Characterization of the Drug Resistance and Transport Properties of Multidrug Resistance Protein 6 (MRP6, ABCC6)1

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ABSTRACT

Mutations in human multidrug resistance protein 6 (MRP6, ABCC6), a member of the MRP family of drug efflux pumps, are the genetic basis of Pseudoxanthoma elasticum, a disease that affects elastin fibers in the skin, retina, and blood vessels. However, little is known about the functional characteristics of the protein, including its potential activity as a resistance factor for anticancer agents. Here, we report the results of investigations of the in vitro transport properties and drug resistance activity of MRP6. Using membrane vesicles prepared from Chinese hamster ovary cells transfected with MRP6 expression vector, it is shown that expression of MRP6 is specifically associated with the MgtA-ATP-dependent transport of the glutathione S-conjugates leukotriene C4 and S-(2, 4-dinitrophenyl)glutathione and the cyclopentapeptide BQ123 but not glucuronate conjugates such as 17β-estradiol 17-(β-D-glucuronide). Analysis of the drug sensitivity of MRP6-transfected cells revealed low levels of resistance to several natural product agents, including etoposide, teniposide, doxorubicin, and daunorubicin. These results indicate that MRP6 is a glutathione conjugate pump that is able to confer low levels of resistance to certain anticancer agents.

INTRODUCTION

The MRP family currently consists of nine members, several of which have been determined to be lipophilic anion pumps that have the facility for conferring resistance to a variety of anticancer agents (1, 2). MRP1, MRP2, and MRP3 mediate the transport of glutathione and glucuronate conjugates and are able to confer resistance to natural product anticancer agents and methotrexate (3–18). MRP1 functions as a ubiquitous component of Phase III of cellular detoxification, and MRP2 is involved in the extrusion of organic anions such as bilirubin glucuronide into the bile (19). By contrast with MRP1 and MRP2, MRP3 is also able to transport monoanionic bile acids such as glycocholate and taurocholate (16, 20), and this feature, in combination with its induction at basolateral surfaces in hepatocytes, suggests that it may function as a backup detoxification system during cholestatic conditions (21–23). MRP4 and MRP5 are cyclic nucleotide efflux pumps that can be deployed by the cell for the purpose of conferring resistance to anticancer and antiviral nucleotide analogs (24–29). In addition, MRP4 appears to differ from MRP5 by virtue of the ability of MRP4 to mediate the transport of glucuronate conjugates and methotrexate (25, 26, 30).

Recently, mutations in MRP6, a protein that has been assigned to the MRP family on the basis of amino acid alignments (31, 32), were determined to be the genetic basis of PXE (33–36), a heritable connective tissue disorder that affects elastic tissues in the body. The primary sites of the disease are the skin, eyes, and cardiovascular system, with corresponding clinical manifestations of redundant sagging skin, visual impairment, intermittent claudicating, blood vessel rupture, and myocardial infarction. Important histopathological features of PXE include abnormal ultrastructural morphology of elastin fibers, including the accumulation of elastic material in the skin and calcification of elastic structures. Although the involvement of MRP6 mutations in PXE has been convincingly demonstrated, little is known about the functional characteristics of the protein or the pathophysiological mechanism whereby its deficiency results in the manifestations of PXE. The properties of the rat MRP6 homologue have been investigated to some extent, and the endothelin receptor antagonist BQ123, but not prototypical conjugates that are established substrates of other MRPs, has been determined to be a transport substrate (37). In addition, the inclusion of MRP6 in the MRP family suggests the possibility that it may be able to confer resistance to anticancer agents, and this feature of the protein has not been investigated. In this study, we sought to gain insight into the functional properties of human MRP6, including its activity as a resistance factor for anticancer agents. In so doing, it is shown that MRP6 is able to transport glutathione conjugates and BQ123 and that it has the facility for conferring low levels of resistance to certain natural product anticancer agents. It is concluded that MRP6 has the capacity to mediate the transport of lipophilic anions and to function as a drug efflux pump.

MATERIALS AND METHODS

Materials. [3H]Etoposide (280 mCi/mmol), [3H]methotrexate (21.2 Ci/mmol), [3H]cyclic AMP (17 Ci/mmol), and [3H]cyclic GMP (6.8 Ci/mmol) were purchased from Moravek (Brea, CA). [3H]LTC4 (130 Ci/mmol), [3H]E217βG (40.5 Ci/mmol), and [3H]glutathione (44.8 Ci/mmol) were purchased from Perkin-Elmer Life Sciences (Boston, MA). [3H]DNP-SG and unlabeled DNP-SG were synthesized from 1-chloro-2,4-dinitrobenzene and labeled or unlabeled glutathione as described previously (38). [3H]BQ123 (20 μCi/mmol) was purchased from Amersham Biosciences (Buckinghamshire, England). Unlabeled E17βG, LTC4, BQ123, daunorubicin, doxorubicin, actinomycin D, pachlaxel, vinblastine, vincristine, and mitoxantrone were obtained from Sigma Chemical Company (St. Louis, MO). Etoposide, teniposide, and cisplatin were obtained from Bristol Myers Squibb (Princeton, NJ). CPT-11 was a gift from Dr. James Gallo.

Expression Vector Construction, Transfection, and Cell Culture. The human MRP6 coding sequence (31) was assembled in Bluescript SK- (Stratagene, La Jolla, CA) from three overlapping PCR fragments. The translation initiation site was modified to CACCATG to conform to the Kozak consensus sequence, and the fidelity of the coding sequence was confirmed by nucleotide sequence analysis. The coding sequence was then inserted into pcDNA3.1 (Invitrogen, Carlsbad, CA) to create pcDNA-MRP6. CHO cells grown in RPMI supplemented with 10% fetal bovine serum were electroporated with 10 μg of either pcDNA-MRP6 or the parental plasmid, and individual G418-resistant colonies were expanded for immunoblot analysis. For insect cell expression, the MRP6 coding sequence was inserted into pVL1392, and baculovirus production and infection of insect cells were accomplished according to the manufacturer’s directions (PharMingen, San Diego, CA).
Generation of MRP6 Polyclonal Antibody and Immunoblot Analysis. A cDNA fragment encoding the linker region of MRP6 (amino acids 848–921) was inserted downstream of the glutathione S-transferase coding sequence in PGEX2T, and the encoded fusion protein was purified from bacterial cultures by the use of glutathione Sepharose beads (Amersham Pharmacia Biotech AB, Upsala, Sweden). Rabbits were immunized with the purified fusion protein, and the specificity of the resulting polyclonal antisera was confirmed by immunoblot analysis of cellular lysates prepared from insect cells infected with MRP6 baculovirus. Cellular lysates and membrane vesicle preparations were subjected to SDS-PAGE, and proteins were electrotransferred to nitrocellulose filters using a wet transfer system as described previously (39). MRP6 was detected using polyclonal MRP6 antibody (1:1000) and horseradish peroxidase-conjugated secondary antibody (Bio-Rad, Hercules, CA).

Preparation of Membrane Vesicles and Transport Experiments. Membrane vesicles were prepared by the nitrogen cavitation method as described previously (40). Transport experiments were performed using the rapid filtration method essentially as described previously (3) and carried out in medium containing membrane vesicles (20 μg), 0.25 mM sucrose, 10 mM Tris-HCl (pH 7.4), 10 mM MgCl₂, 4 mM ATP, 10 mM phosphocreatine, 100 μg/ml creatine phosphokinase, and radiolabeled substrate ± unlabeled substrate in a total volume of 50 μl. Reactions were carried out at 37°C and stopped by the addition of 3 ml of ice-cold stop solution [0.25 mM sucrose, 100 mM NaCl, 10 mM Tris-HCl (pH 7.4)]. Samples were passed through 0.22-μm Durapore membrane filters (Millipore, Bedford, MA) under a vacuum. The filters were washed three times with 3 ml of ice-cold stop solution and dried at room temperature for 30 min. Radioactivity was measured by the use of a liquid scintillation counter.

Analysis of Drug Sensitivity and Etoposide Accumulation. Drug sensitivity was analyzed by the use of a tetrazolium salt microtiter plate assay (CellTiter 96 Cell Proliferation Assay; Promega, Madison, WI). Cells were seeded in triplicate at 8000 cells/well in 96-well dishes in complete medium (CellTiter 96 Cell Proliferation Assay; Promega, Madison, WI). Cells were washed three times with 3 ml of ice-cold stop solution and dried at room temperature for 30 min. Radioactivity was measured by the use of a liquid scintillation counter.

RESULTS

Expression of MRP6 in CHO Cells. CHO cells were transfected with MRP6 expression vector to generate a cellular model with which to examine the properties of MRP6. However, expression of the protein in G418-selected cells was barely enhanced in cells transfected with MRP6 expression vector when compared with cells transfected with parental vector, as determined by immunoblot analysis in which the recombinant protein expressed in insect cells was used as a positive control (Fig. 1, Lanes 3 and 7, respectively). Knowing that it had recently been demonstrated that expression of MRP2 could be dramatically induced in stably transfected cells by the use of the histone deacetylase inhibitor sodium butyrate and that the induced cells were suitable for measuring in vitro transport and drug resistance activities (6), we attempted to enhance the ectopic expression of MRP6 in transfected CHO cells by the use of this agent. Sodium butyrate was indeed effective for this purpose. As shown in Fig. 1, prominent immunoreactive bands were readily detected in lysates prepared from MRP6-transfected cells grown in the presence of sodium butyrate (Lanes 8–10) but not in lysates prepared from similarly treated control-transfected cells (Lanes 4–6). MRP6 migrated as two predominant species of Mr, 162,000 and Mr, 182,000. The smaller of these two protein species migrated with an apparent weight that was comparable with that of the recombinant protein expressed in insect cells (Lane 2), which are unable to synthesize complex polysaccharides. It was therefore inferred that the larger molecular weight species is a more heavily glycosylated form of MRP6. In cell proliferation assays, 2 mM sodium butyrate was found to be nontoxic, and this concentration was used for induction of MRP6 for in vitro transport and drug sensitivity assays.

Analysis of MRP6-dependent Transport Activity. MRP6-dependent transport was assayed on density fractionated membrane vesicles prepared from MRP6-transfected CHO cells treated with sodium butyrate. As shown in Fig. 1B, these membranes were a rich source of MRP6 protein. Parallel experiments were performed on membrane vesicles prepared from similarly treated parental vector-transfected cells to assess the relative contribution of endogenously expressed transporters.

Glutathione and glucuronate conjugates are established substrates of several MRP family members (1, 2). To determine whether these classes of compounds are substrates of MRP6, LTC₄, DNP-SG, and E₂₁₇βG, prototypical glutathione and glucuronate conjugates were used as test compounds. As shown in Fig. 2A, MgATP-stimulated transport of 20 mM LTC₄ was detected for membranes prepared from MRP6-transfected cells. MgATP-stimulated transport of this cysteinyl leukotriene, presumably mediated by endogenously expressed transporters, was also observed for the control membranes. However, the rate and extent of MgATP-energized LTC₄ transport by MRP6-enriched membranes were consistently greater than that observed for the control membranes, indicating the presence of MRP6-dependent transport. Uptake by MRP6-enriched membranes in the presence of MgATP was 0.94 pmol/mg/min when measured at the 5-min time point of the assay. By contrast, uptake by the same membranes in media containing MgAMP and by control membranes in media containing MgATP or MgAMP was only 0.50, 0.67, and 0.41 pmol/mg/min, respectively. MgATP-energized uptake consequent upon expression of MRP6 was also observed for the synthetic glutathione conjugate DNP-SG. When measured at the 5-min time point of the assay, uptake of 1.0 μM DNP-SG by MRP6-enriched membranes in media containing MgATP was 6.7 pmol/mg/min, whereas uptake by the same membranes in the presence of MgAMP or by the control
membranes in the presence of MgATP or MgAMP was only 2.5, 3.8, and 2.8 pmol/mg/min, respectively. As with LTC₄ transport, MgATP-dependent uptake of DNP-SG by the control membranes was observed but was consistently less than that of the MRP6-enriched membranes. By contrast with the two glutathione conjugates, uptake of DNP-SG by the control membranes was only 0.68, 1.5, and 0.84 pmol/mg/min, respectively.

**Osmotic Sensitivity of Transport.** To confirm that MRP6-mediated uptake predominately represented transport into the membrane vesicles as opposed to nonspecific binding to membranes or filters, the osmotic sensitivity of MRP6-mediated uptake of LTC₄ was measured. As shown in Fig. 3, MgATP-dependent uptake of LTC₄ into CHO-MRP6 membrane vesicles increased in proportion to the reciprocal of the sucrose concentration of the transport medium, suggesting that the transported substrate was delivered into an osmotically active compartment. By contrast, the sucrose concentration exerted only a modest effect on radiolabel retained by the same membranes in medium containing MgAMP. This suggested that under nonenergized conditions, radiolabel retention by the membrane vesicles largely represented nonspecific binding as opposed to transport into the intravesicular space.

**Analysis of the Drug Sensitivity of MRP6-transfected CHO Cells.** To gain insight into the drug resistance capabilities of MRP6, the sensitivity of sodium butyrate-induced CHO cells transfected with MRP6 expression vector was compared with similarly treated control transfected cells. As shown in Table 1, CHO-MRP6 cells exhibited enhanced resistance to several natural product anticancer agents. The highest levels of resistance were observed for etoposide and teniposide, two topoisomerase II inhibitors (3.3-fold). Representative growth assays for these two agents are shown in Fig. 4. Enhanced resistance was also observed for two anthracyclines, doxorubicin and daunorubicin (2.5- and 2.3-fold resistance, respectively), and for actinomycin D (3-fold resistance). In addition, low levels of resistance

![Image](image_url)

**Table 1 Drug sensitivity of CHO-MRP6 cells**

<table>
<thead>
<tr>
<th>Drug</th>
<th>IC₅₀ (nM) CHO-pcDNA</th>
<th>IC₅₀ (nM) CHO-MRP6</th>
<th>Relative resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide</td>
<td>440 ± 220</td>
<td>1440 ± 830</td>
<td>3.27¹</td>
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<tr>
<td>Teniposide</td>
<td>64.7 ± 24</td>
<td>216 ± 110</td>
<td>3.33³</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>105 ± 44</td>
<td>238 ± 52</td>
<td>2.27⁷</td>
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<tr>
<td>Doxorubicin</td>
<td>390 ± 170</td>
<td>981 ± 420</td>
<td>2.52²</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>3310 ± 1970</td>
<td>7790 ± 3230</td>
<td>2.35⁴</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>2.21 ± 0.91</td>
<td>6.65 ± 0.47</td>
<td>3.01⁴</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>152 ± 40</td>
<td>103 ± 21</td>
<td>0.68</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>50.0 ± 11</td>
<td>90.8 ± 7.9</td>
<td>0.95</td>
</tr>
<tr>
<td>Vincristine</td>
<td>2.21 ± 0.91</td>
<td>2.21 ± 0.91</td>
<td>0.71</td>
</tr>
<tr>
<td>CPT-11</td>
<td>24.5 ± 7.2</td>
<td>28.8 ± 3.0</td>
<td>1.17</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>407 ± 220</td>
<td>497 ± 350</td>
<td>1.22</td>
</tr>
</tbody>
</table>

¹ Drug concentration that inhibited cell survival by 50%.
² IC₅₀ of CHO-MRP6 transfected/CHO-pcDNA of control transfected.
³ Significantly different from control transflectant (P < 0.01) as determined by the nonparametric two-tailed Wilcoxon test.
⁴ (P < 0.05).

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**Fig. 2. Time course of ATP-dependent uptake of [³H]LTC₄, [³H]DNP-SG, [³H]E₂₁₇βG, and [³H]BQ123 into membrane vesicles. Membrane vesicles (20 μg of protein) prepared from CHO-pcDNA cells (●) or CHO-MRP6 (○) were incubated at 37°C in uptake media containing 20 nM [³H]LTC₄ (A), 1.0 μM [³H]DNP-SG (B), 1.0 μM [³H]E₂₁₇βG (C), 1.0 μM [³H]methotrexate (D), or 1.0 μM [³H]BQ123 (E) and 4 mM MgATP (●) or 4 mM MgAMP (○). Values shown are means ± SE of duplicate measurements. Data were not corrected for the amount of radiolabeled compound that bound to the filters in the absence of vesicles. Representative experiments are shown.**
were observed for the alkylating agent cisplatin (2.4-fold). Increased resistance was not observed for vincristine, vinblastine, CPT-11, mitoxantrone, or paclitaxel. A similar pattern of resistance was observed for the alkylating agent cisplatin (2.4-fold). Increased resistance was not observed for vincristine, vinblastine, CPT-11, mitoxantrone, or paclitaxel. A similar pattern of resistance was observed for vincristine, vinblastine, CPT-11, mitoxantrone, or paclitaxel.

Analysis of Drug Accumulation. Intracellular accumulation of etoposide was assessed in CHO-MRP6 and control-transfected cells. As shown in Fig. 5, the MRP6-expressing cells exhibited reduced accumulation of radiolabeled etoposide compared with control transfected cells, as would be expected were MRP6 functioning as a drug efflux pump. After 15 min of incubation in growth medium containing 0.4 μM [3H]etoposide, accumulation in CHO-MRP6 was 73% of the control cells. A difference in drug accumulation between CHO-MRP6 cells and the control cells was maintained throughout the 60-min time course of the assay.

DISCUSSION

In this study, the functional properties of human MRP6 were investigated to gain insights into its potential for conferring resistance to anticancer agents and into its physiological functions. Analysis of the drug resistance phenotype of MRP6-expressing CHO cells suggests that the protein is able to confer low levels of resistance to several commonly used natural product anticancer agents, including etoposide, doxorubicin, and daunorubicin, as well as to actinomycin D. With regard to its ability to confer resistance to natural product anticancer agents, MRP6 is similar to three other MRP family members (MRP1, MRP2, and MRP3) that have also been determined to confer resistance to members of this class of agents. Our results suggest that the natural product drug resistance phenotype associated with MRP6 is somewhat broader than that of MRP3, which has a drug resistance profile that probably only includes the epipodophyllotoxins etoposide and teniposide (14, 15, 41), but is more restricted than that of MRP1 and MRP2, which have resistance activities that extend to other agents, including Vinca alkaloids (6–13). MRP6 was also found to confer low levels of resistance to cisplatin, an agent that forms glutathione conjugates in the cell and which is also part of the MRP2 drug resistance profile. In terms of potency, the levels of resistance we observed for MRP6 (~2–3-fold) are significantly lower than those described in transfection studies of MRP1 and MRP2 and roughly comparable with resistance levels reported for MRP3-transfected cells (~3-fold; Refs. 1, 14, 15). In considering the resistance profile described in this study, it is worth keeping in mind that we used a system in which MRP6 was induced by the use of sodium butyrate and that this system is probably not optimal for analyzing the resistance properties of a pump whose apparent activity is modest. We anticipate that additional studies using sensitive cell lines in which MRP6 is stably expressed will help to further define the drug resistance properties of the pump.

Using in vitro transport assays, we found that MRP6 is able to mediate the transport of the prototypical glutathione conjugates LTC₄ and DNP-SG and the cyclic pentapeptide BQ123, but not the glucuronate conjugate E₂_{17}BG or cyclic nucleotides. The facility of MRP6 for conjugate but not cyclic nucleotide transport is in accord with relationships observed previously between the structures of MRP family members and their substrate selectivities. MRP family members can be distinguished by the presence or absence of a third (NH₂-terminal) membrane spanning domain (42). Transport of conjugates but not cyclic nucleotides is a consistent feature of characterized MRPs that possess a third membrane spanning domain (MRP1, MRP2, and MRP3), whereas cyclic nucleotide transport is a property of both of the characterized MRPs that do not possess this structural feature (MRP4 and MRP5). Although MRP6 is similar to MRP1, MRP2, and MRP3 in its facility for transporting conjugates, our results suggest at least one potential difference in that whereas glucuronate conjugates are good substrates of the latter pumps, energy-dependent uptake of E₂_{17}BG was not observed in our transport assays of MRP6 activity. The characterization of the in vitro transport prop-

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**Fig. 4.** Analysis of the sensitivity of MRP6-transfected CHO cells to etoposide (A) and teniposide (B). The drug sensitivity of control CHO-pcDNA cells (○) and CHO-MRP6 cells (●) was analyzed using the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfonyl)-2H-tetrazolium, inner salt/phenazine methosulfate assay as described in the “Materials and Methods.” Cells were treated with 2 mM sodium butyrate for 24 h, and the medium was replaced with fresh medium containing various concentrations of drug but not sodium butyrate. The 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfonyl)-2H-tetrazolium, inner salt/phenazine methosulfate assay was performed after 3 days of growth in the presence of drug. Data points, the means of triplicate determinations in a representative experiment.

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**Fig. 5.** Accumulation of radiolabeled etoposide in CHO-MRP6 and control cells. CHO-pcDNA (○) or CHO-MRP6 (●) cells were incubated in the presence of 0.4 μM [3H]etoposide, and drug accumulation was measured at various time points. Data points, the mean of triplicate determinations in a single experiment. A representative experiment is shown.

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**Table 1.** 

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (μM)</th>
<th>CHO-MRP6</th>
<th>CHO-pcDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide</td>
<td>0.1</td>
<td>0.95</td>
<td>0.76</td>
</tr>
<tr>
<td>Etoposide</td>
<td>1.0</td>
<td>0.85</td>
<td>0.70</td>
</tr>
<tr>
<td>Etoposide</td>
<td>10.0</td>
<td>0.75</td>
<td>0.60</td>
</tr>
</tbody>
</table>

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**Fig. 6.** Effect of sodium butyrate on the expression of MRP6. CHO-MRP6 cells (○) and CHO-pcDNA cells (●) were treated with 2 mM sodium butyrate for 24 h, and the medium was replaced with fresh medium for another 24 h. The expression of MRP6 was determined by Western blot analysis. Data points, the means of triplicate determinations in a representative experiment.
properties of MRP6 we describe here are in accord with those of a report that appeared after the completion of our study, and in which transport of glutathione conjugates and BQ123 was detected in experiments using membrane vesicles prepared from insect cells expressing recombinant MRP6 (43). In combination, these studies using membrane vesicles prepared from either MRP6-transfected mammalian cells or insect cells infected with MRP6 baculovirus provide strong evidence in support of the notion that MRP6 is a lipophilic anion pump. They also suggest that the properties of human MRP6 may not be exactly identical to those of the rat orthologue in that the later protein was reported to transport BQ123 but not glutathione conjugates (37).

Although our results and that of Illias et al. (43) indicate that substrates of MRP6 include natural and synthetic glutathione conjugates, the cyclic pentapeptide BQ123 and, by inference from the analysis of the chemosensitivity of transfected cells, certain anticancer agents, the pathophysiological mechanism whereby deficiency of this pump leads to the development of PXE as well as the relevant physiological substrates of the pump, remain to be determined. A puzzling feature of the involvement of MRP6 in PXE is that whereas the disease affects skin, retina, and blood vessels, the initial descriptions of the tissue distribution of MRP6 transcript indicated that its expression is restricted to liver and kidney (31, 32), two organs that are not affected in the disease. In a subsequent report, MRP6 transcript was detected in skin by the use of a reverse transcription-PCR assay (33). However, a recent analysis of the tissue distribution of MRP6 protein in tissues affected in the disease affects skin, retina, and blood vessels, the initial descriptions of the tissue distribution of MRP6 transcript indicated that its expression is restricted to liver and kidney (31, 32), two organs that are not affected in the disease. In a subsequent report, MRP6 transcript was detected in skin by the use of a reverse transcription-PCR assay (33). However, a recent analysis of the tissue distribution of MRP6 protein in tissues affected in the disease...


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