REVIEW ARTICLE

Role of multidrug resistance-associated proteins in cancer therapeutics: past, present, and future perspectives

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Abstract

Cancer, a major public health problem, is one of the world's top leading causes of death. Common treatments for cancer include cytotoxic chemotherapy, surgery, targeted drugs, endocrine therapy, and immunotherapy. However, despite the outstanding achievements in cancer therapies during the last years, resistance to conventional chemotherapeutic agents and new targeted drugs is still the major challenge. In the present review, we explain the different mechanisms involved in cancer therapy and the detailed outlines of cancer drug resistance regarding multidrug resistance-associated proteins (MRPs) and their role in treatment failures by common chemotherapeutic agents. Further, different modulators of MRPs are presented. Finally, we outlined the models used to analyze MRP transporters and proposed a future impact that may set up a base or pave the way for many researchers to investigate the cancer MRP further.

Keywords ABC transporters · Anticancer drugs · Epigenetic alterations · MDR · MRP · MicroRNAs · Organoids

Introduction

By advancing cancer topics, our knowledge of cancer biology is being updated every time. Cancer results in high proliferative growth of abnormal cells with marked changes in the genome properties. Besides, the cancer progression affects the normal biological process of neighboring healthy cells through the invasion of nearby tissues and metastasis to another (Macconaill and Garraway 2010).

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Responsible Editor: Lotfi Aleya

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There have been huge efforts to clarify the basis of cancer biology and develop anti-cancer drugs. Anti-cancer agents recorded a significant jump from conventional cytotoxic chemotherapeutics to targeted and immune-related therapies in the last few decades. The conclusive goal for anti-cancer drugs is to disrupt the tumor cells and control their proliferation to prolong the patient survival time and improve their lives. This can be achieved in many ways. Based on the mechanism of action of anti-cancer drugs, chemotherapeutics can be divided into the following: (1) alkylating agents, which induce intra-strand DNA crosslinks that subvert DNA during replication (e.g., cyclophosphamide); (2) antimetabolites, which inhibit the synthesis of DNA and RNA (e.g., 5-fluorouracil (5-FU)); (3) topoisomerase inhibitors (protein synthesis interferer), which hinder the correct transcription and translation (e.g., irinotecan); and (4) cytotoxic antibiotics, which exert an anti-neoplastic effect through DNA damage and generation of reactive oxygen species (e.g., bleomycin) (Werner et al. 2014). So far, drug industries have produced four main groups of anti-cancer drugs: (1) cytotoxic drugs (alkylating agents, antimetabolites, antibiotics, plant extracts, and various cytotoxic drugs), (2) targeted based agents, (3) hormones and hormones antagonists, and (4) immunomodulators (Arrondeau et al. 2010). In chemotherapy, following the administration of a particular drug, many patients become resistant to this drug. So, anti-cancer drug progress has developed from conventional nonspecific cytotoxic agents, which often kill proliferating normal cells to specific target-based cancer therapy designed to destroy tumor cells only, and on immune-related modulators that help the patient's immune system to defeat tumor cells (Kummar et al. 2010; Mackall et al. 2014).

Targeted therapy works via interference with cancer's specific genes, proteins, or the internal tissue environment (tissue microenvironment) contributing to cancer growth and proliferation. These genes and proteins are mainly settled in cancer or cancer growth-related cells. Various targeted anti-cancer agents have been approved for cancer treatment; these therapies include the following: (a) Hormone therapies are mainly for hormone-sensitive tumors that require specific hormones to proliferate. These therapies act by preventing hormone production or by interfering with its effect. They have been licensed for breast and prostate cancer. (b) Gene expression modulators inhibit protein translation that plays a role in gene expression. (c) Apoptosis inducers induce cancer cells to undergo controlled cell death (apoptosis). (d) Angiogenesis inhibitors prevent the proliferation of new blood vessels to the cancer cells by impairing the function of vascular endothelial growth factor (VEGF), a substance that stimulates new blood vessel formation. (e) Immunotherapies provoke the immune system to damage the cancer cells through monoclonal antibodies (MABs) that recognize particular receptors on the surface of the cancer cells (Aggarwal 2010; Benson et al. 2006; Cole 2014).

Despite the significant advances in understanding the etiology and progression of cancer and developing novel diagnostics and therapeutics, one of the leading causes of cancer treatment failure is multidrug resistance (MDR) (Chang 2011). In the present review, we explained the detailed outlines of cancer drug resistance regarding multidrug resistance-associated proteins (MRPs) and their role in treatment failure. Further, different modulators of MRPs are presented. Finally, we outlined the models used to analyze MRP transporters and proposed a future impact that may set up a base or pave the way for many researchers to investigate the cancer MRP further.

Multidrug Resistance-Associated Proteins (MRP)

Multidrug resistance is a drastic obstacle in cancer therapy and one of the primary reasons for none or little response to therapy. It is active against a single drug or chemically related ones and a whole spectrum of chemotherapeutic drugs, even to ones that have not yet been tabled to the patient. Numerous factors involved in mediating MDR may include host factors, tumor factors, as well as tumor-host interplays. The host factors include genetic variants and drug-drug interactions (Assaraf et al. 2019). The tumor factors are many and involve diminished drug uptake at most via reducing influx transporters, boosting drug efflux via overexpression of MDR efflux transporters of the ATP-binding cassette (ABC) superfamily, or triggering extracellular vesicle-induced drug efflux, deregulation of cell death mechanisms, increased DNA damage repair, deregulation of microRNAs, and epigenetic alterations (Assaraf et al. 2019). Other significant tumor factors are intratumor heterogeneity and cancer stem cell plasticity.

The discovery of these MDR proteins began in 1974 when Victor Ling and Larry Thompson described the stable colchicine-resistant cell clone and discovered that the resistant cells did not allow colchicine to get inside (Ling and Thompson 1974). Further studies reported that the main difference between sensitive and resistant cells was the MRP (Cole et al. 1992). It quickly became apparent that all these proteins have the same features and belong to the ABC superfamily of proteins.

The ABC proteins are energy-dependent efflux pumps with very conserved amino acid (AA) sequences at their nucleotide-binding domain (NBD). They comprise one of the most prominent protein families identified to date and are present in almost all cells of most tissue, mainly the lung, kidney, liver, heart, brain, and skin. The human ABC family includes 48 members. To fit human genetic nomenclature requirements, they were subdivided into seven families: ABCA to ABCG (each named ABC followed by a family letter and a number). Accordingly, ABCB1, known as P-gp, ABC-

subfamily C (ABCC1-6,10,11, and 12 known as MDR-associated proteins 1–9 (MRP1–9 organic anion transporters), and ABCG2, identified as BCRP, are the primary efflux transporters mediating MDR (Baguley 2010) (Dean and Allikmets 2001; Li et al. 2016c).

Several studies declared that different mechanisms could be engaged in the evolution of MDR. They include increased drug detoxification or nucleotide damage, redistribution of intracellular drug accumulation, a shift in drug target molecules, and suppression of drug-induced apoptosis (Lage et al. 2001; Nezami 2019). Nevertheless, overexpression of P-gp and MRP1 is the leading cause of MDR in several tissue cancers (Komdeur et al. 2003). Both proteins are part of ATP-binding cassette protein superfamily (ABC transporters). They cause the outflow of anti-cancer molecules out of tumor cells, thereby lowering their intracellular concentrations (Dean and Allikmets 2001; He et al. 2011) (Fig. 1).

The ATP-binding cassette transporters, subfamily C transporters (ABCC)

The molecular structure of ABCC transporters is one of the significant features of this family. The protein control unit consists of six hydrophobic membrane-crossing helical fragments founding a so-called transmembrane domain (TMD) and a hydrophilic cytoplasmic NBD that harbor specific AA sequences for ABC proteins. In most ABCC transporters, such structure is the same, forming a TMD1-NBD1-TMD2-NBD2 single polypeptide assembly (Fernandez et al. 2002) (Fig. 1).

MRP1/ABCC1

The MRP1 gene is in 16p13.1 chromosome and extended to around 200 kb. It holds 31 exons and 1531 AA with a 180–190 kDa molecular weight (Grant et al. 1997) (Table 1). MRP1 was first identified in MDR doxorubicin-selected lung cancer cell line called H69AR (Cole et al. 1992). MRP1 is composed of two NBDs and three membrane spanning domains (MSDs), namely MSD0, 1, and 2 consisting of 17 transmembrane helices (TM), making it different from the structure of specific ABC transporters that comprises two MSDs involving 6 TMs (Bakos et al. 2000). The two NBDs are distinguished by the existence of ABC accountable for turning ATP to ADP+P, which provides power for transmembrane delivery of solutes by MRP1. The MRP1 efflux characteristics and the substrates' topological polar surface area are correlated (Fernandes and Gattass 2009). The protein molecules playing essential functions in identifying the specificity
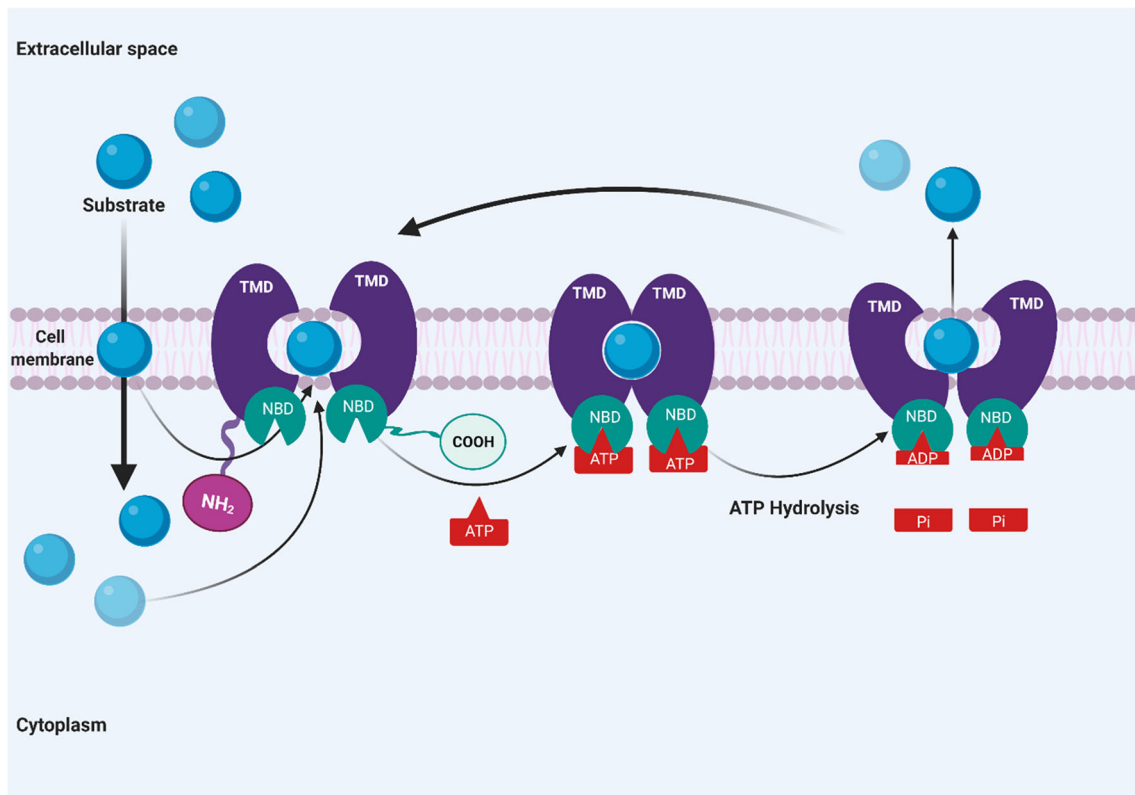

Figure 1 Scheme of the general molecular structure of human ABC subfamily C (long MRP) transporters showing how drug efflux occurred. The transporters are energy-dependent, and upon substrate binding and ATP hydrolysis, they display conformational changes that lead to the substrate's transport process. TMD, transmembrane domain; NBD, nucleotide-binding domain

Table 1 Differences in chromosomal locations, tissues distribution, and physiological substrate specificities of various MRP transporters

Transporter	Chromosome location	Distribution	Physiological substrate specificity	Reference
MRP1	16p3.1	Testes, small intestine, lung, colon, kidney, skin, placenta, skeletal muscle, and blood barriers	GSH conjugates, glucuronide conjugates, sulfate conjugates, and LTC4	Fernandez et al. (2002), Keppler (2011), Michaelis et al. (2009)
MRP2	10q24	Hepatocytes, intestine, kidneys, especially proximal tubules, nerves, urinary bladder, placenta, and CD4$^+$ lymphocytes	GSH conjugates, glucuronide conjugates, and LTC4	Chang (2007), Kranz et al. (2014), Slot et al. (2011)
MRP3	17q21.3	Pancreas, kidney, gut, liver, and adrenal	Glucuronide conjugates DNP-GS	Koike et al. (1997), Slot et al. (2011)
MRP4	13q32	Prostate, ovary, adrenal, pancreas, lung, and skeletal muscle with a low detectable level in the liver	cAMP and cGMP	Kawabe et al. (1999), Kool et al. (1999), Kruh et al. (2001), Zeng et al. (1999)
MRP5	3q27	Prostate, ovary, adrenal, pancreas, lung, and skeletal muscle with a low detectable level in the liver	cGMP and cAMP	Belinsky et al. (2005), Kawabe et al. (1999), Kool et al. (1999)
MRP6	16p13.1	Liver, kidney, pancreas, intestine, and most of the exocrine tissue	GSH conjugates	Reid et al. (2003), Sampath et al. (2002)
MRP7	6p12	Testis, ovary, gut, kidney, and lung	Glucuronide conjugates and GSH conjugates	Belinsky et al. (2005), Chen et al. (2002), Kruh et al. (2001), Wielinga et al. (2002)
MRP8	16q12	Brain and placenta and to a lesser extent to liver and kidney	Glucuronides, bile acids, steroid sulfates	Belinsky et al. (2005), Maeng et al. (2014), Wijnholds et al. (2000)
MRP9	16q12	Brain and placenta and to a lesser extent to liver and kidney	Unknown	Belinsky et al. (2005), Maeng et al. (2014), Wijnholds et al. (2000)

and selectivity of substrates are found in MSD1 and MSD2 as reported in mutagenesis, photo-labeling, and structure-activity relationship studies (He et al. 2011; Iram and Cole 2011).

AA amino acids

MRP1 encodes plasma membrane proteins which have a distinct and vital physiological transport function that mediates the active cellular efflux of different xenobiotics and their metabolites (hydrophobic and hydrophilic antineoplastic agents) against their concentration gradients (drug threshold) (Keppler 2011). MRP1/ABCC1 can transport a broad spectrum of substrates. It has been shown to transport organic anion conjugates, for example, glutathione S-conjugates (Jedlitschky et al. 1994), mono- and di-glucuronides, taurates, and sulfates of bile acids (Jedlitschky et al. 1996). Thus it tends to be the primary conjugate transporter involved in relatively normal detoxification processes (Balcerczyk et al. 2003). Since it can also transport glutathione disulfide, it plays a key role in cellular oxidation processes (Jedlitschky et al. 1997).

MRP1/ABCC1 appears to be expressed in most of all human tissues, higher levels in the testes, small intestine, lung, colon, kidney, skin, placenta, and skeletal muscle (Chang 2007) (Slot et al. 2011), with particular expression in blood-brain, blood test, and blood-cerebrospinal fluid (CSF) barriers (Mercier et al. 2004). MRP1 has been suggested to be overexpressed in leukemias, esophageal cancer, and non-small cell lung cancer (NSCLC) (Nooter et al. 1995). MRP1 levels in the liver are ordinarily low, while the dominant MRP transporter is MRP2 (Keppler 2011) (Table 1).

One of the essential features of MRP1 is the noticeable difference in its substrate specificity among primates and other species, although the AA identity is >90% for all species (Deeley et al. 2006). For example, MRP1 from humans and monkeys can transport estradiol glucuronide and anthracycline agents, such as doxorubicin, whereas this function is missed in mice, canines, and bovine.

MRP1 is involved in the resistance to anthracycline (doxorubicin), vinca alkaloid, and podophyllotoxin, mitoxantrone, methotrexate, as well as alkylating agents (Chen et al. 2003) (Table 2). MRP1 recognizes and outflows some of the newer "targeted" anti-cancer agents that work through modifying signal pathways of tumor growth, proliferation, and metastatic potential. One of these targeted agents is vandetanib (small-molecule tyrosine kinase inhibitor, TKI) that works by blocking the ATP-binding domains of ABC drug transporters. However, the mechanism is still unclear and misunderstood (Brozik et al. 2011). Other targeted anti-cancer agents that interact with MRP1 include the geldanamycin, the farnesyl protein transferase inhibitor lonafarnib, and nutlin-3 (Brozik et al. 2011; Michaelis et al. 2009; Pham et al. 2009; Wang and Johnson 2003). Also, MRP1 can be integrated into multiple physiological and pathophysiological pathways, including

Table 2 The involvement of various MRP transporters in the resistance to different anti-cancer drugs and their common modulators

Transporter	Common anti-cancer agents' resistance*	Common modulators	Reference
MRP1	Anthracyclines, vinca alkaloids, epipodophyllotoxins, folic acid, 5-FU, and methotrexate (MTX)	Ibrutinib and probenecid	Chen et al. (2019), Chen et al. (2003), Jedlitschky et al. (1997), Madon et al. (2000)
MRP2	Anthracyclines, epipodophyllotoxins, vinca alkaloids, cisplatin, and MTX	Probenecid and catechol metabolite	Kool et al. (1997), Kranz et al. (2014), Slot et al. (2008)
MRP3	MTX, etoposide, and teniposide	?	Chu et al. (2006), Huisman et al. (2005)
MRP4	Nucleotide analogs, glucuronide conjugates, MTX	Indomethacin, flavonides, and 3β-acethyl tormentic acid (3ATA)	Kruh and Belinsky (2003), Lee et al. (2000), Smeets et al. (2004)
MRP5	Nucleotide/nucleoside analogs and GSH conjugates	?	Kruh and Belinsky (2003), Lee et al. (2000), Smeets et al. (2004)
MRP6	Anthracyclines, epipodophyllotoxins, and cisplatin	?	Maeng et al. (2014), Sampath et al. (2002)
MRP7	Anthracycline, vinca alkaloids, cisplatin, and taxanes	TKI (nilotinib, imatinib, erlotinib, lapatinib)	Beck et al. (2005), Kao et al. (2003), Ryu et al. (2000)
MRP8	5-FU and MTX	?	Bergen et al. (2000)
MRP9	Unknown	?	-

*Mean that the transporters can also admit resistance to anti-cancer agents containing physiological substrates and their metabolites

inflammatory changes, oxidative defenses (Cole 2014), and the pathogenesis and prognosis of cancer (Yang et al. 2019). Leukotriene C4 (LTC4, a pro-inflammatory arachidonic acid product that is incorporated in asthmatic and allergic reactions as well as smooth muscle constriction (Yonetomi et al. 2015)) is an essential physiological MRP1 substrate (Leier et al. 1994).

MRP2/ABCC2

MRP2 was first cloned from rat liver cells and named canalicular multiple organic anion transporter (cMOAT). It contains 1545 (long MRP) AA residues, is located at the 10q24 chromosome, and shows about 49% AA identity to MRP1 (Table 1). Similarly, with MRP1, MRP2 has three MSD and two NBD features. TM helices were proven necessary for substrates discrimination (Kool et al. 1997; Ryu et al. 2000).

MRP2 is overexpressed in the hepatocytes and intestine, with moderate tissue expression in the kidney, especially proximal tubules, nerves, urinary bladder, placenta, and CD4+ lymphocytes (Huisman et al. 2005; Kranz et al. 2014) (Table 1).

The physiological importance of MRP2 was detected using Mrp2−/− mice (Chu et al. 2006). Researchers suggested MRP2 plays a role in removing endogenous metabolites, xenobiotics, and their metabolites. In the mouse liver, MRP2 transports bilirubin glucuronides to the bile (Chu et al. 2006). MRP2 was reported to confer resistance to many anti-cancer agents such as anthracyclines, as well as vinca alkaloids, camptothecin, tamoxifen, methotrexate, and oxaliplatin, with

remarkable resistance against cisplatin (which not for MRP1) (Kawabe et al. 1999) (Hjorth et al. 2019; Luo et al. 2018; Myint et al. 2019; Valinezhad Sani et al. 2020; Zhang et al. 2019b). Also, MRP2 shows a high affinity to LTC4 like MRP1 (Kawabe et al. 1999) (Table 2).

MRP3/ABCC3

MRP3 is one of the MRPs in which complete coding sequences have been revealed, contains 1527 AA, and is in the 17q21.3 chromosome (Table 1). It has an AA identity of 58 % with MRP1. It is known that MRP3 was predominantly expressed in the pancreas, kidney, gut, liver, and adrenal gland (Kool et al. 1997). MRP3 plays a physiological role in the efflux of organic anions from the cholestatic liver and assists in the enterohepatic circulation of bile acids via the basolateral membranes of enterocytes (Belinsky et al. 2005; Kruh et al. 2001). MRP3 is an organic anion transporter that transports DNP-GS (dinitrophenyl-glutathione) such as MRP1 and MRP2 and may induce resistance to the anti-cancer drugs such as MTX (with a high concentration in a short time), etoposide, teniposide, and glycocholate (Kool et al. 1999). A low level of MRP3 was shown to mediate vincristine resistance in HEK293 cells (Belinsky et al. 2002; Zeng et al. 1999) and chemoresistance in cholangiocarcinoma (PDAC) (Lozano et al. 2020). Further, MRP3 was recently identified as a novel target for treating pancreatic cancer (Adamska et al. 2019b). It is overexpressed in PDAC cell lines and clinical samples. Knockdown of MRP3 in PDAC cell lines reduces cell proliferation by inhibiting STAT3 and HIF1α signaling pathways,

critical regulators of PDAC progression (Adamska et al. 2019b). Moreover, the pharmacological targeting of MRP3 in pancreatic cancer was shown to slow down its progression in animal models and cell lines (Adamska et al. 2019a). These data confirm the role of MRP3 in drug resistance.

MRP4 and MRP5

MRP4 and MRP5 differ from each other in the AA identity. They are in chromosome 13q32 and 3q27.1 and have 1325 and 1437 AA, respectively (Table 1). They have only two MSDs and two NBDs. They are deficient in the extra N-terminal spanning domain present in MRP1 and MRP2 (Borst et al. 2000).

The overexpression of MRP4 and MRP5 mainly presents in the prostate, ovary, adrenal, pancreas, lung, and skeletal muscle with a low detectable level in the liver (Kruh and Belinsky 2003). A survey of the human expressed gene sequence database against the MRP4 showed that MRP4 mRNA exists in most tissues except for bone marrow, vascular endothelium cervix, thymus, and soft tissue. A unique characteristic of MRP4 is its dual localization in polarized cells: it can appear apically and basolaterally depending on the cell type (Lee et al. 2000). For example, MRP4 is found in the basolateral membrane of the human prostate cells. In contrast, it was in the apical membrane of cells of proximal renal tubules (Smeets et al. 2004).

MRP4 and MRP5 are incorporated in the physiological transport of cyclic adenosine monophosphate (cAMP), nucleoside diphosphate, or triphosphate (Reid et al. 2003) and cyclic guanosine monophosphate (cGMP) (Chen et al. 2001; Sampath et al. 2002). The substrates of MRP4 as MDR are effluxing anionic phosphate metabolites and glucuronides substances such as E217βG (Maeng et al. 2014), thiopurine analogs, MTX, and topotecan (Chen et al. 2002; Wielinga et al. 2002), while the substrates of MRP5 are dinitrophenyl-S-glutathione (DNP-SG), cisplatin, purine analogs, and GSH compounds (Wijnholds et al. 2000) (Table 2). Recently, MRP4 has been linked with cell proliferation in various types of cancer, including pancreas, ovary, lung, breast, colon, and osteosarcoma (Colavita et al. 2020; Low et al. 2020). In castration-resistant prostate cancer, MRP4 was overexpressed and mediated the acquired docetaxel resistance, reversed by antiandrogen treatment (Huang et al. 2020; Li et al. 2017). Further, in acute lymphoblastic leukemia, high MRP4 expression is associated with ex vivo MTX resistance (Jaramillo et al. 2019). In PDAC cells, MRP4 was found overexpressed and increased its proliferation by modulating the cAMP efflux, and its pharmacological targeting or silencing decreased cell proliferation through the stimulation of the cAMP/Epac/Rap1 signaling pathway (Carozzo et al. 2019). In ovarian cancer showing Myc overexpression, MRP4 contributes to its aggressiveness and is recommended as a potential

therapeutic target (Jung et al. 2020). MRP4 was reported to be overexpressed in clear cell renal cell carcinoma and essential to regulate its cell proliferation (Colavita et al. 2020). MRP5 was recently shown to be overexpressed in GEM-resistant PDAC cells and successfully targeted via its nitration by nitric oxide–releasing gemcitabine pro-drugs that are encapsulated in liposomes (Masetto et al. 2020). These data suggest the possible roles of MRP4 and MRP5 in the resistance of different cancers to anti-cancer drugs.

MRP6/ABCC6

MRP6 is located in the 16p13 chromosome next to MRP1 with AA identity (40–45%) to other MRP and contains 1503 AA. Its expression occurs mainly in the liver, kidney, pancreas, intestine, and most exocrine tissues (Beck et al. 2005) (Table 1). Mutations in the MRP6 gene were related to pseudoxanthoma elasticum, a congenital disorder of the connective tissue involving impaired vision, skin lesions, and cardiovascular disorders (Bergen et al. 2000). MRP6 was described to transport and confer efflux of glutathione conjugates, anionic cyclopentapeptide BQ123 (the endothelin receptor antagonist), and epipodophyllotoxins (Belinsky et al. 1998; Madon et al. 2000). Recently, in intrahepatic cholangiocarcinoma, MRP6 was expressed and significantly upregulated upon gemcitabine exposure. Interestingly, MRP6 knockdown greatly enhanced gemcitabine-induced cytotoxicity (Yang et al. 2021).

MRP7, MRP8, and MRP9

ABCC10, ABCC11, and ABCC12 are the last identified three members of the MRP family. MRP7 is like MRP1, MRP2, MRP3, and MRP6 in possessing three MSDs and two NBDs (Kao et al. 2003), while the topology of MRP8 and MRP9 is similar to those of MRP4 and MRP5 (Madon et al. 2000). MRP7 is in the 6p12 chromosome, while the MRP8 and MRP9 are closely identical (47% identity), and their genes are at the same site of the 16q12 chromosome (Table 1). MRP7 is expressed in the testis, ovary, gut, kidney, and lung (Takayanagi et al. 2004), while MRP8 and MRP9 are expressed in both the brain and placenta and to a lesser extent in the liver and kidney (Bera et al. 2001).

MRP7 is a lipophilic negatively charged transporter (known as ATP-gated chloride channel). The most common physiological substrates selective for MRP7 are 17β-glucoronsyle estradiol (E217βG) and leukotriene C4 (Chen et al. 2001; Reid et al. 2003). It can confer resistance to some anti-cancer agents, specially taxanes (Huisman et al. 2005), as was determined using HEK293 cells for docetaxel, microtubule-stabilizing agent paclitaxel, vincristine, and vinblastine (Bortfeld et al. 2006). It is also associated with paclitaxel and vinorelbine resistance in NSCLC by increasing their

efflux (Bessho et al. 2009; Oguri et al. 2008). The MRP7-mediated resistance to paclitaxel and vincristine could be reversed using TKIs, imatinib, and nilotinib (Shen et al. 2009) and tandutinib (Deng et al. 2013), as shown in HEK293 cell by blocking the efflux action of MRP7.

MRP8 has a broad spectrum of physiological substrate selectivity of lipophilic anions including glutathione conjugates, LTC4, DNP-SG, monoanionic bile acids glycocholate, E217βG, steroid sulfates dehydroepiandrosterone (DHEAS), estrone 3-sulfate (E13S), folic acid, as well as the substrate of MRP5 and MRP4 (cAMP-cGMP) (Bortfeld et al. 2006; Chen et al. 2001) (Table 2). The drug resistance-promoting ability of MRP8 was assured where it confers resistance to some anti-cancer agents such as 9′-2′- phosphonylmethoxyethyl adenine, the active metabolite of the prodrug adefovir (dipivoxil); zalcitabine; anti-HIV drugs; and 5-FU (Pratt et al. 2005; Uemura et al. 2019). In lung cancer, MRP8 was revealed to confer pemetrexed drug resistance in lung cancer (Uemura et al. 2010). Also, MRP8 expression was shown to significantly increase in alectinib-resistant anaplastic lymphoma kinase-rearranged NSCLC cell lines, and its inhibition increased the sensitivity to alectinib in vitro (Funazo et al. 2020). Overexpression of MRP8 in breast carcinoma subtypes was linked with its aggressiveness and poor prognosis (Yamada et al. 2013).

It has been suggested that MRP9 (ABCC12) may play a role as an anti-cancer resistance transporter protein after expression in human embryonic kidney cells. However, until now, the physiological part of MRP9 and its mechanism in cancer chemotherapy need more elucidation and further research. Recently, the MRP9 gene was identified as an anti-cancer drug-resistant protein (Shi et al. 2020). In lung cancer and colorectal cancer cells, upon exposure to histone deacetylase inhibitors, sodium butyrate, suberoylanilide hydroxamic acid, or trichostatin, the expression level of MRP9 was increased (Shi et al. 2020; Wang et al. 2019).

Role of epigenetic alterations in MDR development

Epigenetics alterations (EA) are changes in the DNA framework independent from sequence changes and are stably transmitted from cell to cell. It has been recognized as a substantial element in establishing non-genetic heterogeneity (Chang et al. 2008). Epigenetic alterations involve DNA methylation and modifications of histone, chromatin, and microRNA (miRNAs). It was reported to drive the drug resistance in cancer (Kagohara et al. 2018; Nowacka-Zawisza and Wisnik 2017). Following chemotherapy, epigenetic events frequently start and mutate the expression level of various MDR genes, such as drug transporters (ABCB1, MDR) (Spitzwieser et al. 2016), pro-apoptotic genes (Death-Associated Protein Kinase (DAPK) and Apoptotic Protease-Activating Factor 1 (APAF1)) (Wilting and Dannenberg 2012), DNA-repair proteins (MutL Homolog 1 (MLH1), Methylguanine-DNA Methyltransferase MGMT)) (Saghafinia et al. 2018), or histone modifiers (Ferraro 2016). DNA methylation, a primary EA in various malignancies (Giri and Aittokallio 2019), is triggered by DNA methyltransferases (DNMT) which contributes to the inhibition of gene transcription resulting in gene silencing (Bird 2002). Aberrant DNA methylation in cancer is linked with chemotherapy administration (Grasse et al. 2018; Yuan et al. 2019), affecting the genes responsible for cell differentiation and proliferation pathways and mitogen-activated protein kinases (MAPK), VEGF, Wingless/Integrated (Wnt), and Tumor Protein p53 (p53) signaling or expression of cell cycle inhibitors (Yuan et al. 2019). The inhibition of DNMT can reverse DNA methylation and restore the expression of essential silenced genes (Berdasco and Esteller 2010). Therefore, therapeutic targeting of EA in malignancies becomes an optimistic attitude to raise the efficiency of multi-treatment regimens and quash MDR (Ahuja et al. 2016).

Role of microRNAs in MDR development

MicroRNAs (miRNAs) are a group of small RNAs that do not encode for any protein but mainly downregulate gene expression at a post-transcriptional level and rarely activate mRNA translation. miRNAs have a role in cancer development, angiogenesis, metastasis, and drug resistance (Peng and Croce 2016).

It was shown that miRNAs regulate the expression of MDR efflux transporters of the ABC superfamily in different tumors. For example, the downregulation of *ABCB1/MDR1* encoding for P-gp by expression of various miRNAs results in the reversal of drug resistance, such as miR-let-7 in ovarian cancer (Boyerinas et al. 2012), miR-200c (Chen et al. 2012) and miR-195 (Yang et al. 2013) in breast cancer, miR-200c in colorectal cancer (Sui et al. 2014), and miR-30a (Li et al. 2016a) and MiR-30 (Du et al. 2018) in advanced gastric cancer. Further, the upregulation of miRNAs in some cancers decreased MRP levels and increased their sensitivities to anti-cancer drugs. For example, in gallbladder cancer, overexpression of miR-145 reduced the level of *ABCC1/MRP1* and sensitized it to cisplatin (Zhan et al. 2016); in the ovarian tumor, miR-490-3p decreased the level of *ABCC2/MRP2* and elevated its response to cisplatin (Tian et al. 2017). Contrarily, in mammary tumors, the downregulation of miR-128 leads to *ABCC5* overexpression and contributes to chemotherapeutic resistance (Zhu et al. 2011).

Interestingly, the miRNAs may also curb the response of malignancies to anti-cancer agents by managing DNA repair genes. In the ovarian tumor, it was revealed that miR-9

downregulated **BRCA1** and restrained DNA damage repair, thus boosted its sensitivity to cisplatin and PARP inhibitors (Sun et al. 2013). The expression levels of miRNAs were found correlated with the response of cancer patients to chemotherapy. The expression values of miR-20b, miR-27a, and miR-181a regarding epirubicin/oxaliplatin/capecitabine chemotherapy regimen in a group of gastric cancer patients were analyzed (Danza et al. 2016). They reported that aberrant expression of these miRNAs associates with a chemotherapeutic response via modulation of **ABCB1/MDR1**, **HIF1A**, and **HIPK2**, suggesting a possible novel therapeutic strategy (Danza et al. 2016). These data reveal that targeting miRNAs might become charming therapeutic plans to target MDR. The roles of miRNAs in MDR, being a potential source of biomarkers and therapeutic targets to overcome MDR, are summarized in Table 3.

Where are we now?

Most researchers evoked many methods to overcome anticancer drug resistance. These strategies relied mainly on introducing new molecules that directly inhibit MRP (inhibitors/modulators). In this regard, we explain a short brief about typical modulators involved in MDR overcoming.

MDR modulators

Chemical drugs and analogs

Ibrutinib as MRP1 modulator

Ibrutinib is TKI that interferes with the cytoplasmic protein in B cell. Therefore, it is approved by FDA to treat chronic lymphocytic leukemia. Zhang et al. found that in human leukemia cell lines, doxorubicin-selected MRP1-overexpressing one (HL60/Adr) and MRP1-transfected cell line (HEK293/MRP1), ibrutinib could significantly boost the cytotoxicity of MRP1 substrates such as daunorubicin, vincristine, and vinblastine and raised their intracellular concentration via blocking the drug efflux function of MRP1 (Zhang et al. 2014). Further, they found that the coadministration of ibrutinib enhanced the vincristine efficacy to suppress the tumor growth of HEK293/MRP1 cells in vivo in nude mice.

Nilotinib, vandetanib, imatinib, erlotinib, lapatinib, mastinib, and tandutinib as MRP7 modulators

They are TKI. They were reported as inhibitors of several ABC transporters such as P-gp, BCRP, and MRP7. They could reverse MRP7-mediated MDR in transfected HEK/MRP7 cells and interfere with the drug efflux function of

MRP7 (Deng et al. 2013). The TKI, vandetanib, was shown to sensitize MRP1-overexpressing C-A120 cells toward vincristine and doxorubicin, increasing their accumulation inside the cell (Zheng et al. 2009).

Verapamil

Verapamil is an antiarrhythmic medication (calcium channel blocker). It sensitizes the lung cancer cell line (H69AR) overexpressing MRP1 transporter to many anthracyclines, such as daunorubicin (daunomycin), vinca alkaloids (vincristine and vinblastine), antifolates (methotrexate), and other cytostatic agents such as acivicin, colchicine, gramicidin-D, and mitoxantrone (Hooijberg et al. 1999).

Pyridine derivatives

Pyridine derivatives are known to target the MDR mediated by P-gp in vitro (Bourichi et al. 2018; Patel et al. 2019) and in vivo (Chen et al. 2004). Derivatives as nicardipine were shown to restore the sensitivity of MRP1-mediated doxorubicin resistance in MES-SA/DX-5 cell (Tatosian and Shuler 2009). It also blocked MRP1-mediated calcein-AM transport in Jurkat-SupT1/Vin cells, overexpressing MRP1 (Ivnitski-Steele et al. 2008). Dihydropyridine derivative, PAK-104P, was found to reverse MRP1-related MDR. It increased the response of doxorubicin-selected MRP1-overexpressing human leukemia cell line (HL60/ADR) to doxorubicin (Vanhoefer et al. 1996). Also, the compound reversed the paclitaxel resistance in this cell line and fibrosarcoma cell line, HT1080/DR4. Further, PAK-104P partially restored the sensitivity of the human epidermoid carcinoma cell line C-A120 overexpressing MRP1 against doxorubicin and completely against vincristine. However, Marbeuf-Gueye et al. reported that PAK-104P was a non-competitive inhibitor of the anthracyclines daunorubicin, pirarubicin, and calcein (Marbeuf-Gueye et al. 2000).

Cyclosporine A and immunosuppressant

It was reported that cyclosporin A enhanced chemosensitization and drug accumulation effects to vincristine and daunorubicin in human MDR large cell lung cancer cells expressing a 190k membrane protein distinct from P-gp (Barrand et al. 1993). Interestingly, Kim et al. used doxorubicin-selected bladder cancer cell line 5637/DR5.5 overexpressing MRP1, which showed to be cross-resistant toward several anti-cancer drugs, such as daunorubicin, vinblastine, or etoposide, and found that cyclosporine A not only enhanced the accumulation of daunorubicin but also reduced its efflux (Kim et al. 1995). Immunosuppressant agents and mTOR inhibitors (mammalian or mechanistic target of rapamycin) such as deforolimus, everolimus, sirolimus

Table 3 Regulating role of various miRNAs to cancer MDR in different tumors

miR regulation	MDR target	Effect(s)	Cancer	Reference(s)
miR-27a ↓ and let-7 ↓	ABCB1/MDR1 ↑	Taxane resistance	Ovarian cancer	Boyerinas et al. (2012)
miR-9 ↑	BRCA1 ↓	Cisplatin resistance	Ovarian cancer	Sun et al. (2013)
miR-200c ↓	ABCB1/MDR1 ↑	Doxorubicin resistance	Mammary tumor	Chen et al. (2012)
		Chemotherapy resistance and metastasis	Colorectal cancer	Sui et al. (2014)
miR-30a ↓	ABCB1/MDR1 ↑	MDR and EMT	Advanced gastric cancer	Li et al. (2016a)
miR-125a ↓	ABCC5/MRP5 ↑	Reverses clinical MDR	Hepatocellular carcinoma	Borel et al. (2012)
miR-519c ↓	ABCG2 ↑	Resistance to the therapy	Colorectal cancer	To et al. (2015)
miR-21 ↑	ABCB1/MDR1 ↑	Resistance to chemotherapy	Pancreatic cancer	Dhayat et al. (2015)
miR-331-5p ↓ & miR-27a ↓	ABCB1/MDR1 ↑	Doxorubicin resistance	Lymphocytic and myeloid leukemia (relapsed)	Feng et al. (2011)
miR-7 ↓	ABCC1/MRP1 ↑	No response to the therapy	Small cell lung cancer	Liu et al. (2015)
miR-495 ↑	ATP7A ↑	MDR	NSCLC	Song et al. (2014)
miR-128 ↓	ABCC5/MRP5↑	Doxorubicin resistance	Mammary tumor	Zhu et al. (2011)
miR-145 ↓	ABCC1/MRP1 ↑	No response to the therapy	Gallbladder cancer	Zhan et al. (2016)

↑: increase, ↓ decrease

(rapamycin), and tacrolimus were reported to interfere with MRP1 and subsequently increased the intracellular anti-cancer drug concentration (Peterson et al. 2017). In T98G cells, with particular regard to tacrolimus, a marked reduction in the transcriptional levels of the MRP1 mRNA was shown, and the intracellular concentration of vincristine was increased 24 h after exposure (Garrido et al. 2011).

Indomethacin

Non-steroidal anti-inflammatory drug (NSAID), indomethacin, was reported to increase BCECF (carboxyfluorescein) accumulation in the murine MRP1-overexpressing PC-V4097 and human HL60/ADR cell lines and inhibit the efflux of the fluorescence dye (Draper et al. 1997). Indomethacin was shown to reverse the MDR by enhancing the toxicity of doxorubicin, daunorubicin, and epirubicin; vincristine; and etoposide compared to the administration of these anti-cancer agents alone (Benyahia et al. 2004).

Phytochemicals

The high biodiversity, bioavailability, and low intrinsic toxicity of natural products encourage the use of new chemical scaffolds for drug progress. Natural phytochemicals such as bioflavonoids and polyphenolic compounds found in curcumin, apigenin, quercetin, and naringenin are frequently favored for their health advantages and documented interaction with MRP1 and other drug-transporting ABC proteins (Li et al. 2010).

Curcumin

Curcumin is extracted from the Indian spice turmeric powder, comprised of curcumin (curcumin I), demethoxycurcumin (curcumin II), and bisdemethoxycurcumin (curcumin III). It has many biological activities, including anti-inflammatory (Bisht et al. 2010), anti-cancer (Aggarwal et al. 2003), and anti-viral properties (Shishodia et al. 2007). It plays an essential role in MDR-linked ABC transporters Pgp, MRP1, and ABCG2 (Limtrakul et al. 2007) (Chearwae et al. 2006). Tetrahydrocurcumin and curcumin I, the major in vivo metabolites of curcumin, showed sensitizing the MRP1-positive cancer cells toward most anti-cancer agents. However, the clinical prevalence of curcumin is limited due to its low oral bioavailability and rapid excretion from the body and less specificity for the target tissue.

Bioflavonoids

Flavonoids are among the most common natural product modulators and include flavonols, flavones, isoflavones, flavanones, and chalcones (Narayana et al. 2001). Many flavonoids are excellent modulators of major ABC drug transporters. They can alter the absorption, distribution, and excretion of drugs by altering the functions of ABC transporters (Cermak and Wolffram 2006; Morris and Zhang 2006).

The interaction of flavonoids with MRP1 was first reported by Versantvoort et al., who showed that the flavonoids genistein, apigenin, biochanin A, and quercetin might inhibit MRP1-mediated transport (Versantvoort et al. 1994). After that, several studies demonstrated that many other flavonoids

aglycones such as baicalein, chalcone, chrysin, chrysoeriol, diosmetin, galangin, isorhamnetin, kaempferol, luteolin, morin, myricetin, naringenin, phloretin, robinetin, silymarin, and tamarixetin could all inhibit MRP1-mediated transport to a varying degree (Leslie et al. 2001; Nguyen et al. 2003; van Zanden et al. 2005).

Therapeutic targeting of epigenetic alterations to reverse MDR

Compared to genetic mutations, epigenetic alterations (EA) are reversible and often accompany diseases, particularly cancer. It influences gene expression without altering DNA sequences. During tumorigenesis, EA are complex and involve multiple steps such as DNA methylation, chromatin remodeling, histone modification, and noncoding RNA. Therefore, it is involved in different cellular processes such as proliferation, apoptosis, invasion, and senescence (Cheng et al. 2019). There have been considerable challenges to develop specific inhibitors to EA (epidrugs) to augment the efficacies of multiple therapy protocols and overcome MDR (Ahuja et al. 2016). Epidrugs are formulated to reprogram cancer cells to invert chemoresistance and classified based on their respective target enzyme. It includes inhibitors of DNA methyltransferase (DNMTi, e.g., 5-azacytidine, decitabine, SGI-110), isocitrate dehydrogenase inhibitors (e.g., ivosidenib and enasidenib), or histone deacetylase inhibitors (HDACi, e.g., vorinostat, romidepsin, or belinostat). DNMTi acts as antitumorigenic agents by inducing hypomethylating and breaking the double-strand DNA and, consequently, G2 phase arrest (Palii et al. 2008). Decitabine was used to restore cisplatin chemosensitivity in refractory patients with ovarian cancer (Zhang et al. 2017b). The targeting of EA by combining two or more agents resulted in optimum response and fewer adverse effects. The combination of DNMTi and HDACi epidrugs is recommended in several studies (García-Domínguez et al. 2018). For example, in sarcoma, using SAHA and HCI-2509 synergistically inhibited the cell viability of EWS-FLI1 and its tumor growth (García-Domínguez et al. 2018). In NSCLC, using DNMTis with HDACis revealed long-lasting and robust clinical responses in many patients (Schiffmann et al. 2016). In other malignancies like hematologic malignancies (Blagitko-Dorfs et al. 2019), colorectal cancer (Sharma et al. 2017), esophageal cancer (Schneider et al. 2017), and pancreatic cancer (Chan et al. 2018), the combined epidrugs were more efficacious. While several pre-clinical and clinical trials are running, FDA has already approved some EA inhibitors for clinical uses (Ball et al. 2017; Cheng et al. 2019) (Table 4).

Monoclonal antibodies

Monoclonal antibodies are often particular and can recognize only specific antigen or receptor sites. Therefore, coupling the active pharmaceutical ingredients with MABs holds a high capacity for site-specific drug delivery. MRP1-specific MABs such as QCRL-1, QCRL-2, QCRL-3, QCRL-4, and QCRL-6 have been chiefly used as valuable tools in experimental studies of different functions and sequences and essential domains of MRP1 (Cole 2014; Hipfner et al. 1994). Several MABs have been mapped to the extracellular epitopes of P-glycoprotein and are eligible to inhibit its drug efflux function (Ritchie et al. 2011). In addition to small-molecule compounds, MABs were developed to modulate or inhibit ABCB1 (Mechetner and Roninson 1992). Among the anti-P-glycoprotein MABs, MRK16 and MRK-17 were the first shown to stop the growth of human MDR tumors in immunodeficient mice (Yano et al. 1999). UIC2 is another MABs derived from BALB/c mice immunized with BALB/c 3T3-1000 cells that overexpress ABCB1 and efficiently block the transport of all investigated ABCB1 substrates (Alam et al. 2018). MRK16 blocks the transport of large substrates such as vincristine and actinomycin D, but not with small and flat molecules such as doxorubicin (Mechetner and Roninson 1992). Given the efficient delivery of MABs to intracellular epitopes, these MABs have little therapeutic potential, although they keep being special tools for experimental studies of MRP1 structure and function.

RNA interference therapy

RNA interference (RNAi), a novel established method in which RNA molecules interfere with target gene expression (Landesman-Milo et al. 2013), has latterly got proper research attention. RNAi demonstrates the potential for establishing new categories of molecular therapeutic drugs that interfere with genes-based diseases, especially those that encode so-called "undruggable" targets, which are not responsive to conventional therapeutics. Interestingly, Nieth et al. showed that transfecting pancreatic and gastric tumor cell lines with MDR1 small interfering RNA (siRNA) significantly inhibited mRNA and protein of MDR1 and lowered the resistance to daunorubicin (Nieth et al. 2003). This implies that RNAi can be used to drive back MDR and retrieve the response to chemotherapeutic agents. However, the delivery of siRNAs by the viral and non-viral vectors to diseased sites for gene therapy is a major challenge (Melamed et al. 2017). Recently, because of their merits, using nanoparticles to deliver RNAi molecules to the target sites has received attention (Xin et al. 2017).

Table 4 FDA-approved drugs for the treatment of epigenetic alterations

Drug	MOA	Commercial	Disease	Company
5-azacitidine	DNMTi	Vidaza	Myelodysplastic syndrome	Pharmion Corporation
Decitabine	DNMTi	Dacogen	Myelodysplastic syndrome	Janssen Pharmaceuticals
Vorinostat	HDACi	Zolinza	Cutaneous T cell lymphoma	Merck
Romidepsin	HDACi	Istodax	Cutaneous T cell lymphoma	Celgene
Belinostat	HDACi	Beleodaq	Peripheral T cell lymphoma	TopoTarget
Panobinostat	HDACi	Farydak	Multiple myeloma	Novartis
Chidamide	HDACi	Epidaza	Peripheral T cell lymphoma	Chipscreen Biosciences

MOA mechanism of action; *DNMTi* DNA methyltransferase inhibitors; *HDACi* histone deacetylase inhibitors

Nanoparticles

Nanomedicine describes the use of nano-objects to prevent, diagnose, and cure disease (Shi et al. 2017). Nanoparticles are fine dispersions or solid particles with particle sizes of 10–1000 nm. In the last two decades, nanomedicines emerged to inhibit the activity of efflux transporters. There are central three mechanisms by which nanoparticles achieve their roles: (1) targeting drugs to the specific tissue through increase local drug gradients, (2) engulfing the drug through endocytosis other than passive diffusion that exposes the drug to the ABC, and (3) blocking or inhibition of ABC expression (RNA interference) (Bar-Zeev et al. 2017; Corbo et al. 2016) (Fig. 2). Liu et al. developed a TAT-improved cell/tissue penetrating nanoparticle for MDR cancer therapy, by which silver nanoparticles showed outstanding antitumor activity in both MDR cells and non-resistant cells.

Moreover, in the in vivo study, these nanoparticles at a dose of 1 nmol/kg were able to strongly suppress the tumor growth in the mice with malignant melanoma, compared with the effective dose of doxorubicin (4.3 μmol/kg) and interestingly with low adverse effects (Liu et al. 2012). Advanced studies reported that Ag nanoparticles directly inhibit the efflux activity of MDR cancer cells (Kovacs et al. 2016). Au (gold) nanoparticles loaded with paclitaxel were endocytosed by both drug-sensitive human lung cancer H460 cells and MDR H460PTX cells overexpressing P-gp and MRP1 (Li et al. 2016b).

These data indicate that these nanoparticles could be a class of nano-drug for MDR cancer therapy.

Models to analyze MRP

Several models were used to study and analyze different MRPs (Fig. 3). These models include cell culture models, which involve cell lines and organoid models. Laboratory animals as immunocompromised mice were also used. Further, *Drosophila melanogaster* is also used.

Cell culture models

Cell lines

Cell lines have a remarkable role in studying the physiological, pathophysiological, and biochemical processes of specific tissues or cells. It describes the changes in the structure, biology, and gene map of the cell under controlled conditions (Ulrich et al. 2002). From 1985 till 1990, the American National Cancer Institute (NCI) allowed the application of murine cell line P388 in studying the mechanisms, biology, and carcinogenic modifications in tumors of human origins. Later, this program has been canceled, and, as a substitute, in vitro primary tissue culture derived from human origin was developed to study these mechanisms (Shoemaker et al. 2002). The in vitro models are two types: either (1) human immortalized cancer cell lines, obtained from patients previously showing primary resistance, or (2) primary cell line cultures directly collected during diagnosis of human cancers, whose sensitivity or resistance to a specific targeted anticancer drug is not evaluated yet.

Cell lines are described as models of drug resistance through the administration of a clinical chemotherapeutical drug to study the mechanism of MDR to develop solutions to overcome it. For example, the first study in establishing an MDR cell line was established by Tsuruo and his colleagues. They used the K562 cell line, a human erythroleukemia cell line, to study the MDR that occurred against the clinical dose (60 nM) of vincristine to treat leukemia (Tsuruo et al. 1983). Amaral et al. reported that the total number of cancer cell lines used in experimental oncology for MDR and drug resistance analysis was 110 cell lines of solid and hematopoietic tumors. Most of them were for solid tumors with 97 cancer cell lines and only 13 cell lines for hematopoietic tumors (Amaral et al. 2019). Examples for cell lines used for the analysis of MDR-associated protein (MRP) are lung cell carcinoma cell line (H69AR), human ovarian cancer cell line A2780 for analysis of MRP1 (Cole et al. 1992; Mahdizadeh et al. 2016), human hepatic cell lines for analysis of MRP2 and MRP3 (Cizkova et al. 2005; Malinen et al. 2019) (Ceballos et al. 2018), colon
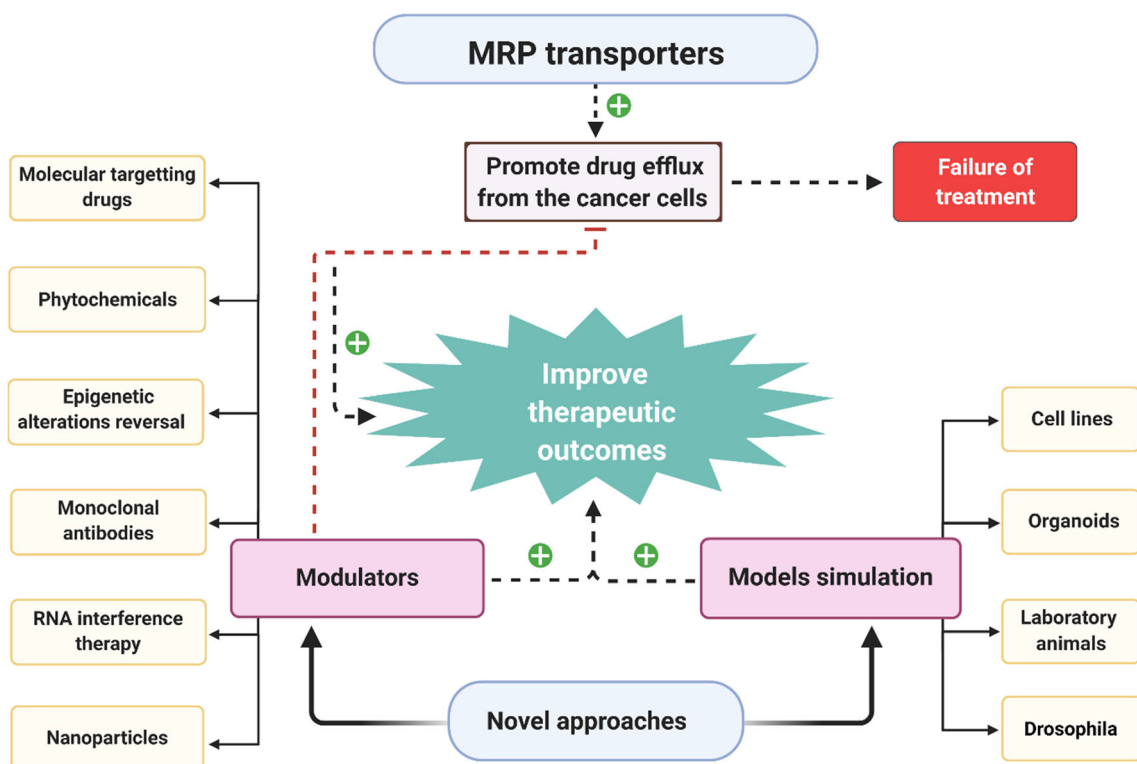
Figure 2 Scheme of MRP efflux transporter role and the developed novel approaches to overcome resistance

cancer cell line for analysis of MRP3 (Kobayashi et al. 2016), and human embryonic kidney cell line (HEK293 cells) for MRP7 (Bortfeld et al. 2006).

Organoids models

Organoids, 3D-developed in vitro cellular structures, are derived mainly from stem cells with the capability of self-renewal and organization into a "mini-copy" of their original organ or tissue (Abugomaa and Elbadawy 2020; Abugomaa
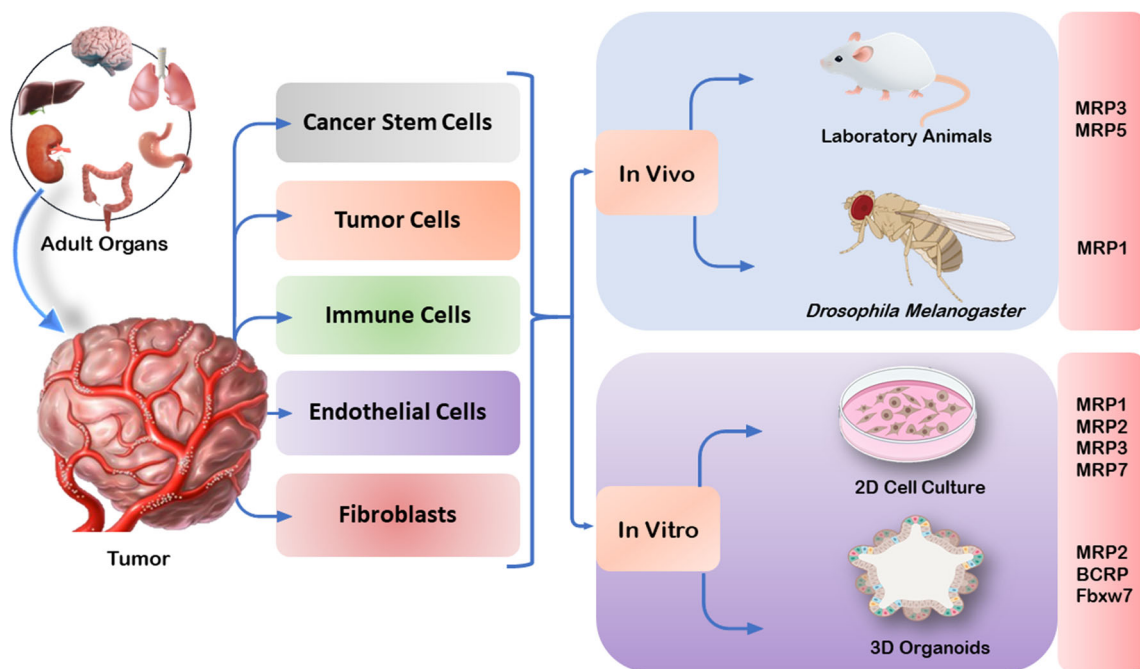

Figure 3 Models to analyze the role of MRP in drug resistance

et al. 2020; Elbadawy et al. 2019a). Organoids can aptly and intimately recapitulate the in vivo architecture and the genetic and molecular signature of their parent tissues or organs (Elbadawy et al. 2018a, 2018b, 2019b; Usui et al. 2018b). In the last decade, organoids were essential tools to support basic medicine and translational research (Abugomaa and Elbadawy 2020) and analyzing the response to therapy (Abugomaa and Elbadawy 2020; Abugomaa et al. 2020; Elbadawy et al. 2021; Usui et al. 2018a).

Researchers began to use the 3D organoids for simulation and detection of the characterization of the ABC family transporter. For example, Zhang et al. were the first to use the 3D small intestinal organoids model (cultured from intestinal crypts) to investigate MRP2-mediated drug transport (Zhang et al. 2019a). They used their established organoids for the demonstration of modulators and inhibitors of MRP2 transporter. They select carboxy-dichlorofluorescein CDF (as MPR2 substrate) and probenecid (as MRP2 inhibitor) to validate the model, and the result assured the ability of MRP2 transport in the organoids (Zhang et al. 2019a). In another study, they continually described the role of intestinal organoids in estimating the function of BCRP transporter using the fluorescent dye as a substrate and Ko143 as an inhibitor. The mRNA expression and immunohistochemical analysis of BCRP revealed that organoid simulation was a valuable tool for detecting BCRP modulators (Zhang et al. 2017a).

Further, Lorenzi et al. employed the intestinal organoid to identify cellular response mediated by Fbxw7 (a member of the F-box protein family that is associated with drug resistance) to various concentrations of 5-FU and showed that the organoids from $fbxw7^{\Delta G}$ (specifically inactivated) are two to three times less sensitive to 5-FU therapy than $fbxw7$-$^{fl/fl}$ (control floxed) ones (Lorenzi et al. 2016). Moreover, small hepatocyte organoids' role in the expression of hepatic transporters and their capacity to convey organic anion substrates were investigated (Oshima et al. 2008). The result showed that transporters such as Oatp1, Oatp2, Ntcp, and MRP2 were increased with time in culture versus a decline in the expression of MRP3 and BCRP (Oshima et al. 2008).

Laboratory animals

Laboratory animal experimentation has been a part of biomedical and molecular research for several years. Animal research was introduced in Greece over 2000 years ago to understand how diseases, drugs, and organisms interact. The laboratory mice used as a model for MDR analysis must be immunocompromised to avoid rejection of the implanted cancer cells such as athymic nude mice (no thymus T cells) and SCID mice (no both B and T cells) (Richmond and Su 2008; Rosa et al. 2014). Rejinold et al. used mice to check the role of curcumin as a nanocarrier for doxorubicin delivery to MDR cancer cells

and to compare the results with that obtained from using cell cultures such as NIH-3T3 (mouse embryonic fibroblast cells), HeLa (human cervical cancer cells), NCI-H460 (human lung carcinoma cells), and HFL1 (human normal lung cells) (Rejinold et al. 2018). Belinsky et al. previously used MRP3 null mice and transfected HEK293 cells to analyze the physiological role of MRP3 in enterohepatic circulation as an anionic transporter and its role to protect the normal tissue against etoposide and endobiotic (Belinsky et al. 2005). Karla et al. demonstrated the expression of MRP5 on the cornea and its role in drug efflux after using a male New Zealand white rabbit's cornea (Karla et al. 2009). Finally, laboratory animals or generally in vivo experiments are the best methods (as they provide the native microenvironment in which tumors grow) to analyze the function and role of MRP transporter in cancer biology. However, due to animal welfare, livability, and ethical considerations, the need for tissue cells mimicking the in vivo experiment was the interest of scientists in the last decades, so organoids (3D tissue culture) were developed.

Drosophila melanogaster model

Drosophila is an alternative in vivo tool for high-throughput screening and validation of several anti-cancer drugs, including methotrexate, aminopterin, acivicin, gefitinib, and erlotinib due to high maintenance of its signaling pathways, brief life cycle, and genetic amenability (Yadav et al. 2016). *D. melanogaster* has a gene closely identical to human MRP1 that encodes a full ABC transporter containing three MSDs and two NBDs. *Drosophila* MRP (DMRP) is the only orthologue of the "long" human MRPs (MRP1, 3, 6, and 7). DMRP has been revealed to be a very active ABC transporter for different organic anions. It could transport MTX (Karasik et al. 2018), which can convey an MDR phenotype such as ABCG2, ABCB1, and ABCC transporters that often interfere with chemotherapy. Additionally, lowered expression of the endogenous DMRP has been revealed to decrease secretion of MRP1 substrate, daunorubicin, in the main insect excretory organ (Chahine et al. 2012). Such information points to the putative functional symmetry of DMRP and long ABCC transporters in vivo.

Summary and future perspectives

In the present review, nine MRPs with different structures, localization, tissue expression, substrate specificities, and functions have been discussed. Physiologically, most MRP family members protect different tissues and organs against several xenobiotic and endogenous substrates as well as their metabolites. In cancer therapeutics, MRPs have been demonstrated to confer resistance to many anti-cancer agents. Recently, there have been several attempts to reverse MRP-

mediated MDR. Notably, small molecular inhibitors, especially TKIs, phytochemicals, miRNA-based therapy, nanomaterials, and MABs, are the main research spots in developing novel MRP modulators. The combination of more than one MRP modulator (hybrid drugs) results in a sophisticated understanding of the pharmacokinetics efflux of this combination by MRP. Progress in developing appropriate research models such as organoids and others will facilitate better understanding and developing effective MRP modulators.

Author contribution Study conception and design: ME, ARE, and HME. Acquisition of data: ME, ARE, HME, RFR, EAM, MA, HS, ASM, AE, AHA, and AHE. Writing and editing of the manuscript: ARE, HME, ME, AA, EAM, RFR, and AHE. Critically reviewed the article: ME, HME, and ARE. All authors have approved the final version of the manuscript.

Data availability All relevant data are within the manuscript.

Declarations

Ethics approval   Not applicable

Consent for publication   • The manuscript is not previously published in the same or very similar form in another journal.
  • The manuscript is not under consideration in other journals.

Conflict of interest   The authors declare no competing interests.

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