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Review Article

Progress and challenges of multidrug resistance proteins in diseases

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Abstract: Chemotherapy remains the first choice for patients with advanced cancers when other treatments are ineffective. Multidrug resistance (MDR) is an unavoidable factor that negatively affects the effectiveness of cancer chemotherapy drugs. Researchers are trying to reduce MDR, improve the effectiveness of chemotherapeutic drugs, and alleviate patient suffering to positively contribute to disease treatment. MDR also occurs in inflammation and genetic disorders, which increases the difficulty of clinically beneficial treatments. The ATP-binding cassette (ABC) is an active transporter that plays an important role in the barrier and secretory functions of many normal cells. As the C subfamily in the ABC family, multidrug resistance proteins (MRPs/ABCCs) export a variety of antitumour drugs and are expressed in a variety of cancers. The present review summarises the role of MRPs in cancer and other diseases and recent research progress of MRP inhibitors to better examine the mechanism and function of MRPs, and establish a good relationship with clinical treatment.

Keywords: Multidrug resistance protein, ATP-binding cassette, cancer, hereditary diseases

Introduction

Chemotherapy is a primary method in advanced cancer treatment, and the emergence of multidrug resistance (MDR) has become a major obstacle to tumour treatment. MDR describes the resistance of tumour cells to different drugs with multiple chemical structures, multiple mechanisms of action and multiple targets, and it is classified as intrinsic or acquired resistance [1, 2]. MDR is characterized by reduced intracellular concentrations of chemotherapeutic drugs and limited efficacy [3, 4]. MDR is a pathophysiological phenomenon within tumour cells involving multiple mechanisms, including tumour factors, host factors and tumour-host interactions [5, 6]. Other mechanisms of MDR are related to the activation of detoxification systems, cell proliferation, activation of DNA repair mechanisms, increased drug excretion or impaired drug uptake, loss of pro-apoptotic factors in nuclear factor kappa B (NF-κB) factors, or overexpression of anti-apoptotic factors [7-10] (**Figure 1**). The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway is involved in the regulation of multiple targets, such as the expression of the ATP-binding cassette (ABC) transporters and NF-κB. It is also a key link in the regulation of MDR and manifests in breast, ovarian and hepatocellular carcinoma (HCC) [11, 12]. Lysosomes also promote hydrophobic anticancer drugs by promoting weak alkaline efflux, and ABC transporters likely localize to lysosomes involved in multidrug resistance [13].

However, one of the common mechanisms of MDR is the promotion of energy-dependent efflux of multiple hydrophobic cytotoxic drugs, and ABC transporters play an important role in this process [14, 15]. Overexpression of the ABC transporter uses the energy provided by adenosine triphosphate (ATP) hydrolysis to expel a variety of cytotoxic drugs from cancer cells, which results in significantly reduced efficacy and the promotion of MDR [16, 17], and it leads to a decrease in the cellular uptake of drugs and an increase in drug pumping, which result in a decrease in intracellular drug con-

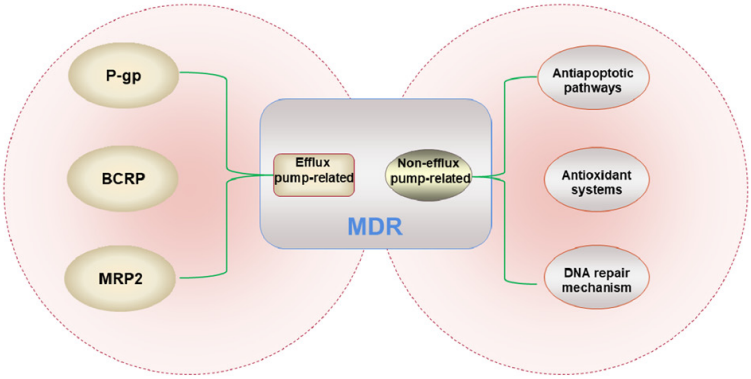

Figure 1. The mechanism of multidrug resistance. MDR are divided into two main categories, namely efflux pump-related and non-ex efflux pump-related. ABC transporter proteins are the main class of identified drug efflux pumps, mainly including P-gp, MRP2 and BCRP. While the main non-ex efflux pump modalities of MDR are antiapoptotic pathways, antioxidant systems and DNA repair mechanisms.

centration and the failure to achieve the desired effect [18, 19]. As mentioned in our previous review, the ABC transporter is activated by ATP and regulates lipid metabolism at the plasma membrane by regulating the import and export of transmembrane substances involved in atherosclerosis, metabolic diseases, atherosclerosis, coronary artery disease and skin diseases [20].

As a subfamily of ABCCs, Multidrug resistance proteins (MRPs) mediate MDR in cancer by secreting various chemotherapeutic drugs or their metabolites from tumour cells [21-23]. MRPs are energy-dependent "drug pump" transmembrane glycoproteins with a broad-spectrum of substrates. MRPs non-directionally exclude intracellular drugs and prevent target-to-target interactions. Drug combinations are the direct cause of multidrug resistance in tumours [24]. Unlike other proteins of the ABC family, MRPs have unique advantages in acquiring multidrug resistance [25]. MRPs are associated with many cancers, but the exact mechanisms are not clear. We reviewed the specific mechanisms of MRP activity in various cancers and summarised the mechanisms of MRP action in other diseases and inhibitors linked to MRPs to highlight the importance of MRPs and provide novel suggestions for clinical treatment.

MRPs belong to the family of ABC transporters

Azad et al. [26] cloned an MRP in 1992 from an H69/AR-resistant cell line and overexpressed it in doxorubicin-resistant H69-AR cells. It is a resistance-related gene functionally similar to P-glycoprotein (P-gp). The MRP family has 13 members, nine of which are associated with tumour resistance: MRP1/ABCC1, MRP2/ABCC2, MRP3/ABCC3, MRP4/ABCC4, MRP5/ABCC5, MRP6/ABCC6, MRP7/ABCC10, MRP8/ABCC11 and MRP9/ABCC12. These nine MRPs use ATP for energy and the transport of endogenous substances and chemotherapeutic drugs. The structure is similar to P-gp, with two transmembrane regions and two ATP-binding domains. Members of the MRP family are divided into two categories. MRP4, MRP5, MRP8, and MRP9 with typical ABC structures (ABCC4, ABCC5, ABCC11, and ABCC12) are "short-term" MRPs, and MRP1, MRP2, MRP3, MRP6, and MRP7 (ABCC1, ABCC2, ABCC3, ABCC6 and ABCC10) are called "long-term" MRPs [27]. The MRP family is widely distributed with localisation to the apical and/or basolateral membranes of hepatocytes, enterocytes, renal proximal tubular cells and blood-brain barrier endothelial cells, and these proteins are is expressed to varying degrees in the liver, kidney, intestine, brain and other tissues [28].

The structure, localisation and family of MRPs

Related information on the structure, localisation and family of MRP1-9 is summarised below and in **Table 1** and **Figure 2**. The molecular structures of MRP1-9 are shown in **Figure 3**, and protein sequences from the unified protein database are described in detail in the Supplementary Materials.

MRP1 was originally found in the human lung cancer cell lines H69 and HL60 [29, 30]. The gene is located on the first chromosome at band 13.1 of the long arm of human chromosome 16. The molecular weight of the MRP1 protein is 190 kDa, and it contains 1531 amino acids and consists of 3 TMDs, 2 NBDs and 1 N-terminal intracellular junction region (L0) (arranged as TMD0-L0-TMD1-NBD1-TMD2-NBD2). NBD participates in the binding and hydrolysis of ATP to provide energy for transport and functions as an antineoplastic drug outflow

Table 1. The information of the MRP family

MRPs	Amino add sequence length	Chromosome location	Related diseases	Ref
MRP1 (ABCC1)	1531	16p13.12	Hepatocellular, esophagus cancer, non-small cell lung cancer, Ovarian cancer	[30, 61-64, 71-73, 111-113]
MRP2 (ABCC2)	1545	10q24.2	Colorectal cancer, Durbin-Johnson syndrome, Hepatocellular carinoma, Acute mycloid leukemia	[39, 71, 72, 95-97, 104, 115-117]
MRP3 (ABCC3)	1527	17q21.33	Hepatocellular carcinoma, Ovarian cancer, Adult acute lymphoblastic leukemia	[39, 71, 72, 104, 111-113]
MRP4 (ABCC4)	1325	13q32.1	Prostaticcancer, Neuroblastoma, Acute myeloid leukemia, Panareatic cancer, Breast cancer, Ovarian cancer	[39, 76, 79, 104, 107, 111-113]
MRP5 (ABCC5)	1437	3q27.1	Lung cancer, Colorectal cancer, Breast cancer, Panaeatic cancer	[61-64, 76, 77, 79, 95-97, 107]
MRP6 (ABCC6)	1503	16p13.12	Pseudo-polychordoma	[118]
MRP7 (ABCC10)	1492	6p21.1	Salivary gland carcinomas	[58]
MRP8 (ABCC11)	1382	16q12.1	Breast cancer, Ovarian cancer, Panaeatic cancer	[76, 77, 79, 107, 111-113]
MRP9 (ABCC12)	1356	16q12.1	Lung cancer, Colorectal cancer	[61-64, 92, 93]

Abbreviations: MRP, Multidrug Resistance Protein; ABC, ATP-Binding Cassette.

pump. TMD is responsible for substrate identification, binding and transport [31]. MRP1 is extensively visualised in various tissues, such as lung, testis, kidney, bone and heart muscle, placenta and macrophages. It is also located in blood-tissue barriers, such as the basement membrane of choroid plexus cells in the blood-cerebrospinal fluid barrier and the trophoblast membrane of bronchial epithelial cells and placental apical commissures [32]. Cells overexpressing MRP1 exhibit low levels of resistance to lycopene, colchicine and vincristine, and moderate resistance to anthracyclines (e.g. etoposide) and vincristine (e.g. pergolide). MRP1 transports a variety of endogenous compounds, such as heavy metal anions, glutathione, glutathione-bound leukotrienes, glucuronic acid and its sulphate conjugates [33]. Because of the dependence of this protein on ATP, glutathione stimulates the transport of various unbound hydrophobic substrates and certain glucosinolate and sulphate conjugates that are resistant to natural product drugs such as periwinkle and epithelial phytotoxins [34].

MRP2 was originally found in human and rat hepatocytes, and it is also called cholinergic MRP (cMRP)/cMOAT. The gene is found on chromosome 10q24, and the protein consists of a total of 1545 amino acids with three MSDs and two NBDs. It is localised to the proximal tubular apical membrane of the kidney, gallbladder epithelial cells, small intestinal epithelial cells, colonic epithelial cells and pulmonary epithelial cells, which is different from other members of the MRP family [22]. Some studies showed that MRP2 led to functional deficiency due to natural mutations, which is associated with Doberman syndrome and associated hyperbilirubinemia, and MRP3 was also involved [35]. Translocation of bilirubin and glucose from the liver to the bile is one of the physiological functions of MRP2. Excretion and protection are the main functions of MRP2 [36]. MRP2 regulates the pharmacokinetics of many drugs by transporting some chemotherapeutic agents, such as antibiotics and heavy metals, and various compounds, specifically lipids bound to glutathione, glucuronide and sulphate, which play large roles in detoxification and chemoprotection [37].

MRP3/MOAT-D is located on chromosome 17q21.3, and it is expressed in the adrenals, small intestine, duodenum, colon, pancreas and gallbladder. There is a high level of MRP3 expression in the liver, small intestine and colon but a low level in the lung, spleen, kidney, stomach and tonsils [38, 39]. MRP3 is an organic ion transporter that transports MRP1 and MRP2 and transport lipid anti-ions such as bile acid and glucagon, but it has poor affinity for GSH-binding compounds [40]. MRP3 is also responsible for the transport of curcumin-O-glucosamine, which is the main metabolite of curcumin in plasma and faeces, from hepato-

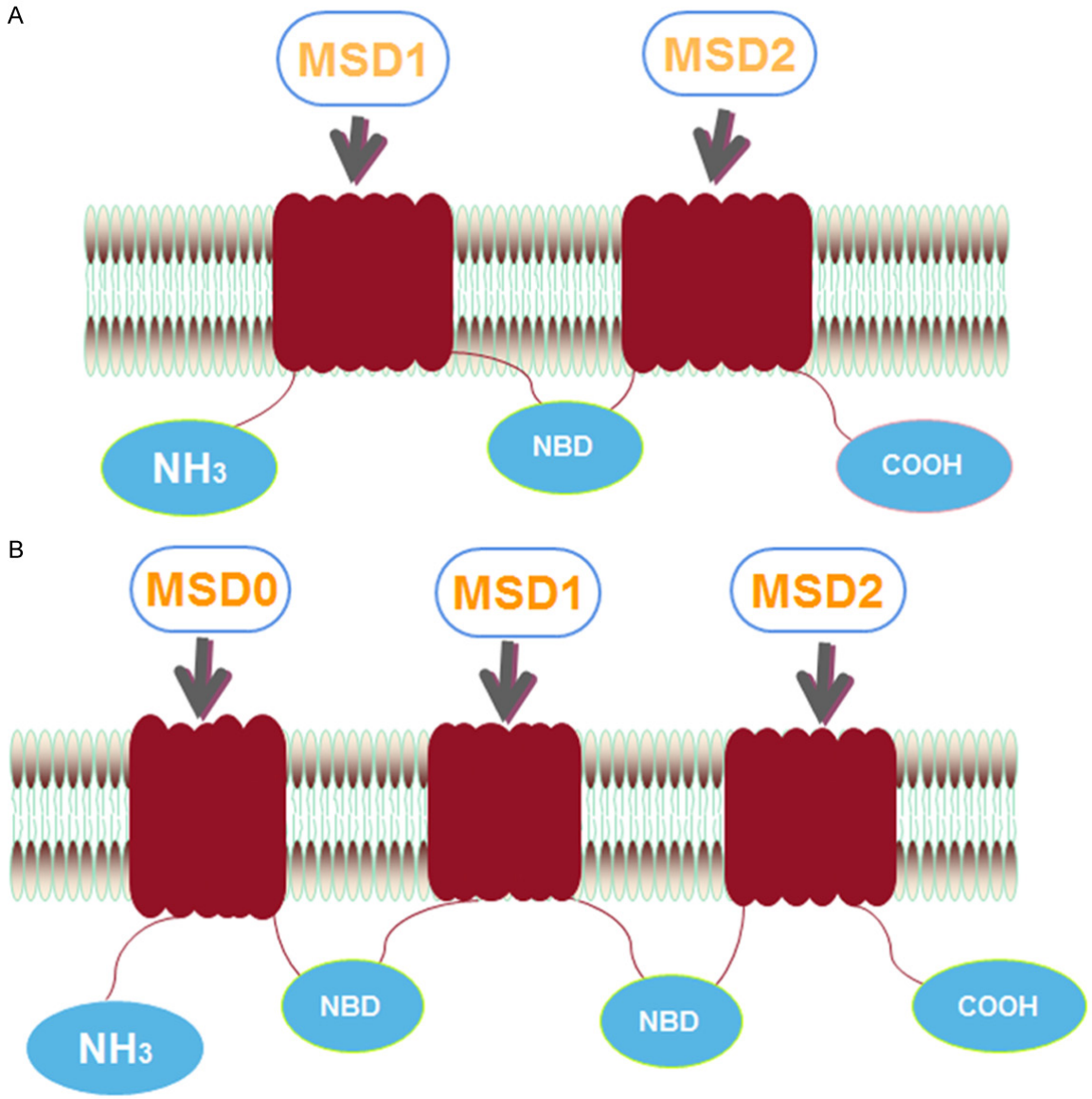

Figure 2. The structure diagram of multidrug resistance protein. A. MRPs are characterized by common structural features: multiple transmembrane (TM) α helices arranged in membrane-spanning domains (MSDs), and intracellular nucleotide-binding domains (NBDs) for ATP binding and hydrolysis. B. "Short-term" MRPs: The basic structure of MRP4, MRP5, MRP8, MRP9. The short MRP is a tetrameric structural domain arrangement consisting of two MSDs and two NBDs. The tetrameric structure of two MSDs and two NBDs is commonly found in the ABC superfamily. "Long-term" MRPs: The basic structure of MRP1, MRP2, MRP3, MRP6, MRP7. The long MRP is an additional NH2-proximal MSD0 outside the four-structure domain arrangement consisting of two MSDs and two NBDs. Abbreviations: MRP, Multidrug Resistance Protein; COOH, Carboxyl Groups; NH3, Amino Groups; MSDs, Membrane-Spanning Domains; NBDs, Intracellular Nucleotide-Binding Domains.

cytes into the bloodstream, and its transformation by glucosylation in enterocytes and hepatocytes [41].

MRP4/MOAT-B was found in a T lymphocyte line in 1996. It encodes 1325 amino acids, and the gene is positioned on the long arm of chromosome 13q32.1. Structurally, MRP4 consists of a typical ABC transport core with two TMDs and two NBDs [42]. MRP4 is concentrated in diverse structures, such as the lung, muscle, pancreas, kidney, prostate, bladder, ovary and testis [42, 43]. MRP4 is a prostatic excretion pump that regulates drug trafficking in the pros-

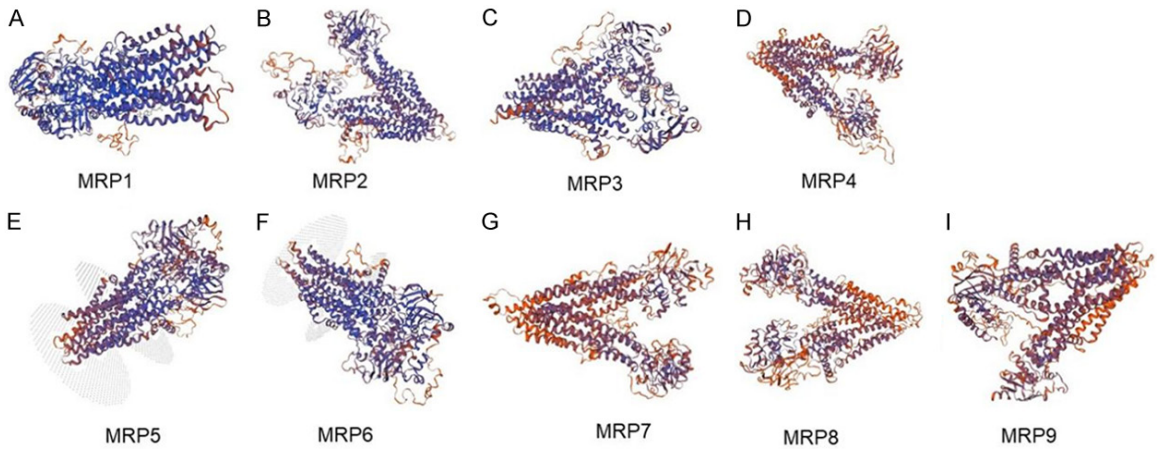

Figure 3. Molecular structures of nine multidrug resistance protein isoforms. It shows the protein fold structure of MRP1-9. A. MRP1; B. MRP2; C. MRP3; D. MRP4; E. MRP5; F. MRP6; G. MRP7; H. MRP8; I. MRP9. Among them, the ligands of MRP1 structure are ADENOSINE-5'-DIPHOSPHATE, ADENOSINE-5'-TRIPHOSPHATE, CHOLESTEROL, MAGNESIUM ION. The ligands of the MRP5 structure are MAGNESIUM ION, and the ligands do not appear in other types of structure diagrams. All the structural diagrams are drawn on the mapping software SWISS-MODEL. The protein sequence of MRP1-9 is input on the software to export the structural diagram.

tate [44]. MRP4 may expel a range of endogenous and heterogeneous organic ionized chemicals from cells, which is different from other C family members. MRP4 regulates the pharmacology and kinetics of several medications as a transporter, including antiviral, antineoplastic, and diuretic drugs [45]. In addition to its action as a drug transporter and renal excretion, MRP4 is also critical in the transmission of cellular signalling molecules, and it is closely linked to active cellular and body activities and physiological processes [46, 47]. MRP4 is also a component in the pathogenesis of metabolic diseases such as obesity and diabetes [48].

The MRP5/MOAT-C gene is located on chromosome 3q27, and the protein contains 1437 amino acids. Some studies found that MRP5 was expressed in a broad range of tissues with highest expression in the heart, brain, lung and skeletal muscle. It is localized in smooth muscle sarcomeres, cardiac myocytes endothelial cells, and cardiomyocytes in the heart. MRP5 is also obviously expressed in the adrenal glands [49].

MRP6, also known as MOAT-E, is situated on chromosome 16, it and encodes a single polypeptide chain of 1503 amino acids with a central MRP structure (with two transmembrane structural domains TMD1 and TMD2 and two cytoplasmic nucleotide-binding structural domains NBD1 and NBD2) [50-52]. MRP6 is primarily located in the liver and kidney, but it is expressed at low or undetectable levels in other tissues, such as the duodenum, colon, brain and salivary glands. MRP6 regulates several key enzymes to produce inorganic pyrophosphate (PPI, an effective inhibitor of ectopic calcification) and prevent its degradation to regulate extracellular purines that participate in ectopic calcification. MRP6 deficiency promoted ectopic calcification and aggravated atherosclerosis [53].

MRP7 was discovered in 2001, and it is located on the 6p12 chromosome. It encodes a protein of 1636 amino acids. It is a 171-kDa protein containing three membrane span domains (MSDs) and two NBDs [54]. MRP7 is most highly expressed in the pancreas, but it is also expressed in the liver, placenta, lungs, kidneys, brain, ovaries, lymph nodes, spleen, heart and colon, and shows low levels in the spleen, stomach, kidneys, heart and brain [55]. MRP7 is a lipophilic ion transporter implicated in the transport of drugs and other endogenous molecules, and it pumps endogenous and heterogeneous biological substrates from the cytoplasm into the extracellular environment [56]. Phosphorylated MRP7 contributes to the dynamic balance of ions and fluids in healthy humans by conducting chloride and bicarbonate ions to the parietal lamellae of epithelial cells within the primary conducting airways and submucosal glands [57, 58].

Table 2. The role of MRPs in cancers

MRPs	Disease	Impact	Mechanism	Ref
MRP1	Non-small cell lung cancer	Aggravate	SLAMF3↑→MRP1↓→Reducing drug resistance	[75]
	Colon cancer	Aggravate	hypoxia↑→HIF-1α↓→MRP1↓→drug resistance↓	[90]
	Renal cell carcinoma	Aggravate	miR-210-3p↓→MRP1↑→drug resistance↑	[84]
MRP1, MRP4	Ovarian cancer	Aggravate	Eicosanes derived from AA↑→SKOV3-R↑→cisplatin-resistance↑activity of cisplatin transfer↑	[108-113]
MRP2	Colorectal cancer	Aggravate	MRP2↑→LTB4↑→circosanoids↑	[95-97]
	Durbin-Johnson syndrome	Aggravate	MRP2↓→CB↑→Inflammatory cytokine release↑→Extracellular regulated kinase↓→MRP2↓	[115-117]
	Hepatocellular carcinoma	Aggravate	CircMRP2↑→miR-665↑→MRP2↑	[118]
	Non-small cell lung cancer	Attenuate	MRP2↑→activation of PARP↑→activation of caspase-3↑→cisplation-resistance↑	[69]
MRP4	Acute myeloid leukemia	Aggravate	MRP4↓→cAMP↑→Proliferation and differentiation of AML cells↑	[104]
	Pancreatic cancer	Aggravate	MRP4↑→the growth of Pancreatic-3↑→EMT↑	[76]
	Breast cancer	Aggravate	MRP4↑→PGE2↑	[107]
MRP7	Endometrial cancer	Aggravate	NEAT1↑→miR-98↓→MRP7↑→drug resistance↑	[82]

Abbreviations: MRP1, Multidrug Resistance Protein 1; MRP2, Multidrug Resistance Protein 2; MRP4, Multidrug Resistance Protein 4; MRP6, Multidrug Resistance Protein 6; LTB4, Leukotriene B4; CB, Conjugated Bilirubin; PARP, Poly (ADP-Ribose) Polymerase; AA, Arachidonic Acid; CAMP, Cyclic Adenosine Monophosphate; EMT, Epithelial-Mesenchymal Transition; PGE2, Prostaglandin E2; IL-1, IL-6, IL-8, Interleukin; NF-kappa B, Nuclear Factor Kappa B; SLAMF3, A Member Of The Signaling Lymphocyte-Activating Molecule Family Of Receptors; HIF-1α, Hypoxia-Inducible Factor; NEAT1, Inhibitors Of MiR-98.

Similar to other members of the family, MRP8 is a complete transport protein with two nucleotide binding regions and 12 transmembrane regions. It has high homology with MRP5 and its gene locus is on chromosome 16q12.1. It is expressed at moderate levels in normal breast and testis tissues and at very low levels in the liver, brain and placenta [59]. The transmembrane protein structure of MRP8 is similar to MRP4 and MRP5, and it possesses just two transmembrane structural domains. MRP8 is poorly expressed in all human tissues other than lung, foetal tissue, kidney, spleen, colon and brain [60].

The MRP9 sequence is similar to MRP8 and was obtained from a cDNA library of human adult liver via cloning. It is detected in gene records of human tissues and other organs, such as the liver, kidney and lung [61-64]. MRP9 sits next to MRP8 on chromosome 16q12.1. MRP9 is represented by a single ATP-binding domain, but the two MSDs each have four transmembrane domains. MRP9 is highly expressed in testis and breast tissues [65].

Mechanisms of MRPs in diseases

MRPs and cancer

Many recent studies showed that MRPs played important roles in cancers. We summarise the related studies of MRPs in cancer below and in **Table 2** and **Figure 5**.

Gastric adenocarcinoma: Mechanisms of chemoresistance are important for the failure of traditional Chinese in the treatment of gastric adenocarcinoma (GAC), which promotes GAC multidrug resistance [66]. Abdulla et al. [67] found MRP1, MRP3, MRP4, MRP5 were significantly expressed in GAC, which may be involved in chemoresistance of GAC. Through the development of the GAC-derived cell line AGS animal model, it was discovered that MRP1 and MRP4 inhibition, as well as the MRP inhibitors diclofenac and probenecid, dramatically improved the responsiveness of AGS cells to sorafenib and docetaxel, which enabled anti-cancer medication in GAC.

Non-small cell lung cancer: Qi et al. [68] found that overexpression of MRP1 promoted multidrug resistance in non-small cell lung cancer (NSCLC). Using the anticancer drug etoposide (VP-16), they found that it exacerbated ROS activation of HIF-1α, switched cellular metabolism to glycolysis in NSCLC, and increased lactate in the extracellular environment, which increased the expression of MRP1. They indicated that the development of MRP1 transporter inhibitors will play an active role in the clinical treatment of NSCLC in the future. Cisplatin resistance is a major obstacle to cisplatin treat-

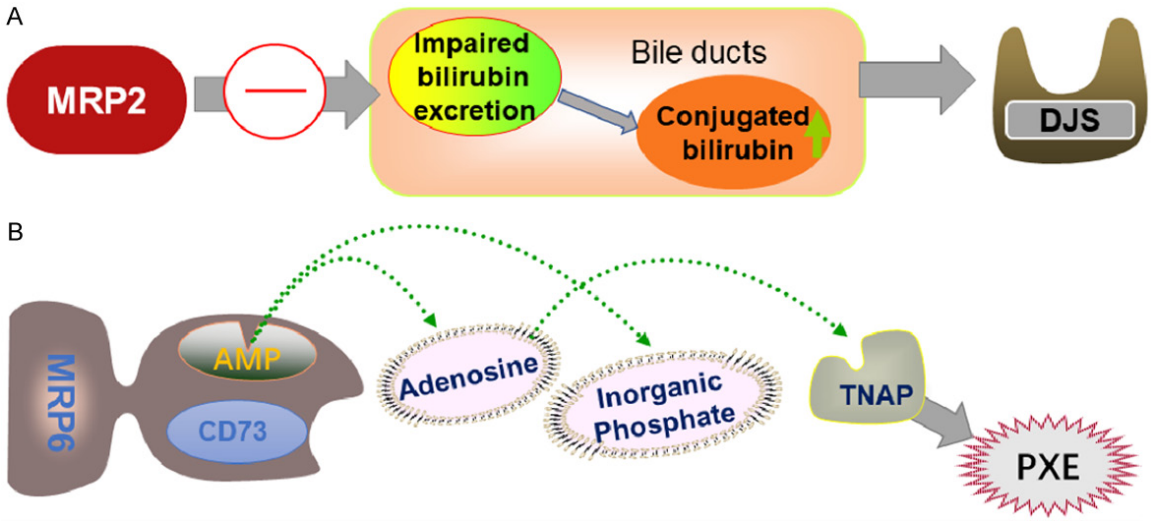

Figure 4. Mechanism of action of multidrug resistance proteins in hereditary diseases. A. Impaired function of MRP2 leads to DJS by impairing bilirubin, which is one of the pathogenic mechanisms of DJS, leading to cholestasis; B. MRP6 secretes AMP and CD73 act together downstream to degrade AMP to adenosine and inorganic phosphate. Adenosine inhibits TNAP expression and activity, thereby regulating PPI. Abbreviations: DJS, Durbin-Johnson Syndrome; PXE, Pseudoxyloma Elasticum.

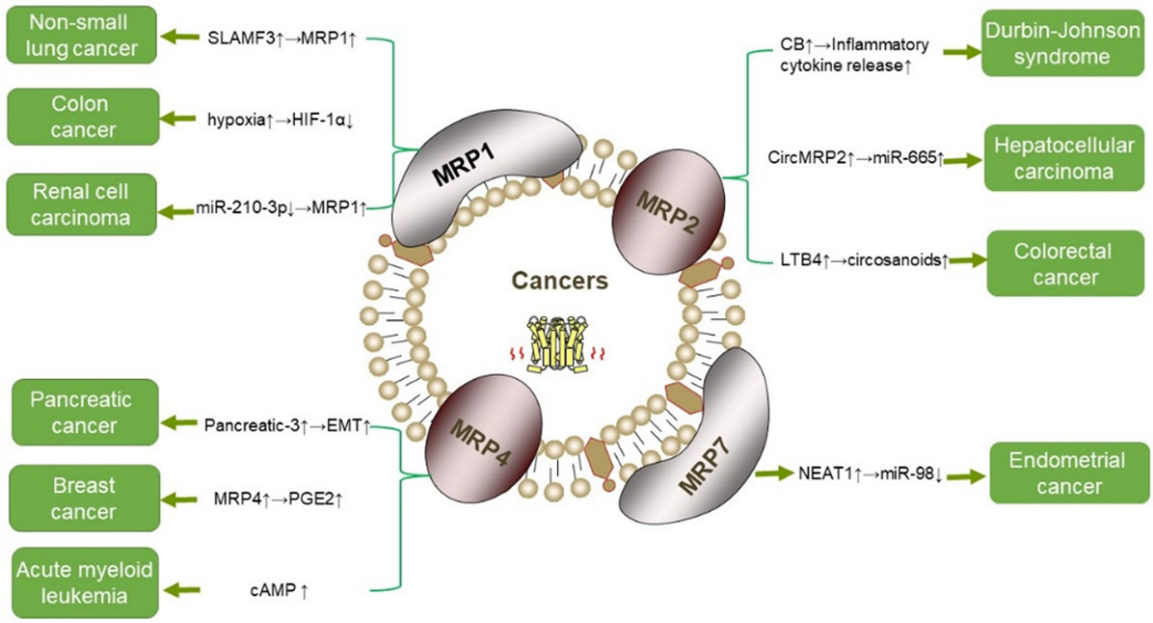

Figure 5. Mechanism of multidrug resistance proteins-mediated cancer. Multidrug resistance is one of the major obstacles leading to clinical treatment of cancer, and multidrug resistance proteins-mediated multidrug resistance plays an important role.

ment of NSCLC. Chen et al. [69] found that reducing MRP2 expression was an important strategy to increase the sensitivity of NSCLC to cisplatin. The cleavage of PARP in cisplatin-resistant NSCLC cells is an important indicator of apoptosis and the activation of caspase-3 apoptotic signalling, and MRP2 knockdown activated PARP and promoted apoptosis in these cells.

Hepatocellular carcinoma: Fouquet et al. [70] found that MRP1 was highly expressed in tumour tissues of HCC, and overexpression of the signalling lymphocyte activating molecule

family member 3 (SLAMF3) in HCC cells specifically reduced MRP1, which reduced multidrug resistance in HCC and facilitated the treatment of HCC [71-73]. SLAMF3 participates in the cell cycle in an RB/PLK-1-dependent manner in HCC cells by regulating the ERK1/2, JNK and mTOR pathways [74]. In addition, the expression of MRP2 also increased, mainly through the upregulation of CircMRP2 and miR-665 [118]. The overexpression of SLAMF3 in HCC may be due to the regulation of cell proliferation and apoptosis and the enhancement of treatment efficacy, but further research is needed to determine the exact mechanism by which SLAMF3 and MRP1 reduce tumour growth [75].

Pancreatic cancer: Pancreatic cancer (PC) is a highly fatal cancer with few symptoms in its early stages. It is normally considered terminal when it is diagnosed and has a poor prognosis. High chemotherapy resistance is one of the characteristics of PDAC and MRPs play a regulatory role in the chemoresistance [76].

Guo et al. [77] established a PDAC mouse model and found that the combination of gemcitabine and rhodopsin reduced the expression levels of P-gp, MRP1 and MRP5, which were beneficial in inhibiting tumour growth and resistance to gemcitabine in mice. However, the exact mechanism is not clear. MRP3 is also considered a therapeutic target for pancreatic cancer. Emodin may promote a reduction of multidrug resistance in PDAC by inhibiting the levels of P-gp, MRP1 and MRP5, but the specific mechanisms are not clear. MRP3 is also considered a therapeutic target for pancreatic cancer. Mutant p53 regulates MRP3 via miR-34C while advancing pancreatic cancer via bioactive lipid lysophosphatidylinositol. Patient survival rate is favourably linked with low expression of the tumour suppressor miR-34C with lower expression levels being linked to lower survival rates. P53 is a cancer suppressor gene. A decrease in proliferation of pancreatic cancer cells in vitro and in vivo was achieved by knocking down ABCC3, which inhibited key regulators of PDAC progression, the STAT3 and HIFI1α signalling pathways [78].

Sahores et al. [76] found that the overexpression of MRP4 accelerated the development of BxPC-3 clonal cell lines in mice, which altered the expression of epithelial mesenchymal transition (EMT) signalling markers and promoted PDAC cell growth. The level of MPP4 expression negatively correlated with the prognosis of PDAC in PDAC patients. Therefore, MRP4 has become a target of gene therapy for PDAC. The expression of MRP4 was higher in PDAC samples, and MRP4 was linked to a more invasive PDAC phenotype. MRP4 is the main protein leading to cAMP efflux, and its inhibition or silencing abolished cell proliferation by activating the cAMP/Epac/Rap1 signalling pathway. The anti-proliferative effect of MRP4 was restored by cAMP, and the cAMP pathway is often activated in pancreatic cancer [79].

Osteosarcoma: He et al. [80] established the human osteosarcoma cell line MG63/DOX that is resistant to adriamycin (ADM) and compared it with the primary cell line GSF-0686. The results showed that the expression of MRP4 in MG63/DOX cells was significantly higher than MG63 cells, which suggests that overexpressed MRP4 may be involved in the ADM resistance of osteosarcoma and promote the drug resistance of osteosarcoma cells. However, the relationship between MRP4 and ADM is not clear.

Endometrial cancer: Chemoresistance is a major factor in the poor prognosis of endometrial cancer (EC) [81]. MRP7 is significantly expressed in EC tissues and associated with poor EC prognosis. Huang et al. [82] found that the tumour suppressor miR-98 inhibited the expression of MRP7, and facilitated resistance to the oncotherapy drug paclitaxel. An inhibitor of miR-98, NEAT1, increased paclitaxel resistance in EC cells by decreasing the expression of miR-98 to upregulate the level of MRP7.

Renal cell carcinoma: Chen et al. [83] showed that miR-210-3p was associated with various cancer pathologies and negatively regulated MRP1. Li et al. [84] showed that the downregulation of miR-210-3p in renal cell carcinoma (RCC) cells increased the expression level of MRP1, which increased multidrug resistance in RCC, but the specific mechanism has not been explained.

Colorectal cancer: Colorectal cancer (CRC) is one of the most common malignancies worldwide [85-87]. CRC is thought to develop from polyps that gradually develop into invasive tumours [88]. High expression of MRP1 posi-

tively correlated with the prognosis of CRC [89]. Lv et al. showed that hypoxia inhibited and reduced HIF-1α, which induced MRP1, and facilitated a reduction of drug resistance in colon cancer. MRP1 was a downstream target gene of HIF-1α, which provided a mechanistic basis for the treatment of HIF-1α-mediated CRC [90].

Inflammation is a risk factor for CRC, and intestinal inflammation and ABC transporter proteins create a link between environmental and potential intestinal carcinogenesis [91-93]. Andersen et al. [94] found that the early events of high expression of the MRP2 gene and low expression of the ABCG2 gene occurred in the CRC-cancer sequence. MRP2 participates in the early process of CRC by transporting LTB4 or MRP2 to transport other eicosanes, and LTB4 and eicosanes promote inflammatory and cancer inflammatory signalling pathways [95-97].

Cholangiocarcinoma: Cholangiocarcinoma (CCA) is a primary liver cancer, and the main obstacle for treatment is the increased resistance of MRP-induced tumours to chemotherapy [98]. Yang et al. [99] found that the expression of MRP5 and MRP6 was significantly upregulated after exposure to the anticancer drug gemcitabine in CCA liver cell lines, which supports the development of MRP6 and MRP5 inhibitors as a treatment for CCA.

Acute myelogenous leukaemia: Acute myelogenous leukaemia (AML) is one of the most common heterogeneous haematological malignancies worldwide [100]. The occurrence and development of AML is due to the disturbance of haematopoietic stem cell differentiation and the excessive proliferation of myeloid progenitor cell clones. Intracellular cAMP is a signalling molecule that regulates cell proliferation, differentiation and apoptosis, and plays an important role in AML [101-103]. Gonzalez et al. [104] induced MRP4 expression and increased cAMP efflux in AML by histamine treatment, and the combination of histamine and MRP inhibitors promoted a reduction in AML cell proliferation in favour of AML treatment. MRP4 regulates the proliferation and differentiation of AML cells by regulating the level of cAMP in AML cell lines.

Breast cancer: Breast cancer (BC), especially metastatic breast cancer, is a leading contributor to morbidity and mortality in women with related diseases [105, 106]. Kochel et al. [107] demonstrated that overexpression of MRP4 was associated with breast cancer. Overexpression of MRP4 increased prostaglandins (PGE2), which are major eicosanoid products in tumours and are detrimental to the prognosis of breast cancer.

Ovarian cancer: Arachidonic acid (AA) metabolism plays an important role in advanced ovarian cancer [108, 109]. Zhang et al. [110] showed that overexpression of MRP1 and MRP4 in cisplatin (DDP)-resistant SKOV3 (SKOV3-R) cells increased the production of AA-derived eicosanoids, which had transduction effects on the drug sensitivity of ovarian cancer DDP capacity to the detriment of ovarian cancer treatment [111-113].

MRPs and hereditary diseases

Durbin-Johnson syndrome: Durbin-Johnson syndrome (DJS) is a hereditary autochthonous recessive disorder featuring conjugated hyperbilirubinemia, which is an increased concentration of bilirubin glucoside in the blood, impaired secretion of anion conjugates of bile in hepatocytes and dark pigmentation of hepatocytes that causes a dark blue or black colouration of the liver in affected individuals [114, 115]. Mutations in the MRP2 gene lead to impaired expression and targeting of MRP2 protein on the cholinesterase membrane, which lead to Durbin-John syndrome that is characterized by conjugated hyperbilirubinemia and defective excretion of organic ions. It is characterized by mutations in the MRP2 gene and impaired MRP2 function, which lead to impaired bilirubin excretion and elevated conjugated bilirubin that result in further cholestasis. Bilirubin is the mechanism by which DJS occurs, and MRP2 is an important driver of bile flow. Downregulated MRP2 expression leads to an excessive release of inflammatory cytokines, which inhibit extracellular regulated kinases in hepatocytes, and a downregulation of MRP2. This vicious cycle exacerbates liver injury [115-117].

Pseudopolychordoma elasticity: Pseudoxyloma elasticum (PXE) is a hereditary infectious disease of the connective tissue [118, 119]. Connective tissue disorder and elastic fibre abnormality are the early manifestations of PXE [120], which is characterized by progressive dystrophy and mineralisation of elasticfi-

bres, including calcification of elastic structures in the skin. Patients with PXE often have skin lesions, vision loss, intermittent coagulation and myocardial infarction [121-123]. Several studies suggested that PXE was caused by mutations in the MRP6 gene, but the process is complex and involves many uncertainties. MRP6 may be associated with the release of ATP from cells, and MRP6 is involved in ATP metabolism and inhibits ectopic calcification. MRP6 deficiency can promote ectopic calcification. MRP6 secretes AMP (adenosine 5-monophosphate), which is converted from ATP by ENPP1 (nucleotide pyrophosphatase/phosphodiesterase) and CD73 (an exo-5-nucleotide) acts together downstream to degrade AMP into adenosine and inorganic phosphate. Adenosine inhibits the expression and activity of TNAP to regulate PPI (**Figure 4**). PPI is an effective calcification inhibitor and a protective endocrine factor that is missing in PXE. TNAP is a tissue nonspecific alkaline phosphatase that degrades pyrophosphate [124-127].

MRPs and other diseases

Acute liver injury: Liver injury is associated with endoplasmic reticulum (ER) stress and NF-κB signalling, and MRP2 is regulated by NF-κB [128, 129]. Huang et al. found significant ER stress, increased MRP2 expression and activation of NF-κB in a carbon tetrachloride (CCl_4)-induced acute liver injury model and a Tg-induced ER stress model in mice. The downregulation of MRP2 expression in the liver increased ER stress and promoted hepatocyte apoptosis and liver injury in mice with CCl_4-induced acute liver injury. The mechanism of increased MRP2 expression in the liver is the activation of NF-κB signalling after ER stress, which alleviates ER stress and acute liver injury [51, 128].

Atopic dermatitis: Atopic dermatitis (AD) is an immune skin disease mediated by T cells [130, 131]. Lee et al. established Jurkat cells and mouse CD4 T-cell models with AD, and found that MRP1 physically bound to kamanol in activated T cells, in which reduced the expression and phosphorylation of JNK in the treatment of atopic dermatitis [132].

Prostate inflammation: Prostate inflammation (PI) is often accompanied by symptoms of the lower urinary tract, and the urethra plays an important role in the urinary cycle [133]. Alexandre et al. [134] used histological and cGMP level analyses and found that PI dysfunction decreased urethral contractility and the expression of MRP5, which may modulate inflammatory processes, increased intracellular cGMP (guanosine cyclophosphate) accumulation in urethral tissues, and significantly relaxed smooth muscle, which may adversely affect urethral tissues.

Kawasaki disease: Kawasaki disease (KD) was first reported in 1967 [135]. It is a systemic vasculitis syndrome that primarily affects coronary vasculitis. It is an acute self-limited vasculitis and acute febrile disease of unknown cause [136, 137]. It typically occurs in children under 5 years of age and as a feature of hyperhaemoglobinaemia [138]. KD may cause coronary artery aneurysms, ischaemic heart disease, myocardial infarction, and death [139-141]. Intravenous immunoglobulin (IVIG) is the first choice for the treatment of KD, but McCrindle found IVIG resistance such as recurrence or persistent fever after treatment [142]. MRP4 is a mediator of prostaglandin E1 and prostaglandin E2 efflux, and an MRP4 single nucleotide polymorphism may influence Kawasaki disease. Because the triggering factor of PGE2 expression in the acute phase of Kawasaki disease is IVIG, there is a certain correlation between the change in plasma PGE2 levels and IVIG resistance. However, there is uncertainty about the role of MRP4 single nucleotide polymorphisms in IVIG resistance and other roles for MRP4 in the pathogenesis of KD.

Ulcerative colitis: Ulcerative colitis (UC) is a type of chronic colitis that belongs to inflammatory bowel diseases, with clinical manifestations comprised of rectal bleeding, persistent diarrhoea and belly pain [143]. Several studies showed that the MRP7/CFTR gene and protein were involved in the occurrence and development of UC. Marco et al. [120] used MRP7/CFTR knockout mice and discovered that CFTR downregulation was responsible for increased expression of inflammatory interleukin 6 (IL-6), tumour necrosis factor-α (TNF-α) and NF-κB in the mouse intestine, which resulted in an inflammatory response. NF-κB is a key inflammatory regulator that is activated by a variety of stimuli, including bacterial components (such as lipopolysaccharide), proinflammatory cytokines (such as TNF-α and IL-1), viruses and DNA

proliferators. The activation of transcriptional NF-κB promotes an increase in ILs, such as IL-1, IL-6 and IL-8, and participates in the inflammatory response [144].

Progress of MRP inhibitors

Meloxicam

COX inhibitors reduce multidrug resistance by inhibiting the expression of ATP-binding cassette transporters, which is beneficial to the anticancer drug doxorubicin for the treatment of tumours [145]. Chen et al. [146] revealed the role of a specific COX-2 inhibitor, meloxicam, by developing a human A549 lung cancer model. A549 cells had increased accumulation of a substrate of intracellular MRP, doxorubicin, which helped inhibit the development of lung cancer by reducing the expression levels of MRP1 and MRP4.

Lapatinib

Lapatinib inhibits the phosphorylation of EGFR, AKT and P38 in breast cancer globulin, reduces the expression of MRP1, and promotes the toxicity of tumour-globulin cells [147]. Kwon et al. [148] found that blocking the PI3K/AKT and p38/MAPK signalling pathways reduced MRP1 levels in doxorubicin-treated tumour spheroids. These results indicated that lapatinib suppresses adriamycin-induced MRP1 expression by inhibiting the PI3K/AKT and p38MAPK signalling pathways, which may be an effective agent for the treatment of breast cancer.

HOXA10

Multidrug resistance is a major obstacle in the treatment of chronic myeloid leukaemia (CML) with the anticancer drug doxorubicin [149]. HOXA10 is a member of the HOX gene family and it is frequently expressed in CML [150]. Ying et al. [151] found that knockdown of HOXA10 inhibited the expression of P-gp and MRP1, which indicated that HOXA10 was a potential target for reducing multidrug resistance in CML.

Conclusion and future

Multidrug resistance is increasingly recognised as a major obstacle to cancer treatment. Multidrug resistance proteins are involved in the occurrence and development of various cancers. As the C subfamily of the ABC family, MRPs play an important role in the multidrug resistance of various cancers and are closely related to the occurrence and development of other systemic diseases. EBP50 knockdown in HepG2 cells, the respective substrates of MRP and breast cancer resistance protein (BCRP), reduced the activities of P-gp and MRP, but not BCRP. These results suggest that EBP50 regulates ET activity. MRP-1 is implicated in multidrug resistance and was described as prognostic in high-risk patients with soft-tissue sarcoma. The expression of MRP-1 is elevated in colorectal adenocarcinoma tissues, and patients with negative expression of MRP-1 have a better prognosis. Therefore, MRP-1 may be a reference indicator for clinical diagnosis and prognosis. Other multidrug resistance proteins also play irreplaceable roles in various cancers.

The development of MRP inhibitors is expected to improve the efficacy of anticancer drugs and be beneficial to the treatment of other diseases. However, to overcome MDR in cancer, a gap between in vitro/in vivo research of MRPs modulators and therapeutic applications remains, and the discovery of specific MRP inhibitors is currently lacking. Therefore, to overcome chemoresistance in clinical practice, very powerful and selective MRP inhibitors and sizable MDR cancer cohorts with thorough clinicopathological data are needed. The combined use of MRP inhibitors and anticancer drugs is expected to become the development trend in cancer treatment.

Although ABC transporter proteins play an important role in the development of multidrug-resistant cancers, efforts to target these transporter proteins have not been successful. Future strategies to combat multidrug resistance are likely going to include the following: (1) the use of bioinformatics for customized treatment; (2) continuous research on new pathways relating ABC transporter proteins to diseases, including MDR; and (3) accelerating anticancer drug development platforms through the use of high-throughput and the packaging of new or current chemotherapeutic agents as nanodrugs to boost medication delivery to drug-resistant cancer cells. By using novel medicines and cutting-edge technologies as tactics for

attacking ABC-transporting proteins and multidrug resistance, such as nanoparticles, monoclonal antibodies, and gene technologies, anticancer drug delivery to resistant cells may be increased. Combination therapies that maximise chemosensitivity should also be further investigated. These methods may hold the solution to the growing issue of malignancies with medication resistance.

We should also investigate the cause of multidrug resistance from the MRP family to understand the mechanism of cancer, genetics and other diseases from various aspects and whether the MRP family is related to other causes that affect the disease. Given these unanswered questions, we have much work to do in the future.

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Disclosure of conflict of interest

None.

Abbreviations

AA, Arachidonic Acid; ABC, ATP-Binding Cassette; AD, Atopic Dermatitis; ADM, Adriamycin; AML, Acute Myelogenous Leukemia; BC, Breast Cancer; CCA, Cholangiocarcinoma; cMRP, Cholinergic MRP; CML, Chronic Myeloid Leukemia; CRC, Colorectal Cancer; DJS, Durbin-Johnson Syndrome; EC, Endometrial Cancer; EMT, Epithelial Mesenchymal Transformation; ER, Endo plasmic Reticulum; GAC, Gastric Adenocarcinoma; HCC, Hepatocellular Carcinoma; IL-6, Inflammatory Interleukin 6; IVIG, Intravenous Immunoglobulin; KD, Kawasaki Disease; MDR, Multidrug Resistance; MRPs/ABCCs, Multidrug Resistance Proteins; MSD, Membrane Span Domains; NF-κB, Nuclear Factor KappaB; NSCLC, Non-Small Cell Lung Cancer; PC, Pancreatic Cancer; P-gp, P-Glycoprotein; PGE2, Prostaglandin; PI, Prostate Inflammation; PXE, Pseudoxyloma Elasticum; RCC, Renal Cell Carcinoma; SLAMF3, Signaling Lymphocyte Activation Molecule Family Member 3; TNF-α, Tumor Necrosis Factor-α; UC, Ulcerative Colitis.

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Plessmann U, Münch S, Abou-El-Ardat K, Makowka P, Acker F, Enssle JC, Cremer A, Schnütgen F, Kurrle N, Chapuy B, Löber J, Hartmann S, Wild PJ, Wittig I, Hübschmann D, Kaderali L, Cox J, Brüne B, Röllig C, Thiede C, Steffen B, Bornhäuser M, Trumpp A, Urlaub H, Stegmaier K, Serve H, Mann M and Oellerich T. The proteogenomic subtypes of acute myeloid leukemia. Cancer Cell 2022; 40: 301-317, e312.

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Supplementary Materials

The protein sequences of human MRP1-9 from the Unified Protein Data Bank are described as follows.

1. Multidrug resistance-associated protein 1 ● Homo sapiens (Human)

2. ATP-binding cassette sub-family C member 2 ● Homo sapiens (Human)

3. ATP-binding cassette sub-family C member 3 ● Homo sapiens (Human)

4. ATP-binding cassette sub-family C member 4 ● Homo sapiens (Human)

5. ATP-binding cassette sub-family C member 5 ● Homo sapiens (Human)

6. ATP-binding cassette sub-family C member 6 ● Homo sapiens (Human)

7. ATP-binding cassette sub-family C member 10 ● Homo sapiens (Human)

8. ATP-binding cassette sub-family C member 11 ● Homo sapiens (Human)

9. ATP-binding cassette sub-family C member 12 ● Homo sapiens (Human)

Multidrug resistance-associated protein 1 ● Homo sapiens (Human) amino acid sequence:

>sp|P33527|MRP1_HUMAN Multidrug resistance-associated protein 1 OS=Homo sapiens OX=9606 GN=ABCC1 PE=1 SV=3

MALRGFCSADGSDPLWDWNVTWNTSNPDFTKCFQNTVLVWVPCFYLWACFPFYFLYLSRH

DRGYIQMTPLNKTKTALGFLLWIVCWADLFYSFWERSRGIFLAPVFLVSPTLLGITMLLA

TFLIQLERRKGVQSSGIMLTFWLVALVCALAILRSKIMTALKEDAQVDLFRDITFYVYFS

LLLIQLVLSCFSDRSPLFSETIHDPNPCPESSASFLSRITFWWITGLIVRGYRQPLEGSD

LWSLNKEDTSEQVVPVLVKNWKKECAKTRKQPVKVVYSSKDPAQPKESSKVDANEEVEAL

IVKSPQKEWNPSLFKVLYKTFGPYFLMSFFFKAIHDLMMFSGPQILKLLIKFVNDTKAPD

WQGYFYTVLLFVTACLQTLVLHQYFHICFVSGMRIKTAVIGAVYRKALVITNSARKSSTV

GEIVNLMSVDAQRFMDLATYINMIWSAPLQVILALYLLWLNLGPSVLAGVAVMVLMVPVN

AVMAMKTKTYQVAHMKSKDNRIKLMNEILNGIKVLKLYAWELAFKDKVLAIRQEELKVLK

KSAYLSAVGTFTWVCTPFLVALCTFAVYVTIDENNILDAQTAFVSLALFNILRFPLNILP

MVISSIVQASVSLKRLRIFLSHEELEPDSIERRPVKDGGGTNSITVRNATFTWARSDPPT

LNGITFSIPEGALVAVVGQVGCGKSSLLSALLAEMDKVEGHVAIKGSVAYVPQQAWIQND

SLRENILFGCQLEEPYYRSVIQACALLPDLEILPSGDRTEIGEKGVNLSGGQKQRVSLAR

AVYSNADIYLFDDPLSAVDAHVGKHIFENVIGPKGMLKNKTRILVTHSMSYLPQVDVIIV

MSGGKISEMGSYQELLARDGAFAEFLRTYASTEQEQDAEENGVTGVSGPGKEAKQMENGM

LVTDSAGKQLQRQLSSSSSYSGDISRHHNSTAELQKAEAKKEETWKLMEADKAQTGQVKL

SVYWDYMKAIGLFISFLSIFLFMCNHVSALASNYWLSLWTDDPIVNGTQEHTKVRLSVYG

ALGISQGIAVFGYSMAVSIGGILASRCLHVDLLHSILRSPMSFFERTPSGNLVNRFSKEL

DTVDSMIPEVIKMFMGSLFNVIGACIVILLATPIAAIIIPPLGLIYFFVQRFYVASSRQL

KRLESVSRSPVYSHFNETLLGVSVIRAFEEQERFIHQSDLKVDENQKAYYPSIVANRWLA

VRLECVGNCIVLFAALFAVISRHSLSAGLVGLSVSYSLQVTTYLNWLVRMSSEMETNIVA

VERLKEYSETEKEAPWQIQETAPPSSWPQVGRVEFRNYCLRYREDLDFVLRHINVTINGG

EKVGIVGRTGAGKSSLTLGLFRINESAEGEIIIDGINIAKIGLHDLRFKITIIPQDPVLF

SGSLRMNLDPFSQYSDEEVWTSLELAHLKDFVSALPDKLDHECAEGGENLSVGQRQLVCL

ARALLRKTKILVLDEATAAVDLETDDLIQSTIRTQFEDCTVLTIAHRLNTIMDYTRVIVL

DKGEIQEYGAPSDLLQQRGLFYSMAKDAGLV

Human MRP1:

Seq Identity

90.52%

Template

6uy0.1. A Multidrug resistance-associated protein 1

Cryo-EM structure of wild-type bovine multidrug resistance protein 1 (MRP1) under active turnover conditions

ATP-binding cassette sub-family Cmember 2 ● Homo sapiens (Human) amino acid sequence:

>sp|Q92887|MRP2_HUMAN ATP-binding cassette sub-family C member 2 OS=Homo sapiens OX=9606 GN=ABCC2 PE=1 SV=3

MLEKFCNSTFWNSSFLDSPEADLPLCFEQTVLVWIPLGYLWLLAPWQLLHVYKSRTKRSS

TTKLYLAKQVFVGFLLILAAIELALVLTEDSGQATVPAVRYTNPSLYLGTWLLVLLIQYS

RQWCVQKNSWFLSLFWILSILCGTFQFQTLIRTLLQGDNSNLAYSCLFFISYGFQILILI

FSAFSENNESSNNPSSIASFLSSITYSWYDSIILKGYKRPLTLEDVWEVDEEMKTKTLVS

KFETHMKRELQKARRALQRRQEKSSQQNSGARLPGLNKNQSQSQDALVLEDVEKKKKKSG

TKKDVPKSWLMKALFKTFYMVLLKSFLLKLVNDIFTFVSPQLLKLLISFASDRDTYLWIG

YLCAILLFTAALIQSFCLQCYFQLCFKLGVKVRTAIMASVYKKALTLSNLARKEYTVGET

VNLMSVDAQKLMDVTNFMHMLWSSVLQIVLSIFFLWRELGPSVLAGVGVMVLVIPINAIL

STKSKTIQVKNMKNKDKRLKIMNEILSGIKILKYFAWEPSFRDQVQNLRKKELKNLLAFS

QLQCVVIFVFQLTPVLVSVVTFSVYVLVDSNNILDAQKAFTSITLFNILRFPLSMLPMMI

SSMLQASVSTERLEKYLGGDDLDTSAIRHDCNFDKAMQFSEASFTWEHDSEATVRDVNLD

IMAGQLVAVIGPVGSGKSSLISAMLGEMENVHGHITIKGTTAYVPQQSWIQNGTIKDNIL

FGTEFNEKRYQQVLEACALLPDLEMLPGGDLAEIGEKGINLSGGQKQRISLARATYQNLD

IYLLDDPLSAVDAHVGKHIFNKVLGPNGLLKGKTRLLVTHSMHFLPQVDEIVVLGNGTIV

EKGSYSALLAKKGEFAKNLKTFLRHTGPEEEATVHDGSEEEDDDYGLISSVEEIPEDAAS

ITMRRENSFRRTLSRSSRSNGRHLKSLRNSLKTRNVNSLKEDEELVKGQKLIKKEFIETG

KVKFSIYLEYLQAIGLFSIFFIILAFVMNSVAFIGSNLWLSAWTSDSKIFNSTDYPASQR

DMRVGVYGALGLAQGIFVFIAHFWSAFGFVHASNILHKQLLNNILRAPMRFFDTTPTGRI

VNRFAGDISTVDDTLPQSLRSWITCFLGIISTLVMICMATPVFTIIVIPLGIIYVSVQMF

YVSTSRQLRRLDSVTRSPIYSHFSETVSGLPVIRAFEHQQRFLKHNEVRIDTNQKCVFSW

ITSNRWLAIRLELVGNLTVFFSALMMVIYRDTLSGDTVGFVLSNALNITQTLNWLVRMTS

EIETNIVAVERITEYTKVENEAPWVTDKRPPPDWPSKGKIQFNNYQVRYRPELDLVLRGI

TCDIGSMEKIGVVGRTGAGKSSLTNCLFRILEAAGGQIIIDGVDIASIGLHDLREKLTII

PQDPILFSGSLRMNLDPFNNYSDEEIWKALELAHLKSFVASLQLGLSHEVTEAGGNLSIG

QRQLLCLGRALLRKSKILVLDEATAAVDLETDNLIQTTIQNEFAHCTVITIAHRLHTIMD

SDKVMVLDNGKIIECGSPEELLQIPGPFYFMAKEAGIENVNSTKF

Human MRP2:

Seq Identity

51.02%

Template

5uj9.1. A bovine multidrug resistance protein 1 (MRP1), Multidrug resistance-associated protein 1

Cryo-EM structure of bovine multidrug resistance protein 1 (MRP1)

ATP-binding cassette sub-family Cmember 3 ● Homo sapiens (Human) amino acid sequence:

>sp|O15438|MRP3_HUMAN ATP-binding cassette sub-family C member 3 OS=Homo sapiens OX=9606 GN=ABCC3 PE=1 SV=3

MDALCGSGELGSKFWDSNLSVHTENPDLTPCFQNSLLAWVPCIYLWVALPCYLLYLRHHC

RGYIILSHLSKLKMVLGVLLWCVSWADLFYSFHGLVHGRAPAPVFFVTPLVVGVTMLLAT

LLIQYERLQGVQSSGVLIIFWFLCVVCAIVPFRSKILLAKAEGEISDPFRFTTFYIHFAL

VLSALILACFREKPPFFSAKNVDPNPYPETSAGFLSRLFFWWFTKMAIYGYRHPLEEKDL

WSLKEEDRSQMVVQQLLEAWRKQEKQTARHKASAAPGKNASGEDEVLLGARPRPRKPSFL

KALLATFGSSFLISACFKLIQDLLSFINPQLLSILIRFISNPMAPSWWGFLVAGLMFLCS

MMQSLILQHYYHYIFVTGVKFRTGIMGVIYRKALVITNSVKRASTVGEIVNLMSVDAQRF

MDLAPFLNLLWSAPLQIILAIYFLWQNLGPSVLAGVAFMVLLIPLNGAVAVKMRAFQVKQ

MKLKDSRIKLMSEILNGIKVLKLYAWEPSFLKQVEGIRQGELQLLRTAAYLHTTTTFTWM

CSPFLVTLITLWVYVYVDPNNVLDAEKAFVSVSLFNILRLPLNMLPQLISNLTQASVSLK

RIQQFLSQEELDPQSVERKTISPGYAITIHSGTFTWAQDLPPTLHSLDIQVPKGALVAVV

GPVGCGKSSLVSALLGEMEKLEGKVHMKGSVAYVPQQAWIQNCTLQENVLFGKALNPKRY

QQTLEACALLADLEMLPGGDQTEIGEKGINLSGGQRQRVSLARAVYSDADIFLLDDPLSA

VDSHVAKHIFDHVIGPEGVLAGKTRVLVTHGISFLPQTDFIIVLADGQVSEMGPYPALLQ

RNGSFANFLCNYAPDEDQGHLEDSWTALEGAEDKEALLIEDTLSNHTDLTDNDPVTYVVQ

KQFMRQLSALSSDGEGQGRPVPRRHLGPSEKVQVTEAKADGALTQEEKAAIGTVELSVFW

DYAKAVGLCTTLAICLLYVGQSAAAIGANVWLSAWTNDAMADSRQNNTSLRLGVYAALGI

LQGFLVMLAAMAMAAGGIQAARVLHQALLHNKIRSPQSFFDTTPSGRILNCFSKDIYVVD

EVLAPVILMLLNSFFNAISTLVVIMASTPLFTVVILPLAVLYTLVQRFYAATSRQLKRLE

SVSRSPIYSHFSETVTGASVIRAYNRSRDFEIISDTKVDANQRSCYPYIISNRWLSIGVE

FVGNCVVLFAALFAVIGRSSLNPGLVGLSVSYSLQVTFALNWMIRMMSDLESNIVAVERV

KEYSKTETEAPWVVEGSRPPEGWPPRGEVEFRNYSVRYRPGLDLVLRDLSLHVHGGEKVG

IVGRTGAGKSSMTLCLFRILEAAKGEIRIDGLNVADIGLHDLRSQLTIIPQDPILFSGTL

RMNLDPFGSYSEEDIWWALELSHLHTFVSSQPAGLDFQCSEGGENLSVGQRQLVCLARAL

LRKSRILVLDEATAAIDLETDNLIQATIRTQFDTCTVLTIAHRLNTIMDYTRVLVLDKGV

VAEFDSPANLIAARGIFYGMARDAGLA

Human MRP3:

Seq Identity

57.22%

Template

5uj9.1. A bovine multidrug resistance protein 1 (MRP1), Multidrug resistance-associated protein 1

Cryo-EM structure of bovine multidrug resistance protein 1 (MRP1)

ATP-binding cassette sub-family Cmember 4 ● Homo sapiens (Human) amino acid sequence:

>sp|O15439|MRP4_HUMAN ATP-binding cassette sub-family C member 4 OS=Homo sapiens OX=9606 GN=ABCC4 PE=1 SV=3

MLPVYQEVKPNPLQDANLCSRVFFWWLNPLFKIGHKRRLEEDDMYSVLPEDRSQHLGEEL

QGFWDKEVLRAENDAQKPSLTRAIIKCYWKSYLVLGIFTLIEESAKVIQPIFLGKIINYF

ENYDPMDSVALNTAYAYATVLTFCTLILAILHHLYFYHVQCAGMRLRVAMCHMIYRKALR

LSNMAMGKTTTGQIVNLLSNDVNKFDQVTVFLHFLWAGPLQAIAVTALLWMEIGISCLAG

MAVLIILLPLQSCFGKLFSSLRSKTATFTDARIRTMNEVITGIRIIKMYAWEKSFSNLIT

NLRKKEISKILRSSCLRGMNLASFFSASKIIVFVTFTTYVLLGSVITASRVFVAVTLYGA

VRLTVTLFFPSAIERVSEAIVSIRRIQTFLLLDEISQRNRQLPSDGKKMVHVQDFTAFWD

KASETPTLQGLSFTVRPGELLAVVGPVGAGKSSLLSAVLGELAPSHGLVSVHGRIAYVSQ

QPWVFSGTLRSNILFGKKYEKERYEKVIKACALKKDLQLLEDGDLTVIGDRGTTLSGGQK

ARVNLARAVYQDADIYLLDDPLSAVDAEVSRHLFELCICQILHEKITILVTHQLQYLKAA

SQILILKDGKMVQKGTYTEFLKSGIDFGSLLKKDNEESEQPPVPGTPTLRNRTFSESSVW

SQQSSRPSLKDGALESQDTENVPVTLSEENRSEGKVGFQAYKNYFRAGAHWIVFIFLILL

NTAAQVAYVLQDWWLSYWANKQSMLNVTVNGGGNVTEKLDLNWYLGIYSGLTVATVLFGI

ARSLLVFYVLVNSSQTLHNKMFESILKAPVLFFDRNPIGRILNRFSKDIGHLDDLLPLTF

LDFIQTLLQVVGVVSVAVAVIPWIAIPLVPLGIIFIFLRRYFLETSRDVKRLESTTRSPV

FSHLSSSLQGLWTIRAYKAEERCQELFDAHQDLHSEAWFLFLTTSRWFAVRLDAICAMFV

IIVAFGSLILAKTLDAGQVGLALSYALTLMGMFQWCVRQSAEVENMMISVERVIEYTDLE

KEAPWEYQKRPPPAWPHEGVIIFDNVNFMYSPGGPLVLKHLTALIKSQEKVGIVGRTGAG

KSSLISALFRLSEPEGKIWIDKILTTEIGLHDLRKKMSIIPQEPVLFTGTMRKNLDPFNE

HTDEELWNALQEVQLKETIEDLPGKMDTELAESGSNFSVGQRQLVCLARAILRKNQILII

DEATANVDPRTDELIQKKIREKFAHCTVLTIAHRLNTIIDSDKIMVLDSGRLKEYDEPYV

LLQNKESLFYKMVQQLGKAEAAALTETAKQVYFKRNYPHIGHTDHMVTNTSNGQPSTLTI

FETAL

Human MRP4:

Seq Identity

39.97%

Template

7m69.1. A Metal resistance protein YCF1

E1435Q Ycf1 mutant in inward-facing wide conformation

ATP-binding cassette sub-family Cmember 5 ● Homo sapiens (Human) amino acid sequence:

>sp|O15440|MRP5_HUMAN ATP-binding cassette sub-family C member 5 OS=Homosapiens OX=9606 GN=ABCC5 PE=1 SV=2

MKDIDIGKEYIIPSPGYRSVRERTSTSGTHRDREDSKFRRTRPLECQDALETAARAEGLS

LDASMHSQLRILDEEHPKGKYHHGLSALKPIRTTSKHQHPVDNAGLFSCMTFSWLSSLAR

VAHKKGELSMEDVWSLSKHESSDVNCRRLERLWQEELNEVGPDAASLRRVVWIFCRTRLI

LSIVCLMITQLAGFSGPAFMVKHLLEYTQATESNLQYSLLLVLGLLLTEIVRSWSLALTW

ALNYRTGVRLRGAILTMAFKKILKLKNIKEKSLGELINICSNDGQRMFEAAAVGSLLAGG

PVVAILGMIYNVIILGPTGFLGSAVFILFYPAMMFASRLTAYFRRKCVAATDERVQKMNE

VLTYIKFIKMYAWVKAFSQSVQKIREEERRILEKAGYFQSITVGVAPIVVVIASVVTFSV

HMTLGFDLTAAQAFTVVTVFNSMTFALKVTPFSVKSLSEASVAVDRFKSLFLMEEVHMIK

NKPASPHIKIEMKNATLAWDSSHSSIQNSPKLTPKMKKDKRASRGKKEKVRQLQRTEHQA

VLAEQKGHLLLDSDERPSPEEEEGKHIHLGHLRLQRTLHSIDLEIQEGKLVGICGSVGSG

KTSLISAILGQMTLLEGSIAISGTFAYVAQQAWILNATLRDNILFGKEYDEERYNSVLNS

CCLRPDLAILPSSDLTEIGERGANLSGGQRQRISLARALYSDRSIYILDDPLSALDAHVG

NHIFNSAIRKHLKSKTVLFVTHQLQYLVDCDEVIFMKEGCITERGTHEELMNLNGDYATI

FNNLLLGETPPVEINSKKETSGSQKKSQDKGPKTGSVKKEKAVKPEEGQLVQLEEKGQGS

VPWSVYGVYIQAAGGPLAFLVIMALFMLNVGSTAFSTWWLSYWIKQGSGNTTVTRGNETS

VSDSMKDNPHMQYYASIYALSMAVMLILKAIRGVVFVKGTLRASSRLHDELFRRILRSPM

KFFDTTPTGRILNRFSKDMDEVDVRLPFQAEMFIQNVILVFFCVGMIAGVFPWFLVAVGP

LVILFSVLHIVSRVLIRELKRLDNITQSPFLSHITSSIQGLATIHAYNKGQEFLHRYQEL

LDDNQAPFFLFTCAMRWLAVRLDLISIALITTTGLMIVLMHGQIPPAYAGLAISYAVQLT

GLFQFTVRLASETEARFTSVERINHYIKTLSLEAPARIKNKAPSPDWPQEGEVTFENAEM

RYRENLPLVLKKVSFTIKPKEKIGIVGRTGSGKSSLGMALFRLVELSGGCIKIDGVRISD

IGLADLRSKLSIIPQEPVLFSGTVRSNLDPFNQYTEDQIWDALERTHMKECIAQLPLKLE

SEVMENGDNFSVGERQLLCIARALLRHCKILILDEATAAMDTETDLLIQETIREAFADCT

MLTIAHRLHTVLGSDRIMVLAQGQVVEFDTPSVLLSNDSSRFYAMFAAAENKVAVKG

Human MRP5:

Seq Identity

36.60%

Template

6uy0.1. A Multidrug resistance-associated protein 1

Cryo-EM structure of wild-type bovine multidrug resistance protein 1 (MRP1) under active turnover conditions

ATP-binding cassette sub-family C member 6·Homo sapiens (Human) amino acid sequence:

>sp|O95255|MRP6_HUMAN ATP-binding cassette sub-family C member 6 OS=Homo sapiens OX=9606 GN=ABCC6 PE=1 SV=2

MAAPAEPCAGQGVWNQTEPEPAATSLLSLCFLRTAGVWVPPMYLWVLGPIYLLFIHHHGR

GYLRMSPLFKAKMVLGFALIVLCTSSVAVALWKIQQGTPEAPEFLIHPTVWLTTMSFAVF

LIHTERKKGVQSSGVLFGYWLLCFVLPATNAAQQASGAGFQSDPVRHLSTYLCLSLVVAQ

FVLSCLADQPPFFPEDPQQSNPCPETGAAFPSKATFWWVSGLVWRGYRRPLRPKDLWSLG

RENSSEELVSRLEKEWMRNRSAARRHNKAIAFKRKGGSGMKAPETEPFLRQEGSQWRPLL

KAIWQVFHSTFLLGTLSLIISDVFRFTVPKLLSLFLEFIGDPKPPAWKGYLLAVLMFLSA

CLQTLFEQQNMYRLKVLQMRLRSAITGLVYRKVLALSSGSRKASAVGDVVNLVSVDVQRL

TESVLYLNGLWLPLVWIVVCFVYLWQLLGPSALTAIAVFLSLLPLNFFISKKRNHHQEEQ

MRQKDSRARLTSSILRNSKTIKFHGWEGAFLDRVLGIRGQELGALRTSGLLFSVSLVSFQ

VSTFLVALVVFAVHTLVAENAMNAEKAFVTLTVLNILNKAQAFLPFSIHSLVQARVSFDR

LVTFLCLEEVDPGVVDSSSSGSAAGKDCITIHSATFAWSQESPPCLHRINLTVPQGCLLA

VVGPVGAGKSSLLSALLGELSKVEGFVSIEGAVAYVPQEAWVQNTSVVENVCFGQELDPP

WLERVLEACALQPDVDSFPEGIHTSIGEQGMNLSGGQKQRLSLARAVYRKAAVYLLDDPL

AALDAHVGQHVFNQVIGPGGLLQGTTRILVTHALHILPQADWIIVLANGAIAEMGSYQEL

LQRKGALMCLLDQARQPGDRGEGETEPGTSTKDPRGTSAGRRPELRRERSIKSVPEKDRT

TSEAQTEVPLDDPDRAGWPAGKDSIQYGRVKATVHLAYLRAVGTPLCLYALFLFLCQQVA

SFCRGYWLSLWADDPAVGGQQTQAALRGGIFGLLGCLQAIGLFASMAAVLLGGARASRLL

FQRLLWDVVRSPISFFERTPIGHLLNRFSKETDTVDVDIPDKLRSLLMYAFGLLEVSLVV

AVATPLATVAILPLFLLYAGFQSLYVVSSCQLRRLESASYSSVCSHMAETFQGSTVVRAF

RTQAPFVAQNNARVDESQRISFPRLVADRWLAANVELLGNGLVFAAATCAVLSKAHLSAG

LVGFSVSAALQVTQTLQWVVRNWTDLENSIVSVERMQDYAWTPKEAPWRLPTCAAQPPWP

QGGQIEFRDFGLRYRPELPLAVQGVSFKIHAGEKVGIVGRTGAGKSSLASGLLRLQEAAE

GGIWIDGVPIAHVGLHTLRSRISIIPQDPILFPGSLRMNLDLLQEHSDEAIWAALETVQL

KALVASLPGQLQYKCADRGEDLSVGQKQLLCLARALLRKTQILILDEATAAVDPGTELQM

QAMLGSWFAQCTVLLIAHRLRSVMDCARVLVMDKGQVAESGSPAQLLAQKGLFYRLAQES

GLV

Human MRP6:

Seq Identity

47.64%

Template

6uy0.1. A Multidrug resistance-associated protein 1

Cryo-EM structure of wild-type bovine multidrug resistance protein 1 (MRP1) under activeturnover conditions

ATP-binding cassette sub-family Cmember 10 ● Homosapiens (Human) amino acid sequence:

>sp|Q5T3U5|MRP7_HUMANATP-binding cassette sub-family C member 10 OS=Homo sapiens OX=9606 GN=ABCC10 PE=1 SV=1

MERLLAQLCGSSAAWPLPLWEGDTTGHCFTQLVLSALPHALLAVLSACYLGTPRSPDYIL

PCSPGWRLRLAASFLLSVFPLLDLLPVALPPGAGPGPIGLEVLAGCVAAVAWISHSLALW

VLAHSPHGHSRGPLALALVALLPAPALVLTVLWHCQRGTLLPPLLPGPMARLCLLILQLA

ALLAYALGWAAPGGPREPWAQEPLLPEDQEPEVAEDGESWLSRFSYAWLAPLLARGACGE

LRQPQDICRLPHRLQPTYLARVFQAHWQEGARLWRALYGAFGRCYLALGLLKLVGTMLGF

SGPLLLSLLVGFLEEGQEPLSHGLLYALGLAGGAVLGAVLQNQYGYEVYKVTLQARGAVL

NILYCKALQLGPSRPPTGEALNLLGTDSERLLNFAGSFHEAWGLPLQLAITLYLLYQQVG

VAFVGGLILALLLVPVNKVIATRIMASNQEMLQHKDARVKLVTELLSGIRVIKFCGWEQA

LGARVEACRARELGRLRVIKYLDAACVYLWAALPVVISIVIFITYVLMGHQLTATKVFTA

LALVRMLILPLNNFPWVINGLLEAKVSLDRIQLFLDLPNHNPQAYYSPDPPAEPSTVLEL

HGALFSWDPVGTSLETFISHLEVKKGMLVGIVGKVGCGKSSLLAAIAGELHRLRGHVAVR

GLSKGFGLATQEPWIQFATIRDNILFGKTFDAQLYKEVLEACALNDDLSILPAGDQTEVG

EKGVTLSGGQRARIALARAVYQEKELYLLDDPLAAVDADVANHLLHRCILGMLSYTTRLL

CTHRTEYLERADAVLLMEAGRLIRAGPPSEILPLVQAVPKAWAENGQESDSATAQSVQNP

EKTKEGLEEEQSTSGRLLQEESKKEGAVALHVYQAYWKAVGQGLALAILFSLLLMQATRN

AADWWLSHWISQLKAENSSQEAQPSTSPASMGLFSPQLLLFSPGNLYIPVFPLPKAAPNG

SSDIRFYLTVYATIAGVNSLCTLLRAVLFAAGTLQAAATLHRRLLHRVLMAPVTFFNATP

TGRILNRFSSDVACADDSLPFILNILLANAAGLLGLLAVLGSGLPWLLLLLPPLSIMYYH

VQRHYRASSRELRRLGSLTLSPLYSHLADTLAGLSVLRATGATYRFEEENLRLLELNQRC

QFATSATMQWLDIRLQLMGAAVVSAIAGIALVQHQQGLANPGLVGLSLSYALSLTGLLSG

LVSSFTQTEAMLVSVERLEEYTCDLPQEPQGQPLQLGTGWLTQGGVEFQDVVLAYRPGLP

NALDGVTFCVQPGEKLGIVGRTGSGKSSLLLVLFRLLEPSSGRVLLDGVDTSQLELAQLR

SQLAIIPQEPFLFSGTVRENLDPQGLHKDRALWQALKQCHLSEVITSMGGLDGELGEGGR

SLSLGQRQLLCLARALLTDAKILCIDEATASVDQKTDQLLQQTICKRFANKTVLTIAHRL

NTILNSDRVLVLQAGRVVELDSPATLRNQPHSLFQQLLQSSQQGVPASLGGP

Human MRP7:

Seq Identity

33.71%

Template

7mpe.1. A Metal resistance protein YCF1

Cryo-EM structure of the yeast cadmium factor 1 protein (Ycf1p)

ATP-binding cassette sub-family C member 11 ● Homo sapiens (Human) aminoacid sequence:

>sp|Q96J66|MRP8_HUMAN ATP-binding cassette sub-family C member 11 OS=Homo sapiens OX=9606 GN=ABCC11 PE=1 SV=1

MTRKRTYWVPNSSGGLVNRGIDIGDDMVSGLIYKTYTLQDGPWSQQERNPEAPGRAAVPP

WGKYDAALRTMIPFRPKPRFPAPQPLDNAGLFSYLTVSWLTPLMIQSLRSRLDENTIPPL

SVHDASDKNVQRLHRLWEEEVSRRGIEKASVLLVMLRFQRTRLIFDALLGICFCIASVLG

PILIIPKILEYSEEQLGNVVHGVGLCFALFLSECVKSLSFSSSWIINQRTAIRFRAAVSS

FAFEKLIQFKSVIHITSGEAISFFTGDVNYLFEGVCYGPLVLITCASLVICSISSYFIIG

YTAFIAILCYLLVFPLAVFMTRMAVKAQHHTSEVSDQRIRVTSEVLTCIKLIKMYTWEKP

FAKIIEDLRRKERKLLEKCGLVQSLTSITLFIIPTVATAVWVLIHTSLKLKLTASMAFSM

LASLNLLRLSVFFVPIAVKGLTNSKSAVMRFKKFFLQESPVFYVQTLQDPSKALVFEEAT

LSWQQTCPGIVNGALELERNGHASEGMTRPRDALGPEEEGNSLGPELHKINLVVSKGMML

GVCGNTGSGKSSLLSAILEEMHLLEGSVGVQGSLAYVPQQAWIVSGNIRENILMGGAYDK

ARYLQVLHCCSLNRDLELLPFGDMTEIGERGLNLSGGQKQRISLARAVYSDRQIYLLDDP

LSAVDAHVGKHIFEECIKKTLRGKTVVLVTHQLQYLEFCGQIILLENGKICENGTHSELM

QKKGKYAQLIQKMHKEATSDMLQDTAKIAEKPKVESQALATSLEESLNGNAVPEHQLTQE

EEMEEGSLSWRVYHHYIQAAGGYMVSCIIFFFVVLIVFLTIFSFWWLSYWLEQGSGTNSS

RESNGTMADLGNIADNPQLSFYQLVYGLNALLLICVGVCSSGIFTKVTRKASTALHNKLF

NKVFRCPMSFFDTIPIGRLLNCFAGDLEQLDQLLPIFSEQFLVLSLMVIAVLLIVSVLSP

YILLMGAIIMVICFIYYMMFKKAIGVFKRLENYSRSPLFSHILNSLQGLSSIHVYGKTED

FISQFKRLTDAQNNYLLLFLSSTRWMALRLEIMTNLVTLAVALFVAFGISSTPYSFKVMA

VNIVLQLASSFQATARIGLETEAQFTAVERILQYMKMCVSEAPLHMEGTSCPQGWPQHGE

IIFQDYHMKYRDNTPTVLHGINLTIRGHEVVGIVGRTGSGKSSLGMALFRLVEPMAGRIL

IDGVDICSIGLEDLRSKLSVIPQDPVLLSGTIRFNLDPFDRHTDQQIWDALERTFLTKAI

SKFPKKLHTDVVENGGNFSVGERQLLCIARAVLRNSKIILIDEATASIDMETDTLIQRTI

REAFQGCTVLVIAHRVTTVLNCDHILVMGNGKVVEFDRPEVLRKKPGSLFAALMATATSS

LR

Human MRP8:

Seq Identity

34.41%

Template

7mpe.1. A Metal resistance protein YCF1

Cryo-EM structure of the yeast cadmium factor 1 protein (Ycf1p)

ATP-binding cassette sub-family C member 12 ● Homo sapiens (Human) amino acid sequence:

>sp|Q96J65|MRP9_HUMAN ATP-binding cassette sub-family C member 12 OS=Homo sapiens OX=9606 GN=ABCC12 PE=1 SV=2

MVGEGPYLISDLDQRGRRRSFAERYDPSLKTMIPVRPCARLAPNPVDDAGLLSFATFSWL

TPVMVKGYRQRLTVDTLPPLSTYDSSDTNAKRFRVLWDEEVARVGPEKASLSHVVWKFQR

TRVLMDIVANILCIIMAAIGPVILIHQILQQTERTSGKVWVGIGLCIALFATEFTKVFFW

ALAWAINYRTAIRLKVALSTLVFENLVSFKTLTHISVGEVLNILSSDSYSLFEAALFCPL

PATIPILMVFCAAYAFFILGPTALIGISVYVIFIPVQMFMAKLNSAFRRSAILVTDKRVQ

TMNEFLTCIRLIKMYAWEKSFTNTIQDIRRRERKLLEKAGFVQSGNSALAPIVSTIAIVL

TLSCHILLRRKLTAPVAFSVIAMFNVMKFSIAILPFSIKAMAEANVSLRRMKKILIDKSP

PSYITQPEDPDTVLLLANATLTWEHEASRKSTPKKLQNQKRHLCKKQRSEAYSERSPPAK

GATGPEEQSDSLKSVLHSISFVVRKGKILGICGNVGSGKSSLLAALLGQMQLQKGVVAVN

GTLAYVSQQAWIFHGNVRENILFGEKYDHQRYQHTVRVCGLQKDLSNLPYGDLTEIGERG

LNLSGGQRQRISLARAVYSDRQLYLLDDPLSAVDAHVGKHVFEECIKKTLRGKTVVLVTH

QLQFLESCDEVILLEDGEICEKGTHKELMEERGRYAKLIHNLRGLQFKDPEHLYNAAMVE

AFKESPAEREEDAGIIVLAPGNEKDEGKESETGSEFVDTKVPEHQLIQTESPQEGTVTWK

TYHTYIKASGGYLLSLFTVFLFLLMIGSAAFSNWWLGLWLDKGSRMTCGPQGNRTMCEVG

AVLADIGQHVYQWVYTASMVFMLVFGVTKGFVFTKTTLMASSSLHDTVFDKILKSPMSFF

DTTPTGRLMNRFSKDMDELDVRLPFHAENFLQQFFMVVFILVILAAVFPAVLLVVASLAV

GFFILLRIFHRGVQELKKVENVSRSPWFTHITSSMQGLGIIHAYGKKESCITYHLLYFNC

ALRWFALRMDVLMNILTFTVALLVTLSFSSISTSSKGLSLSYIIQLSGLLQVCVRTGTET

QAKFTSVELLREYISTCVPECTHPLKVGTCPKDWPSRGEITFRDYQMRYRDNTPLVLDSL

NLNIQSGQTVGIVGRTGSGKSSLGMALFRLVEPASGTIFIDEVDICILSLEDLRTKLTVI

PQDPVLFVGTVRYNLDPFESHTDEMLWQVLERTFMRDTIMKLPEKLQAEVTENGENFSVG

ERQLLCVARALLRNSKIILLDEATASMDSKTDTLVQNTIKDAFKGCTVLTIAHRLNTVLN

CDHVLVMENGKVIEFDKPEVLAEKPDSAFAMLLAAEVRL

Human MRP9:

Seq Identity

38.04%

Template

5uj9.1. A bovine multidrug resistance protein 1 (MRP1), Multidrug resistance-associated protein 1

Cryo-EM structure of bovine multidrug resistance protein 1 (MRP1)