG2 function at the BBB may not be pharmacologically achievable (Kalvass et al. 2013).

Development of approaches to successfully modulate ABCG2 activity at the BBB depends largely on improving and validating reliable BBB models for extrapolation of rodent data to humans. First, the overlapping substrate and inhibitor specificity of human and mouse ABCG2 supports the use of mouse models to evaluate the clinical, physiological, and pharmacological roles of ABCG2, especially at the BBB (Bakhsheshian et al. 2013b). Second, ABCG2 levels are reported to be similar (less than twofold difference) between murine and human BBB (Uchida et al. 2011). Third, any model must take into account the overlapping substrate specificity of ABCG2 and ABCB1 and ABCC4, all at the BBB. A recent study identified D-luciferin as a specific probe for bioluminescence imaging of ABCG2 function in vivo at the BBB (Bakhsheshian et al. 2013a). This novel method will allow for better understanding of the kinetics of transporter activity at the BBB. The study further demonstrated that ABCG2 plays a role in limiting the biodistribution of a specific substrate, and the possibility for saturable transporter inhibition at the BBB using pharmacologic levels of inhibitor, which was not possible before for ABCG2. Such tools will aid drug discovery studies with novel modulators of the transporter and/or new methods to increase drug delivery to the brain.

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