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Review article

Multidrug resistance-associated protein 4 in pharmacology: Overview of its contribution to pharmacokinetics, pharmacodynamics and pharmacogenetics

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ABSTRACT

MRP4 is an ABC membrane transporter involved in clinical outcomes as it is located in many tissues that manages the transport and the elimination of many drugs. This review explores the implication of MRP4 in clinical pharmacology and the importance of its genetic variability. Although there is no specific recommendation regarding the study of MRP4 in drug development, it should be considered when drugs are eliminated by the kidney or liver or when drug-drug interactions are expected.

1. Introduction

The transport of xenobiotics across organ membranes is mediated by transporters related to the ATP-binding cassette (ABC) transporter or the Solute Carrier (SLC) superfamilies. The present review focuses on MRP4 (Multidrug resistance-associated protein 4), the fourth member of the ABCC family (*ABCC4* gene). MRP4 acts as an unidirectional export pump for conjugates which contributes to cellular detoxification. This transporter has been much less considered than other important members of the ABC superfamily such as the P-glycoprotein (P-gp, ABCB1). However, MRP4 obviously has an important role in clinical pharmacology since it contributes to the export of xenobiotics and it is known to be associated with situations of multi-drug resistance.

MRP4 is encoded by the *ABCC4* gene (MRP4 refers to the protein). Its substrates are mainly organic anions and glucuronide conjugates. [1,2] According to Genecards (https://www.genecards.org/cgi-bin/carddisp.pl?gene=ABCC4&keywords=ABCC4) this gene is located on the minus strand of chromosome 13 (GRCh38/hg38: 95,019,829-95,301,475). The related protein is composed of 1325 amino acids and has a molecular mass of 149.5 kDa. Alternative splicing leads to 4 isoforms of MRP4.

So far, only isoform #1 has been studied. It is expressed in different organs such as the brain, liver, kidneys and blood cells [3] (Fig. 1). MRP4 contains two transmembrane domains (TMDs) and two nucleotide binding domains (NBDs) where the catalytic sites are found [4] (Fig. 2).

2. The roles of MRP4 in pharmacology

2.1. Substrates, inhibitors and related clinical application fields

Table 1 shows the main substrates and inhibitors of MRP4 as reported by Ivanyuk et al. and Russel et al. [5,6]. The drugs are related to 9 different clinical domains. Several substrates belong to cardiovascular, anti-infectious and anti-cancer drugs. In most cases these substrates are also inhibitors.

2.2. The role of MRP4 in drug pharmacokinetics

MRP4 is present in multiple organs and can modify cellular exposure to drugs or metabolites with different consequences. Here, we address the expected role of MRP4 in major organs involved in pharmacokinetics. Most of the studies listed below were performed in animals or derived from in vitro data. Extrapolation from these studies to clinical pharmacokinetics in humans requires careful interpretation.

2.2.1. Kidney

MRP4 is localized at the apical membrane of kidney proximal tubules (Fig. 1B) where it participates in the elimination of many drugs [2]. Various studies have shown that the absence of MRP4 can lead to an accumulation of the drugs in kidney cells and significantly modify their tubular excretion.

This phenomenon has been demonstrated for cephalosporins when

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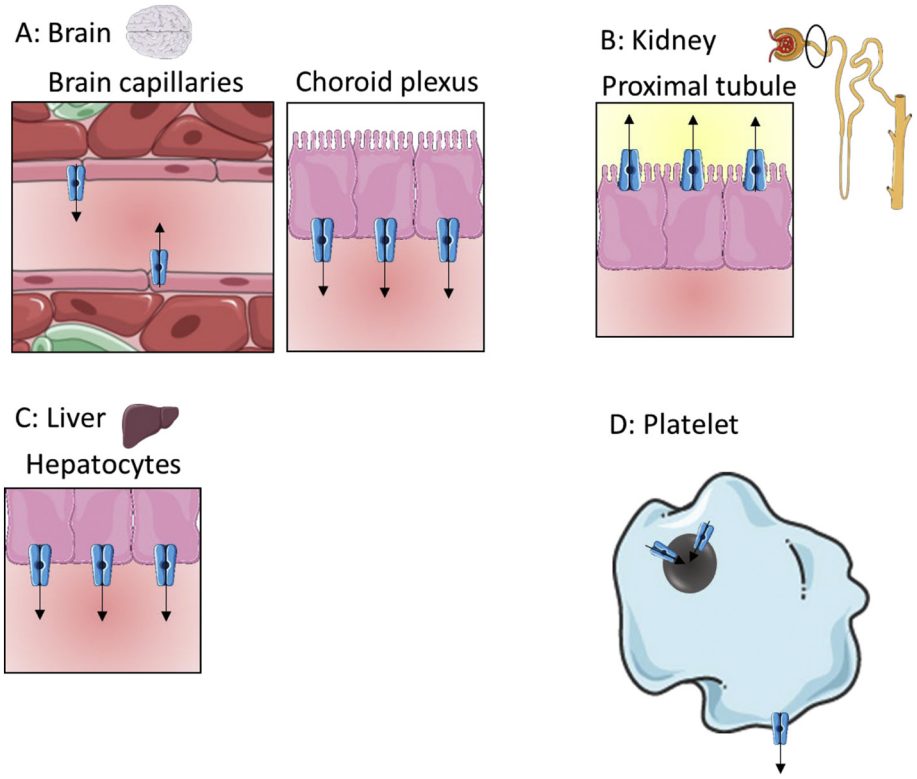

Fig. 1. MRP4 tissue localization. Arrows indicate the substrate transport direction. (A) MRP4 is localized at the basolateral membrane of the choroid plexus epithelium and also at the luminal side of brain capillaries. (B) In the kidney, MRP4 is localized at the apical side of proximal tubules. (C) In the liver, it is expressed at the basolateral side of hepatocytes. (D) In platelets, it can be found at the dense granule as well as at the plasma membrane.

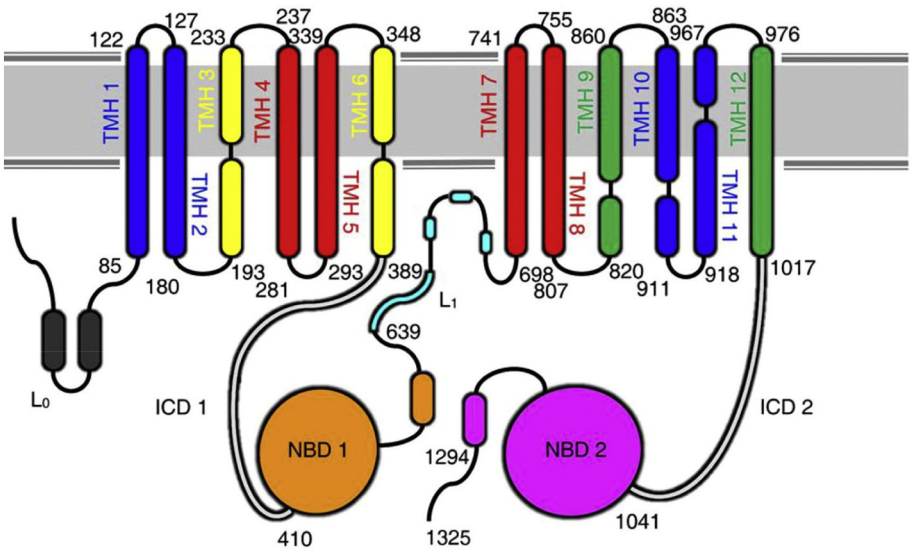

Fig. 2. MRP4 structure. Recent determination taken from and reprinted with permission from Chantemargue et al. [4]. TMH = Transmembrane helix, L1 and L0 = Linker 1 and 0, NBD = nucleotide binding domain, ICD = intra-cytoplasmic domain.

administered to mice [7]. Ci et al. reported that intra-kidney concentrations of ceftizoxime and cefazolin was 2 to 3-fold higher in *Mrp4*$^{-/-}$ mice compared to wild-type mice. The accumulation of the two drugs in the kidney was found to decrease the renal clearances (about 10-fold and 3-fold, respectively) of both drugs, but was not associated with a significant modification in their steady-state plasma concentrations [7].

In a very similar study, Hasegawa et al. observed that the clearance of two different diuretics (hydrochlorothiazide and furosemide) was reduced of about 35 to 40% in *Mrp4*$^{-/-}$ mice [8]. In deficient mice, the intra-kidney concentration of hydrochlorothiazide was almost doubled as compared to wild-type mice. Here again, the accumulation in the kidney and decrease in the renal excretion of the diuretics was not associated with a modification in drug plasma concentrations (similar area under the time-concentration (AUC) values of furosemide in deficient and control mice).

The same research team also demonstrated that the absence of MRP4 could double the intra-kidney concentrations of tenofovir and adefovir, two antiviral agents with strong and selective activity against retroviruses [9]. For both drugs, the renal luminal efflux clearance was estimated to be 37% in *Mrp4*$^{-/-}$ mice and 46% in wild-type mice [9].

2.2.2. Brain

MRP4 is localized in the basolateral membrane of the choroid plexus

Table 1
MRP4 substrates and inhibitors reported in the literature and their related clinical application fields, adapted from Russel and Ivanyuk [5,6].

Drugs	Substrates (Yes/No/ND) (Km if available)	Inhibitor (Yes/No/ND) (IC50 if available)	Clinical application field: drug class
Simvastatin	ND	Yes[a]	Cardiovascular system: hypolipidemic agents
Dipyridamole	ND	Yes (< 1–12 μM)	Cardiovascular system: antithrombotic agents
Ticlopidine	ND	Yes	
Furosemide	Yes	Yes	Cardiovascular system: *Diuretics*
Hydrochlorothiazide	Yes	Yes[a]	
Irbesartan	ND	Yes (10 μM)	Cardiovascular system: *Renin-angiotensin system*
Losartan	ND	Yes[a]	
Olmesartan	Yes (26 μM)	Yes	
DHEAS	Yes (2 μM)	Yes	Endocrinology: *Sex corticosteroids*
Estradiol-17β-glucuronide	Yes (30 μM)	Yes	
Tamoxifen	ND	Yes[a]	
Cefazoline	Yes[a] (80 μM)	Yes	Anti-infectious agents: *β-lactam antibiotics*
Cefmetazole	Yes[a] (28 μM)	Yes	
Cefotaxime	Yes	Yes	
Ceftizoxime	Yes[a] (18 μM)	Yes	
Piperacillin	Yes[a]	ND	
Nitrofurantoin	ND	Yes[a]	Anti-infectious agents: *Other antibacterials*
Sulfasalazine	ND	Yes[a]	
Micafungin	ND	Yes[a]	Anti-infectious *Antifungal agents*
Adefovir	Yes[a] (> 1000 μM)	ND	Anti-infectious agents: *Antiviral agents*
Tenofovir disoproxil fumarate	Yes[a] (> 1000 μM)	ND	
Leucovorin	Yes (640 μM)	Yes	Antineoplastic agents
Methotrexate	Yes[a] (220–1300 μM)	Yes	
Mitoxantrone	ND	No (enhanced [^{3}H]-MTX efflux)	
Sorafenib	ND	Yes[a]	
Topotecan	Yes	ND	
Mycophenolic acid	Yes	Yes[a]	Immunosuppressants
Celecoxib	35 (μM)	Yes	Non-steroidal anti-inflammatory drugs
Flurbiprofen	ND	Yes[a]	
Ibuprofen	ND	Yes[a]	
Indomethacin	5–22 (μM)	Yes[a]	
Naproxen	ND	Yes[a]	
Sulindac	Yes (2 μM)	Yes[a]	
Allopurinol	ND	No (Enhanced urate efflux)	Anti-gout and uricosuric drugs
Benzbromarone		Yes[a]	
Probenecid	Yes (100 μM)	Yes	
Edaravone and glucuronide	Yes (9.8 μM)	ND	Central nervous system drugs: *Others*
Sildenafil	Yes (20 μM)	Yes	Other xenobiotics

[a] Indicates substantial contribution of MRP4 to drug transport or important inhibition potency (i.e. for substrates: drug eliminated by tubular secretion for at least 25% of its total clearance, predominantly through MRP4; for inhibitors, Ki or IC50 within the 10-fold range of plasma unbound maximal concentration, or when a pharmacokinetic interaction clinically significant was reported). ND indicates no data. Km: Michaelis Menten's constant; IC 50: half maximal inhibitory concentration.

epithelium and also at the luminal side of brain capillaries (Fig. 1A) [10]. It reduces the transfer of many xenobiotics into the brain by extruding them from blood capillaries to the plasma. The impact of this phenomenon has been explored for different classes of drugs.

Some authors have focused on anticancer drugs because accumulation into the brain can promote neurotoxicity. Leggas et al. reported that 6 h after an intravenous injection of 2 mg/kg of topotecan, whole-brain concentration of the drug was approximatively six times higher in *Mrp4*$^{-/-}$ mice than in wild-type mice [11]. Similarly, they observed that topotecan concentrations in cerebrospinal fluid 3 h after the perfusion were about 10-fold higher in *Mrp4*$^{-/-}$ mice. Of note, DeVries et al. showed that BCRP (breast cancer resistance protein) and P-gp could also contribute to this phenomenon [12]. In another study performed in mice with a similar design, it was also observed that methotrexate, raltitrexed (two folate analogues) and cyclophosphamide (an alkylating agent) can significantly accumulate in the brain when MPR4 is not functional [13].

Oseltamivir is an anti-influenza virus drug whose active moiety is called Ro 64–0802. Two hours after an injection of 1 mM of Ro 64–0802 to mice, Ose et al. reported that its amount in the brain was about 5-times higher in *Mrp4*$^{-/-}$ as compared to control mice [14] (0.32 nmol versus 0.060 nmol). However, the authors also considered organic anion transporter 3 (OAT3/SLC22A8), which is present in the abluminal and luminal membranes of brain capillaries and acknowledged that is difficult to clearly assess its role in brain distribution of the drug. This enlightens an important point: whatever the drug, multiple transporters are involved in membrane crossing processes and it is very difficult to discriminate their respective contributions.

2.2.3. Liver

MRP4 is localized at the basolateral membrane of human (Fig. 1C), rat, and mouse hepatocytes. It is also present in the human hepatoma HepG2 cells. It transports, among multiple substances, reduced glutathione and bile salts [15]. Only a few comprehensive studies concerning the impact of MRP4 liver expression on drug pharmacokinetics have been performed. Most of the data derived from in vitro studies.

Using different vesicular models expressing MRP4 or not, Ferslew et al. demonstrated that enalaprilat (the active metabolite of enalapril, an antihypertensive drug) is a substrate of MRP4 using human sandwich-cultured hepatocytes. The authors observed that the hepatic basolateral efflux clearance of enalaprilat was significantly reduced in presence of the MRP4 inhibitor MK-571 [16].

Interestingly, many transporters, including MRP4, are probably up regulated in the case of primary biliary cirrhosis and ingestion of toxic doses of acetaminophen [17]. In these situations, changes in hepatobiliary efflux transporters expression might modify the process of drug elimination. Indeed, Aleksunes et al. observed increased mRNA and protein expressions of multidrug resistance-associated proteins 2–4 (Mrp2–4) in mouse liver after exposure to a hepatotoxic dose of acetaminophen [18,19]. In another study, they showed that mice treated with acetaminophen reached maximal MPR4/3 up regulation in 48 h and that mice pre-treated with acetaminophen had less hepatotoxicity than those treated with placebo [20]. Consequently, the authors concluded that an increased expression of efflux transporters may help to prevent the accumulation of potentially toxic compounds within hepatocytes, thus contributing to acquired resistance [21].

Methotrexate (MTX) is the most widely recommended drug for the treatment of rheumatoid arthritis and is frequently associated to leflunomide in order to increase its clinical efficacy. MTX is a substrate of MRP4. Le Wang et al. [22] reported that, in mice, leflunomide significantly decreases the bile excretion of both MTX and its metabolite (7-hydroxy-MTX) and that it increases their concentrations in the liver, kidneys and plasma. Additionally, they observed an up regulation of MRP4 and MRP3 and a down regulation of MRP2 gene expression in the liver. These results suggest an enhanced basolateral efflux of MTX when associated to leflunomide.

2.2.4. Peripheral blood mononuclear cells (PBMC)

Only few data are available to explore the links between the pharmacokinetics of drugs and MRP4-related transport in PBMC.

Neutropenia is a common side effect when treating children for serious infections with long courses of antibiotics. In a study of approximately 100 children, Hahn et al. [23] observed that homozygous patients for *MRP4* c.3348 A > G given a prolonged therapy with β-

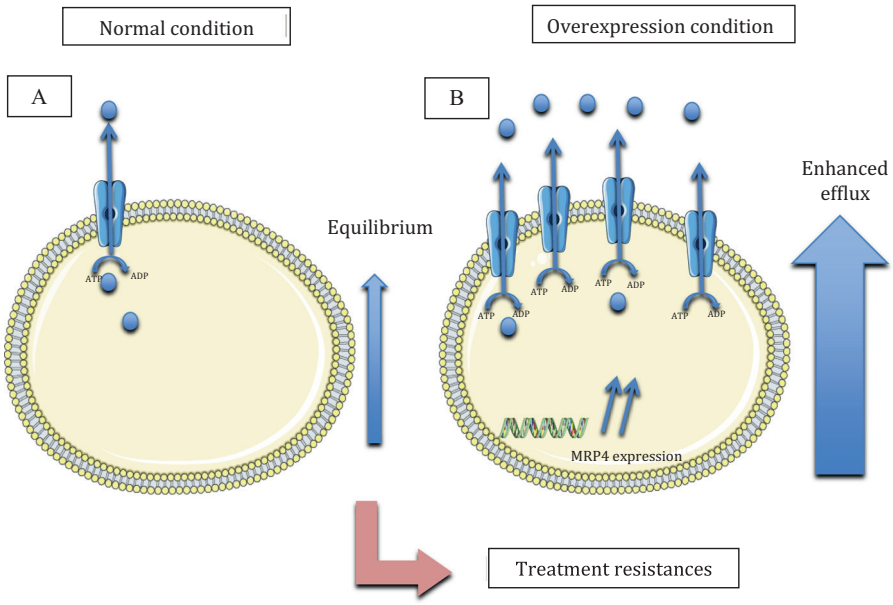

Fig. 3. Impact of MRP4 overexpression on drug efflux. Cells expressing MRP4 (blue) A. In normal cell life conditions; B. in case of overexpression (long term treatment for cancer, infection…), substrate (blue dots) efflux is increased. This may result in resistance to treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lactam (penicillin, cephalosporin or carbapenem) were 5.3 times (95% CI: 0.6–49.2) more likely to develop neutropenia ($p = 0.171$); though the pharmacokinetics of the antibiotics remains unchanged in these patients.

Ganciclovir (GCV) is the most widely used treatment for cytomegalovirus infections. However, neutropenia is a frequent associated adverse effect leading to a decrease in the GCV dose or discontinuation of the therapy, thereby favoring viral resistance. In renal transplant patients, Billat et al. [24] observed a significant association between GCV-triphosphate intracellular concentrations and the decrease in the neutrophil count over the first 3 months of GCV treatment. The authors identified one MRP4 genetic variant contributing to the decrease of neutrophils count [25] (see Section 3.2: genetic polymorphisms).

2.3. The role of MRP4 in drug pharmacodynamics

MRP4 is not considered to be a drug target but it can modify drug pharmacokinetics (as mentioned above), which can contribute to side effects or changes in drug efficacy (i.e. a decrease in MRP4 activity can enhance toxicity by decreasing drug elimination from cells; (Fig. 3). In addition, MRP4 is directly involved in physiological functions such as platelet aggregation and it participates in the mechanism of drug action. As shown in Fig. 3, MRP4 has an impact on the response to treatment.

2.3.1. The role of MRP4 in platelets

In platelets, MRP4 is mainly located at the dense granule membrane and to a lesser extent at the plasma membrane (Fig. 1D) [26]. At the dense granule membrane, it promotes the storage of ADP which is required for platelet activation and aggregation whereas at the plasma membrane, it promotes efflux from the platelet.

It was reported that patients suffering from Hermansky-Pudlak syndrome (i.e. the δ-storage pool deficiency; a defect in dense granule components) have no MRP4 at the dense granule membrane [26,27]. These patients present extensive bleeding. Mattiello et al. reported that aspirin and salicylic acid can be transported by MRP4 both at the dense granule and at the plasma membrane [28]. After inhibition of MRP4 by dipyridamole (a phosphodiesterase 5 inhibitor) and MK-571, they observed an increase in aspirin and salicylic acid concentrations in the cytoplasm of platelets and a higher COX-1 activity. Additionally, it seems that aspirin modifies the expression of MRP4. In fact, Mattiello et al. observed an increased expression of MRP4 at the plasma membrane in patients treated by aspirin after coronary artery bypass graft surgery [28]. Massimi et al. [29] confirmed these results as they also observed that platelets MRP4 mRNA was more abundant in patients with chronic aspirin treatment than in patients treated for < 1 month. Additionally, patients with higher MRP4 mRNA levels had higher serum Thromboxane B2 levels and collagen-induced platelet aggregation (i.e., parameters signing higher platelet aggregation). This suggests that MRP4 has a role in reducing aspirin inhibition of COX-1 when it is overexpressed in platelets.

Temperilli et al. observed a similar phenomenon with other NSAIDs [30]. They found a higher expression of MRP4 (mRNA and protein levels) and an increase in ADP-induced platelet aggregation in osteoarthritis patients given NSAIDs for > 4 weeks. They also demonstrated that DAMI cells (human megakaryocytic cell line) treated with celecoxib, diclofenac, and naproxen had increased expression of MRP4 mRNA. These results suggest that NSAIDs treatment can result in MRP4 overexpression in platelets.

A recent work by Mendes-Silverio et al. [31] suggests that MRP4 plays an additional role in platelets. BAY 60–2770 is a soluble guanylyl cyclase activator that potently inhibits human platelet aggregation and adhesion through overstimulation of the cGMP-PKG signaling pathway [32]. In the presence of the MRP4 inhibitor MK 571, the anti-aggregating effect of BAY 60–2770 in collagen- and thrombin-activated platelets was significantly increased. Pre-incubation with MK 571 increased the intracellular and decreased the extracellular levels of cGMP (cyclic GMP) in response to BAY 60–2770, while the cyclic AMP (cAMP) levels remained unchanged. This resulted in an increase of the phosphorylation of vasodilator-stimulated phosphoprotein at serine 239 in BAY 60–2770-treated platelets. In labelled platelets, BAY 60–2770 reduced the intracellular Ca2 + levels, an effect significantly potentiated by MK 571. Flow cytometry assays showed that BAY 60–2770 reduced integrin αIIbβ3 (GPIIb/IIIa) activation, which was further reduced by MK 571 treatment. Blocking MRP4-mediated efflux of cGMP may be a potential mechanism to enhance the antiplatelet efficacy of soluble guanylyl cyclases activators.

In the light of these in vitro findings, further studies have been performed in MRP4 deficient mice models. Decouture et al. [33] showed that arterial occlusion was delayed and tail bleeding time was prolonged in mice lacking MRP4 as compared to control mice.

2.3.2. MRP4 and cancer

The expression of MRP4 in cancer cells is also pivotal for treatment

issues as the protein can efflux many anticancer drugs or interfere with physiopathological processes.

Ho et al. [34] showed that MRP4 mRNA and protein levels were increased in prostate cancer cells. However, this overexpression was lower in patients pre-operatively treated with androgen castrative therapy, compared to uncastrated prostate cancer patients who had normal testosterone levels. This suggests an androgenic regulation of the transporter. The authors concluded that these data strongly suggested that MRP4 is an androgen-regulated gene important in the progression to prostate cancer and may be a potential drug target. These findings were confirmed using docetaxel resistant C4–2 (C4–2/D) cells (castration resistant prostate cancer cell line) that present an overexpression of MRP4. In fact, treatment with dihydrotestosterone increased MRP4 expression in C4–2/D cells whereas antiandrogenic treatments reversed the sensitivity of these cells to docetaxel chemotherapy by decreasing MRP4 overexpression [35].

Another study performed in CEM cells (human T-lymphoblastic leukemia cell line) demonstrated the role of MRP4 overexpression in 6-mercaptopurine (6-MP) resistance. In this case, MRP4 was up-regulated in tumorous cells but influx transporters were also down-regulated, which resulted in an increase of the efflux of 6-MP and a better survival rate of resistant cells [36]. In clinical settings, the overexpression of both MRP4 and MRP1 were significantly associated with poor prognosis in neuroblastoma [37,38]. These examples clearly show that overexpression of MRP4 in cancer cells contribute to treatment resistances.

MRP4 also manages the efflux of cAMP in human myeloid leukemia cells (U937, HL-60 and KG-1a) and inhibition of MRP4 is associated with an increase in intracellular cAMP, leading to the end of proliferation and promotion of cell differentiation [39]. MRP4 was also found to be highly expressed in non-small cell lung cancer. The inhibition of MRP4 expression with shRNA inhibited cell growth and increased the percentage of cells in G1 phase [40].

2.3.3. MRP4 in infectious diseases

Turizziani et al. isolated PMBC from HIV patients and healthy donors and measured MRP4 mRNA expression in lymphocytes T CD4 cells [41]. They observed that MRP4 mRNA expression was significantly higher in HIV patients. Moreover, they showed that treatments can modify MRPs and P-gp mRNA expression.

Clemente et al. [42] studied lymphocytes infected with HIV type-$1_{NL4.3}$, CEM and CEM3TC (overexpressing MRP4) cells treated with zidovudine, emtricitabine and tenofovir (MRP4 substrates) with or without different NSAIDs (ibuprofen, indomethacin and probenecid; MRP4 inhibitors). They observed a reduced efflux of zidovudine (AZT) in presence of these previously quoted inhibitors. Interestingly, the antiretroviral activity (measured by the decrease of p24 antigenemy (Agp24) during 3 days following infection) in infected lymphocytes and CEM3TC cells was significantly enhanced by NSAIDs mediated inhibition of MRP4. They also demonstrated that activation of peripheral blood lymphocytes from healthy donors with Phytohaemagglutinin can increase MRP4 expression from 6 to 8% to 25–60%. Additionally, after incubation with AZT, it was observed that MRP4 levels were increased by approximately 10% in total lymphocytes. The authors suggested that MRP4 inhibition can improve anti-retroviral treatment and proposed a possible mechanism of resistance of HIV by MRP4 overexpression. Adachi and al. [43] demonstrated a similar phenomenon with GCV treatment, by demonstrating that cells overexpressing MRP4 are more resistant to GCV cytotoxic effects.

3. Variability of MRP4 activity and consequences in clinical pharmacology

3.1. Drug-drug interactions

Drug-drug interactions concerning efflux transporters can lead to increased intracellular substrate concentrations through transport inhibition. The increase of transporter expression at the cell membrane can lead to drug exclusion from the cells and to the increase in drug blood concentrations with several consequences depending on the drug properties (increased activity or toxicity or increased elimination of the drugs by the kidney). This section lists examples related to drug-drug interaction with MRP4.

3.2. Antiviral therapies

As discussed above, it was demonstrated in HIV-1 infected T cells that the inhibition of MRP4 by NSAIDs such as ibuprofen and indomethacin led to a significant increase of activity of nucleoside reverse transcriptase inhibitors (zidovudine, abacavir, lamivudine and tenofovir) [42].

Diclofenac is a MRP4 inhibitor [44] and tenofovir is a substrate of MRP4 [9]. A case study has reported a HIV patient treated for a long period of time with tenofovir who developed a severe, biopsy-proven, acute tubular necrosis with proximal tubule dysfunction, after introduction of diclofenac [45]. In a retrospective study conducted in HIV patients, 14.6% of the patients developed acute kidney injury shortly after initiating diclofenac treatment [46], suggesting that the drug-drug interaction between diclofenac and tenofovir is clinically relevant.

Other antiretroviral drugs might be involved in drug-drug interaction with tenofovir. In a study conducted in HIV patients of African origin, an increase in tenofovir trough concentrations was found in patients given lopinavir/ritonavir when compared to other therapies (i.e. tenofovir/emtricitabine/nevirapine; tenofovir/emtricitabine/zidovudine or tenofovir/emtricitabine/efavirenz). Nevertheless, the mean GFR (calculated using the CKD-EPI formula) was not substantially altered after 48 weeks of treatment compared to baseline (-8.2 mL/min/1.73 m^2, $P < 0.05$) [47]. The authors did not conclude whether the increase in tenofovir concentration was due to an inhibition of influx (by Organic anion transporter OAT1) or efflux (by MRP4 or MRP2). Knowing that lopinavir and ritonavir are mild OAT1/3 and MRP4/2 inhibitors [48,49] and that tenofovir is mainly eliminated by OAT1 and MRP4 [50], it was reported that tenofovir renal clearance can be decreased by 17,5% in HIV patients treated by lopinavir/ritonavir [51].

3.3. Anticancer therapies

MTX is a substrate of both MRP4 and MRP2 and its transport (and that of its glucuronide conjugates) was found to be inhibited by NSAIDs [44,52] in vesicular transport assays.

When concomitantly administered with MTX, NSAIDs (including indomethacin, ibuprofen, and naproxen) increase its exposure and toxicity. For example, Dupuis et al. reported that the use of MTX with NSAIDs in one patient increased mean MTX half-life [53]. Tracy et al. [54] also reported that the apparent systemic clearance of MTX was significantly reduced in patients treated with magnesium trisalicylate, ibuprofen and naproxen. Thyss et al. [55] analysed retrospectively 118 cycles of high dose MTX and demonstrated that simultaneous administration of ketoprofen is associated with prolonged detectable MTX levels.

Irinotecan is a drug known to cause severe diarrhea and is another substrate of MRP4. It has been shown that inhibition of cAMP-MRP4 mediated efflux by irinotecan increases cAMP intracellular level near the plasma membrane. This enables the formation of MRP4-CFTR (Cystic fibrosis transmembrane conductance regulator) macromolecular complex (linked by PDZ motif) that activates the CFTR channel and causes diarrhea [56].

An in vitro study illustrated the role of MRP4 in resistance to oxazophorine drugs. HepG2 (human liver cancer cell line) and HepG2-MRP4 cells were treated with cyclophosphamide (CP) and ifosfamide (IF) for 48 h, with or without inhibitors. The inhibition of CP and IF's MRP4 dependent transport by either DL-buthionine-(*S*,*R*)-sulfoximine, celecoxib, diclofenac or MK571 caused an increase in cytotoxicity in

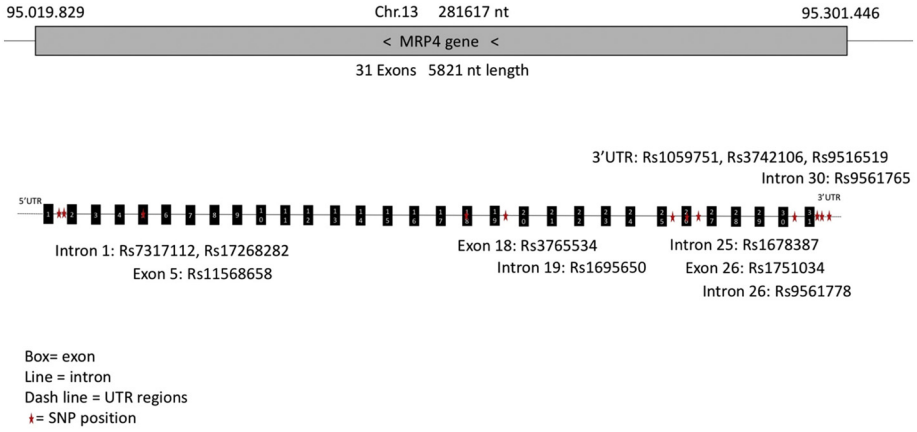

Fig. 4. Overview of relevant SNPs. In grey, MRP4 gene localization on chromosome 13. Black boxes represent exons, full lines correspond to introns and dash lines to untranslated regions. Red stars show the different SNPs listed in this review. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
List of the 12 *ABCC4* variants associated with substantial clinical consequences (according to https://www.pharmgkb.org).

Variant ID	Nucleotide change (consequences)	Drug impacted	Consequences	Level of proof	Ref
rs1059751	c.*879T > C (3′-UTR SNP)	Tenofovir	Increase of beta2-microglobulinuria in tenofovir HIV patients related to kidney tubular dysfunction	3	[65]
rs1751034	c.3348G > C/A (Missense Variant)	Tenofovir	*ABCC4* c.3348G allele carriers had higher TFV-DP concentrations than wild type carriers.	2B	[66]
rs3742106	c.*38T > G (3′-UTR SNP)	Tenofovir	Patients carrying *ABCC4* c.*38 TG or GG genotype had, on average, a 30% higher mean tenofovir plasma concentration than patients carrying the TT genotype *ABCC4* c.*38G allele carriers had 20% higher 3TC-triphosphate concentrations than non-carriers	3	[67]
		Zidovudine			[68]
rs11568658	c.559G > T (Missense Variant)	Latanoprost	*ABCC4* c.559 T carrier had significantly lower decrease in intraocular pressure than non-carriers at day 7 and day 30 of latanoprost treatment.	3	[69]
		(Val)ganciclovir	*ABCC4* c.559 T carriers had significant higher risk of neutropenia following valganciclovir treatment than non-carriers. Decrease of MRP4 mediated efflux in vesicular transport assay		[25]
		Methylated arsenic metabolites ($MMA(GS)_2$			[70]
rs1678387	g.240795A > G (Intronic variant)	Biphosphonates	Allele A is weakly associated with an increased likelihood of Osteonecrosis when treated with Bisphosphonates as compared to allele G.	3	[71]
rs16950650	g.183269G > A (Intron variant)	Cisplatin Irinotecan	Variant allele carriers had shorter overall survival for small-cell lung cancer when treated by ironotecan and cisplatin than wild type carriers.	3	[72]
rs17268282	g.33387C > A (Intron variant)	Furosemide	This variant was associated with weight loss when using furosemide in decompensated heart failure patients.	3	[73]
rs3765534	c.2269G > A (Missense Variant)	Azathioprine, Mercaptopurine	Increase of 6-Thioguanine nucleotide levels and decrease of white blood cells in carriers of the variant.	3	[74]
rs7317112	g.35178T > C (Intron variant)	Methotrexate (MTX)	Wild type genotype was associated with more frequent mucositis in Acute lymphoblastic leukemia patients treated with MTX	3	[75]
rs9516519	c.*1372A > G/C (3′-UTR SNP)	Methotrexate (MTX)	TT genotype was associated with higher MTX plasma levels compared to GG + GT genotype when exposed to MTX in children with acute Leukemia, B-Cell.	3	[76]
rs9561765	g.275458C > T (Intron variant)	Imatinib	*ABCC4* TT genotype was associated with reduced time to progression disease in gastrointestinal stromal tumors	3	[77]
rs9561778	g.244986C > T (Intron variant)	Cyclophosphamide	This variant was associated with gastrointestinal toxicity and leukopenia/ neutropenia when using Cyclophosphamide based combination in breast cancer patient	3	[78]

Nucleotide changes are given according to *ABCC4* transcript variant 1 (i.e. NM_005845.4) or to the RefSeq for intronic variants. PharmGKB criteria for levels of evidence [79] are the following: **2B**: Annotation for a variant–drug combination with moderate evidence of an association. The association must be replicated, but there may be some studies that do not show statistical significance, and/or the effect size may be small. **3**: Annotation for a variant–drug combination based on a single significant (not yet replicated) study or annotation for a variant–drug combination evaluated in multiple studies but lacking clear evidence of an association.

Table 3
Minor allelic frequencies (MAF) of MRP4 variants in different ethnic groups.

MAF	AFR	AMR	EAS	EUR	SAS
< 1%	rs3765534; rs11568658		rs9516519; rs17268282; rs11568695	rs3765534; rs16950650; rs11568695	rs11568695
1–10%	rs9561765; rs17268282; rs1678387	rs9561765; rs3765534; rs17268282; rs16950650; rs1678387; rs11568695; rs11568658	rs3765534; rs16950650	rs9561765; rs17268282; rs1678387; rs11568658	rs9561765; rs9516519; rs3765534; rs17268282; rs16950650; rs1678387; rs11568658
10–20%	rs9561778; rs16950650; rs11568695	rs9561778; rs9516519	rs11568658	rs9561778; rs9516519; rs1751034	rs9561778; rs1751034
> 20%	rs9516519; rs3742106; rs1751034; rs10597751; rs7317112	rs7317112; rs3742106; rs1751034; rs1059751	rs9561778; rs9561765; rs7317112; rs3742106; rs17510334; rs1678387; rs1059751	rs7317112; rs3742106; rs1059751	rs7317112; rs3742106; rs1059751

AFR: Africans, AMR: Americans, EAS: East Asian, EUR: European, SAS: South Asian.

HepG2-MRP4 cells compared to untransfected cells [57]. According to these results, there is a probable drug-drug interaction between oxazophorine and some NSAIDs associated with MRP4 inhibition.

3.4. Genetic polymorphisms

According to dbSNP (https://www.ncbi.nlm.nih.gov/projects/SNP/), 30,185 SNPs were reported for *MRP4*, two thirds of which are located in intronic sequences. Some of them have direct or indirect clinical implications (see Fig. 4, Tables 2 and 3). In this section, only *MRP4* variations unambiguously associated with clinical outcomes have been discussed.

MRP4 transports many antivirals and anticancer drugs. In all the studies listed in Table 1, variants were associated with drug toxicities, efficacy or pharmacokinetics. The direct effects of MRP4 variants can be difficult to ascertain, since drugs can be transported by other transporters bearing polymorphisms, contributing to the differences observed in clinical outcomes. Some studies also suffer from lack of power. For example, MTX is transported by MRP4 and MRP2 with different affinities [58]. The reduced function of one transporter due to a genetic variation (or to the inhibition through drug-drug interaction) can be compensated by overexpression of the second transporter. In the case of PMEA (9-(2-phosphonylmethoxyethyl)adenine)), initially described as a MRP4 substrate, an up regulation of BCRP in various tissues was described in MRP4 Knock Out mice and was associated with decreased tissue concentrations of PMEA [59]. Based on this observation, it has been confirmed that BCRP transports and confers resistance to the purine prodrug Bis(POM)PMEA also known as adefovir dipivoxil used in treatment for Hepatitis B. MRP4 expression in kidneys was also found to be increased in MRP2 deficient rats strain as compared to wild type rats but the efflux of cAMP (a MRP4 substrate) was not increased [60]. Both of these transporters are expressed at the apical membranes of proximal tubule cells and this study suggested that MRP4 can take over MRP2 substrates but it has not been tested with common substrates of these transporters. Indeed, the urinary excretion of cysteinyl leukotrienes and acetaminophen–glucuronide conjugate known as MRP2 substrates were increased in MRP2 deficient rat and Dubin-Johnson patients [61–63], suggesting a compensatory MRP4 transporter up regulation.

4. Conclusion

This review provides a better understanding regarding MRP4 drug transport and its implication in efficacy or toxicity. Based on recommendations from the International Transporter Consortium [64], regulatory instances such as the European Medicines Agency (EMA) and the Food and Drugs Administration (FDA) currently recommend investigating the role of only 7 transporters in the process of drug development (i.e. OAT1, OAT3, OCT2, OATP1B1, OATP1B1, P-gp and BCRP). MRP4 is not yet included in the list. Special attention should be given to MRP4 when dealing with anti-cancer, anti-infectious drugs or NSAIDs.

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