Intestinal P-glycoprotein, which is encoded by the MDR1 gene, plays an important role in the absorption and presystemic elimination of many xenobiotics. Hence, an understanding of the factors regulating its expression and function is of substantial interest. In addition to genetic factors, exposure to drugs such as rifampin can profoundly affect its expression. So far, the mechanisms by which rifampin induces MDR1 expression are poorly understood. Recent studies demonstrate that the nuclear receptor PXR (pregnane X receptor) is involved in xenobiotic induction of CYP3A4. Because CYP3A4 and MDR1 are often co-induced, we investigated whether a similar mechanism is also involved in MDR1 induction. The human colon carcinoma cell line LS174T was used as an intestinal model to study induction because in these cells the endogenous MDR1 gene is highly inducible by rifampin. The 5′-upstream region of human MDR1 was examined for the presence of potential PXR response elements. Several binding sites were identified that form a complex regulatory cluster at about −8 kilobase pairs. Only one DR4 motif within this cluster is necessary for induction by rifampin. We conclude that induction of MDR1 is mediated by a DR4 motif in the upstream enhancer at about −8 kilobase pairs, to which PXR binds.

The MDR1 gene product P-glycoprotein (P-gp) plays an important role in the transport of hydrophobic xenobiotics and peptides from the inside to the outside of cells. Initially discovered in cancer cells as a mechanism responsible for resistance against certain cytostatic drugs (reviewed in Ref. 1), it was later shown that P-gp is also expressed in different nonmalignant cells of various organs. In agreement with its assumed physiologic role as a defense mechanism against potential toxic substances present in the diet and from environmental exposure, it is expressed in the brush border membrane of the mature enterocytes, the canicular membrane of hepatocytes, the brush border of proximal renal tubular cells, and the luminal side of endothelial cells of brain capillaries (2, 3).

In the gut P-gp functions as an efflux pump, actively transporting substances back into the intestinal lumen (4) and, hence, has an important role for the absorption and presystemic elimination of many chemicals including drugs. The level of intestinal P-gp expression shows wide interindividual differences (5) controlled by both genetic and environmental factors. Recently a genetic polymorphism of the MDR1 gene has been reported that affects the P-gp expression in the epithelial cell lining of the small intestine (6). In addition to this genetic polymorphism, environmental factors can affect the expression of P-gp. A number of drugs and steroid hormones have been shown to induce P-gp expression (7–11). For instance, the antibiotic rifampin not only induces intestinal cytochrome P 450 3A4 enzyme but also elicits a significant increase of intestinal P-gp (11). As a consequence, the plasma concentrations of orally administered digoxin are dramatically reduced.

So far the mechanisms by which rifampin and other inducing substances cause induction are poorly understood. Induction appears to take place at the transcriptional level, as MDR1 mRNA expression is elevated after treatment with inducers (8, 10, 12). Recent studies indicate that the nuclear receptor NR1I2 (pregnane X receptor (PXR)) (13) mediates xenobiotic induction of CYP3A4 genes by binding to PXR response elements in the upstream regulatory region of these genes (14–18). Since CYP3A4 and MDR1 seem to be co-induced at least by some compounds (11, 12), we investigated whether a similar PXR-dependent mechanism is also involved in MDR1 induction. In this study we used the human colon carcinoma cell line LS174T as a model to elucidate the molecular mechanisms of MDR1 induction by rifampin because in these cells the endogenous MDR1 gene is highly inducible by rifampin. By DNA binding assays and transfections, we identified a distinct PXR binding site, a DR4 nuclear receptor response element, that is essential for MDR1 induction by rifampin.

EXPERIMENTAL PROCEDURES

Plasmid Constructs—The reporter gene plasmid containing 10.2 kb of the MDR1 upstream regulatory region (p-10224) was constructed by ligating the corresponding NcoI fragment of the BAC clone CTB-60P12 (Research Genetics; GenBank™ accession number AC002457), which contains the 5′ part of the MDR1 locus, into the NcoI site of pGL3-Basic (Promega). The correct orientation was verified by sequencing. p-10224 encompasses the MDR1 sequence from bases −10224 to +261. Unidirectional deletion mutants of p-10224 were constructed using the double-stranded Nested Deletion kit (Amersham Pharmacia Biotech). The precise starting point of the deletion mutants was determined by sequencing. The MDR1 downstream promoter region encompassing the sequence between bases −1974 and +281 (19) was amplified by PCR out of human genomic DNA using the primers 5′-ACG GTA CCA AGG ACT GTT GAA AGT-3′ and 5′-ATG GAT CCA ACC CCA CTG GGT CCC CAT-3′, which introduce KpnI and BamHI sites, respectively. The PCR fragment digested with KpnI and BamHI was ligated into KpnI/BamHI-digested pGL3-Basic, creating p-1974, and sequenced. To create p-1803,
Induction of Intestinal MDR1 by Rifampin

p-1974 was digested with KpnI and BglII and the ends filled in and religated. The MDR1 promoter fragment (−7975 to −7013) containing the cluster of nuclear receptor response elements was amplified by PCR out of the above-mentioned BAC clone with primers 5′-TCT GGT AGC AGG AGC TGC-3′ containing a KpnI site, and 5′-ATG AGA TAT CCA GTC TCT TCC-3′, introducing a BglII site. The KpnI/BglII-digested PCR fragment was ligated between the KpnI and HindIII sites, creating p-7975/7013/T/TK, and sequenced. p-7975/7012−1804 was constructed by ligating a KpnI/BglII fragment from p-7975/7013/TK, which contained the promoter sequence between −7975 and −7013, into KpnI/BglII-digested p-1974.

Site-directed mutagenesis of the DR4(I) and ER6/DR4(III) motifs was performed within p-7975/7013/TK by using primers that contained two mutated bases in the center of each half-site (mutated bases are underlined and in italics): DR4(I), 5′-CAT TGT TGT AAT TTC TGT CTC-3′ and 5′-AGC AAC AAG TTA GAA CAG TG-5′; ER6/ DR4(III), 5′-GAG TTC ATT TGT TAT TAA ACA AGA AAC TGT ATG-3′ and 5′-CAT AGA TTT CTT TGT TGT TAT ACA AAC AAT GAA CTC-3′. The DR4(I)/ER6/DR4(III) double mutation was obtained by site-directed mutagenesis within the DR4(I)-mutated plasmid with the ER4(DR4)/DR4(III)-mutated primers. All mutations were verified by sequencing. Dimers of DR4(I) and ER6/DR4(III) were obtained by self-ligation of site-specific double-stranded oligonucleotides adenylated at BamHI/BglII sites and cloning into the BglII site of the modified pGL3-Basic vector with the TK promoter described above. Dimers with the motifs in the same orientation as in the MDR1 gene were identified by sequencing.

The open reading frame of human PXR was amplified out of LS180 cells using the primers 5′-TCG ATT ACC ATG GAT GGC GAG ACC-3′, introducing an EcoRI site and an optimized Kozak consensus sequence and 5′-CGT CTA GAT CAG CTA CCT GTG ATG CCG AAC A-3′, which introduces an Xbal site. The EcoRI/Xbal-digested PCR fragment was ligated into appropriately digested pCDNA3 (Invitrogen), creating pCD-PXR and sequenced.

Cell Culture, Transfection, and Reporter Gene Assays—The human colon adenocarcinoma cell line LS174T (20) was obtained from ATCC. Cells were cultured in Dulbecco’s modified Eagle medium (Life Technologies) buffered with 25 mM HEPES, supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin (Life Technologies), 1% nonessential amino acids (Biochrom), 1 mM sodium pyruvate (Life Technologies), 2 mM L-glutamine (Biochrom), and 10% fetal calf serum (Biochrom). Cells were grown at 37 °C, 5% CO2 in a humidified incubator. One day before transfection, 5.0 ml of cell lysate, and luminescence was measured immediately for 4 s with an AutoLumat Plus (Berthold, Germany).

RESULTS

Induction of Endogenous MDR1 in LS174T Cells by Rifampin and Other CYP3A4 Inducers or PXR Activators—Expression of intestinal P-glycoprotein had been shown to be induced by rifampin in vivo (11). To investigate the mechanisms of induction in the intestine, we used the intestinal cell line LS174T as a model. LS174T cells showed a time- and concentration-dependent induction of MDR1 by rifampin (Fig. 1). When LS174T cells were exposed to rifampin for 4–48 h, a biphasic induction was observed that peaked at about 8 h, declined thereafter to a low at 16 h, and increased again (Fig. 1A). When LS174T cells were treated with increasing concentrations of rifampin ranging from 0.1 μM to 10 μM, MDR1 induction was maximal between 5 and 10 μM rifampin (Fig. 1B). Thus, LS174T cells are an appropriate model to investigate the mechanisms of intestinal MDR1 induction because the endogenous MDR1 gene is highly inducible by rifampin.

Recently, it has been reported that the induction of CYP3A4 by rifampin is mediated through the nuclear receptor PXR (18), to which rifampin binds directly (24). Because CYP3A4 and MDR1 are supposed to be co-induced (12), we hypothesized that a similar mechanism is also involved in MDR1 induction. Therefore, LS174T cells were incubated with additional drugs already known to induce CYP3A4 or to be an activator or ligand for PXR. Fig. 2 shows that apart from rifampin, which is one of

RNA Preparation and Northern Blotting—Preparation of polyadenylated RNA and Northern blot analysis were done as described previously (25). Radiolabeled cDNA probes were synthesized using the DNA labeling II Kit (Ambion). To synthesize a probe for MDR1, the MDR1 cDNA fragment of pMDR V15 (23) was used. The GAPDHmouse DNA fragment was used as a probe specific for glyceraldehyde-3-phosphate dehydrogenase.

Electrophoretic Mobility Shift Assays—Gel mobility shift assays were performed as previously described (18) with modifications. Briefly, hPXR and hXRα were synthesized from pcDNA-PXR and pCMX-hXRα (generously provided by R. Schule) expression vectors, respectively, using the TNT Quick Coupled transcription/translation reticulocyte system (Promega). Nuclear response elements were prepared by annealing 1 μl each of two complementary oligonucleotide stocks (100 μM) in 48 μl of 10 mM Tris-Cl pH 7.8 and 1 mM EDTA, 300 mM NaCl. For annealing of the annealed oligonucleotides, 2 μl of 10× RB100 (200 mM Tris-Cl, pH 7.5, 100 mM MgCl2, 1 mM NaCl, 10 mM dithiothreitol), 20 μCi of [γ-32P]dCTP, 1 μl of 5 μM dATP, dGTP, and dTTP, 0.5 μl of Klenow fragment (2.5 units) and H2O to a final volume of 20 μl were incubated at 30 °C for 15 min and purified through Sephadex G-25 columns (MicroSpin® G-25 columns, Amersham Pharmacia Biotech).

Binding reactions consisted of 10 mM HEPES, pH 7.8, 60 mM KCl, 0.2% Nonidet P-40, 60 μg/ml dithiothreitol, 2 μg of poly(dI-dC), 10,000 cpm labeled probe, and 1 μl of synthesized hPXR and/or hXRα in a final volume of 20 μl. If necessary, reactions were filled up with unprogrammed lysate. In competition experiments, unlabeled competitor oligonucleotides were added before the addition of in vitro translated protein(s). Samples were incubated on ice for 20 min after the synthesized proteins had been added, and the protein-DNA complexes were resolved on a pre-electrophoresed 5% polyacrylamide gel in 44.5 mM Tris, 44.5 mM borate, and 1 mM EDTA (pH 8.3) at 200 V and room temperature. Gels were dried and autoradiographed at −80 °C overnight.

Oligonucleotides for Electrophoretic Mobility Shift Assays—ER6/ DR4(III) wild type sense, 5′-GAT CCC ATT TGA TAA ACA AGT TCA AAG T-3′; ER6/DR4(III) wild type antisense, 5′-GAT CTA CTT TAC TGT TAT ATC AAT CCT AGA AAT GGA CTC-3′. The DR4(I)/ER6/DR4(III) double mutation was obtained by site-directed mutagenesis within the DR4(I)-mutated plasmid with the ER4(DR4)/DR4(III)-mutated primers. All mutations were verified by sequencing. Dimers of DR4(I) and ER6/DR4(III) were obtained by self-ligation of site-specific double-stranded oligonucleotides adenylated at BamHI/BglII sites and cloning into the BglII site of the modified pGL3-Basic vector with the TK promoter described above. Dimers with the motifs in the same orientation as in the MDR1 gene were identified by sequencing.

The open reading frame of human PXR was amplified out of LS180 cells using the primers 5′-TCG ATT ACC ATG GAT GAG ACC-3′, introducing an EcoRI site and an optimized Kozak consensus sequence and 5′-CGT CTA GAT CAG CTA CCT GTG ATG CCG AAC A-3′, which introduces an Xbal site. The EcoRI/Xbal-digested PCR fragment was ligated into appropriately digested pCDNA3 (Invitrogen), creating pCD-PXR and sequenced.

Cell Culture, Transfection, and Reporter Gene Assays—The human colon adenocarcinoma cell line LS174T (20) was obtained from ATCC. Cells were cultured in Dulbecco’s modified Eagle medium (Life Technologies) buffered with 25 mM HEPES, supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin (Life Technologies), 1% nonessential amino acids (Biochrom), 1 mM sodium pyruvate (Life Technologies), 2 mM L-glutamine (Biochrom), and 10% fetal calf serum (Biochrom). Cells were grown at 37 °C, 5% CO2 in a humidified incubator. One day before transfection, 5.0 ml of cell lysate, and luminescence was measured immediately for 4 s with an AutoLumat Plus (Berthold, Germany).
the most potent inducers, reserpine, nifedipine, clotrimazole, RU486, and corticosterone were also strong inducers. Weaker induction was seen with carbamazepine, 5β-pregnane-3,20-dione, 6,16α-dimethylpregnenolone, dexamethasone, and pregnenolone-16α-carbonitrile, and no induction of MDR1 was observed after treatment with coumestrol. With the exception of 6,16α-dimethylpregnenolone, reserpine, and carbamazepine, for which no EC50 values have been reported, concentrations used to induce MDR1 in LS174T cells exceeded reported EC50 values for ligand activation of hPXR (14, 15, 24). Regarding the nearly identical pharmacological profile of MDR1 induction in LS174T cells and hPXR activation, we suppose that MDR1 induction by rifampin is mediated by a PXR-dependent mechanism.

PXR/RXRα Heterodimers Bind to Three DR4 Motifs in a Cluster of Nuclear Response Elements—The previously published proximal promoter region of MDR1 (up to approximately –2 kb) (19) was not involved in induction by rifampin in LS174T cells (Fig. 5A). Unidirectional deletion mutants of this region also did not reveal any induction by rifampin (data not shown). By computer-aided analysis with the Lasergene program package (DNASTAR), we looked for potential PXR binding sites in 20 kb of the MDR1 upstream region (sequence is available in GenBank™ accession number AC002457). PXR had been shown to bind to AG(G/T)TCA repeats of DR3, DR4, DR5, and ER6 organization (15). We identified a cluster of potential PXR binding sites at about –28 kb from the MDR1 promoter (Fig. 3) comprising three DR4 motifs (numbered I, II, and III, starting from 5′) and one DR3 and ER6 motif, all overlapping one another with at least one half-site. DR4(I) was the only motif for PXR with two consensus AG(G/T)TCA half-sites; all the others had one or two mismatches in one half-site.

Electrophoretic mobility shift assays (Fig. 4, A and B) with wild type and mutated versions of each motif revealed that PXR binds specifically as a heterodimer with RXRα to all three DR4 wild type motifs (DR4(III) and ER6 are coincident, since the two elements are too nested) but not to the mutated forms. DR3 was not able to bind PXR/RXRα heterodimers, even in its wild type form (Fig. 4B). PXR/RXRα heterodimers did not bind to DR4(I) or DR4(II) as strongly as to ER6/DR4(III). Binding to the latter motif is as strong as to the DR3 motif of CYP3A23 (Fig. 4A). Competition experiments with the corresponding unlabeled wild type and mutated versions of the motifs further...
proximal

The regulatory cluster conferred inducibility by rifampin to the MDR1 gene. The 1 kb fragment comprises bases −7975 to −7013. These include the cluster from −7864 to −7817, which is depicted in a larger magnification. DR4 motifs are numbered serially from the 5′ to the 3′ direction. Also shown is the previously published proximal promoter region (19).

FIG. 3. Position of MDR1 promoter elements. The figure shows the position of the regulatory cluster containing several potential nuclear response elements in relation to the transcription start site of the human MDR1 gene. The 1 kb fragment comprises bases −7975 to −7013. This region by itself is not inducible by rifampin, as the regulatory cluster was fused to the proximal promoter region of which a 1-kb sequences further downstream are required for induction. To show the previously published proximal promoter region (19).

The data presented in Fig. 2 have provided evidence that PXR is likely to be the endogenous factor present in LS174T cells that mediates induction. To demonstrate that PXR can activate transcription of MDR1, an expression plasmid for hPXR was co-transfected with p-7975/7013TK. As can be seen in Fig. 5C, co-transfection of PXR activated transcription of the reporter gene even in the absence of rifampin. Treatment with rifampin led to a further increase in induction (about 3-fold). Therefore it can be concluded that induction by rifampin of the MDR1 enhancer can be mediated by PXR. Altogether these data indicate that PXR is the endogenous factor present in LS174T cells mediating induction by rifampin.

DISCUSSION

Due to the central role that intestinal P-gp plays in the absorption and presystemic elimination of many chemicals, including medicines, an understanding of the factors regulating its expression is of importance both from a clinical and toxicological point of view. Because the mechanisms of induction are poorly understood, we investigated the molecular mechanisms by which rifampin induces MDR1 gene expression using an intestinal cell line. Rifampin was selected because it is a powerful inducer of intestinal P-gp both in human duodenal biopsies (11) and in a cell line (12), whereas for other inducers, only in vitro data are available, thus raising doubts if results obtained in cell lines with these substances can be extrapolated for the human in vivo situation. Since a time- and concentration-dependent induction of MDR1 by rifampin was observed in the colon carcinoma cell line LS174T, it proved a suitable model for intestinal MDR1 induction. The biphasic induction is indicative of a two-stage mechanism of induction by rifampin. The first and immediate increase can be explained by activation of pre-existing factors, probably PXR, and is therefore supposed to be independent of de novo protein biosynthesis. The second increase, starting at about 24 h, however, probably required de novo protein biosynthesis. This would imply that additional genes are induced by rifampin, which then participate in MDR1 induction. The reason for the decrease in MDR1 expression between 8 and 16 h is unclear and remains to be elucidated.

The reported co-induction of CYP3A4 and MDR1 (11, 12) and the recently identified involvement of PXR in xenobiotic induction of CYP3A genes (18) prompted us to investigate whether PXR is also involved in induction of MDR1. Treatment of LS174T cells with the known CYP3A4 inducers reserpine, clotrimazole, RU486, carbamazepine, dexamethasone, and pregnenolone-16a-carbonitrile (12, 22, 26) and the known activators for PXR, nifedipine, corticosterone, 5β-pregnane-3,20-dione, and 6,16a-dimethylpregnenolone (14–17), induced MDR1. Only the PXR activator coumestrol did not induce MDR1. Induction of MDR1 by other drugs apart from rifampin, known as CYP3A4 inducers and PXR activators, provided evidence that PXR is probably the factor responsible for induction of MDR1 in LS174T cells. In agreement with this hypothesis, PXR mRNA is expressed in LS174T cells (data not shown).
PXR/RXRα heterodimers bind specifically to DR4 and ER6/DR4 motifs. A and B, electrophoretic mobility shift assays using in vitro translated proteins bound to radiolabeled oligonucleotides corresponding to unmutated or mutated (mut) potential PXR binding sites of the MDR1 regulatory cluster or the PXR binding site of CYP3A23 as a positive control. Binding reactions contained (+) or lacked (−) the indicated proteins. Complexes of PXR/RXRα heterodimers and the oligonucleotides are marked by an arrow. The band of lower molecular weight seen in the lanes with only one of the two proteins derived from the unprogrammed reticulocyte lysate, as it was also detected when unprogrammed lysate was used alone (shown in C). The intensity of this band varied between experiments and probes used. C, competition experiment with radiolabeled wild type DR4(I) as probe and unlabeled wild-type (DR4(I)) or mutated DR4(I) (DR4(I)mut) as competitor. The numbers indicate the n-fold molar excess to which the competitor was added. Specific complexes are marked by an arrow.
We identified an enhancer element at about –8 kb of the MDR1 upstream region that contains several nuclear receptor binding motifs and mediates induction by rifampin in LS174T cells. Within this enhancer element, there are three DR4 motifs (numbered I-III from 5′ to 3′) and one DR3 and ER6 motif, respectively, all overlapping with at least one half-site. A similar complex organization of nuclear response elements has also been reported in the distal enhancer module (XREM) of
CYP3A4, which mediates the hPXR-dependent induction by xenobiotics in co-operation with a proximal promoter element (18). In contrast to CYP3A4, such a proximal promoter element is missing in MDR1. As shown by us, the proximal promoter region of MDR1 cannot be induced by rifampin. Similar to the XREM of CYP3A4, only one out of several motifs to which PXR binds is necessary for induction. In the XREM of CYP3A4, a DR3 motif mediates induction (18), whereas in MDR1 it is the DR4(I) motif, which is the only consensus motif present in MDR1. Mutation of the ER6/DR4(III) motif in the MDR1 enhancer was associated with an increased induction. A similar observation has been made with the mutated ER6 motif in the CYP3A4 XREM (18). Therefore it is quite likely that there are factors in LS174T cells that bind to the ER6/DR4(III) and probably exert a suppressive effect on the activity of DR4(I). In agreement with this, dimers of ER6/DR4(III) cannot be induced, although PXR binds in vitro to the motif. The ER6 motif in the proximal promoter of CYP3A23 also showed binding of PXR but did not mediate PXR-dependent induction (27). It is a common feature of all these imperfect ER6 motifs, to which PXR binds in vitro but which do not mediate induction, that a more or less well conserved DR4 motif is contained within the ER6. It is probably due to the imperfect nature of these ER6 motifs that other factors can bind to them or to the enclosed degenerate DR4 with higher affinity than PXR. Likely candidates could be the nuclear receptors COUP-TFI, LXR, and CAR, which all bind to degenerate DR4 motifs (28–30). LXR and COUP-TFI are expressed in LS174T cells (data not shown). Competition of different nuclear receptors, which exert opposing effects on MDR1 expression, could explain the pronounced interindividual variability in MDR1 induction by rifampin observed in humans (9, 11). The magnitude of induction is probably dependent on the relative amounts of competing factors. Consequently, the total amount of PXR alone does not determine the extent of induction. On the other hand, mutations in the PXR response elements that change the binding affinity of PXR or competing factors can also cause the observed variability of MDR1 induction in different individuals.

The DR4(I) motif mediating induction of MDR1 is the first physiological PXR response element of DR4-type, whereas previously described PXR response elements in CYP3A promoters were all of ER6 and DR3-type. This confirms results obtained with synthetic AG(G/T)TCA repeats of different spacing, which suggest the existence of DR4 and DR5 motifs in PXR-regulated gene promoters (15). The degenerate DR4(II) motif to which PXR binds in vitro is not necessary for induction. Other factors in addition to PXR probably bind to DR4(II) in LS174T cells.

Co-transfection of an expression plasmid for hPXR directly demonstrated that PXR mediates induction of MDR1 through the identified enhancer. Moreover, PXR activates the reporter gene with the MDR1 enhancer even in the absence of rifampin treatment. Co-transfection probably changes the relative amounts of PXR and competing factors, leading to an increased binding of PXR to its binding sites in the MDR1 enhancer. Transcriptional activation then might be due to the presence of endogenous ligands for PXR in LS174T cells. As reported previously, pregnant women are likely candidates for endogenous ligands (16).

This study provides evidence that a similar mechanism is responsible for induction of CYP3A4 and MDR1 by xenobiotics. The induction of both genes requires nuclear receptor response elements in proximal promoter and/or enhancer regions to which PXR binds. Recently it has been shown in knockout mice that PXR is necessary for induction of CYP3A (31). Whether this is also true for MDR1 induction remains to be clarified. CYP3A4 and P-gp are believed to constitute a physiological barrier in the intestine that prevents the absorption of harmful chemicals contained in the diet (32). When the organism is exposed to increasing concentrations of xenobiotics, induction seems to be a mechanism to strengthen the barrier function in the intestine by coordinated up-regulation of both the drug metabolizing enzyme and the drug transporter. The question arises of whether additional drug-metabolizing enzymes or drug transporters, which can contribute to barrier function, are also up-regulated by a similar PXR-dependent mechanism.

Acknowledgments—We thank Dr. R. Schule (Klinik fuer Tumoriologie, University of Freiburg, Germany) for kindly providing us with pCMX-hRXRα plasmid.
Nuclear Receptor Response Elements Mediate Induction of Intestinal MDRI by Rifampin
Anke Geick, Michel Eichelbaum and Oliver Burk

J. Biol. Chem. 2001, 276:14581-14587.
doi: 10.1074/jbc.M010173200 originally published online January 31, 2001

Access the most updated version of this article at doi: 10.1074/jbc.M010173200

Alerts:
• When this article is cited
• When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 32 references, 13 of which can be accessed free at http://www.jbc.org/content/276/18/14581.full.html#ref-list-1