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REVIEW ARTICLE

ABC Transporters: Regulation and Association with Multidrug Resistance in Hepatocellular Carcinoma and Colorectal Carcinoma

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Abstract: For most cancers, the treatment of choice is still chemotherapy despite its severe adverse effects, systemic toxicity and limited efficacy due to the development of multidrug resistance (MDR). MDR leads to chemotherapy failure generally associated with a decrease in drug concentration inside cancer cells, frequently due to the overexpression of ABC transporters such as P-glycoprotein (P-gp/MDR1/ABCB1), multidrug resistance-associated proteins (MRPs/ABCCs), and breast cancer resistance protein (BCRP/ABCG2), which limits the efficacy of chemotherapeutic drugs. The aim of this review is to compile information about transcriptional and post-transcriptional regulation of ABC transporters and discuss their role in mediating MDR in cancer cells.

This review also focuses on drug resistance by ABC efflux transporters in cancer cells, particularly hepatocellular carcinoma (HCC) and colorectal carcinoma (CRC) cells. Some aspects of the chemotherapy failure and future directions to overcome this problem are also discussed.

Keywords: ABCB1**,** ABCC2, ABCG2, chemotherapy, hepatocellular carcinoma, colorectal carcinoma, multidrug resistance, transcriptional regulation.

1. INTRODUCTION

Multidrug resistance (MDR) is a phenotype that is associated with tumor cells gaining a cross-resistance to a large range of drugs with different cellular targets and structures and is characterized by diminished intracellular drug accumulation leading to treatment failure [1, 2]. Either intrinsic or acquired resistance can produce chemotherapeutic failure and malignant tumor progression. Intrinsic resistance occurs when some inherent characteristic of the cancer cells, already present at diagnosis, prevents the drugs from working from the beginning of therapy. Acquired drug resistance can be developed during treatment of tumors that were initially sensitive and can be caused by mutations arising during therapy, as well as through various other adaptive responses, such as increased expression of the therapeutic target and activation of alternative compensatory signaling pathways [3]. MDR arises *via* many unrelated mechanisms, such as increased drug efflux, decreased drug influx, intracellular drug sequestration, drug inactivation or lack of activation, specific drug metabolism or detoxification, alterations in drug target susceptibility, activation of survival responses, evasion of apoptosis, improved DNA repair, epigenetic changes and the influence of the local tumor microenvironment, tumor molecular and genetic heterogeneity, among others [3-5]. Among these, one of the most important and best characterized mechanisms of MDR is the overexpression of ATP binding cassette (ABC) efflux transporters in cancer cells, which pump out chemotherapeutic drugs, decreasing their intracellular concentrations [6, 7] (Fig. **1**). The involvement of ABC

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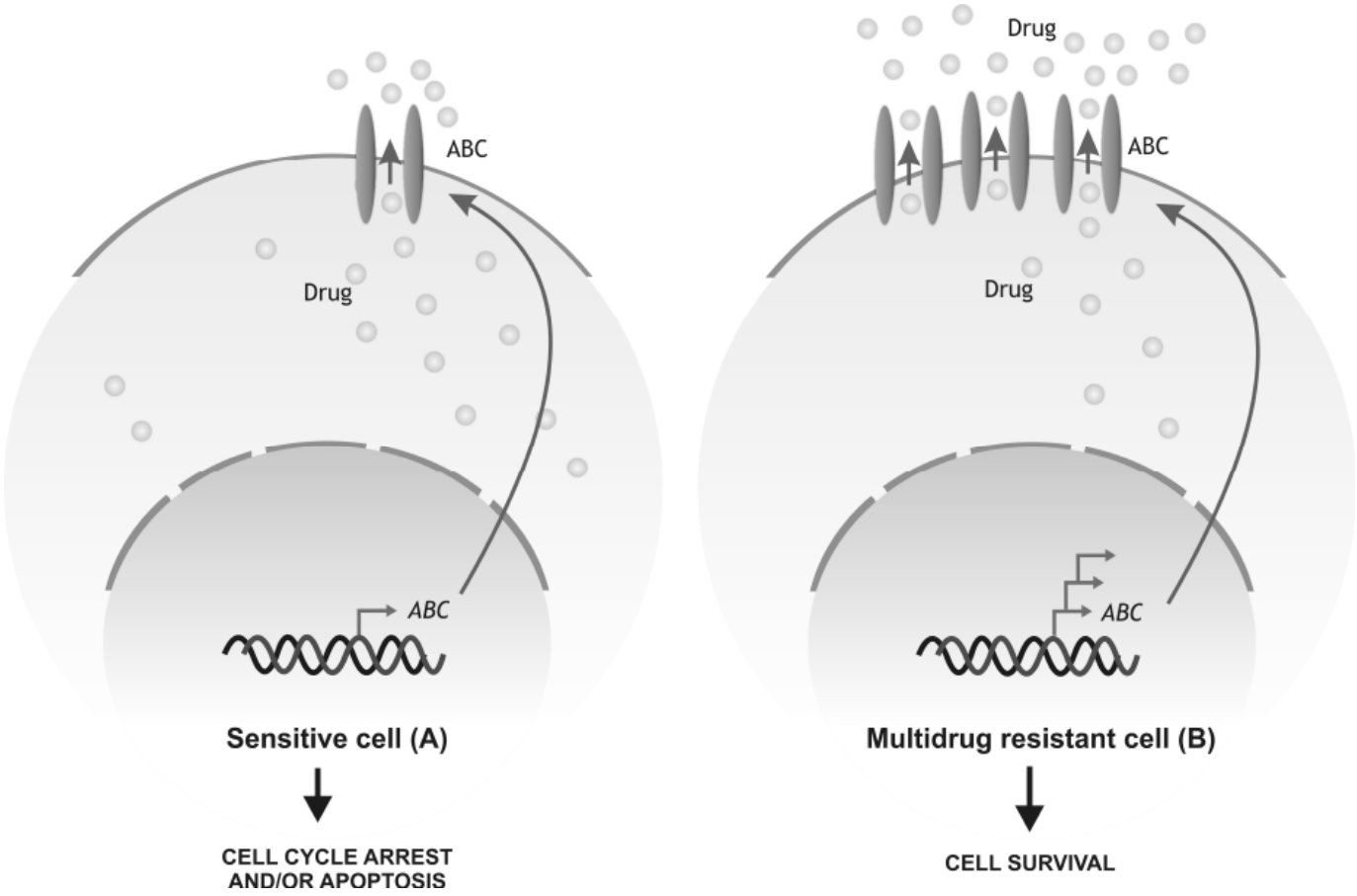

Fig. (1). Comparison between a drug sensitive cell (**A**) and a multidrug resistant cell (**B**). Overexpression of ABC transporters increases drug efflux diminishing intracellular drug concentration.

transporters including P-glycoprotein (P-gp/MDR1/ ABCB1), multidrug resistance-associated proteins (MRPs/ABCCs), and breast cancer resistance protein (BCRP/ABCG2) in cancer resistance is a very interesting topic to study since overcoming their action could result in the restoration of chemosensitivity.

The expression of ABC transporters is highly regulated, particularly at the transcriptional level, suggesting a potential target for modulation of the MDR phenotype. To broaden the understanding of the regulating mechanisms of ABC transporter expression, the options that are being developed nowadays to revert drug resistance will be detailed.

2. REGULATION OF ABC TRANSPORTER EXPRESSION

ABC transporter expression is regulated at different levels. In this section the transcriptional and post-transcriptional mechanisms of regulation of P-gp, MRPs and BCRP are described in detail. All the information is also synthetized in Table **1**.

2.1. Regulation of P-gp/MDR1/ABCB1 Expression

Cloning of the promoter of human *MDR1* gene encoding P-gp (GenBank Nr: M29423) was followed by the study of the regulation of the expression of this gene [8]. P-gp expression, as well as the expression of other transporter proteins, is dynamically regulated at the transcriptional level by nuclear receptors that act as xenosensors, among others. Particularly, the pregnane X receptor (PXR, *NR1I2*) and the constitutive androstane receptor (CAR, *NR1I3*) [9, 10], which exhibit overlapping ligand specificity, constitute a network of regulatory effectors modulating drug metabolism and transport. Nuclear receptor activation has been characterized both by reporter gene and ligand competition assays and is correlated with the induction of the metabolism through cytochrome P450 [11, 12]. The antibiotic rifampicin, and other therapeutic agents, has been identified as a potent and specific agonist of human PXR [13-15]. PXR activation by rifampicin results in an increase of P-gp expression. Also, the antiparasitic benznidazole and the diuretic spironolactone are able to induce P-gp through the activation of PXR [16,

Table 1. Mechanism of ABC transporter regulation.

ABC Transporter	Mechanism of Regulation		References
P-gp/MDR1/ABCB1	Transcriptional	PXR, CAR	[9-17]
		Epigenetic modification in *MDR1 locus*	[18]
		p53, Ras, c-Raf, c-Raf kinase	[19-25]
		NF-κB, AP-1	[26]
		miR-27a, miR-138	[34]
	Post-transcriptional	mRNA stabilization	[32, 33, 25]
		miR-223, miR-145	[27, 29]
MRPs/ABCCs	Transcriptional	AP-1, Sp1, HNF-1, HNF-3β, C/EBPα, C/EBPβ	[36, 37]
		PXR, CAR, AhR, FXR, GR (MRP2)	[38-41]
		Nrf2 (MRP1, MRP2, MRP3, MRP4)	[42-45]
		PPAR-α (MRP1)	[46]
		ER-α, PXR(MRP3)	[50-52]
	Post-transcriptional	mRNA stabilization	[54,55
		miRNAs	[56, 60]
		Alternative open reading frames (MRP2)	[61]
BCRP/ABCG2	Transcriptional	PRB, AhR, ER-α, HIF-1α	[63-69]
		Nrf2, NF-κB	[63]
		Methylation of promoter region	[74, 75]
	Post-transcriptional	miR-519c, miR-520h, miR-328, miR-181a, miR-487a	[77-81]

17]. In addition, chemotherapeutic drugs are capable of inducing specific epigenetic modifications in the *MDR1 locus*, concomitant with P-gp upregulation through transcriptional activation and also with participation of a potential post-transcriptional component. It has been established that the mechanisms are not mutually exclusive and are dependent on *MDR1* promoter methylation state [18]. *MDR1* promoter activity could also be modulated by the tumor suppressor protein p53 [19-22]. While wild-type p53 represses *MDR1* promoter activity, mutant forms of p53 enhance its activity. The expression of *MDR1* is also regulated by oncogenes such as Ras, c-Raf, and c-Raf kinase [23–25]. These proteins are capable of activating the *MDR1* promoter. Nuclear factor NF-κB subunit (NF-κB) and AP-1 transcription factors directly bind to the promoter region of the *MDR1* gene. The induction or repression produced by these transcription factors depends on the cell line and the presence of co-regulators [26]. P-gp expression can also be regulated at the post-transcriptional level. MicroRNAs (miRNAs) are a class of short, noncoding RNA molecules that can regulate gene expression. Through bioinformatics analysis, several miRNAs that can bind to the 3'UTR of *MDR1* mRNA were found [27]. Besides, Bruhn *et al.* [28] recently demonstrated that shortening of the *MDR1* 3'-UTR causes loss of miRNA-dependent translational control leading to elevated *MDR1* protein levels. Some miRNA such as miR-223 and miR-145 negatively regulates the expression of P-gp by direct action on the 3'-UTR of *MDR1* mRNA [27, 29]. However, different miRNAs can regulate P-gp expression indirectly. For example, miR-27a and miR-138 modulate P-gp expression by inhibiting Frizzled 7/β-catenin pathway in HCC cells or NF-κB/p65 in leukemia cells, respectively [30, 31]. In addition, several drugs regulate P-gp expression by stabilizing *MDR1* mRNA such as ivermectin in a murine hepatocyte cell line [32] or cytotoxic drugs like doxorubicin, cytarabine, colchicine, colcemid, or vinblastine, in leukemia cells, in which also a translational block was overcome such that the stabilized mRNA was translated and P-gp expressed [33]. It was also described a transcriptional regulation of P-gp by miRNAs [34]. Both miR-27a and miR-138 can also regulate P-gp expression transcriptionally [34]. It was proposed that *MDR1* transcriptional regulation by miR-27a and

miR-138 may occur through two possible scenarios: (1) direct miRNA hybridization with an active promoter and (2) triplex structure formation (double-stranded DNA/RNA) stabilized by argonaute 2. Finally, P-gp mRNA endoribonuclease attack can be prevented by the binding of an oncoprotein expressed in cancerous liver cells called CRD-BP, also known as insulin growth factor 2 binding protein 1 (IGF2BP1), to *MDR1* mRNA [35].

2.2. Regulation of MRPs/ABCCs Expression

Regulation of MRPs expression takes place at different levels. The most common phenomenon is transcriptional regulation and involves changes in the rate of mRNA synthesis. Detailed studies of transcription factor binding sites are only available for human *MRP2* promoter, although they do not cover the whole regulatory sequences [36, 37]. Nevertheless, the bioinformatic analysis of promoters up to -2650 bp upstream of the transcription initiation site revealed binding sites for transcription factors such as AP-1, SP-1, HNF-1, HNF-3β, C/EBP-α and C/EBP-β. In addition, nuclear receptors are key regulators of MRP2 expression by endo- and xenobiotics. As described for P-gp regulation, PXR has been shown to mediate MRP2 modulation by several drugs and other xenobiotics [38, 39]. In addition, CAR, the aromatic hydrocarbon receptor (AhR) and the farnesoid X receptor (FXR, NR1H4) also mediate MRP2 transcriptional regulation, particularly by drugs like phenobarbital, aromatic xenobiotics and bile salts, respectively [40, 41]. Moreover, the *MRP2* promoter harbors glucocorticoid response elements (GRE) and antioxidant response elements (ARE) mediating the effect of glucocorticoids *via* the glucocorticoid receptor and pro-oxidant compounds *via* the nuclear factor erythroid 2-related factor 2 (Nrf2) on the transporter expression, respectively [37–42]. MRP1, MRP2 and MRP4 were shown to be positively regulated by Nrf2 [43–45], whereas MRP1 is negatively regulated by the peroxisome proliferator-activated receptor α (PPARα, *NR1C1*) in the small intestine [46]. Rifampicin, a strong PXR agonist, failed to induced MRP1 [47, 48], suggesting a minor role of PXR in MRP1 regulation, in clear opposition to the situation described for P-gp and MRP2.

The comparison of *MRP2* and *MRP3* promoter activities using reporter systems showed that the activity of *MRP3* promoter was only 4% of that of *MRP2* promoter [37], in accordance with the low basal MRP3 expression in human liver [49]. PXR was described as a modulator of basal MRP3 expression [50]. Nevertheless, treatment with PXR agonists not always leads to a further induction [39]. Estrogen receptor α (ER-α, *NR3A1*) mediates the induction of hepatic MRP3 by ethynylestradiol both in rat [51] and human models [52], albeit the *MRP3* promoter does not bear classical estrogen response elements. It was found that MRP3 regulation takes place through a non-canonical way involving the transcription factor AP-1 [51, 52]. Different studies assessing the regulation of other MRPs by endo- and xenobiotics have been performed. Nevertheless, little information about the nuclear receptors and/or transcription factors mediating these processes is available.

Post-transcriptional regulation of MRPs is a less frequent mechanism. In this regard, mRNA stabilization leads to augmented mRNA levels without an increase in the transcription rate. This phenomenon was already described for P-gp [32, 33, 53]. However, it is still unknown whether it also contributes to MRPs regulation. Additionally, MRPs can undergo translational regulation in which a change in the protein expression takes place without a concomitant change in the mRNA synthesis rate, as described in ethynylestradiol- and pregnancy-associated cholestasis [54, 55]. Moreover, miRNAs have also been shown to modulate MRP1 [56], MRP2 [57], MRP3 [58], MRP4 [59] and MRP5 [60] translation. Thus, any chemical affecting the expression of regulatory miRNAs could modulate the expression of these transporters. For MRP2, it was also described as a translational regulation due to the use of alternative open reading frames [61].

2.3. Regulation of BCRP/ABCG2 Expression

The regulation of BCRP can occur at transcriptional, post-transcriptional or post-translational level. An epigenetic regulation of this transporter was similarly reported. *BCRP* human promoter was initially characterized in 2001 by Bailey-Dell *et al.* [62]. It bears several regulatory elements including the estrogen response element (ERE), the progesterone response element (PRE), the hypoxia response element (HRE), ARE, the aryl hydrocarbon response element (AhRE) and the active NF-kB response element [63]. Thus, ligands capable of activating nuclear receptors and transcription factors which interact with the above mentioned regulatory elements can modulate BCRP expression. In this regard, regulation of BCRP by progesterone *via* progesterone receptor B (PRB) [64] and by romidepsin through the AhR has been already described [65]. BCRP is also regulated by hypoxic conditions through the hypoxia-inducible factor 1α (HIF-1α) [66]. Several authors demonstrated that estradiol can

modulate BCRP expression *via* ER-α. In this regard, some studies showed upregulation of the BCRP gene and protein by estradiol [67–69], while other studies showed downregulation of BCRP by estradiol possibly through a post-transcriptional regulation [70–72]. Such controversial data could result from cell- or organ specific regulation or the experimental systems used in each case; also the interaction between hormones and other regulatory factors could be the reason of the contradictory data [73].

In addition to transcriptional regulation, increased BCRP levels in drug resistant cell lines were reported to be associated with hypomethylation or unmethylation of a particular site in the promoter region [74, 75]. Also miRNAs can downregulate BCRP; they bind to the 3′ UTR of the *BCRP* mRNA and exert a negative modulation of transcript stability and protein translation [76]. There have been identified several miRNAs that modulate BCRP by interacting directly with *BCRP* 3′UTR and determine the sensitivity of cancer cells to chemotherapeutic drugs, including miR-519c, miR520h, miR328 [77-79], miR-181a [80] and miR-487a [81].

3. HEPATOCELLULAR CARCINOMA

The primary liver cancer originates in the liver and its occurrence is increasing rapidly every year. Worldwide, liver cancer is the sixth most common cancer (782,000 new cases in 2012) and the second cause of cancer-related death (745,000 cases in 2012) [82]. Among genders, it is the fifth most common cancer in men (554,000 new cases; 521,000 deaths) and the ninth in women (228,000 new cases; 224,000 deaths). The ratio of mortality to incidence for liver cancer is 0.95, which means that this cancer has a very poor prognosis [82].

Among the various types of primary liver cancers like hepatocellular carcinoma (HCC), cholangiocarcinoma, angiosarcoma, hepatoblastoma, fibrosarcoma, leiomyosarcoma and rhabdomyosarcoma, HCC is the most common form, being responsible for 80-90% of the primary malignant liver tumors in adults. HCC, also called malignant hepatoma, arises from the liver parenchymal cells (hepatocytes) [83].

HCC is one of the few cancers with well-defined major risk factors, which generally transform healthy liver to HCC liver through fibrosis and cirrhosis. Most common risk factors include chronic hepatitis B and C viral infection (HBV and HCV), alcoholic liver diseases caused by excessive alcohol intake, type 2 diabetes, obesity, metabolic disorders and non-alcoholic steatohepatitis (NASH) as part of non-alcoholic fatty liver diseases (NAFLD) and aflatoxin B1-contaminated food intake [84]. Metabolic and genetic diseases associated with HCC include hemochromatosis, Wilson's disease, α-1 antitrypsin disease, tyrosinemia, glycogen-storage disease types I and II, and porphyrias. Other risk factors may include cigarette smoking and exposure to oral contraceptives. HCC incidence varies according to age, ethnicity, gender (HCC occurs more often in males, with a ratio of 2:1-4:1) and geographical distribution [84].

There are about 30 publically available HCC cell lines that have played important roles in cancer studies for both dissecting molecular mechanisms and developing new drugs. These cell lines represent primary HCCs with high fidelity, thus laying the rationale for their testing as preclinical models. The most commonly HCC cell lines used include BEL-7402, C3A, Hep3B, HepG2, HUH7, JHH-1, PLC/PRF/5 (Alex), SNU-182, SNU-387, SNU-449, SNU-761 and SNU-878 [85, 86].

3.1. HCC Treatment

Although most of the risk factors of HCC are known, the underlying mechanisms responsible for the conversion of healthy hepatic cells to neoplastic cells are still ambiguous. Hepatocarcinogenesis is a highly complex multistep process, and the molecular pathogenesis of HCC involves different genetic and epigenetic aberrations and alterations in multiple signaling pathways leading to heterogeneity not only between different HCCs but also within a single tumor nodule [87].

The therapy strategies are broadly divided into curative and palliative treatment. Whereas curative treatments (such as surgery, liver resection and transplantation and locoregional therapies like radiofrequency ablation) are applied to the HCC patients who are in early stages, palliative care is provided to the patients in intermediate (locoregional therapies like transarterial embolization) and advanced (systemic treatments such as radiation, chemotherapy and targeted therapy) stages of HCC [83]. Unfortunately, HCC is characterized as an asymptomatic disease in the initial stages, which most often leads to a late diagnosis. In the advanced stages, only systemic treatments can be used [88]. Nevertheless, HCC is one of the most lethal types of tumor and it is notoriously difficult to treat due not only to the long latent period before detection that leads to aggravated liver dysfunction and makes systemic drug delivery ineffective, but also to MDR and severe drug-related adverse effects from therapy. The complexity

and heterogeneity of HCC tumors also contributes to the failure of therapy, since multiple signaling pathways are dysregulated preventing a single drug from being fully effective [89]. Regarding radiotherapy, the liver and its primary tumors are highly radioresistant, which leads to the ineffectiveness of this type of treatment [88].

The complete failure of chemotherapy and radiotherapy in previous years gradually shifted HCC treatment to molecular targeted therapies, leading to the approval of sorafenib therapy (Nexavar, BAY 43-9006; Bayer HealthCare Pharmaceuticals - Onyx Pharmaceuticals) for HCC by the European Medicine Agency (EMA) and the U.S. Food and Drug Administration (FDA) in 2007 [90–92]. Sorafenib inhibits cell surface tyrosine kinase receptors (*e.g.*, VEGFR-1, VEGFR-2, VEGFR-3; PDGFR-β, c-KIT, FLT-3 and RET) as well as downstream intracellular serine/threonine kinases of the RAF/MEK/ERK pathway (*e.g.*, Raf-1, wild-type B-Raf and mutant B-Raf) leading to a dual mechanism of action by targeting tumor cell proliferation and tumor angiogenesis [91]. In addition, sorafenib is capable of inducing apoptosis in HCC and others tumor cell lines [91, 93]. Indeed, sorafenib is the only approved drug for advanced HCC and it is the standard systemic therapy for this pathology, however, it only prolongs median survival and the time to progression by nearly 3 months in patients with advanced HCC [94]. One of the main reasons underlying the impaired sensitivity to sorafenib is that a considerable number of HCCs are refractory to the drug due to intrinsic and acquired resistance, and the majority of these HCC patients show disease progression even after an initial satisfactory response [95]. In addition, many patients require dose reduction to minimize adverse effects exerted by sorafenib (hand-foot skin reaction, rash/desquamation, weight loss, alopecia, diarrhea, nausea, abdominal pain, dyspepsia, fatigue, hypertension, thromboembolic and cardiac ischemic events) [94].

Nowadays, no single agent or combination therapies have been shown to impact outcome after sorafenib failure and there is no available second-line treatment for patients with intolerance or failure to this drug [96, 97].

3.2. MDR and ABC Transporters in HCC Chemotherapy

Although chemotherapy has become one of the main treatments for cancers, HCC is a chemorefractory malignancy [98]. MDR limits the application of liver cancer chemotherapy, and it is also a major cause of liver cancer recurrence and metastasis [99-101]. Data show that the incidence rate of MDR in primary liver cancer is 84.6%-100%, thus solving MDR during chemotherapy is of great significance to the treatment of this malignancy [99]. The ABC transporters of particular relevance to cancer chemotherapy in HCC are P-gp, MRP1, MRP2, MRP3 and BCRP [102-105]. In this regard, these ABC transporters are overexpressed in HCC, thus promoting intrinsic drug resistance. Expression of P-gp is increased in human HCC compared to normal liver tissue, cirrhotic liver and liver from individuals with chronic cholestasis [106-109]. Similarly, MRP1, -2, -3 expressions were significantly increased in human HCC samples when compared to normal liver tissue, cirrhotic liver and liver from individuals with chronic cholestasis [104, 107, 109-113]. Roelofsen *et al.* [114] found that MRP1 protein levels are highly increased in both HepG2 cells and immortalized hepatocytes compare to normal hepatocytes. In another study, Nies *et al.* [105] described that *MRP2* and *MRP3* mRNA expression in human HCC tissue was at least 10-fold higher than *MRP1* mRNA expression. On the other hand, BCRP expression was higher in human HCC tissue than both cirrhotic paired tissue and normal tissue [115–117]. Also, BCRP protein and mRNA expression was found to be highest in the most undifferentiated HCC cell lines, and this was related to a higher functional activity of this ABC transporter [115]. Additionally, the expression of the aforementioned ABC transporters can be induced by chemotherapeutic drugs, thus resulting in acquired MDR. Several models of MDR in HCC cell lines were developed *in vitro* by exposing HCC cell lines to progressively increasing concentrations of certain chemicals. These studies demonstrated that cells resistant to conventional chemotherapeutics drugs, overexpressed ABC transporters and exhibited decreased intracellular drug accumulation compared to parental cells. For example, HCC cells resistant to paclitaxel, epirubicin, and doxorubicin exhibited higher expression of P-gp [103, 118–122] whereas HCC cells resistant to cisplatin presented higher expression of MRP2 and MRP3 [123] and HCC cells resistant to mitoxantrone and doxorubicin showed overexpression of BCRP [103, 119]. In these studies, it was demonstrated that these one drug-resistant cells also exhibit cross-resistance to other drugs which are also ABC transporter substrates [118–120, 122]. Sun *et al.* [102] showed that expression of P-gp and BCRP was amplified in subcutaneous tumors generated in nude mice with adriamycin-resistant HCC cells compared to parental HCC cells. Also, P-gp and BCRP expression was augmented in HCC tissues from post-

transarterial chemoembolization (TACE) patients contrarily to patients without TACE [102]. Hoffmann *et al.* [124] and Sukowati *et al.* [115] showed that exposure of parental HCC cells to gemcitabine and doxorubicin also resulted in upregulation of some ABC transporters.

Taken together, intrinsic and acquired drug resistance mediated by ABC transporters are mainly responsible for the failure of the systemic chemotherapy, which provides only marginal effect on survival in HCC patients [125]. Noteworthy, an increased expression and function of transmembrane drug efflux pumps in HCC is associated with poor clinical prognosis and biological aggressiveness. For instance, P-gp overexpression was associated with a shorter recurrence-free interval, increased disease progression and poor survival and thus might be a useful prognostic factor for HCC [126, 127]. In addition, it was reported a significant association between P-gp overexpression, tumor aggressiveness and metastatic potential during tumor progression in experimental rat liver tumor [128]. In HCC, some single nucleotide polymorphisms (SNPs) in the *MRP1* gene have been shown to affect the function of MRP1 and were associated with a higher risk of recurrence [129] and a poor survival [130]. In the same way, Wang *et al.* [111] found that the mean survival time of post-operative HCC patients with negative *MRP1* expression was longer than that of patients with positive expression and that the positive rate of *MRP1* gene expression was increased as the degree of HCC differentiation decreased. Since MDR in HCC is related to *MRP1* gene overexpression, the authors concluded that poor differentiation, malignancy and worse prognosis are consistent with MDR in HCC and that *MRP1* gene is expected to be an indicator of clinical prognosis [111]. In line, Vander Borght *et al.* [110] reported that *MRP1* mRNA levels were significantly higher in HCCs with poor survival, *i.e.* in tumors classified as having the worst prognosis. Also, they found high MRP1 expression in poorly differentiated HCCs, large tumors and microvascular invasive tumors [110]. Regarding BCRP, it was reported that cells positive for this ABC member might play a central role in hepatocarcinogenesis and in the maintenance of the cancer cell hierarchy of human HCC, with BCRP positive cells residing at the higher rank in that hierarchy [131]. Shi *et al.* [132] identified side population cells from HCC cell lines with stepwise metastatic potentials that showed high expression of BCRP and similar characteristics of self-renewal, high clonogenicity and remarkable chemoresistance. Also, BCRP was found to be overexpressed in patients with recurrent HCC and it was confirmed as a prognostic factor for predicting relapse-free survival [133]. In another work, the expression of BCRP in HCC tissues and cell lines showed tendencies of association with unfavorable clinical and pathological factors, and had a close relationship with tumorigenicity, proliferation, drug resistance and metastasis ability [134]. Related to this, the upregulation of BCRP in liver with HCC was greater in pathological poorly differentiated grade than in well-differentiated HCC [115, 116]. Overall survival in HCC patients with high expression of BCRP was reduced in elderly patients and thus this transporter may be a powerful predictor of prognostic value in these patients [116].

Finally, sorafenib is a substrate of ABC proteins and an association between ABC proteins upregulation and sorafenib resistance was established in HCC cell lines. In this regard, Huang *et al.* [135] demonstrated that BCRP mediated the efflux of sorafenib whereas Colombo *et al.* [136] showed that P-gp was found not only in the cell membrane but also on lysosomes and that sorafenib resistance was mediated by P-gp-mediated lysosomal sequestration. In line, Rigalli *et al.* [137] showed that the phytoestrogen genistein increased P-gp and MRP2 protein expression and activity, correlating well with an elevated sorafenib resistance in HepG2 cells. In these studies, co-treatment with inhibitors for these ABC proteins reverted sorafenib resistance thus augmenting its cytotoxicity [135–137]. Regarding sorafenib treatment effect on ABC transporters expression, Hoffmann *et al.* [138] and Ye *et al.* [121] showed that sorafenib reduced the expression of *MDR1* and *MRP2* mRNA in Huh7 cells and the levels of P-gp protein in doxorubicin-resistant HepG2 cells, respectively. However, long-term exposure of HCC cells to sorafenib induced resistance to sorafenib due to sorafenib-resistant HCC cell lines exhibited increased expression of P-gp, MRP1, -2 and -3 and BCRP [101, 139–141]. Sorafenib-resistant HCC cell lines also had a higher survival rate without apoptosis and enhanced migratory and invasive abilities, compared to parental cells [101, 139]. Chow *et al.* [101] suggest that advanced HCC patients with acquired sorafenib resistance may have enhanced tumor growth or distant metastases, which raises the concern of long-term sorafenib treatment in advanced HCC patients who have developed sorafenib resistance. Related to this, MRP3 protein was highly expressed in the HCC tissues from patients that never responded to sorafenib treatment but not in those who did [140]. In the study of Liang *et al.* [142] P-gp was significantly induced by hypoxia in the presence of sorafenib in HCC cells and HCC tissues from patients clinically resistant to sorafenib exhibit increased intratumor hypoxia compared

with HCC tissues from patients before treatment or sensitive to sorafenib. The authors concluded that the hypoxia caused by the antiangiogenic effects of sustained sorafenib therapy induce sorafenib resistance.

4. COLORECTAL CANCER

Colorectal cancer (CRC) is one of the most frequent causes of cancer-related death in industrialized countries [143, 144], being the second most common cancer in men and the third most in women [145]. The proportion of patients that achieve 5-year of survival after diagnosis is less than 15% [146]. Thus, premature detection and treatment is an imperative issue to reduce the morbidity and the rate of mortality.

As previously stated for HCC, CRC is a complex disease in which multiple signaling pathways are dysregulated. Mutations, diet and intestinal microbiota were suggested to be involved in CRC development. Around 15-20% of all CRC are due to inherited mutations in one or more genes that generate the development of adenomas or carcinoma [147, 148]. In this regard, it was reported that the adenomatous polyposis coli (APC) tumor suppressor gene is frequently mutated in CRC resulting in dysregulated Wnt signaling [149]. APC forms a protein complex that controls the stability and sub-cellular localization of CTNNB1 (β-catenin), an integral part of the cell cytoskeleton as well as a significant transcriptional factor in Wnt signaling, that regulates downstream inflammatory pathways, cell cycle and proliferation. In an experimental model, loss of APC blocks differentiation and leads to hyperproliferation and growth of stem cells in the small and large intestine resulting in the disruption of the normal crypt-villus axis [150, 151]. As a result, benign and dysplastic adenomas are expanded [152]. A recent experimental work demonstrates that APC restoration stimulates cellular differentiation and reinstates crypt homeostasis in CRC [153]. This mutation is present in familial adenomatous polyposis (FAP), an inherited disorder in which polyps are formed in the epithelium of the large intestine. These polyps are benign, but malignant transformation may occur. Although FAP is inherited, the vast preponderance of CRC is sporadic. For that reason, it is believed that the frequency of carcinogenesis is determined by the penetrance of the mutation as well as the aggressiveness of environmental factors [154]. It is known that amines and nitrates can be transformed by colonic bacteria in potent procarcinogens such as *N*-nitrosamines [155, 156]. Indeed, numerous food-derived carcinogens could contribute to CRC development. *In vivo* and *in vitro* investigations as well as epidemiological studies establish the contribution of heterocyclic amines such as 2-amino-1-methyl-6-phenylimidazol[4,5-b]pyridine (PhIP) in mutagenesis and subsequently carcinogenesis [157, 158]. This compound is present in cooked meat or fish and is transported by ABC family members [159–161].

Nearly 70 human colorectal cancer cell lines were obtained from a range of sources and are widely used to explore tumor biology, experimental therapy and biomarkers. Among the most used cell lines Caco-2, LS180, LS174T; HCT116, HT29, LoVo, T84 can be mentioned [162, 163].

4.1. CRC Treatment

Unfortunately, as occurs with HCC, generally CRC presents a late diagnosis. CRC management depends on the location and stage of the disease. Generally, resection of the bowel with the adjacent lymph nodes is the first choice of treatment. Then adjuvant chemotherapy, with or without radiation, could be applied. Sometimes, chemotherapy is used before surgery to reduce the tumor size before resection (neoadjuvant chemotherapy) [164].

Drugs such as the antimetabolite 5-fluorouracil (5-FU) and agents that potentiate its action (folinic acid; capecitabine, methotrexate, *etc.*), camptothecin derivatives, oxaliplatin and cisplatin are used for systemic chemotherapy [165]. With the better understanding of CRC pathogenesis, the introduction of epidermal growth factor receptor (EGFR) targeted therapy, *e.g.* the anti-EGFR monoclonal antibodies cetuximab or panitumumab, was indicated. Given the better response rate and the progression-free survival in comparison with monotherapy [166], the most common regimens for CRC are FOLFOX (folinic acid, 5-fluoruracil and oxaliplatin) and FOLFIRI (folinic acid, 5-fluoruroacil and irinotecan) [66][166]. However, these therapies are accompanied by side effects such as nausea, vomiting, diarrhea, neutropenia, alopecia, peripheral neurotoxicity, among others.

4.2. MDR and ABC Transporters in CRC Chemotherapy

As in many types of cancer, chemotherapy usually results toxic and/or unsuccessful. Cancer cells are provided with numerous mechanisms for survival: upregulation of ABC transporters that limit drug uptake or enhance drug efflux, increased drug metabolism, drug compartmentalization, blocked apoptosis, altered cell cycle, *etc.* [167]. As was indicated before for HCC, intrinsic or acquired overexpression of ABC transporters is one the major causes of MDR in CRC that leads

to chemotherapeutic failure. For example, high P-gp expression has been observed at the time of colon cancer diagnosis being associated with the intrinsic resistance. This resistance was also observed in different colon cancer cell lines [168-170]. As stated previously, the major ABC proteins involved in cancer MDR are P-gp, MRPs and BCRP. In general, a strong negative correlation was found between ABC protein levels, response to chemotherapy and prognosis [171].

Efflux of endo- and xenobiotics, including anticancer agents, out of the cells trough ABC proteins could be significant for the early stages of CRC, as well as for the CRC treatment outcome. Changes in ABC transporter activity may have a critical role in the efflux of numerous substrates involved in intestinal inflammation observed in different situations such as inflammatory bowel disease and CRC [172]. Environmental agents, microbes and diet, among others factors, may raise the levels of molecules that are ABC transporters substrates, thus affecting their transcriptional regulation. Indeed, low ABC transporter levels might promote CRC by increasing intracellular concentration of carcinogenic or inflammatory substrates. Disruption of the *mdr1a* gene results in colitis and later intestinal adenocarcinomas in mice [173] suggesting that the risk of inflammation-related CRC appears when P-gp protein activity is missing. Similarly, a significant transcriptional downregulation of BCRP compared to normal tissue leads to higher concentrations of carcinogens such as PhIP in human colorectal adenomas as well as in APC deficient mice. On the other hand, MRP2 and MRP1 protein expressions did not change in adenomas when compared to healthy tissue [174]. Another study demonstrated that the mRNAs encoding for P-gp, MRP1 and MRP3 were greatly expressed in normal colorectal mucosa and that expression was diminished or unchanged in cancerous tissues in comparison with noncancerous specimens. Conversely, Hinoshita *et al.* [175] found that the protein and mRNA levels of MRP2 were very low in normal colorectal mucosa and were increased in cancer tissue being associated with cisplatin but not 5-FU resistance. Nakamura *et al.* [176] found that Caco-2 cells express lower *MDR1* mRNA levels than human duodenal enterocytes, but similar to normal colorectal mucosa and colorectal adenocarcinoma; whereas Caco-2 *MRP1* mRNA levels were lower than in human samples. In addition, *MRP2* mRNA was also lower in Caco-2 cells compared to human duodenal enterocytes although was hardly detected in normal or cancerous colorectal samples. Based on these results it was suggested that deficiencies in ABC expression precedes cancer development as early events in the colorectal adenoma-carcinoma sequence. Accordingly, Micsik *et al.* [177] found that P-gp activity was decreased in primary colorectal cancer tissue compared to surrounding healthy mucosa, whereas MRP1 activity displayed no significant alteration. Hlatava *et al.* [178] found downregulation of *MDR1* and *BCRP* mRNAs and MRP2 upregulation in colorectal tumors collected before the first line of 5-FU treatment in comparison with control tissues. In agreement, Andersen *et al.* [172] recently detected low *MDR1* and *BCRP* and high *MRP2* mRNA levels in morphologically normal tissues surrounding the tumor, in CRC tissue as well as in mild/moderate and severe dysplasia tissue, when compared to the expression in tissues from healthy individuals. Thus, some transporter deficiencies could increase CRC susceptibility promoting the adenoma-carcinoma sequence by higher genotoxic effects. In CRC P-gp expression was correlated with the pathological grading of tumors, having lower expression in poorly differentiated tumors and higher levels in well differentiated ones [179]. Although a poor prognosis for neuroblastoma and acute myeloid leukemia was related to higher P-gp levels [180, 181], its prognostic value in CRC is uncertain. Weinstein *et al.*, [182] correlated the presence of P-gp in colon adenocarcinoma with an increased incidence of tumor vessel invasion and lymph node metastases. In another work, an overexpression of P-gp has been associated with apoptosis inhibition and an increased risk of cancer development in a mouse model [183]. Others authors were unable to find a correlation between P-gp levels and survival [184]. The inconsistency among the findings in different reports may come from the study design, the patient population, the stage of the tumor development, the time of sample collection (before or after chemotherapeutic), *etc.*

ABC expression is generally upregulated by therapeutic agents in cancer cells. It was reported that P-gp and BCRP levels were significantly increased in Caco-2 cells after chronic exposure to imatinib [185]. Several anticancer drugs (such as vincristine, tamoxifen, ifosfamide, paclitaxel, *etc.*) were able to induce P-gp *via* PXR activation affecting the accumulation of known P-gp substrates in LS180 cells [186]. The vitamin D3 metabolite 1,25-dihydroxycholecalciferol increased P-gp expression and activity in LS174T cells and this effect was further amplified by the combination with ketoconazole [187]. Auto-induction of colchicine efflux was reported as a consequence of induction of P-gp protein expression in LS180 cells [188]. BCRP is overexpressed in many types of advanced cancer and confers resistance to anticancer drugs [135, 189–191]. In-

duction of BCRP was also detected after treatment with anticancer agents. Indeed, its cDNA was identified in human colon carcinoma cells S1-M1-80 after exposure to mitoxantrone [192] and an increase in *BCRP* mRNA was also observed in HT29 cells resistant to the same drug [193]. Irinotecan (or CPT-11) is a pro-drug, whose metabolite 7-ethyl-10-hydroxy-camptothecin (SN-38) is able to inhibit the nuclear enzyme topoisomerase I [194]. It is used as a first-line of therapy in combination with others antitumor drugs for metastatic CRC [195], however, irinotecan and topotecan resistance is frequently observed. BCRP overexpression accompanied by expression of stem cell surface markers have been involved in treatment failure, tumor recurrence and expansion in CRC [196, 197]. Candeil *et al.* [195] demonstrated that *BCRP* mRNA levels in hepatic metastases derived from CRC are increased after irinotecan-based therapy. The basal expression of BCRP is Nrf2-dependent. Pharmacological activation of Nrf2 or genetic interventions have been reported to prevent oxidative stress-associated diseases and cancer [198, 199]. Alteration in Nrf2 pathway itself does not necessarily promote cancer initiation, but can lead to increased proliferation [200]. In colon carcinoma HT29 cells only BCRP was found to be down-regulated by Nrf2 knockdown among the studied ABC transporters [201]. The estrogenic compounds ethynylestradiol and genistein, were able to upregulate the mRNA and protein levels as well as the activities of P-gp and MRP2 in Caco-2 cells without affecting BCRP. Cytotoxicity assays proved a good correlation of MRP2 and P-gp upregulation with increased resistance to cell death induced by 1-chloro-2,4-dinitrobenzene (an MRP2 substrate precursor) and by paraquat (a P-gp substrate) [202]. Although the cytotoxicity was evaluated with noxious substances it can be speculated that the same effects may occur with chemotherapeutic agents. In this regard, it was reported that MRP2 is an important factor in drug resistance in colon cancer patients receiving cisplatin treatment [175]. MRP2 levels were also increased in SW620 and LoVo cells exposed to oxaliplatin generating cross-resistance to 5-FU, etoposide, cisplatin, vincristine and epirubicin [203].

5. OVERCOMING MDR IN HCC AND CRC

Efflux of drugs by ABC transporters decreases intracellular drug concentration causing failure of chemotherapy. Therefore, the inhibition of ABC transporter activity either by co-administrating inhibitors or by suppressing its protein expression has been suggested as effective approaches to sensitize drug-resistant cancer cells to anticancer drugs. In this section several methods designed to reverse the resistance mediated by ABC transporters are detailed. These strategies include the use of synthetic inhibitors, natural products, biological agents (siRNA and miRNA), inhibitors of ABC transporter regulating pathways, monoclonal antibodies, ultrasound waves and new drug delivery system (nanoparticles) (Table **2**). All the strategies described below are shown schematically in Fig. (**2**).

5.1. Synthetic Inhibitors

Considering P-gp, three generations of synthetic inhibitors were developed. First-generation inhibitors (such as verapamil, cyclosporine A, erythromycin, tamoxifen, *etc.*) have high toxicity and low efficacy at tolerable doses. Both verapamil and cyclosporine A have been assessed in clinical trials but high doses of these drugs were required in patients to reverse MDR and serious side effects were observed [204, 205]. Afterwards, second-generation of P-gp inhibitors were developed to improve efficacy and to reduce secondary effects. The analogue of cyclosporine A, PSC833 (valspodar) was 10- to 20-fold more potent than its precursor in reversing MDR in cell lines [206, 207] and also effective in solid tumor MDR models in animals [208]. However, clinical trials demonstrated that PSC833 impaired drug metabolism and excretion of co-administered drugs. Consequently, patients were exposed to higher serum concentrations of chemotherapeutic agents with risk of toxicity [209, 210]. Third-generation of P-gp inhibitors, such as tariquidar (XR9576) at nanomolar concentration, were more specific and effective. This compound potentiates the antitumor activity of doxorubicin without significant toxicity in mice with resistant colon tumors [211] and do not seem to produce pharmacological interactions in phase I clinical trials [212, 213]. More promising results are nowadays expected from phase II and III clinical studies.

Phenothiazines and structurally-related compounds are also P-gp inhibitors even more potent than verapamil. They increase the cytotoxic effect produced by doxorubicin on both sensitive and resistant colon adenocarcinoma cell lines [214]. Other P-gp inhibitors such as all-trans retinoic acid (ATRA) and its derivative 6-OH-11-O-hydroxyphenanthrene (IIF, pat. WIPO W000/117143) reduced P-gp synthesis in LoVo/MDR cells [215].

A lipophilic 7-modified camptothecin analogue (ST1481) was able to reverse BCRP-associated resistance in a mitoxantrone-resistant HT29 colon carcinoma cell line [216]. Despite a large number of reports

Table 2. Strategies to overcome multidrug resistance targeting ABC transporters in HCC and CRC.

		ABC Transporter	References
Synthetic inhibitors	First generation inhibitors (verapamil, cyclosporine A, erythromycin, tamoxifen, etc).	P-gp	[204,205]
	Second generation inhibitors (valspodar)	P-gp	[206-210]
	Third-generation inhibitors (tariquidar)	P-gp	[211-215]
	ST1481	BCRP	[216-218]
	Probenecid, MK571	MRP2	[219, 220]
Natural products	Steroidal saponin (from *Trilluim tschonoskii*)	P-gp, MRPs (1, 2, 3, 5)	[228]
	Crude extracts from *Antrodia Camphorata* and C-phycocyanin extracted from *Spirulina platensis*	P-gp	[235, 236, 242]
	Shikonin (from *Lithospermum erythrorhizon)*	P-gp (*via* SIRT1)	[249,250]
	Isocorydine derivative *(*from *Dicranostigma leptopodum)*	P-gp and BCRP (*via* IGF2BP3)	[238]
	Epigallocatechin-3-gallate derivative Y6 (green tea)	BCRP (*via* HIF-1α)	[244]
	Compounds obtained from *Salvia miltiorrhiza*	P-gp	[252]
	Curcumin	P-gp	[253,254]
	Sipholenol A (a marine-derived triterpene)	P-gp	[255]
	Fumitremorgin C (a fungal toxin)	BCRP	[256]
Biological Agents (siRNA and miRNA)	siRNA	P-gp, MRPs, BCRP	[99,140,257,258]
	Promoter-driven ABC transporter antisense constructs	P-gp, MRP2	[259,260]
	shRNA	P-gp	[261]
	Overexpression of miR-223, miR-27a, miR-133a, miR-326	P-gp	[27,30,263]
	Overexpression of miR-122 and miR-503	P-gp, MRP1	[264,265]
	miR-519c	BCRP	[267]
	miR-297	MRP2	[268]
Inhibitors of ABC transporter regulating pathways	SIRT1 silencing	P-gp	[269,270]
	COX-2 and AP-1 inhibition, inactivation of ERK, JNK, p38 signal transduction pathways	P-gp	[270, 271]
	Transfection with TFPI-2	P-gp, MRP1	[272]
	HIF-1α degradation and NF-κB inactivation	P-gp	[142]
	AMPK/mTOR/HIF-1α pathway	P-gp, MRP1	[273, 274]
	SLAMF3	MRP1	[275]
	inhibiton of PI3K/AKT/mTOR and RAS/ERK pathways	P-gp	[139]
	JNK1/c-jun signaling pathway	BCRP	[276]
	galectin-3 knockdown	P-gp, MRP1, MRP2	[277]
	NF-κB signaling inhibition	P-gp	[278-281]
Monoclonal Antibodies	MRK-16	P-gp	[284,286]
Ultrasound waves		P-gp, MRP1	[287-289]

(Table 2) contd….

		ABC Transporter	References
New drug delivey system (nanoparticles)	Lipid doxorubicin and curcumin NPs	P-gp	[293]
	Co-administration of recombinant mutant human TNF-α and a sublethal dose of chemicals (doxorubicin, mitomycin and 5-FU) and hydroxyapatite NPs	P-gp, BCRP	[295]
	Polymeric NPs of low-density lipoprotein loaded with cholesterol-conjugated *MDR1* siRNA and N-succinyl chitosan loaded with doxorubicin	P-gp	[297]
	Chitosan-graf t-D-α-tocopheryl polyethylene glycol 1000 doxorubicin-loaded NPs	P-gp	[299]
	N-octyl-O-sulfate chitosan (NOSC), and its paclitaxel (PTX)-encapsulated micelles (PTX-M)	P-gp	[300]
	Low molecular weight heparin NPs modified by glycyrrhetinic acid and lactobionic acid and loaded with doxorubicin	P-gp	[302]
	2-(9-anthracenylmethylene)-hydrazinecarbothioamide *via* conjugation with the cell-penetrating peptide TAT (transactivator of transcription) modified gold NPs	P-gp	[304]
	Synthesized folate (FA)-conjugated selenium NPs	P-gp, MRP1, BCRP	[298]
	Combination of FA, monoclonal P-gp antibodies and miR-122-loaded gold NPs	P-gp	[301]
	Lactobionic acid-conjugated D-α-tocopheryl polyethylene glycol 1000 succinate NPs	P-gp	[303]
	Mitoxantrone encapsulated in a dual functional galactosyl group (Gal-P123) modified liposome.	BCRP	[305]

about the discovery of BCRP inhibitors, only few have examined their clinical efficacy in humans [217, 218].

Also, structurally different compounds (probenecid, MK571, *etc*.) were able to inhibit MRPs activities in rat intestine and colon carcinoma cell lines [219, 220]. It was recently reported that the aromaticity and lipophilicity affect inhibitory activities whereas anionic charge is not required for inhibitory capability [221].

Most of the results reported about synthetic inhibitors of ABC transporters were obtained in *in vitro* systems. The clinical use of these experimental tools has been scarcely investigated *in vivo* or has resulted unsuccessful until now. The reason is related to several problems such as toxicity or safety and poor knowledge of the pharmacokinetic properties of compounds with novel chemical structures [7, 222]. Indeed, many of them also inhibit cytochrome P450 and impair drug clearance, putting a risk of toxicity and adverse effects in normal cells [223].

5.2. Natural Products

Besides synthetic ABC inhibitors, there are several promising anti-MDR strategies evolving. Natural compounds extracted from fruits, vegetables, mushrooms, oilseeds, herbs, bacteria and animals, as well as its derivatives obtained by chemical modifications, are able to modulate ABC proteins and exhibit less cytotoxicity than the synthetic ABC inhibitors previously described [224]. In multidrug resistant HCC cell lines these compounds suppressed the expression and/or activity of P-gp, MRPs and/or BCRP and thus increased the sensitivity and intracellular accumulation of sorafenib and other chemotherapy drugs [225–249]. Some of them also inhibited xenografts tumor formation *in vivo* in mice [228, 236]. Some works studied the mechanism of action of these natural compounds. For example, extracts from *Antrodia camphorata* and C-phycocyanin extracted from *Spirulina platensis* act by inhibiting the cyclooxygenase-2 (COX-2) pathway, which is involved in the development of the MDR phenotype and in the inhibition of apoptosis, *via* the downregulation of P-gp, p-AKT, NF-κB and AP-1 [235, 236, 242]. In addition, it was found that shikonin, from *Lithospermum erythrorhizon,* downregulates the expression of the class III histone deacetylase sirtuin 1 (SIRT1), which induces P-gp upregulation and associates with tumor progression and resistance to sorafenib and other drugs [249, 250]. An isocorydine derivative from *Di*

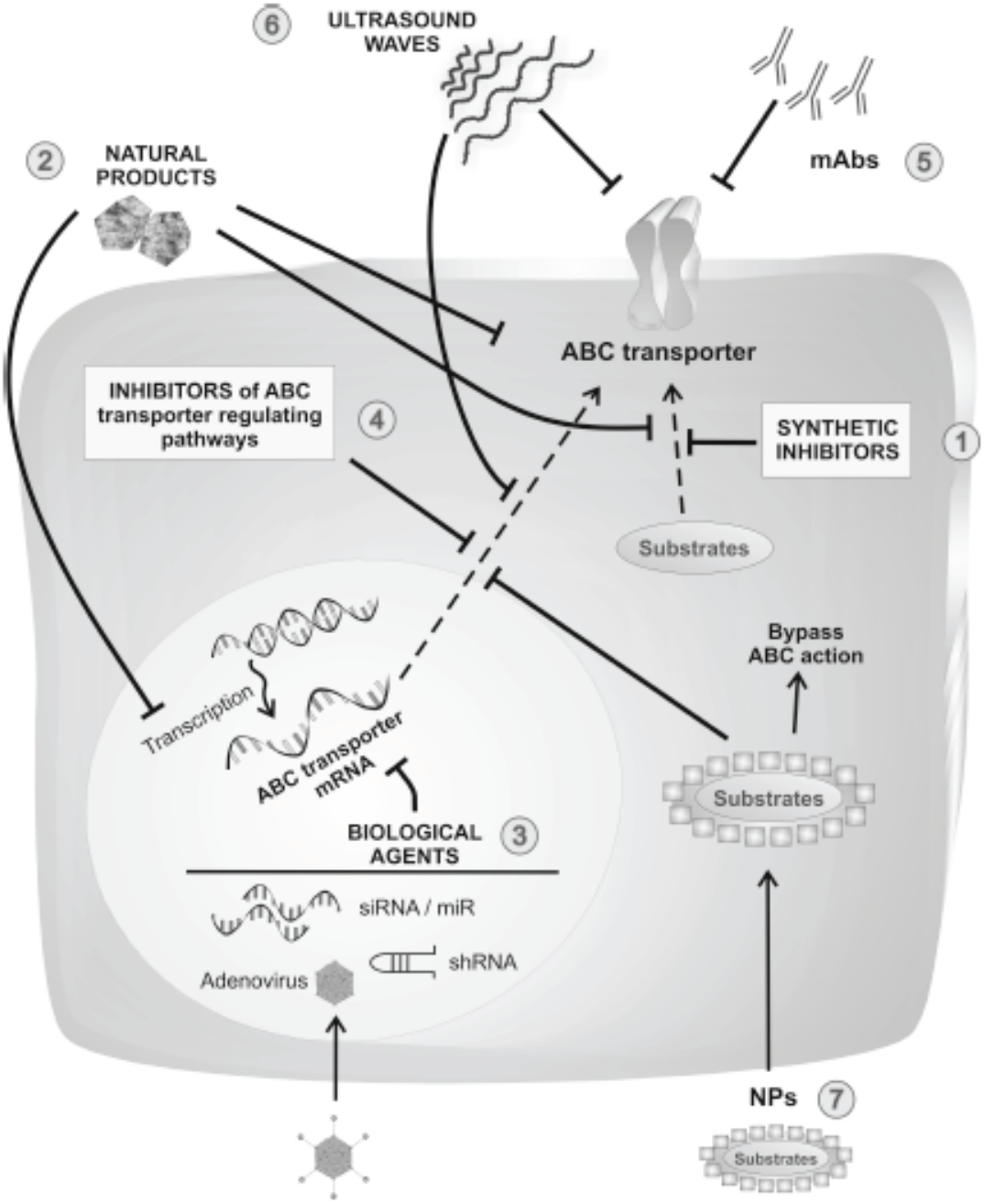

Fig. (2). Strategies to reverse MDR mediated by ABC transporters. Several mechanisms to overcome MDR are presented. Synthetic inhibitors that affect ABC transporters activity (1), natural products which could inhibit ABC transporters activity, expression or alter their regulating pathways (2), biological agents such as siRNA, shRNA or adenovirus affecting ABC transporter expression (3), inhibitors of ABC transporter regulating pathways (4), monoclonal antibodies (mAbs) against ABC transporters (5), ultrasound waves that decrease ABC transporter levels (6) and ABC transporter substrate encapsulation by different nanoparticles (NPs) bypassing ABC action or inhibiting ABC transporter expression (7).

cranostigma leptopodum attenuates cell growth and P-gp and BCRP expression by inhibiting IGF2BP3 expression (like IGF2BP1, IGF2BP3 is an oncoprotein expressed in HCC cells) [238] whereas the epigallocatechin-3-gallate derivative Y6, extracted from the green tea, decreases the expression of HIF-1α [244] which in turn is a BCRP modulator. Therefore, these natural products show strong MDR reversal activity and could be used as adjunctive agents for hepatic cancer chemotherapy. Similarly, natural products were used to obtain the fourth generation of P-gp inhibitors that sensitize resistant colon cancer cells [251]. Com-

pounds obtained from *Salvia miltiorrhiza* enhance doxorubicin and irinotecan cytotoxicity in a P-gp overexpressing CRC cell line almost certainly by downregulating its mRNA and protein levels and inhibiting its ATPase activity [252]. Curcuminoids suppress P-gp expression and increase the anticancer activity of 5-FU in colon cancer cell lines [253]. Besides, in an *in situ* cancerous colon perfusion model in rat, it was demonstrated that curcumin inhibits P-gp activity increasing irinotecan absortion [254]. Similarly sipholenol A, a marine-derived triterpene, efficiently inhibits P-gp in cancer cells representing a potential reversal agent for the treatment of multidrug resistance [255]. Fumitremorgin C (FTC), a fungal toxin that strongly and specifically inhibits BCRP, overcomes resistance to mitoxantrone, doxorubicin and topotecan *in vitro* [256].

5.3. Biological Agents

Another approach for drug resistance reversal is the use of biological agents such as small interfering RNAs siRNA and microRNAs (miRNAs) to downregulate the expression of ABC family members. The transient inhibition of *MDR1* [257], *MRPs* [99, 140] and *BCRP* [258] genes by siRNA enhanced and selectively restored the sensitivity of MDR-resistant HCC cells to anticancer drugs. In addition, animal experiments suggested that silencing *MRP* genes with siRNA inhibited tumor growth *in vivo* [99]. Alternatively, adenoviral delivery of alpha fetoprotein promoter-driven anti-MDR1 ribozymes constructed to allow specific gene transfer to HCC cells, completely restored the chemosensitivity to anticancer drugs [259]. In the same way, transfection of HCC cells with adenoviral vectors using cytomegalovirus promoter-driven MRP2 antisense constructs demonstrated the specific reversal of MRP2-related drug resistance in these cells, even after the generation of HCC tumors in nude mice [260]. On the other hand, MDR can be reversed by short hairpin RNA (shRNA)-mediated *MDR1* long-term suppression in MDR-resistant HCC cells [261]. In addition, the upregulation of ABC transporters in HCC is associated with miRNAs downregulation. Borel *et al.* [109] found in paired HCC patient samples the dysregulation of 90 miRNAs in HCC compared with adjacent healthy liver, and an inverse relation between ABC and miRNA expression in individual patients. In addition, Zhuo *et al.* [262] reported differentially expressed miRNA profiles in five drug-resistant HCC sublines compared to the parental HCC cell line. In relation with this, in HCC lines the overexpression of miR-223, miR-27a, miR-133a and miR-326 generated the downregulation of P-gp [27, 30, 263], whereas the overexpression of miR-122 and miR-503 generated the downregulation of P-gp and MRP1 [264, 265], at both mRNA and protein levels, sensitizing these cells to anticancer drugs. Until now, no report exists about the reversal of P-gp mediated MDR *via* miRNA modulation in CRC. It was reported that downregulation of miR-145 in Caco-2 cells induced P-gp expression and activity but not *MDR1* mRNA level. In the same study, miR-145 negatively modulates P-gp expression and function through the repression of mRNA by direct interaction with its 3′UTR [29]. Regarding BCRP, it was observed that its overexpression generates resistance to 5-FU and irinotecan substrates *in vitro* [266]. In tumors from patients with CRC sensitive to chemotherapy low levels of BCRP expression were found compared to surrounding normal colon tissues. Conversely, in patients not responding to 5-FU-based chemotherapy, the tumor was found to have higher BCRP levels than the adjacent colon tissues. The high expression of BCRP was associated with the simultaneous overexpression of the mRNA binding protein HUR and a low expression of miR-519c since this miRNA is a known regulator of both proteins [267]. The authors suggest that miR-519c could also be a feasible drug target to modulate BCRP expression to reverse MDR in CRC chemotherapy. Similarly, it was reported that miR-297 was downregulated in human CRC and that MRP2, a predicted target of miR-297, progressively increased with the tumor stage [268]. The authors found a negative correlation between miR-297 and MRP2 mRNA levels in CRC. They also suggest that the findings may be useful to predict MDR in patients and to design personalized therapy for CRC patients. Thus, ABC transporter silencing and miRNA-based gene therapies provide valuable approaches to make MDR human carcinoma cells sensitive to chemotherapy drugs.

5.4. Inhibitors of ABC Transporter Regulating Pathways

As mentioned before, ABC expression and activity are regulated by different intracellular signaling pathways that could enlarge the spectrum of pharmacological targets for overcoming MDR in cancer. For example, SIRT1-silencing by the use of SIRT1 SMART small interfering RNA duplex or shRNA targeting SIRT1 sensitized HCC cells to anticancer treatments [269, 270]. Celecoxib, a selective inhibitor of COX-2, enhanced the sensitivity of HCC cells to chemotherapy drugs in a process mediated by the downregulation of P-gp expression by COX-2 and AP-1 and also by the inactivation of ERK, JNK and p38 MAPK signal transduction pathways [271]. Transfection of chemo-

resistant HCC cells with tissue factor pathway inhibitor-2 (TFPI-2), which plays an important role in inhibiting cell metastasis and tumor invasion, improved sensitivity to drugs and the mechanism involves the p38-mediated downregulation of *MDR1* and *MRP1* gene expression [272]. On the other hand, it is known that HCCs clinically resistant to sorafenib, exhibit increased intratumoral hypoxia compared to HCCs before treatment or HCCs sensitive to sorafenib, and the resistance is mediated by HIF-1α and NF-κB activation. In addition, P-gp is significantly induced by hypoxia in the presence of sorafenib [142]. In this relation, EF24, a molecule having structural similarity to curcumin, overcomes sorafenib resistance through HIF-1α degradation and NF-κB inactivation in HCC and the combination of EF24 and sorafenib showed synergic effects against metastasis both *in vivo* and *in vitro*. In this study, synergistic tumor growth inhibition effects were also observed in subcutaneous and orthotopic hepatic tumors in mice [142]. Metformin, a commonly used biguanide antidiabetic drug with anti-proliferative properties, downregulated the expression of P-gp and MRP1 and reversed MDR in human HCC cells [273, 274]. Metformin targeted the AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) pathway and suppressed HIF-1α, a downstream protein of mTORC1, which in turn regulated the expression of P-gp and MRP1 [273]. Also, metformin downregulated P-gp through the inhibition of the NF-κB signaling pathway [274]. In another work, an inverse correlation between signaling lymphocytic activation molecule family member 3 (SLAMF3) and MRP1 expression was found in HCC patient samples and HCC cell lines, and the overexpression of SLAMF3 in HCC cells induced specifically MRP1 dysfunction and improved sensitivity to sorafenib [275]. Combining sorafenib with the specific inhibitors of PI3K/AKT/mTOR and RAS/ERK pathways MK-22062HCL and PD0325901, respectively, synergistically inhibited cell growth and decreased *MDR1* gene expression in sorafenib-resistant HCC cell lines [139]. Regarding CRC, JNK1/c-jun signaling pathway was involved in BCRP-mediated MDR in the human colon cancer cell line SW1116 resistant to hydroxycamptothecin (HCPT). The inhibition of the JNK1/c-jun pathway reduce the expression level and transport function of BCRP and could be suitable for reversing BCRP-mediated drug resistance in HCPT-resistant colon cancer cells [276]. A study from Lee *et al.* [277] demonstrated that galectin-3 knockdown increased the intracellular concentration of epirubicin in Caco-2 cells by suppressing the mRNA expression of galectin-3, β-catenin, *MDR1*, *MRP1* and *MRP2*, and downregulating the expression of P-gp among other proteins. It is known that P-gp expression is regulated by NF-κB/p65 and inhibition of NF-κB leads to downregulation of P-gp expression [278-280]. Related to this, it was reported that long-term treatment with TNF-α reduced NF-κB signaling resulting in the downregulation of P-gp in the human HCT15 colorectal carcinoma cell line, favoring its chemosensitization [281]. Thus, targeting signaling pathways implicated in the regulation of ABC proteins may be a promising way to affect the ABC profile and overcome clinical MDR.

5.5. Monoclonal Antibodies

The monoclonal antibodies developed against P-gp, MRK-16 and MRK-17, have shown to reverse drug resistance mediated by P-gp both *in vivo* and *in vitro*. MRK-16 inhibited actinomycin D and vincristine efflux, and MRK-17 affected the proliferation of MDR cells [282-286]. In an *in vivo* model of HCC, MRK-16 was tested in mice bearing a tumor derived from Alex cells and from an Alex MDR clone. Immunotherapy with MRK-16 suppressed the *in vivo* growth of tumors derived from both cell lines [286]. Regarding CRC, MRK-16 monoclonal antibody was able to reverse vincristine resistance in HT-29 mdr1 tumor-bearing mice increasing the median survival time [284].

5.6. Ultrasound Waves

Another less explored strategy in HCC is the use of ultrasound waves [287–289]. Ultrasound waves enhanced the cellular uptake and cytotoxicity of chemotherapeutic agents in drug-resistant HCC cells [289], *via* decreasing P-gp and MRP1 protein and mRNA levels and increasing apoptosis through the raise of Bax protein expression [288]. Thus, ultrasound wave-mediated reversal of MDR may lead to the development of a novel strategy of using a targeted, non-invasive physical approach that would resensitize the MDR cancer cells to chemotherapy.

5.7. New Drug Delivery System (Nanoparticles)

Finally, the development of new drug delivery systems that can bypass the ABC family of transporters such as nanoparticles (NPs) are used extensively to deliver antitumor chemicals to specific target cells/tissues of patients. Highly efficient targeted delivery is crucial for successful anticancer chemotherapy. In this regard, NPs improve the drug therapeutic index and overcome dose-limiting side effects, lack of selectivity, tissue toxicity, limited drug access to tumor tissues, high drug doses, and emergence of multiple drug resistance with

conventional or combination chemotherapy. Examples of NPs include polymers, solid lipids, metals, quantum dots, dendrimers, liposomes, micelles, magnetic NPs, silica NPs and cell penetrating peptides (for a review of nanoparticles see [290-292]).

Some of these NPs reversed MDR by decreasing the expression of P-gp, MRP1 and/or BCRP and suppressed cell growth and induced apoptosis in MDR HCC cells [293-298]. For example, lipid doxorubicin and curcumin NPs reduced P-gp and Bcl-2 protein and mRNA levels [293, 294]. Also the co-administration of recombinant mutant human TNF-α and a sublethal dose of chemicals (adriamycin, mitomycin and 5-FU) and hydroxyapatite NPs inhibited *MDR1* and *BCRP* gene expression [295]. Polymeric NPs of low-density lipoprotein loaded with cholesterol-conjugated *MDR1* siRNA and N-succinyl chitosan loaded with doxorubicin decreased *MDR1* levels [297]. Other NPs reversed MDR by blocking or bypassing P-gp pump action [299-304] or by inhibiting BCRP-mediated drug efflux [305]. For example, chitosan-graf t-D-α-tocopheryl polyethylene glycol 1000 doxorubicin-loaded NPs greatly enhanced cell cytotoxicity and apoptosis of drug-resistant HCC cells as compared to adriamycin and this can be attributed to P-gp blocking by these NPs [299]. The efficacy of a synthesized amphiphilic graft copolymer, N-octyl-O-sulfate chitosan (NOSC), and its paclitaxel (PTX)-encapsulated micelles (PTX-M) resulted from a combination of the inhibiting P-gp effect of NOSC and the bypassing P-gp action of the intact PTX-M [300]. Conversely, the low molecular weight heparin NPs modified by glycyrrhetinic acid and lactobionic acid and loaded with doxorubicin are internalized *via* energy-dependent endocytosis and thus can bypass P-gp pump [302]. In the same way, Wang *et al.* [304] developed a drug delivery system that loads the anticancer molecule 2-(9-anthracenylmethylene)-hydrazinecarbothioamide *via* conjugation with the cell-penetrating peptide TAT (trans-activator of transcription) modified gold NPs, that effectively prevent drug efflux due to their size being much larger than that of P-gp channel. As stated before, this drug delivery system has the advantage of targeting only HCC cells. For example, the synthesized folate (FA)-conjugated selenium NPs increase the sensibility of HCC cells overexpressing the FA receptor, which transports the captured drugs into the cell by receptor-mediated endocytosis, and MDR HCC cells by inhibition of P-gp, MRP1 and BCRP proteins expression. These NPs could be used as a cancer-targeted carrier of the metal-based anticancer drug ruthenium polypyridyl [298]. Likewise, another option is the combination of FA, monoclonal P-gp antibodies (for targeting MDR cancer cells) and miR-122 (downregulated in high metastatic liver cancer cells)-loaded gold NPs [301]. Another example are the lactobionic acid-conjugated D-α-Tocopheryl polyethylene glycol 1000 succinate NPs that were developed as a potential asialoglycoprotein receptor (ASGPR)-targeted nanocarrier that effectively inhibit P-gp for etoposide efflux specifically in HCC cells, since these cells overexpress this receptor in their membranes [303]. Similarly, the encapsulation of mitoxantrone in a dual functional galactosyl group (Gal-P123) modified liposome enhance its therapeutic efficacy against HCC cells by simultaneously targeting the Gal-P123 receptor overexpressed in these cells (ASGPR) and inhibiting BCRP-mediated antitumor drug efflux [305]. Some of these NPs also restored the chemotherapeutic sensitivity in mouse models and in clinical samples [293–296, 299-303, 305]. Therefore, the development of targeted drug delivery systems offers the potential for high accumulation of chemotherapeutics within the cancer-affected organ through means of active and passive targeting to overcome MDR, thereby reducing the unwanted exposure of cytotoxic agents to healthy tissue.

CONCLUSION

It is largely known that one of the major obstacles in the successful chemotherapy of cancer is the overexpression of ABC transporters such as P-gp, MRPs and BCRP, that leads to the MDR phenotype. One of the challenges to overcome MDR is to achieve higher drug concentrations inside the tumor cells and therefore a better therapeutic outcome. It is considerable interesting to study the pathways involved in the regulation of ABC transporters in tumor cells, particularly those that are not involved in the regulation of ABC transporters in normal cells. Thus, new targets could be proposed preserving the normal functioning of non-tumor cells avoiding all the known adverse effects.

LIST OF ABBREVIATIONS

ABC = ATP Binding Cassette

BCRP = Breast cancer resistance protein

CRC = Colorectal cancer

HCC = Hepatocellular carcinoma

MDR = Multidrug resistance

miRNA = microRNA

MRPs = Multidrug resistance associated proteins

P-gp = P-glycoprotein

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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