The cytochromes P450 (CYPs) superfamily consists of heme-containing monooxygenases that play an important role in the oxidative metabolism of endogenous substances, natural compounds, and xenobiotics. The CYP3A4 gene product is the most abundant CYP that is expressed in human liver and is involved in the metabolism of drugs, steroids, and environmental procarcinogens (reviewed in Ref. 1). The expression of the CYP3A4 is transcriptionally activated by many natural and xenobiotic compounds. This induction of the CYP3A4 gene by xenobiotic compounds, in turn, can cause drug-drug interactions. One such example is the antibiotic rifampicin, a well known inducer of the human CYP3A4 gene, which then increases the clearance of immunosuppressant cyclosporine A, oral contraceptives, glucocorticoid derivatives, and calcium channel blockers. Recently, the orphan nuclear receptor, steroid and xenobiotic receptor (SXR) (also called pregnane X receptor (PXR)), has been isolated (2–5). SXR is highly expressed in the liver and small intestine and regulates the CYP3A4 gene. SXR forms heterodimer with retinoid X receptor (RXR) on xenobiotic-response elements (XREs), located in the promoter region of the CYP3A4 gene. A variety of known CYP3A4 inducers such as rifampicin, clotrimazole, and nifedipine bind to SXR as ligands and stimulate transcription of the CYP3A4 (3–6).

Ligand-dependent interaction with coactivators activates transcription, and ligand-independent interaction with corepressors represses basal transcription by certain nuclear receptors such as thyroid hormone receptors (TRs) and retinoic acid receptors (RARs) (7, 8). Recent studies revealed that the various inducers of the CYP3A4 recruit the nuclear receptor coactivators such as steroid receptor coactivator-1 (SRC-1) to the ligand-binding domain (LBD) of SXR (2, 3, 9, 10). However, it is not known whether SXR represses basal transcription. NCoR (nuclear receptor corepressor) and SMRT (silencing mediator for retinoid and thyroid receptors) mediate basal repression by unliganded nuclear hormone receptors (11, 12). In the present study, we analyzed the silencing ability of SXR and its interaction with the corepressors (NCoR and SMRT) in CYP3A4 gene regulation.

EXPERIMENTAL PROCEDURES

Reagents and Chemicals—Rifampicin, corticosterone, and triiodothyronine (T3) were obtained from Sigma. Ketoconazole was kindly provided by Janssen Research Foundation (Beerse, Belgium). Troglitazone was kindly provided by Sankyo Co. Ltd. (Tokyo, Japan).

Plasmids—Human SXR in pCDG1 was kindly provided by Dr. R. M. Evans, the Salk Institute, La Jolla, CA (4). Mouse NCoR in pCEP4 (Invitrogen) and human SMRT in pCMX were described previously (13). A schematic diagram of the GAL4 or VP16 fusion constructs used is shown in Fig. 1. GAL4 SXR-LBD and GAL4 SRC-1-RID were constructed by ligating the LBD of human SXR (amino acids 107–434) (10) and nuclear receptor-interacting domain (RID) containing three LXXLL motifs in human SRC-1 (amino acids 595–780) (14) into the pM expression vector (CLONTECH, Palo Alto, CA), respectively. VP16 SXR-LBD and VP16 SRC-1-RID were constructed by ligating the same amino acid
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To determine the silencing ability of SXR and its interaction with the corepressors (NCoR and SMRT) on the CYP3A4 gene, transient transfection assays were performed. Human SXR expression plasmid and a reporter plasmid, XREM-CYP3A4-LUC, containing the enhancer and promoter of the CYP3A4 driving luciferase gene expression (18, 19) were cotransfected into a human liver-derived cell line, HepG2. Previously, it has been reported that CYP3A4 expression is induced by rifampicin in cultured HepG2 cells (20). We then examined SXR regulation of CYP3A4 gene expression in the absence or presence of rifampicin. As shown in Fig. 2, SXR showed a weak basal activation (2.3-fold) rather than repression in the absence of ligand. Rifampicin treatment stimulated SXR-mediated transcription by −100-fold. Cotransfection of NCoR did not show a significant change in SXR expression. However, cotransfection of SMRT repressed not only basal but also rifampicin-induced transcriptional activity of SXR. This result suggests that SMRT, but not NCoR, may be involved in SXR-mediated gene repression both in the absence and presence of ligands.

We then generated a series of fragments of SXR, fused to the DNA-binding domain (DBD) of the yeast transcription factor GAL4, to test their transcriptional activity on five copies of a GAL4 upstream activation sequence reporter (5× UAS-TK-LUC) in HepG2 cells (Fig. 3). The GAL4 SXRP-LBD (amino acids 107–434) showed basal repression and rifampicin-induced transcriptional activity of SXR. This result suggests that SMRT, but not NCoR, may be involved in SXR-mediated gene repression both in the absence and presence of ligands.

RESULTS

To determine the silencing ability of SXR and its interaction with the corepressors (NCoR and SMRT) on the CYP3A4 gene, transient transfection assays were performed. Human SXR expression plasmid and a reporter plasmid, XREM-CYP3A4-LUC, containing the enhancer and promoter of the CYP3A4 driving luciferase gene expression (18, 19) were cotransfected into a human liver-derived cell line, HepG2. Previously, it has been reported that CYP3A4 expression is induced by rifampicin in cultured HepG2 cells (20). We then examined SXR regulation of CYP3A4 gene expression in the absence or presence of rifampicin. As shown in Fig. 2, SXR showed a weak basal activation (2.3-fold) rather than repression in the absence of ligand. Rifampicin treatment stimulated SXR-mediated transcription by −100-fold. Cotransfection of NCoR did not show a significant change in SXR expression. However, cotransfection of SMRT repressed not only basal but also rifampicin-induced transcriptional activity of SXR. This result suggests that SMRT, but not NCoR, may be involved in SXR-mediated gene repression both in the absence and presence of ligands.

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LBD, we observed another repression domain in the DBD of SXR (amino acids 41–107). The two GAL4 constructs that contain both DBD and LBD (amino acids 1–434 and 41–434) have less rifampicin-induced transcriptional activity than the GAL4 SXR-LBD (amino acids 107–434) (Fig. 3).

Using a mammalian two-hybrid assay in HepG2 cells, we tested whether the silencing function of SXR-LBD is mediated by interaction with corepressors. The homologous regions of nuclear receptor-interacting domains in SMRT and NCoR were fused to the transactivation domain of VP16 (VP16 SMRT-RID and VP16 NCoR-RID in Fig. 1) (16, 17). As a control experiment, we used VP16 SRC-1-RID, which contains the nuclear receptor-interacting domain (10, 26). GAL4 and VP16 fusion constructs were cotransfected with a 5× UAS-TK-LUC reporter plasmid. As shown in Fig. 4, when GAL4 SXR-LBD was used, VP16 SRC-1-RID increased transcriptional activity in the presence of rifampicin, suggesting rifampicin-induced interaction of SXR with SRC-1 (10). Importantly, whereas co-transfection of VP16 NCoR-RID did not show significant change in GAL4 SXR-LBD-mediated transcription, cotransfection of VP16 SMRT-RID increased basal transcription in the absence of rifampicin. Transcription of GAL4 SXR-LBD also was significantly increased by cotransfection of VP16 SMRT-RID in the presence of rifampicin. Taken together, the data show that not only basal but also rifampicin-induced transcriptional activity of SXR was suppressed by SMRT (Fig. 2) and is likely due to interaction with SMRT in the absence or presence of rifampicin in HepG2 cells. Of note, rifampicin-induced activation of GAL4 SXR-LBD with VP16 alone in Fig. 4 is less than that of GAL4 SXR-LBD in Fig. 3, which is probably due to different amounts of total transfected DNA, GAL4 SXR-LBD, and reporter DNA used with the two studies. When GAL4 empty vector was used, no VP16 construct (VP16 SMRT-RID, VP16 NCoR-RID, or VP16 SRC-1-RID) increased the luciferase activity (data not shown).

To examine the effect of rifampicin on SMRT-SXR interaction, the interactions between SXR and the two corepressors (NCoR and SMRT) were also examined using the reverse configuration of GAL4 or VP16 fusion constructs in HepG2 cells. The analysis of TR interaction with NCoR or SMRT was used as a control. As recently reported, NCoR, but not SMRT, specifically interacted with TR-LBD (16, 17). The addition of T3 dissociated the TR and NCoR interaction (Fig. 5A). In contrast, SMRT, but not NCoR, interacted with SXR-LBD (Fig. 5B).

Furthermore, rifampicin increased the interaction between SMRT and SXR-LBD. These mammalian two-hybrid assays suggest that the ligands of SXR may increase the interaction with both the coactivator, SRC-1, and the corepressor, SMRT. We also used CV-1 cells instead of HepG2 cells to test the specificity. In the absence of ligand, SMRT, but not NCoR, interacted with SXR-LBD in CV-1 cells. However, rifampicin treatment neither increased nor decreased the interaction of SXR with SMRT (data not shown). In addition, GST pull-down assays using 35S-labeled SXR with GST SMRT-RID or GST NCoR-RID failed to show ligand-dependent interaction of SXR with both corepressors (data not shown). Therefore, ligand-dependent interaction of SXR with SMRT in HepG2 cells may require other cell-specific factor(s) or post-transcriptional modification.

The induction of the CYP3A4 enzyme is mainly explained by the xenobiotic-induced transactivation of SXR. On the other hand, the inhibition of the CYP3A4 enzyme by xenobiotics, such as the drugs nefazodone, clarithromycin, erythromycin, itraconazole, and ketoconazole, is generally thought to be the inhibition of the enzyme activity at post-transcriptional level (1). Ketoconazole, an anti-fungal agent, is known as a strong inhibitor of CYP3A4. It inhibits the CYP3A4 enzyme with low Ki value by forming a complex with the CYP3A4 enzyme (1, 21, 22). However, as shown in Fig. 6, ketoconazole partially inhibited corticosterone-induced SXR activation. Of note, ketoconazole treatment alone showed a weak agonistic activity (~8-fold). This result suggest that ketoconazole may act as an antagonist only when the SXR is activated by its agonist such as corticosterone.

To understand the mechanism of the antagonistic activity by ketoconazole, the effect of ketoconazole for the interaction of SXR with SMRT or SRC-1 was analyzed by a mammalian two-hybrid assay in HepG2 cells (Fig. 7). Constitutive interaction of SXR with SMRT or SRC-1 was enhanced by rifampicin or corticosterone treatment. On the other hand, ketoconazole dissociated the interaction of SXR with SMRT or SRC-1 to near basal level. Thus, ketoconazole may inhibit corticosterone-induced transactivation by disrupting SXR-coactivator interaction directly.
DISCUSSION

The nuclear hormone receptors (NRs) such as TRs and RARs repress gene transcription in the absence of ligands. The repression is mediated by the interaction of the NRs with nuclear corepressors such as NCoR and SMRT (7, 8, 11, 12). SXR belongs to the same subfamily of the NRs as TRs and RARs, which heterodimerize with RXRs and mediate ligand-dependent transcription. SXR regulates various members of the CYP enzymes including CYP3A4, CYP3A11, and CYP2C8 (24, 25). The basal level of the CYP3A11 mRNA was increased in the SXR null mouse, indicating that SXR may have a repression function in vivo (24). In the present study, we showed that unliganded SXR exhibited basal repression on the heterologous promoter. Two repression domains were located in the LBD.

**FIG. 5.** In vivo interaction of corepressors with TR and SXR. The expression plasmids encoding GAL4 NCoR-RID or GAL4 SMRT-RID (0.1 µg) were cotransfected with 0.5 µg of VP16 TR-LBD (A) or VP16 SXR-LBD (B), 5× UAS-TK-LUC reporter plasmid (1.5 µg), and CMV-β-galactosidase control vector (0.1 µg) in HepG2 cells. Cells were treated with 1 µM T3 (A) or 10 µM rifampicin (B) for 24 h. The corrected luciferase activity was calculated as -fold luciferase activity with 1-fold basal activity defined as the luciferase activity with GAL4 NCoR and VP16 alone or GAL4 SMRT and VP16 alone in the absence of the ligand. The results are expressed as the mean ± S.D. of the representative experiments (panel A and GAL4 NCoR experiment in panel B, n = 3) or triplicate sample in three separate experiments (GAL4 SMRT experiment in panel B, n = 9). The asterisk (*) denotes significant difference from the luciferase value of the column that represents GAL4 SMRT and VP16 alone or GAL4 SMRT and VP16 SXR-LBD in the absence or presence of rifampicin (p < 0.0001).

**FIG. 6.** Ketoconazole partially inhibits corticosterone-induced SXR transcription. The expression plasmid encoding SXR (0.1 µg) was cotransfected with reporter plasmid XREM-CYP3A4-LUC (1.5 µg) and CMV-β-galactosidase control vector (0.1 µg) in HepG2 cells. Cells were treated with different concentrations of corticosterone and/or ketoconazole for 24 h. The corrected luciferase activity was calculated as -fold luciferase activity with 1-fold basal activity defined as the luciferase activity with the empty expression vector in the absence of the ligand. The results are expressed as the mean ± S.D. (n = 3).

**FIG. 7.** The effect of ketoconazole on the interaction of SXR with SMRT or SRC-1. The expression plasmids encoding GAL4 SMRT-RID (A) or GAL4 SRC1-RID (B) (0.1 µg) were cotransfected with VP16 SXR-LBD (0.5 µg), 5× UAS-TK-LUC reporter plasmid (1.5 µg), and CMV-β-galactosidase control vector (0.1 µg) in HepG2 cells. Cells were treated with 10 µM rifampicin, 10 µM corticosterone, or 5 µM ketoconazole for 24 h. The corrected luciferase activity was calculated as -fold luciferase activity with 1-fold basal activity defined as the luciferase activity with GAL4 SMRT and VP16 empty vector (A) or GAL4 SRC-1 and VP16 empty vector (B) in the absence of the ligand. The results are expressed as the mean ± S.D. (n = 3).
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and DBD of SXR. We found the repression function of the LBD-SXR was mediated by the specific interaction with SMRT. We have not analyzed how the DBD-SXR mediates repression. Similar to SXR, we reported previously that the DBD of TR contains an inhibitory region, which prevents full-length wild-type TR transcriptional activation in the GAL4 chimeric receptor system (26). Mathur et al. (27) reported a corepressor protein, PSF (polypyrimidine tract-binding protein-associated splicing factor), which binds to the DBD of type II nuclear hormone receptors such as TRs and RXRs. They showed that PSF interacts with Sin3A and mediates silencing through the recruitment of histone deacetylases. Importantly, although thyroid hormone (T3) dissociates TR-NCoR interaction, the levels of TR-bound PSF and Sin3A remain unchanged (27). It will be interesting to test the interaction of DBD-SXR with PSF. When we used the CYP3A4 promoter, we failed to observe basal repression. However, cotransfection of SMRT, but not NCoR, inhibited the SXR transcription. We and others reported previously that conformational change(s) of NRs induced by the specific hormone-response elements may influence the nature of binding to coactivators such as SRC-1 (28, 29). In our mam-malian two-hybrid assays, SXR showed constitutive interaction with both SRC-1 and SMRT. The relative balance of SXR interaction with coactivators and corepressors may determine the specific promoter activity. It also will be important to know whether the basal transcriptional activities by SXR depend on the specific XREs of the promoters.

We showed that SXR specifically interacts with SMRT, but not NCoR. While our work was in progress, Synold et al. (30) reported preferential recruitment of SMRT by SXR in CV-1 cells, consistent with our result. Although NCoR and SMRT share a similar structure in their C-terminal nuclear receptor-interacting domains, recent studies demonstrated that there is specificity in terms of NR recruitment of corepressors. TRβ1 preferentially interacts with NCoR, whereas RARα preferentially interacts with SMRT (16, 17). (I/L)XXII motifs and the adjacent α helical structure within the nuclear corepressor IDs are critical for mediating interactions with NRs (31, 32). NCoR contains three IDs, whereas SMRT has two IDs (17, 33). In vitro and in vivo interaction studies using fragments and chimeric mutants of IDs revealed that the preferences of TR and RAR interaction with the distinct corepressors are due to the sequence differences in the IDs (16, 17). Vitamin D receptor has also been reported to have preferred interaction with SMRT similar to SXR (34). It would be interesting to know which ID(s) of SMRT is important for the specific interaction with SXR.

In HepG2 cells, the SXR-SMRT interaction was unexpectedly increased by rifampicin or corticosterone treatment. In CV-1 cells, we failed to observe such ligand-dependent interaction of SXR with SMRT. Synold et al. (30) showed that the anti-cancer drug paclitaxel, but not doxetaxel, disrupted the SXR-SMRT interaction, whereas both drugs induced SXR-SRC-1 interaction in CV-1 cells. Although we have not analyzed SXR-SMRT interaction using paclitaxel and doxetaxel in HepG2 cells, the effect of xenobiotics on SXR-SMRT interaction may be different among different tissues. In fact, the agonist-induced recruitment of corepressors in the specific cell is not restricted to the SXR. Smith et al. (35) have reported that SMRT inhibits 4-hydroxytamoxifen agonist activity of estrogen receptor α in HepG2 cells.

The long QT syndrome is a group of disorders characterized by a prolonged QT interval, and this disorder promotes the specific type of life-threatening ventricular tachycardia, torsades de pointes. The long QT syndrome can be inherited or acquired as an adverse response to electrolyte abnormalities, bradycardia, or drugs that include ketoconazole, which inhibits CYP activities (1). Using human liver microsomes, Maurice et al. (21) reported that ketoconazole is a strong and selective inhibitor of the CYP3A4. It has been generally considered that imidazole derivatives such as ketoconazole are able to interact with various CYPs of liver microsomes, thereby inhibiting some monoxygenase activities (1). However, we showed that ketoconazole disrupted both SXR-SMRT and SXR-SRC-1 interactions and partially inhibited corticosterone-stimulated SXR transcription on the CYP3A4 promoter in HepG2 cells. Blumberg et al. (4) reported that the cocktails of endogenous steroids containing corticosterone additively increase human SXR-mediated transcription. Thus, it is possible that many endogenous steroid hormones in serum may additively stimulate SXR transcription in vivo. It has been reported that the plasma concentration of ketoconazole after 1 h of oral administration of a 200-mg single dose is 6.2 µg/ml (i.e. 11.7 µM) (36). Ketoconazole may inhibit the endogenous steroid-induced transcription in vivo to alter the CYP3A4 transcription.

In summary, our results suggest that the differential interaction of coactivators and corepressors induced by various xenobiotics may alter SXR-mediated transcription. Furthermore, the effects of ketoconazole on the CYP3A4 gene suppression may explain, in part, drug-induced inhibition of the CYP3A4 action at transcriptional level.

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REFERENCES

1. Thummel, K. E., and Wilkinson, G. R. (1998) Annu. Rev. Pharmacol. Toxicol. 38, 389–430
2. Kliwer, S. A., Moore, J. T., Wade, L., Staudinger, J. L., Watson, M. A., Jones, S. A., McKee, D. D., Oliver, B. B., Willson, T. M., Zetterstrom, R. H., Perlmann, T., and Lehmann, J. M. (1998) Cell 92, 73–82
3. Lehmann, J. M., McKee, D. D., Watson, M. A., Wilson, T. M., Moore, J. T., and Kliwer, S. A. (1998) J. Clin. Invest. 102, 1016–1023
4. Blumberg, B., Sabbagh, W. J., Jaygulal, H., Bolado, J., van Meter, C. M., Ong, E. S., and Evans, R. M. (1998) Genes Dev. 12, 3195–3205
5. Bertilsson, G., Heidehr, J., Svensson, K., Asman, M., Jendeberg, L., Sydow-Buckman, M., Ohlsson, R., Postland, H., Blomquist, P., and Berkenstam A. (1998) Proc. Natl. Acad. Sci. U. S. A. 95, 12208–12213
6. Waxman, D. J. (1999) Arch. Biochem. Biophys. 369, 11–23
7. Mccaruso, N., Lanz, R. B., and O'Malley, B. W. (1999) Endocr. Rev. 20, 321–344
8. Glass, C. K., and Rosenfeld, M. G. (2000) Genes Dev. 14, 121–141
9. Jones, S. A., Moore, L. B., Shenk, J. L., Wilsely, G. B., Hamilton, G. A., McKee, D. D., Tomkinson, N. C., LeChuyse, E. L., Lambert, M. H., Willson, T. M., Kliwer, S. A., and Moore, J. T. (2000) Mol. Endocrinol. 14, 27–39
10. Takeshita, A., Kibuchi, N., Oka, J., Taguchi, M., Shishiba, Y., and Ozawa, Y. (2001) Eur. J. Endocrinol. 145, 513–517
11. Horlein, A. J., Naar, A. M., Heinzel, T., Torchia, J., Gless, B., Kurokawa, R., Ryan, A., Kamei, Y., Siderström, M., Glass, C. K., and Rosenfeld, M. G. (1995) Nature 377, 409–412
12. Chen, J. D., and Evans, R. M. (1995) Nature 377, 454–457
13. Misić, S., Schomburg, L., Yen, P. M., and Chin, W. W. (1998) Endocrinology 139, 2483–2500
14. Takeshita, A., Yen, P. M., Misić, S., Cardona, G. R., Liu, Y., and Chin, W. W. (1996) Endocrinology 137, 3584–3597
15. Vasavada, H. A., Ganguly, S., Germino, F. J., Wang, Z. X., and Weissman, S. M. (1991) Proc. Natl. Acad. Sci. U. S. A. 88, 10797–10800
16. Cohen, R. N., Putney, A., Wondraford, F. E., and Holenberg, A. N. (2000) Mol. Endocrinol. 14, 900–914
17. Cohen, R. N., Brazeck, T., Kim, B., Chovek, M., Wondraford, F. E., and Holenberg A. N. (2001) Mol. Endocrinol. 15, 1049–1061
18. Goodwin, B., Hodgson, E., and Liddle, C. (1999) Mol. Pharmacol. 56, 1329–1339
19. Moore, L. B., Parks, D. J., Jones, S. A., Bledsoe, R. C., Conaler, T. G., Stimmel, J. B., Goodwin, B., Liddle, C., Blanchard, S. G., Willson, T. M., Collins, J. L., and Kliwer, S. A. (2000) J. Biol. Chem. 275, 15122–15127
20. Sumida, A., Fukun, S., Yamamoto, I., Matsuda, H., Nanhara, M., and Azuma, J. (2000) Biochem. Biophys. Res. Commun. 276, 756–760
21. Maurice, M., Pichard, L., Dajout, M., Fabre, I., Joyeux, H., Domergue, J., and Maurrel, P. (1992) FASEB J. 6, 752–758
22. Beck, D. J., Stevenson, P., and Tji, J. P. (1989) Br. J. Clin. Pharmacol. 28, 166–170
23. Deleted in proof
24. Staudinger, J. L., Goodwin, B., Jones, S. A., Hawkins-Brown, D., Mackenzie,
Inhibition of SXR-mediated Transcription by Xenobiotics

K. I., LaTour, A., Liu, Y., Klaassen, C. D., Brown, K. K., Reinhard, J., Willson, T. M., Koller, B. H., and Kliewer, S. A. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 3369–3374

25. Xie, W., Radominska-Pandya, A., Shi, Y., Simon, C. M., Nelson, M. C., Ong, E. S., Waxman, D. J., and Evans, R. M. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 3375–3380

26. Liu, Y., Takeshita, A., Nagaya, T., Banahmad, A., Chin, W. W., and Yen, P. M. (1998) Mol. Endocrinol. 12, 34–44

27. Mathur, M., Tucker, P. W., Samuels, H. H. (2001) Mol. Cell. Biol. 21, 2298–2311

28. Takeshita, A., Yen, P. M., Ikeda, M., Cardona, G. R., Liu, Y., Koibuchi, N., Norwitz, E. R., and Chin, W. W. (1998) J. Biol. Chem. 273, 21554–21562

29. Wood, J. R., Likhite, V. S., Loven, M. A., and Nardulli, A. M. (2001) Mol. Endocrinol. 15, 1114–1126

30. Synold, T. W., Dussault, I., and Forman, B. M. (2001) Nat. Med. 7, 584–590

31. Hu, X., and Lazar, M. A. (1999) Nature 402, 93–96

32. Hu, X., Li, Y., and Lazar, M. A. (2001) Mol. Cell. Biol. 21, 1747–1758

33. Webb, P., Anderson, C. M., Valentine, C., Nguyen, P., Marinmutlu, A., West, B. L., Baxter, J. D., and Kashner, P. J. (2000) Mol. Endocrinol. 14, 1976–1985

34. Tagami, T., Lutz, W. H., Kumar, R., and Jameson, J. L. (1998) Biochem. Biophys. Res. Commun. 253, 358–363

35. Smith, C. L., Nawaz, Z., and O’Malley, B. W. (1997) Mol. Endocrinol. 11, 657–666

36. Huang, Y. C., Colaizzi, J. L., Bierman, R. H., Woestenborghs, R., and Heykants, J. (1986) Antimicrob. Agents Chemother. 30, 296–210