Chapter 2
Clinical Relevance of Multidrug-Resistance-Proteins (MRPs) for Anticancer Drug Resistance and Prognosis

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Abstract Chemoresistance in cancer is frequently associated with elevated levels of multidrug transporters. While P-glycoprotein is the best known, the majority of multidrug transporters belong to the Multidrug Resistance Protein (MRP) family, also known as the ABCC family, which includes MRP1–9. These proteins are typically found in the plasma membrane of cells, where they efflux a broad range of both physiological substrates and xenobiotics, including anticancer drugs. Consistent with the removal of chemotherapeutics from the cancer cell, high expression of several MRPs has been linked to poorer outcome in a variety of cancer types, suggesting these proteins represent targets for therapy. In this review we will describe the range of reported substrates for MRP1–9 in vitro, discuss associations between the MRP family and patient outcome, and investigate the evidence that MRP family members contribute directly to drug resistance based on in vivo models and patient data. We will also discuss the value of MRP expression as a prognostic marker and its potential role in selecting treatment protocols and examine existing and novel strategies to target MRPs.

Keywords Cancer • MRP • ABCC • Multidrug resistance • Chemotherapy

Abbreviations

ABC	ATP binding cassette
ABCC	ATP binding cassette sub-family C
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia

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BCRP/ABCG2	Breast cancer resistance protein
CSC	Cancer stem-like cell
CLL	Chronic lymphoblastic leukaemia
ESCC	Esophageal squamous cell carcinoma
EFS	Event-free survival
ESFT	Ewing's sarcoma family of tumours
GSH	Glutathione
HER2	Human epidermal growth factor receptor 2
MDR	Multi-drug resistance
miRNA	MicroRNA
MRP	Multidrug resistance protein
NSCLC	Non-small cell lung cancer
OS	Overall survival
P-gp	P-glycoprotein
RNAi	RNA interference
SCLC	Small cell lung cancer
shRNA	Short hairpin RNA
siRNA	Small interfering RNA
SNPs	Single nucleotide polymorphisms

2.1 Introduction

The net uptake of drugs into cells is regulated by both import and export mechanisms, with the latter commonly mediated by ABC transporters. Not surprisingly, elevated levels of ABC transporters are frequently observed in cancer cells compared to their normal counterparts and the role of ABC transporters in chemoresistance has been an area of major research interest more than three decades. P-glycoprotein (P-gp, MDR1, ABCB1) stands out for conferring the most extensive resistance to the broadest range of compounds [152] and has received by far the most attention, followed by the Breast Cancer Resistance Protein (BCRP, ABCG2). However, at least a dozen other family members have been demonstrated to efflux chemotherapeutics and mediate chemoresistance in vitro, the majority of which belong to the ABCC subfamily, commonly referred to as the Multidrug Resistance Protein (MRP) family. For the majority of MRP family members, the ability to confer drug resistance in vitro is well established, and a large number of reports describe associations between their expression in tumours and patient outcome. To date, however, compelling evidence for a clinically relevant role in multidrug resistance is very limited. This chapter will examine the ability of MRPs to efflux chemotherapeutics in vitro, the available evidence for their importance in clinical drug resistance and mediating therapeutic responses, their potential prognostic value, and possible approaches to more clearly define their roles.

2.2 The ABCC/MRP Subfamily

The ABCC (or MRP) subfamily of ABC transporters consists of 12 members, 9 of which function as energy-dependent transporters, including MRP1–6 (ABCC1–6) and MRP7–9 (ABCC10–12). The remaining members of the ABCC subfamily, CFTR (ABCC7), SUR1 (ABCC8) and SUR2 (ABCC9), are either ion channels or ion channel regulators. The MRPs are often further subdivided into the short MRPs (MRP4, MRP5, MRP8, MRP9), which contain two membrane-spanning domains and two nucleotide binding domains, and the long MRPs (MRP1, MRP2, MRP3, MRP6, MRP7), which contain an additional *N*-terminal membrane-spanning domain. The long MRPs are mostly closely related to MRP1, with 46, 56 and 45 % identity for MRP2, MRP3 and MRP6, respectively, although the identity of MRP7 to long and short MRPs is comparable [35, 142]. The short MRPs are also generally more closely related, with MRP5 and MRP8 exhibiting 42 and 46 % identity with MRP9, while MRP4 is less closely related (31 %) [142]. For more detailed discussion of the structure and evolutionary relationships between family members, the reader is referred to previous comprehensive reviews [33, 35, 142]. Of the MRPs, all except MRP9 [118] have been shown to efflux chemotherapeutics and, therefore, have the potential to contribute to drug resistance in cancer. Drugs established as MRP substrates are listed in Table 2.1. As with P-gp and ABCG2, transporters of the MRP family are also present in a range of pharmacological barriers including in the gastrointestinal tract, the blood–brain barrier and the proximal tubules of the kidney where they contribute to the vectorial transport of their substrates [153]. Consequently, they are key contributors to the absorption, distribution and elimination of cancer drugs. Table 2.2 lists the localisation of MRP family members in different pharmacological barriers and cell types.

2.3 Specificity of MRPs for Chemotherapeutic Agents

A variety of compounds with differing mechanisms of action have been identified as MRP substrates (Table 2.1), ranging from traditional DNA damaging cytotoxics (doxorubicin) to antifolates (methotrexate) and microtubule damaging agents (vincristine). In contrast to P-gp, which effluxes unmodified neutral and positively charged hydrophobic drugs, members of the MRP family also efflux a range organic anions and drugs modified by Phase II metabolism, including glutathione (GSH), glucuronide and sulphate conjugates, or (in the case of MRP1) efflux some drugs in a GSH-dependent manner. There is significant overlap in the substrate profiles of the family members, particularly within the long and short MRP subfamilies. Each of the long MRPs, for instance, effluxes etoposide (Table 2.1), while each of the short MRPs effluxes nucleoside analogues. Interestingly, MRP7, which has comparable sequence identity to both short and long MRPs, effluxes both these drug classes.

To date there are few examples of targeted agents as substrates of MRP family members. Sorafenib was shown to be an MRP2 substrate [141] while sunitinib has

Table 2.1 Anticancer substrates of MRP1–9

	Class	Drug	Experimental method	References
MRP1	Alkylating agents	Chlorambucil (GSH conjugate)	Stable transfectant	[5, 104]
		Melphalan (GSH conjugate)	Membrane vesicles	[5, 69]
	Anthracenedione	Mitoxantrone	Drug-resistant cell line	[14, 105, 143]
			Membrane vesicles	
			Stable transfectant	
	Anthracyclines	Daunorubicin (GSH conjugate)	Drug-resistant cell line	[14, 27, 128, 126]
			Knockout cell line	
			Stable transfectant	
		Doxorubicin (GSH conjugate)	Drug-resistant cell line	[14, 27, 52, 128, 126]
			Knockout cell line	
			Stable transfectant	
		Epirubicin	Stable transfectant	[27]
	Antifolates	Methotrexate	Membrane vesicles	[61]
			Stable transfectant	
		ZD1694	Stable transfectant	[61]
	Arsenic-based	Arsenate (conversion to arsenite)	Stable transfectant	[27, 93, 128]
			Knockout cell line	
		Arsenite (GSH conjugate)	Knockout cell line	[27, 93, 128]
			Stable transfectant	
	Epipodophyllotoxins	Etoposide (glucuronide conjugate; stimulated by GSH)	Drug-resistant cell line	[14, 27, 52, 128, 69, 133]
			Membrane vesicles	
			Knockout cell line	
			Stable transfectant	
		Teniposide	Knockout cell line	[128]
	Camptothecins	Irinotecan	Drug-selected cells	[23, 150]
		SN-38	Drug-selected cells	[23, 150]
			Membrane vesicles	
	Microtubule damaging	Colchicine	Drug-selected cells	[27, 75, 78]
			Stable transfectant	
	Taxane	Taxol	Stable transfectant	[27]
	Vinca alkaloids	Vinblastine	Drug-resistant cell line	[14, 27, 52]
			Stable transfectant	
		Vincristine (GSH co-transport)	Drug-resistant cell line	[14, 27, 52, 99, 128]
			Knockout cell line	
			Stable transfectant	

(continued)

Table 2.1 (continued)

	Class	Drug	Experimental method	References
MRP2	Anthracyclines	Doxorubicin	Stable transfectant	[31, 77]
		Epirubicin	Stable transfectant	[31]
	Antifolates	GW1843	Stable transfectant	[61]
		Methotrexate	Membrane vesicles	[4, 61]
			Stable transfectant	
		ZD1694	Stable transfectant	[61]
	Arsenic oxoanion	Arsenite	Stable transfectant	[37, 93]
	Camptothecins	Irinotecan	Animal studies	[22]
		SN-38	Animal studies	[22]
	Epipodophyllotoxins	Etoposide (stimulated by GSH)	Stable transfectant	[31]
	Platinum-containing	Cisplatin (GSH dependent)	Stable transfectant	[31, 77]
	Taxanes	Docetaxel	Stable transfectant	[67]
		Paclitaxel	Stable transfectant	[67]
	Vinca alkaloid	Vinblastine (stimulated by GSH)	Stable transfectant	[42, 158]
		Vincristine (stimulated by GSH)	Stable transfectant	[31, 77]
MRP3	Antifolates	Methotrexate	Stable transfectant	[81]
	Epipodophyllotoxins	Etoposide	Membrane vesicles	[81, 173]
			Stable transfectant	
		Teniposide	Stable transfectant	[81]
	Vinca alkaloid	Vincristine	Stable transfectant	[175]
MRP4	Alkylating agent	Cyclophosphamide	Stable transfectant	[156]
	Camptothecins	10-hydroxy-camptothecin	Stable transfectant	[156]
		Irinotecan	Stable transfectant	[114, 156]
		Rubitecan	Stable transfectant	[156]
		SN-38	Stable transfectant	[114, 156]
	Purine analogues	6-mercaptopurine, Azathioprine	Stable transfectant	[20]
		6-thioguanine	Stable transfectant	[20]
		Methotrexate	Stable transfectant	[89, 156]
MRP5	Anthracyclines	Doxorubicin	Stable transfectant	[125]
	Antifolates	Methotrexate	Membrane vesicles	[125, 165]
			Stable transfectant	
		Pemetrexed	Stable transfectant	[125]
	Platinum-based	Cisplatin	Stable transfectant	[125]
		Oxaliplatin	Stable transfectant	[125]
	Purine analogues	5-fluorouracil, 5′-deoxy-5′-fluoridine	Membrane vesicles	[125]
			Stable transfectant	
		Azathioprine, 6-mercaptopurine	Stable transfectant	[168]
		6-thioguanine	Stable transfectant	[125, 168]

(continued)

Table 2.1 (continued)

	Class	Drug	Experimental method	References
MRP6	Actinomycines	Actinomycin D	Stable transfectant	[9]
	Anthracyclines	Daunorubicin	Stable transfectant	[9]
		Doxorubicin	Stable transfectant	[9]
	Epipodophyllotoxins	Etoposide	Stable transfectant	[9]
		Teniposide	Stable transfectant	[9]
	Platinum-containing	Cisplatin	Stable transfectant	[9]
MRP7	Anthracyclines	Daunorubicin	Stable transfectant	[63]
	Camptothecins	SN-38	Stable transfectant	[63]
	Epipodophyllotoxins	Etoposide	Stable transfectant	[63]
	Epothilones	Epothilone B	Stable transfectant	[63]
	Platinum-containing	Cisplatin	Stable transfectant	[151]
	Pyrimidine analogues	Cytarabine	Animal studies	[62, 63]
			Stable transfectant	
		Gemcitabine	Stable transfectant	[63]
	Taxanes	Docetaxel	Stable transfectant	[62, 63]
		Paclitaxel	Stable transfectant	[62, 63]
	Vinca alkaloids	Vincristine	Stable transfectant	[62, 63]
		Vinblastine	Stable transfectant	[62]
		Vinorelbine	Drug selected cells	[13]
MRP8	Antifolates	Methotrexate	Stable transfectant	[21]
	Purine analogues	5-fluorouracil	Stable transfectant	[53]

Stable transfectant: cells transfected with vector containing specific MRP construct, resulting in specific overexpression of the MRP
Membrane vesicles: inside out membrane vesicles prepared from cell lines, with uptake of substrates into vesicles determined
Drug-resistant cell line: cell line selected for high transporter expression in vitro by continuous culture in the presence of a cytotoxic agent
Knockout cell line: cells derived from knockout mice lacking a particular transporter, or cells expressing an RNAi construct targeting a transporter
Animal studies: studies performed in whole animals

been identified as a weak substrate of MRP4 [66]. However, since a range of tyrosine kinase inhibitors has been identified as MRP inhibitors, including imatinib, nilotinib and cediranib (MRP1 inhibitors [38, 58, 155]) and lapatanib, erlotinib and masatinib (MRP7 inhibitors [72, 85]), it remains possible that some of these agents may be MRP substrates.

While the list of established substrates for MRP family members is quite extensive, it should be recognised that the majority of these were determined to be substrates using cell lines selected for high transporter expression in vitro by continuously culturing in the presence of a cytotoxic drug, cell lines overexpressing individual transporters or as "inside-out vesicles" derived from these cell lines [50]. These systems, while often well controlled, do not necessarily reflect typical endogenous transporter expression levels. Furthermore, transport of a substrate in vitro does not necessarily imply physiological relevance in vivo, with the latter dependent on both the affinity of the substrate for the transporter and the achievable concentration of the substrate

Table 2.2 Localisation of MRP family members relevant to drug disposition

	Pharmacological barrier/cell	Cellular localization	References
MRP1	Blood–brain barrier	Apical (luminal)	[149, 177]
	Blood–cerebrospinal fluid barrier	Basolateral	[127]
	Blood–testis barrier	Basolateral	[157]
	Placenta	Apical	[146]
	Bronchial epithelium	Basolateral	[137]
MRP2	Intestinal epithelium	Apical (luminal)	[48]
	Hepatocytes	Apical (canalicular)	[15, 122]
	Kidney proximal tubules	Apical (luminal)	[136]
MRP3	Intestinal epithelium	Basolateral	[138]
	Hepatocytes	Basolateral (sinusoidal)	[79]
MRP4	Hepatocytes	Basolateral (sinusoidal)	[129]
	Blood–brain barrier	Apical (luminal)	[90, 109, 177]
	Blood–cerebrospinal fluid barrier	Basolateral	[90]
	Kidney proximal tubules	Apical (luminal)	[159]
MRP5	Blood–brain barrier	Apical (luminal)	[109, 177]
MRP6	Hepatocytes	Basolateral (sinusoidal)	[102]
	Kidney proximal tubules	Basolateral	[51, 139]

in vivo. Furthermore, the transport of some substrates is dependent on or modulated by endogenous molecules, as exemplified by the glutathione dependence of both doxorubicin and vincristine transport by MRP1 [14, 27, 52, 128, 99] (Table 2.1). Validation of drugs as transporter substrates using MRP knockout mice has the potential to be informative, although care is required with the interpretation of these data as the affinity of some MRP substrates varies markedly between the mouse and human transporters. Human MRP1, for example, confers resistance to anthracyclines, whereas mouse MRP1 does not [147], while cGMP has a very low affinity for mouse MRP4 compared to human MRP4 [32]. On the other hand, Mrp1$^{-/-}$ mice show increased sensitivity to etoposide [100, 166], Mrp2$^{-/-}$ mice show elevated plasma methotrexate, Mrp4$^{-/-}$ mice have higher levels of plasma and cerebrospinal fluid topotecan [90] and Mrp7$^{-/-}$ mice are more sensitive to paclitaxel [64], these findings validated these drugs as physiologically relevant substrates of their respective transporters.

2.4 Association of MRPs With Cancer Survival

2.4.1 MRP1

MRP1 was the first of the family to be identified [26] and as a result, it has been the focus of the majority of clinical and in vitro studies. MRP1 expression has been reported in a variety of cancer types, including chronic lymphoblastic leukaemia (CLL) [111], non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [12], prostate cancer [160], gastric carcinoma [41], esophageal squamous cell

carcinoma (ESCC) [112], colorectal cancer [46], endometrial carcinoma [82], glioma [1], retinoblastoma [19], acute myeloid leukaemia (AML) [91], acute lymphoblastic leukaemia (ALL) [7], breast cancer [44], Ewing's Sarcoma Family of Tumours (ESFT) [131] and neuroblastoma [55, 113]. The presence of MRP1 in this broad range of adult and childhood cancer tissues is consistent with the hypothesis that MRP1 may have an important role in cancer biology. Supporting this, MRP1 expression has been associated with the time to a first event (event-free survival, EFS) and overall survival (OS). More specifically, MRP1 mRNA expression has been linked with poor survival rates in NSCLC [95, 96], neuroblastoma [55, 113], childhood and adult AML [134] and ALL [40, 124]. Similarly, protein expression of this ABC transporter has been linked with an adverse outcome in both adult breast cancer [44] and nasopharyngeal carcinoma [87] and childhood cancers (ESFT; [131]). In contrast, although expressed, MRP1 protein levels have been reported as showing no association with EFS in breast cancer [17], ovarian carcinomas [68] and ALL [148] or OS in AML [43].

Consistent with increased ABC transporter protein expression as a mechanism by which cells develop multidrug resistance, MRP1 mRNA and protein expression have been identified as increased in post-treatment and metastatic samples compared to normal and diagnosis tissues, respectively, in a variety of solid tumours [1, 19, 80]. Similarly, MRP1 expression has been linked with adverse tumour grade in primary epithelial ovarian carcinoma [3]. Taken together, these data suggest a role for MRP1 in the progression of cells from a normal to a malignant phenotype. However, despite this, very few studies have described a significant link between MRP1 expression and patient response to therapy [12, 65, 68, 119], although this likely reflects the complexity of the chemotherapeutic response in patients.

2.4.2 MRP2

Similar to studies investigating MRP1, both MRP2 protein and mRNA expression have been reported as predictive of a worse OS in oesophageal squamous cell carcinoma [172], gall bladder carcinoma [74], breast cancer [101], NSCLC [45], AML [145], and adult and child ALL [124]. An association with a shorter EFS in breast cancer [101] and both adult and child ALL [124] has also been reported. Furthermore, MRP2 also appears to be involved in the response of cells to therapy. For example, in oesophageal squamous cell carcinoma tumour samples, MRP2 mRNA and protein expressions were increased after treatment with MRP2 substrates [172].

2.4.3 MRP3

Unlike MRP1 and MRP2, the prognostic significance of MRP3 expression at the protein level is yet to be evaluated. However, increased mRNA expression levels have been linked to a poor OS and EFS in ALL [124, 145], AML [145] and

pancreatic carcinoma [80]. In contrast, high MRP3 mRNA has been correlated with better outcome in neuroblastoma [59].

2.4.4 MRP4

Although MRP4 expression in cancer has been described [124, 145], studies investigating the clinical relevance of MRP4 are limited and inconsistent. Although a correlation between high MRP4 expression and poor patient survival has been described in epithelial ovarian carcinoma [3] and neuroblastoma [114], low MRP4 protein expression in prostate cancer was linked to a worse EFS and prostate-specific Gleason score [103]. Interestingly, MRP4 expression has been shown to be significantly higher in colorectal and pancreatic carcinoma tumour specimens compared with normal tissue [60], and in polyps from *ApcMin*/+ mice compared with normal mucosa [60, 80], consistent with a role in tumour development. Furthermore, *Abcc4* deficiency reduces systemic exposure to oral Dasatinib [49], possibly through reducing oral absorption.

2.4.5 MRP5

A correlation between MRP5 mRNA expression and both overall and EFS has been described in adult and child ALL [124] and, consistent with a causative role in cancer development, mRNA is increased in pancreatic carcinoma compared to normal tissue [80] and in lung cancer patients exposed to platinum drugs [117]. However, no association between MRP5 mRNA levels and patient survival was described in AML [145], suggesting the role of MRP5 is not consistent across all cancer types.

2.4.6 MRP6

To our knowledge only one study has evaluated MRP6 expression in cancer tissues; MRP6 mRNA was expressed in 98 % of ALL patients and was predictive of EFS and OS in both adult and child ALL [124], suggesting a role in the biology of ALL. However, since MRP6 overexpression induced only low-level resistance to chemotherapeutics in vitro (less than threefold increase in IC_{50} [9]), its ability to contribute to chemoresistance in vivo would seem limited.

2.4.7 MRP7

Although MRP7 has been well characterised in vitro (Table 2.1; [62, 63]), the prognostic significance of this protein is yet to be investigated. However, incubation with MRP7 substrates increased expression of the transporter in NSCLC [13] and in

salivary gland adenocarcinoma [106] cell lines, and MRP7 expression was inversely correlated with paclitaxel sensitivity in 17 non-small cell lung cancer (NSCLC) cell lines [117], suggesting MRP7 is important for the response of cells to specific substrates in cancer.

2.4.8 MRP8

The prognostic significance of MRP8 has been examined exclusively in breast cancer and the data are conflicting. Although MRP8 has been associated with a poor prognosis in all subtypes except luminal A [171], mRNA and protein expression were decreased in cancer compared to normal breast tissue [144]. In addition, SNPs within MRP8 have also been linked with cancer risk in 270 Japanese patients [120] but this association was not observed in European cohorts [8, 86]. Therefore, it is likely that MRP8 is similar to MRP3 and MRP6, since despite an association with patient survival in some cases, there is no clear evidence that MRP8 has a specific role in cancer development or the response of cancer cells to therapy.

2.5 Validation of Multidrug Resistance Proteins as Therapeutic Targets

Despite the multitude of clinical correlations between the expression of MRP family members and outcome, evidence of a causative link between MRP expression and clinical multidrug resistance is largely absent. A number of factors contribute to the difficulty of establishing causality subsequent to validation as a therapeutic target. Firstly, drug resistance in the clinic is frequently multifactorial. In additional to enhanced drug efflux, which may be mediated by multiple transporters, alterations in the ability of cancer cells to take up drugs, and alterations affecting the ability of drugs to kill cells, including increased drug metabolism activity, increased DNA repair capacity, alterations to the cell cycle, and increased resistance to apoptosis, can all contribute to multidrug resistance. Secondly, many of the clinical correlations described above have been determined in the context of combination chemotherapy that may include both substrates and non-substrates for a given transporter. Thirdly, the cohorts examined frequently contain multiple cancer subtypes and/or consist of patients treated under differing chemotherapeutic protocols, and have been conducted retrospectively rather than prospectively, or have been conducted solely with diagnosis samples with no measure of MRP expression at relapse. Finally, few if any of the studies described above have been able to account for the possibility of tumour heterogeneity, which may limit the ability to detect MRP expression in the tumour cell subpopulations that allow relapse [148]. This consideration is also relevant for cancer stem-like cell (CSC) populations, which express a variety of ABC transporters [34, 73, 178, 135], that may allow them to remain viable after therapy, leading to re-population of the tumour and patient relapse.

In the absence of compelling clinical data, the knockout of MRPs in genetically modified mouse cancer models can provide opportunities to formally assess their role in drug resistance. Mice deficient in MRP1 [100, 167], MRP2 [24, 108, 161], MRP3 [10, 174], MRP4 [11, 90, 98], MRP5 [32], MRP6 [51, 76] and MRP7 [64] have all been previously described, however to date, only the MRP1 knockout mouse has been crossed to a genetic cancer mouse model. In these experiments, the TH-MYCN mouse, a clinically relevant model of the paediatric solid tumour neuroblastoma [164] was crossed with an Mrp1 knockout ($Mrp1^{-/-}$) mouse [18]. To examine tumour intrinsic effects, as opposed to pharmacokinetic effects, tumours were harvested from $Mrp1^{+/+}$ or $Mrp1^{-/-}$ mice and engrafted into secondary recipients. In tumours lacking Mrp1, the response to the MRP1 substrates vincristine and etoposide was significantly enhanced, with a two to threefold delay in tumour growth, while response to cisplatin and cyclophosphamide, neither of which are effluxed by MRP1, was unaffected by MRP1 status [18]. These data provide direct evidence that MRP1 mediates chemoresistance in vivo. Comparable approaches may be of value for determining the role of other MRPs in chemoresistance, although as mentioned in Sect. 2.3 above, the affinity of some MRP substrates varies markedly between the mouse and human transporters, limiting the ability to extrapolate to humans.

2.6 Can Knowledge of MRP Expression Improve Patient Outcome?

2.6.1 MRP Expression as a Marker of Patient Prognosis

While MRP expression in tumours is frequently associated with outcome, it is less clear whether their expression has additional prognostic value beyond standard predictors of outcome. In breast cancer and ovarian cancer, where histological subtypes are more clearly defined, MRP expression appears to correlate with a more aggressive phenotype. MRP1 was more frequently expressed in both high-risk resistant triple-negative (Human Epidermal Growth Factor Receptor 2 (HER2), oestrogen and progesterone receptor negative) breast cancer [171] and stage 1C endometrial carcinoma [82] than in other subtypes. Furthermore, expression of MRP1 predicted a worse OS in these groups [82, 171], consistent with the classical markers of adverse prognosis in these subtypes [30, 36]. Similarly, MRP8 was more common in HER2 enriched and luminal A subtypes, where it predicts an adverse outcome [171], consistent with the poor survival associated with these patient groups [57]. Furthermore, increased MRP2 mRNA expression has been linked with poor survival in oestrogen receptor negative patients [101] which is linked to an adverse survival compared to receptor positive patients [39]. Therefore, since increased MRP expression identifies a similar population to that of the current well-established markers of patient outcome in breast and ovarian cancer, a role for MRP expression in improving patient prognosis in this scenario is unclear. However, more generally, while associations between MRP expression and clinical outcome have been frequently described, only relatively few studies have addressed whether MRP

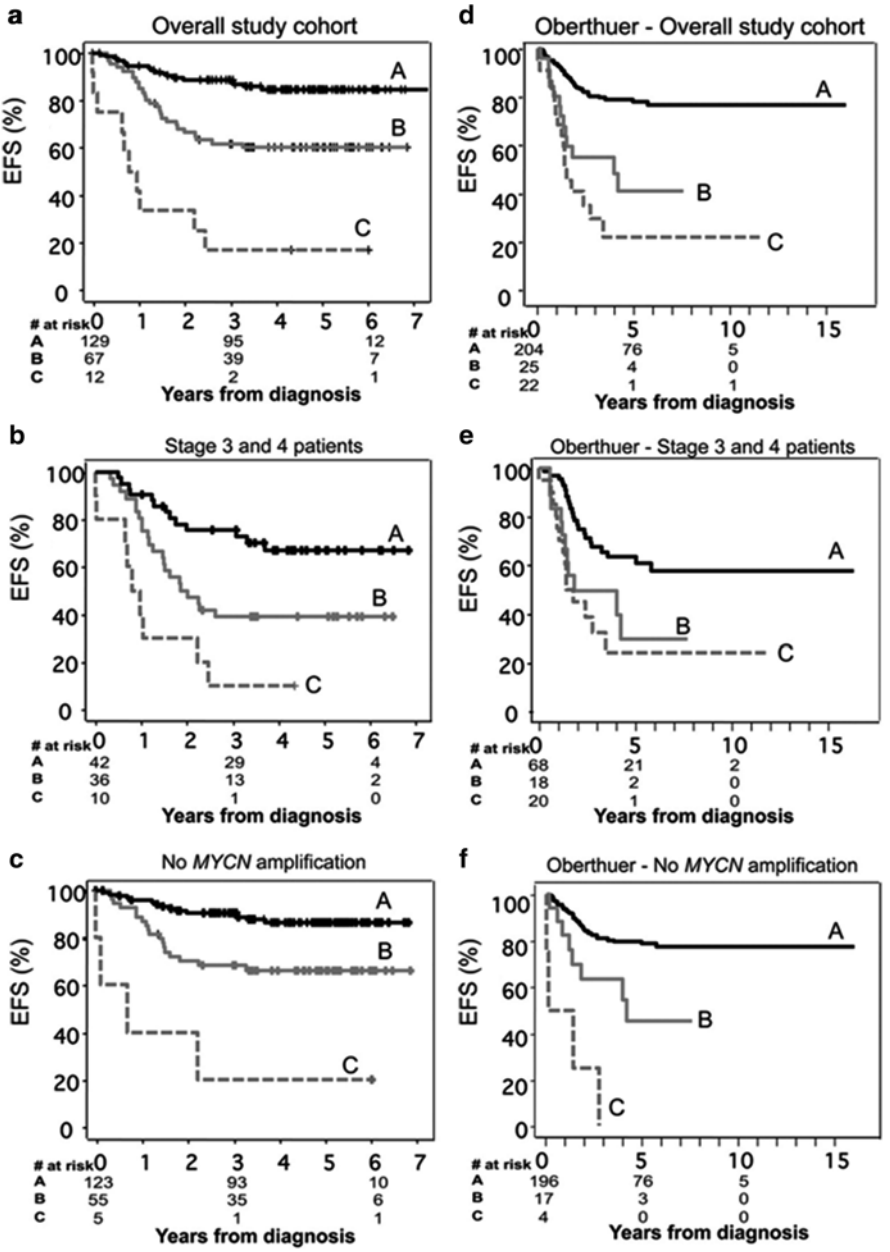

Fig. 2.1 Prognostic significance of ABCC gene expression in neuroblastoma. (**a**) Combined expression of the ABCC1, ABCC3 and ABCC4 genes and cumulative event-free survival (EFS) in 209 patients with neuroblastoma. Patients were categorized into eight clusters on the basis of their combined ABCC1, ABCC3, and ABCC4 expression pattern. Kaplan–Meier survival analysis of these clusters revealed three statistically distinct groupings (Groups A, B, and C), which were associated with the risk of relapse associated with individual ABCC gene expression. Group A

expression is informative independent of established predictors of outcome [3, 87, 95, 114, 134]. The prognostic value of the MRP family, therefore, remains to be firmly established in any cancer, at least at the level of a single gene. It is possible, however, that the combined expression of several MRPs may be of prognostic value. The combined expression of MRP1 (ABCC1), MRP3 (ABCC3), and MRP4 (ABCC4) stratified neuroblastoma patients into groups having excellent, intermediate, or poor outcome (Fig. 2.1), and is one of the most powerful independent prognostic markers yet identified for this disease [59].

2.6.2 MRP Expression as a Method to Stratify Patients for Therapy

If we assume that an MRP family member contributes to response to therapy, expression of that MRP might be exploited to select more effective therapeutic options. For instance, patients with high expression of MRP may be treated with a non-MRP substrate chemotherapeutic, thereby avoiding the resistance generated by efflux of the agent.

In addition to expression at the protein and mRNA levels, specific single nucleotide polymorphisms (SNPs) in genes of the MRP family (particularly MRP1) have also been associated with patient survival [2, 16, 154, 121] and response to therapy [154, 163], including alterations in drug plasma levels [2], response to exogenous and endogenous substrates [28, 29, 94, 84], and increased chemotherapy-induced side effects (cardiotoxicity) [84, 140, 169, 162]. Therefore, similar to the basic expression of MRPs in cancer, it would be advantageous to stratify patients with a SNP conferring a more aggressive phenotype, to more extensive therapy, and/or include those substrates unaffected by the expression of a specific SNP. However, as we have described, the response of cells to chemotherapy is dependent on multiple factors and so it is unlikely that the use of a non-MRP substrate in patient treatment would completely bypass the resistance of tumours to therapy.

Fig. 2.1 (continued) included only those patients whose tumours displayed low levels of ABCC1 and ABCC4 and high levels of ABCC3, reflecting "favourable" ABCC gene expression. Group B consisted of patients whose tumours displayed only one unfavourable risk factor with respect to the three ABCC genes analysed (i.e., ABCC1 high, ABCC4 high, or ABCC3 low), and Group C comprised patients whose tumours exhibited two or more unfavourable ABCC risk factors. Similar associations between combined ABCC gene expression and increasingly poor outcome were also observed in subgroups of patients (**b**) with stage 3 or 4 disease or (**c**) whose tumours lacked MYCN amplification. (**d**) Combined expression of the ABCC1, ABCC3, and ABCC4 genes and cumulative EFS in 251 neuroblastoma patient samples analysed by Oberthuer et al. [116]. Patients in the Oberthuer et al. cohort were categorized into eight groups as described for panel (**a**) above. These groupings were also strongly predictive of EFS in subgroups of patients (**e**) with unfavourable (stages 3 and 4) disease or (**f**) with non–MYCN-amplified disease. At 0, 3, and 6 years from diagnosis [Panels (**a**), (**b**), and (**c**)], or 0, 5, and 10 years from diagnosis [Panels (**d**), (**e**), and (**f**)], the number of patients at risk of relapse are shown. Figure reproduced from [59], with permission

2.7 MRPs as Targets for Therapy

2.7.1 Small Molecule Modulators

Assuming that MRP transporters contribute significantly to clinical multidrug resistance, it will be critical to establish whether MRPs can be successfully targeted to either reverse drug resistance, or at least allow a broader therapeutic window for drugs that are at or approaching their maximum tolerated dose. Therefore, a variety of strategies have been employed to abolish the resistance caused by MRPs. The most common of these is the use of small molecule inhibitors which, prevent binding or efflux of substrates, thus enhancing the efficacy of chemotherapeutics [152]. Although many small molecule inhibitors of MRPs have been evaluated in vitro and shown good inhibition of efflux activity and enhanced the effects of MRP substrates (Table 2.1), sulindac, an inhibitor of MRP1 ([115], clinicaltrials.gov) is the only modulator to progress through in vivo studies to clinical trials. Several hypotheses have been suggested as to why a lack of correlation exists between the responses observed using in vivo models and behaviour in clinical studies, including differences in pharmacokinetics of combination therapies in mice and humans, leading to unpredicted toxicities. Furthermore, the cellular heterogeneity that exists in patient tumours, in addition to differences in basal MRP expression and pharmacokinetic activity, cannot be modelled effectively using in vitro cell line and in vivo mouse models.

Inhibitors of P-glycoprotein (discussed in detail elsewhere in this volume) have been extensively examined in clinical studies and several P-gp inhibitors, also reported to inhibit MRP1, have been evaluated in Phase I clinical trials [123, 132]. However, only one MRP inhibitor, sulindac, has been examined in a Phase II clinical trial, given in combination with epirubicin in patients with advanced melanoma, where no unacceptable toxicity was observed (ClinicalTrials.gov). Despite the limited MRP inhibitor trials, extensive studies modulating P-gp have identified a range of challenges associated with ABC transporter protein inhibition. For instance, pharmacokinetic interactions between modulators and chemotherapeutics often limit the normal efflux, absorption and metabolism of therapeutics, leading to unacceptable plasma levels. Therefore, it is essential to appreciate the normal physiological role of these proteins when developing inhibitors.

An ideal modulator would have high specificity and potency, good bioavailability, absence of toxicity in combination with chemotherapeutics and be screened/designed specifically for MRP inhibition. As with early generation P-gp inhibitors, MRP inhibitors have typically been drugs previously identified for other purposes. Sulindac, for example, is a non-steroidal anti-inflammatory drug [115], while MK-571 was developed as a cysteinyl leukotriene receptor antagonist [92]. Modulators optimised specifically for MRP inhibition would be expected to be more effective. In addition to non-specific modulators, the only clinical trial evaluating sulindac enrolled advanced cancer patients, after failure of initial chemotherapy protocols [115]. As a result, tumours in this cohort may have acquired multiple alternative

mechanisms of resistance, which may also contribute to clinical outcome. Ideally, clinical studies with more stringent criteria and objectives should be employed, including evaluating modulators in ABC transporter expressing cancer types at diagnosis, using MRP substrate chemotherapeutics, effective monitoring of patient side effects/toxicity and effect on MDR phenotype [152].

2.7.2 Monoclonal Antibodies

In addition to the traditional inhibition of MRP efflux activity by small molecule modulators, several strategies to prevent MRP activity are currently under investigation. Targeting general cancer cell-specific mechanisms using monoclonal antibodies has been a successful strategy in a variety of leukaemias and solid tumours [88]. However, although a large number of MRP antibodies are currently available and have shown activity in vitro, an antibody targeting an MRP is yet to be evaluated in vivo. In the case of MRP1, in addition to ineffective inhibition, the lack of progression to in vivo studies has also been linked with the intracellular binding of currently available antibodies and subsequent inability to generate antibodies to the extracellular domains [25].

2.7.3 RNA Interference

Although RNA interference (RNAi) targeting MRPs has proved valuable in vitro, there are limited studies investigating the use of RNAi in vivo. Significant alterations in tumour mass or substrate accumulation after treatment with substrates and MRP1 siRNA [170] or MRP2 shRNA by adenovirus [107] in vivo have been described, suggesting this is a plausible strategy for MRP inhibition. In addition, several microRNAs have been associated with expression of MRPs, particularly MRP1 in vitro [54, 83, 97]. However, as a single miRNA has multiple mRNA targets [6], it is likely that the addition of an MRP inhibitory miRNA to a cell will induce effects on additional mRNA species and pathways. Therefore, to confirm inhibition of MRP by a particular RNA species as a viable strategy, more extensive validation in vivo is required.

It must be remembered that MRPs are also expressed on the surface of non-cancer cells and so targeting the malignant cell specifically by RNAi represents a challenge. However, recent studies have suggested the use of bio-nanocapsules, which display a molecule capable of recognising a tumour cell-specific target, such as HER2 in breast and ovarian cancer. Consequently, capsules deliver RNAi only to abnormal cells, inducing target protein knockdown [110].

2.8 Are There Roles for MRPs in Cancer Progression Other Than in Drug Resistance?

Although the focus of most studies has been the role of MRPs in drug resistance and the subsequent effects on cancer patient prognosis, there is some suggestion that MRPs may influence patient outcomes by alternative mechanisms [47]. The efflux of endogenous substrates, such as glutathione and sulphur conjugates [56, 176], leukotriene C_4 [92], bilirubicin, bile salts [70], 17-beta-D-glucuronide, cAMP and cGMP [20, 71] by MRPs is well described and the ability of cells to successfully maintain cellular homeostasis in conditions of stress, such as chemotherapy insult, may also represent a targetable mechanism. Furthermore, MRPs have also been linked with normal [130] and cancer [59] cell migration in vitro and also tumour formation in a transgenic mouse model of neuroblastoma [59], suggesting a possible secondary role for these proteins in cancer development in addition to traditional efflux activity.

2.9 Summary

In this chapter we have described the wide range of known anticancer substrates of MRPs, and the correlations between expression and patient outcome in a variety of cancer types. However, whether these associations will improve the prediction of patient prognosis above existing markers is yet to be fully examined. Furthermore, there is some difficultly in confirming a causative role for MRPs in cancer, since although some substrates induce expression of MRPs in tissues, multiple factors contribute to drug resistance. In addition, clinical correlative studies routinely involve patients who have been treated with differing chemotherapeutic protocols, both between and within a cancer type. A better understanding of the role of MRPs in patient outcome may lead to expression of MRPs being usefully employed to stratify patients with increased expression for more intensive therapy or treatment with a non-MRP substrate. However, only one MRP inhibitor has been evaluated in clinical trials, although monoclonal antibodies and RNAi techniques are currently showing promise as novel strategies for MRP inhibition. Therefore, until these multidrug transporter proteins are shown to have clear causative roles in drug resistance, we must question whether MRP inhibition will be a viable therapy in combination with traditional therapeutics.

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