cDNA cloning and inducible expression of human multidrug resistance associated protein 3 (MRP3)

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Abstract Previously, we cloned rat MRP3 as a candidate for an inducible transporter for the biliary excretion of organic anions [Hirohashi et al. (1998) Mol. Pharmacol. 53, 1068–1075]. In the present study, we cloned human MRP3 (1527 amino acids) from Caco-2 cells. Human MRP3 is predominantly expressed in liver, small intestine and colon; hepatic expression of MRP3 was observed in humans but not in normal rats. In HepG2 cells, the expression of MRP3 was induced by phenobarbital. These results suggest that MRP3 may act as an inducible transporter in the biliary and intestinal excretion of organic anions.

Key words: Multidrug resistance associated protein; Canalicular multispecific organic anion transporter; GS-X pump; Multidrug resistance; Biliary excretion

1. Introduction

Many organic anions including conjugated metabolites are excreted into the bile across the bile canalicular membrane via a primary active transporter referred to as the canalicular multispecific organic anion transporter (cMOAT/multidrug resistance associated protein 2 (MRP2)) [1–7], a member of the GS-X pump family [8–10]. The substrate specificity of cMOAT/MRP2 has been examined by comparing the transport properties across the bile canalicular membrane using normal and mutant rats (such as TR^- and Eisai hyperbilirubinemic rats (EHBR)) whose cMOAT/MRP2 function is hereditarily defective [1–7]. These mutant rats suffer from jaundice due to the impaired biliary excretion of bilirubin glucuronide via cMOAT/MRP2 and, therefore, are a good animal model for Dubin-Johnson syndrome in humans [1–7]. Recently, we and others have cloned rat and human cMOAT/MRP2 cDNA based on the homology with human MRP1 [11–15], and have clarified the mechanism for the mutation in mutant rats and patients suffering from Dubin-Johnson syndrome [11,14,16,17]. In addition, functional analysis of the cloned cDNA product has been performed [15,18–20].

However, kinetic studies with isolated bile canalicular membrane vesicles (CMVs) suggested the presence of multiple transport systems for the biliary excretion of organic anions and conjugated metabolites across the bile canalicular membrane [21,22]. As candidate molecules for the putative transporter(s), we have recently cloned two additional transporters referred to as MRP-like protein (MLP) 1 and 2 [23]. Sequence alignment indicated that MLP2 is the rat homologue of human MRP3 located on chromosome 17 [23,24]. Northern blot analysis indicated that MLP1 is predominantly expressed in the liver of both SD rats and EHBR, whereas hepatic expression of MRP3 is observed only in EHBR [23]. In addition, MRP3 is markedly induced in Sprague-Dawley rat liver by treatments which elevated the plasma concentration of bilirubin or bilirubin glucuronide, and by phenobarbital (PB) [25]. Although the full sequence of human MRP1, cMOAT/MRP2 and 5 has been reported [13,16,26–28], only a partial sequence is available for MRP3 [24,29]. The purpose of the present study was to clone the full length of human MRP3 and to examine its expression in order to investigate the possible involvement of this transporter in the biliary excretion of organic anions.

2. Materials and methods

2.1. Cell culture and RNA isolation

Total RNA was prepared from Caco-2 cells, HepG2 cells and human liver by a single-step guanidinium thiocyanate procedure. RNA isolation from Caco-2 cells was performed at 0, 5, 7, 10 and 15 days after becoming confluent. In order to examine the inducibility of MRP3 in HepG2 cells, 0, 1, 2 and 10 mM PB was added to the medium 7 days after becoming confluent. The HepG2 cells were removed for isolation of RNA on day 10. A human liver specimen (female Caucasian, 28 years old) was provided by SRI International (Menlo Park, CA). Poly(A)$^+$ RNA was purified using Oligotex-dT30 (Takara Shuzo, Kyoto, Japan).

2.2. Amplification of cDNA fragments and preparation of the cDNA probe

cDNA fragments were amplified by RT-PCR according to the method described previously [14,30] with total RNA of human liver as a template using an RNA-PCR kit (Takara Shuzo). For PCR, the degenerated primers were prepared on the basis of the conserved amino acid sequence in the ABC region of human MRP1 [26,30]. The sequences of the forward and reverse primers were 5′-dGAGAAGGTGGGCATCGTGGG(AGTC)CG(AGTC)AC(AGTC)GG-3′ and 5′-dGTCCACGGCTGC(AGTC)GT(AGTC)GC(TC)TC(AG)TC-3′, respectively [30]. The amplified PCR product (421 bp) was subcloned into the *Eco*RV site of pBluescript II SK^- (Stratagene, La Jolla, CA) and the sequence was determined [30]. This 421 bp cDNA fragment was used as the probe for Northern blot analysis or library screening [30]. Northern blot analysis was performed according to the method described previously [14,30] except that a Multiple Tissue Northern Blot (Clontech Laboratories, Palo Alto, CA) was used to determine the expression in human tissues.

2.3. Library construction and screening

The cDNA library was constructed with a Lambda ZAP II vector (SuperScript Choice System, Life Technologies, Gaithersburg, MD) [14]. Packaging of recombinants into the λ-phage was performed using a kit (Gigapack II Gold packaging Extract, Stratagene) [14]. After two rounds of screening, single positive colonies were isolated. Following co-infection with the M13 helper phage (ExAssist, Stratagene), the cDNA was excised in a pBluescript II SK^- plasmid and rescued by SOLR strain [14].

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3. Results

3.1. Cloning of human MRP3 from Caco-2 cells

In order to clone human MRP3 cDNA, RT-PCR was performed with degenerated primers using RNA from human liver. The cDNA fragment with 421 bp was amplified and its amino acid identity was 89.5% with rat MRP3, 68.7% with human cMOAT/MRP2 and 72.4% with human MRP1. Based on the high homology with rat MRP3, this fragment was regarded as the partial sequence of human MRP3.

Since the quality of the human liver specimen was not good enough to prepare a cDNA library, Caco-2 cells were chosen as the source of mRNA, since Northern blot analysis showed relatively high expression of human MRP3 in these cells cultured for 10 days after becoming confluent. A full-length cDNA with an open reading frame of 1527 amino acid residues was cloned for human MRP3 with two highly conserved ABC regions (Fig. 1). The identity of the amino acid sequence of MRP3 between humans and rats was 82.5%. The pattern of the hydropathy plot of MRP3, analyzed with the method by Eisenberg et al. [31], resembles that of MRP1 and cMOAT/MRP2 (Fig. 2). A BLAST search of the National Center for Biotechnology Information database showed that, at deduced amino acid levels, human MRP3 exhibits high overall identity with several ABC proteins such as human MRP1 and cMOAT/MRP2 (56.4% and 45.9%, respectively), rather than human MDR1 (20.6%).

3.2. Tissue distribution of human MRP3

Northern blot analysis indicated that human MRP3 mRNA is highly expressed in liver, colon, and small intestine, with low expression in lung, spleen and kidney (Fig. 3). Although the tissue expression pattern of MRP3 in humans resembles that in rats, the liver was exceptional in that hepatic expression is observed in normal humans, but not in normal rats (Fig. 3) [23]. To confirm the expression of MRP3 in human liver, Northern blot analysis was performed using poly(A)$^+$ RNA (5 μg) from another human liver specimen. The density of the band was about one-third that of human cMOAT/MRP2 (data not shown).

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1     MDALCGSGELGSKFWDSNLSVHTENPDLTPCFQNSLLAWVPCIYLWVALPCYLLYLRHHC
61    RGYIILSHLSKLKMVLGVLLWCVSWADLFYSFHGLVHGRAPAPVFFVTPLVVGVIMLLAT
121   LLIQYERLQGVQSSGVLIIFWFLCVVCAIVPFRSKILLAKAEGEISDPFRFTTFYIHFAL
181   VLSALILACFREKPPFFSAKNVDPNPYPETSAGFLSRLFFWWFTKMAIYGYRHPLEEKDL
241   WSLKEEDRSQMVVQQLLEAWRKQEKQTARHKASAAPGKNASGEDEVLLGARPRPRKPSFL
301   KALLATFGSSFLISACFKLIQDLLSFINPQLLSILIRFISNPMAPSWWGFLVAGLMFLCS
361   MMQSLILQHYYHYIFVIGVKFRTGIMGVIYRKALVITNSVKRASTVGEIVNLMSVDAQRF
421   MDLAPFLNLLWSAPLQIILAIYFLWQNLGPSVLAGVAFMVLLIPLNGAVAVKMRAFQVKQ
481   MKLKDSRIKLMSEILNGIKVLKLYAWEPSFLKQVEGIRQGELQLLRTAAYLHTTTFTWM
541   CSPFLVTLITLWVYVYVDPNNVLDAEKAYVSVSLFNILRLPLNMLPQLISNLTQASVSLK
601   RIQQFLSQEELDPQSVERKTISPGYAITIHSGTFTWAQDLPPTLHSLDIQVPKGALVAVV
661   GPVGCGKSSLVSALLGEMEKLEGKVHMKGSVAYVPQQAWIQNCTLQENVLFGKALNPKRY
721   QQTLEACALLADLEMLPGGDQTEIGEKGINLSGGQRQRVSLARAVYSDADIFLLDDPLSA
781   VDSHVAKHIFDHVIGPEGVLAGKTRVLVTHGISFLPQTDFIIVLADGQVSEMGPYPALLQ
841   RNGSFANFLCNYAPDEDQGHLEDSWIALEGAEDKEALLIEDTLSNHTDLTDNDPVTYVVQ
901   KQFMRQLSALSSDGEGQGRPVPRRHLGPSEKVQVTEAKADGALTQEEKAAIGTVELSVFW
961   DYAKAVGLCTTLAICLLYVGQSAAAIGANVWLSAWTNDAMADSRQNNTSLRLGVYAALGI
1021  LQGFLVMLAAMAMAAGGIQAARVLHQALLHNKIRSPQSFFDTTPSGRILNCFSKDIYVVD
1081  EVLAPVILMLLNSFFNAISTLVVIMASTPLFTVVILPLAVLYTLVQRFYAATSRQLKRLE
1141  SVSRSPIYSHFSETVTGASVIRAYNRSRDFEIISDTKVDANQRSCYPYIISNRWLSIGVE
1201  FVGNCVVLFAALFAVIGRSSLNPGLVGLSVSYSLQVTFALNWMIRMMSDLESNIVAVERV
1261  KEYSKTETEAPWVVEGSRPPEGWPPRGEVEFRNYSVRYRPGLDLVLRDLSLHVHGGEKVG
1321  IVGRTGAGKSSMTLCLFRILEAAKGEIRIDGLNVADIGLHDLRSQLTIIPQDPILFSGTL
1381  RMNLDPFGSYSEEDIWWALELSHLHTFVSSQPAGLDFQCSEGGENLSVGQRQLVCLARAL
1441  LRKSRILVLDEATAAIDLETDNLIQATIRTQFDTCTVLTIAHRLNTIMDYTRVLVLDKGV
1501  VAEFDSPANLIAARGIFYGMARDAGLA
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Fig. 1. Deduced amino acid sequence of cloned human MRP3. The nucleotide binding domains are indicated by an underline.

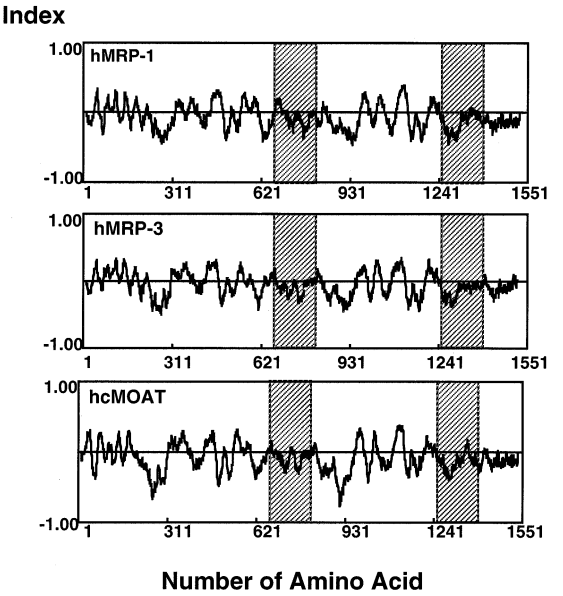

Fig. 2. Hydropathy plot of MRP family members. The pattern of the hydropathy plot, analyzed with the method described by Eisenberg et al. [31], was compared in human MRP1, cMOAT/MRP2 and MRP3. ABC regions are indicated by a shadow.

3.3. Induction of human MRP3 in HepG2 cells

Induction of human MRP3 was studied in HepG2 cells, since this cell line has been widely used to study the induction of metabolic enzymes such as P450 [32]. Northern blot analysis indicated that the expression of human MRP3 in HepG2 cells was enhanced by PB in a concentration-dependent manner (Fig. 4). Moreover, expression of MRP1 and cMOAT/MRP2 was also observed at higher PB concentrations (10 mM).

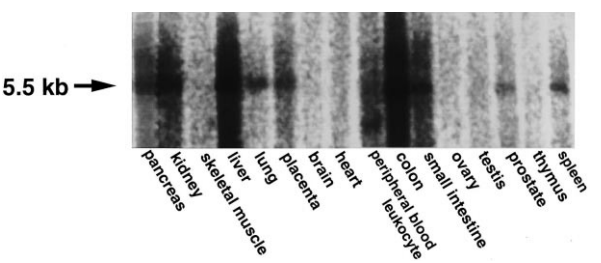

Fig. 3. Tissue expression of MRP3. The expression of MRP3 in human tissues was examined by Northern blot analysis using Multiple Tissue Northern Blot (Clontech Laboratories) with the ^{32}P-labeled carboxy-terminal ABC region.

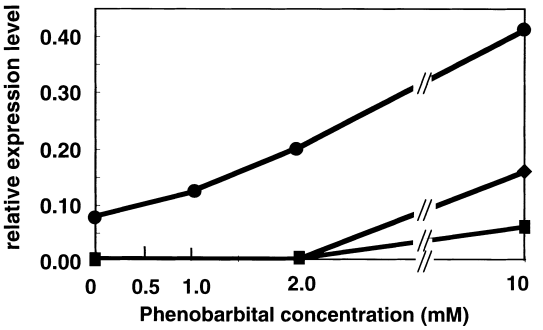

Fig. 4. Induction of MRP family members in HepG2 cells by phenobarbital. At 10 days after becoming confluent, HepG2 cells were treated with phenobarbital. The expression of MRP1 (■), cMOAT/MRP2 (♦) and MRP3 (●) was examined by Northern blot analysis. The relative expression level was determined by normalizing the expression of transporters with that of G3PDH.

4. Discussion

Multiplicity of active efflux transport systems in rats has been shown not only by kinetic studies using CMVs but also using molecular biology techniques [22,23]. In normal rat liver, cMOAT/MRP2 and MLP1 are expressed, whereas in EHBR liver, MLP1 and MLP2 (MRP3) are expressed [23]. Moreover, hepatic expression of MRP3 in Spraque-Dawley rats was induced by PB and by treatments which elevated the plasma concentration of bilirubin and/or its glucuronide [25]. In the present study, cloning of the human homologue of rat MRP3 was performed to investigate the multiplicity of biliary excretion. The alignment of the deduced amino acid sequence (Fig. 1) and the hydropathy plot of human MRP3 (Fig. 2) revealed that this protein belongs to the MRP family which may contain 17 transmembrane domains [33].

Extensive expression of human MRP3 was observed in liver (see Section 3 and Fig. 3), which is in marked contrast to rats [23], although this has not been established in general since liver specimens from only two human subjects were examined. It is possible that the expression of human MRP3 may have been induced by many factors and, therefore, the expression level of MRP3 may be involved in possible interindividual differences in biliary excretion. This hypothesis is supported by the in vitro finding that MRP3 was induced in HepG2 cells (Fig. 4). Although CYP enzymes are also induced by PB in vivo and also in HepG2 cells in vitro [32], the mechanism for this induction is not necessarily the same for the two proteins. Such an example has been reported for the hepatic induction of mdr1 and CYP3A enzymes [34]. The inducers for both proteins overlap, irrespective of the fact that the DNA binding proteins required for the induction are different [35].

In the present study, we could detect significant induction of MRP1 and cMOAT/MRP2 by PB in HepG2 cells, although a higher PB concentration was required than for MRP3 (Fig. 3). This finding is consistent with the previous in vivo finding that PB, at a dose of 80 mg/kg i.p. for 4 days, could induce MRP3, but not MRP1 or cMOAT/MRP2 to a significant level [25]. This inducible nature of some MRP family members by chemical carcinogens and antineoplastic drugs has been reported previously. Kauffmann et al. [36] reported the induction of cMOAT/MRP2, but not that of MRP1, in cultured rat hepatocytes by cisplatin, 2-acetylaminofluorene (AAF) and cycloheximide. Recently, they analyzed the 5′-flanking region of rat cMOAT/MRP2 and showed that the induction by AAF and probably by cisplatin is related to the downstream of base −250 in the flanking region, which contains Sp1 and PEA3 regions [37]. Moreover, they reported that the 5′-flanking region between bases −581 and −436 may be necessary for the induction of this transporter by PB in a rat hepatoma cell line, H4IIE [37]. Simultaneous induction of MRP1, cMOAT/MRP2 and MRP3 has also been observed in some doxorubicin-resistant non-small cell lung cancer cells and in cisplatin-resistant colon carcinoma cells [24,29]. Although Ishikawa and his collaborators identified the factors for the simultaneous induction of MRP1 and γ-glutamylcysteine synthetase, a rate determining enzyme for glutathione synthesis [9], further studies of the promoter region of MRP3 are required to determine the mechanism of induction.

The results of the present study may have some implications for the transport properties in CMVs. We found that the ATP-dependent uptake of glutathione conjugates and other non-conjugated organic anions in CMVs from humans is 5–10 times lower than that in rat CMVs, whereas the uptake of glucuronide conjugates was comparable between the two species [38]. This difference could be accounted for not only by a species difference in the substrate-specific transport characteristics of cMOAT/MRP2, but also by a difference in the population of transporters expressed on the bile canalicular membrane, i.e. if it is assumed that the ability of human cMOAT/MRP2 to transport all ligands examined previously is lower than that of rat cMOAT/MRP2, the species difference in the transport activity in CMVs can be accounted for by the hypothesis that the biliary excretion of organic anions is predominantly mediated by cMOAT/MRP2 in rats, whereas the contribution of MRP3 may be significant in humans.

The extensive expression of MRP3 in intestine may be related to the intestinal excretion of organic anions. Recently, using an Ussing chamber, Fujita et al. [39] suggested the presence of an active transport system for calcein on the brush border membrane of intestinal epithelium. However, by comparing the disposition of 1-naphthol glucuronide between normal and TR^- rats, it has been suggested that cMOAT/MRP2 may not be responsible for the intestinal excretion of this conjugated metabolite [40]. Moreover, Caco-2 cells can extrude 2′,7′-bis(2-carboxyethyl)-5(6)-carboxyfluorescein and 2,4-dinitrophenyl *S*-glutathione across both membranes in an ATP-dependent manner [41,42]. Together with the expression of MRP3 in Caco-2 cells, it is possible that MRP3 might be involved in the intestinal transport of organic anions.

In conclusion, we cloned cDNA encoding the full length of human MRP3. Expression of MRP3 was induced by PB in HepG2 cells. Although the function and localization of this cDNA product remain to be clarified, it is possible that this inducible transporter may be involved in the biliary and intestinal excretion of organic anions in humans.

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