Regulation of ATP-binding Cassette Sterol Transporters ABCG5 and ABCG8 by the Liver X Receptors α and β*

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Mutations in the ATP-binding cassette (ABC) transporters ABCG5 and ABCG8 have recently been shown to cause the autosomal recessive disorder sitosterolemia. Here we demonstrate that the ABCG5 and ABCG8 genes are direct targets of the oxysterol receptors liver X receptor (LXR) α and LXRβ. Diets containing high cholesterol markedly increased the expression of ABCG5/G8 mRNA in mouse liver and intestine. This increase was also observed using synthetic ligands of LXR and its heterodimeric partner, the retinoid X receptor. In situ hybridization analyses of tissues from LXR agonist-treated mice revealed that ABCG5/G8 mRNA is located in hepatocytes and enterocytes and is increased upon LXR activation. In addition, expression of the LXR target gene ABCA1, previously implicated in the control of cholesterol absorption, was also dramatically up-regulated in jejunal enterocytes upon exposure to LXR agonists. These changes in ABC transporter gene expression were not observed in mice lacking LXRs. Furthermore, in the rat hepatoma cell line FTO2B, LXR-dependent transcription of the ABCG5/G8 genes was cloheximide-resistant, indicating that these genes are directly regulated by LXRs. The addition of ABCG5 and ABCG8 to the growing list of LXR target genes further supports the notion that LXRs serve as sterol sensors to coordinately regulate sterol catabolism, storage, efflux, and elimination.

Cholesterol homeostasis is maintained by a series of regulatory pathways to control the synthesis of endogenous cholesterol, the absorption of dietary sterol, and the elimination of cholesterol and its catabolic end products, bile acids. Transcriptional control of many genes vital to these processes can be attributed to two families of transcription factors: the sterol regulatory element-binding proteins (SREBPs),1 especially SREBP-2, which control the production of key enzymes in cholesterol biosynthesis (for review, see Ref. 1), and the liver X receptors LXRα and LXRβ, which regulate the expression of genes involved in cholesterol efflux, storage, catabolism, and elimination (for review, see Ref. 2). LXRs are ligand-activated transcription factors that are members of the nuclear hormone receptor superfamily. LXRs are bound and activated by a specific class of naturally occurring oxysterols (3–5) as well as a recently described nonsteroidal synthetic agonist, T0901317 (6, 7). LXRs bind DNA as obligate heterodimers with the retinoid X receptors (RXRs) and can be activated by either LXR agonists or RXR ligands. The RXR/LXR heterodimer binds to a DNA sequence comprised of two direct repeats of the hexanucleotide motif AGGTCA separated by four bases, referred to as an LXR response element of the DR4 type (8). Upon binding ligand, LXR undergoes a conformational change that recruits coactivator proteins and enhances transcription of the target gene.

Increasing evidence suggests that the RXR/LXR heterodimer serves as a sensor that responds to high intracellular sterol concentrations by increasing the expression of genes that reduce the cellular sterol load. In rodents, high cholesterol feeding results in the production of oxysterols in the liver (9) that activate LXRs thereby increasing expression of cholesterol 7α-hydroxylase and promoting cholesterol conversion to bile acids for excretion (10). Mouse lacking LXR proteins accumulate large quantities of esterified cholesterol in their livers following the consumption of dietary cholesterol (10, 11).2 LXRs also play a major role in orchestrating cholesterol efflux from cholesterol-loaded macrophages by up-regulating two ATP-binding cassette transporters, ABCA1 and ABCG1 (6, 12–15), and apolipoprotein E, which serves as an acceptor of effluxed cholesterol in the formation of high density lipoprotein particles (16). LXR activation also promotes the formation of cholesterol esters by increasing expression of SREBP-1c and steroyl-CoA desaturase, resulting in increased production of oleic acid, the preferred substrate for cholesterol esterification (7, 17, 18).

Administration of synthetic LXR or RXR agonists to mice has multiple effects on cholesterol metabolism (7, 17, 19). Serum high density lipoprotein cholesterol and phospholipid levels are increased, and the biosynthesis and secretion of both bile acids and cholesterol are enhanced in treated mice (6, 7).3 Cholesterol absorption is reduced in LXR agonist-treated mice, and this reduction is associated with a dramatic increase in ABCA1 expression in the intestine (6). Moreover, cholesterol absorp-

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1 The abbreviations used are: SREBP, sterol-regulatory element-binding protein; ABC, ATP-binding cassette; LXR, liver X receptor; RXR, retinoid X receptor; mpk, mg/kg of body weight; FXR, farnesoid X receptor; PPAR, peroxisome proliferator-activated receptor.

2 J.-M. Lobaccaro and D. J. Mangelsdorf, unpublished observation.

3 J. Repa, S. Turley, D. Mangelsdorf, and J. Dietschy, unpublished data.

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tion was recently reported to be increased in abca1-knockout mice, suggesting that this ATP-binding cassette transporter may serve to efflux cholesterol back into the intestinal lumen for elimination (6, 20).

Two other members of the ABC transporter family, ABCG5 and ABCG8, have also recently been implicated in mediating the secretion of sterols from the liver and efflux of dietary sterols from the gut. Mutations in either of the genes encoding these two proteins cause the autosomal recessive disorder sitosterolemia (21, 22). The diagnostic finding in this disorder is markedly elevated serum levels of the plant sterol β-sitosterol, which is normally present in only trace amounts (23). Individuals with sitosterolemia exhibit hyperabsorption of β-sitosterol, as well as other sterols, and have markedly reduced secretion of sterols into the bile. The expression of ABCG5 and ABCG8 are both increased in cholesterol-fed mice, suggesting that ABCG5 and ABCG8, as well as ABCA1, are regulated by the LXR-dependent expression of a family of ABC transporters in the liver and intestine.

In this report, we provide unequivocal evidence that ABCG5 and ABCG8 are direct target genes of LXRs in liver and intestine. Furthermore, using in situ hybridization, we show that the levels of ABCG5 and ABCG8, as well as ABCA1, are dramatically increased in hepatocytes and enterocytes treated with an LXR agonist. These data provide strong evidence that the maintenance of dietary sterol homeostasis is coordinately regulated by the LXR-dependent expression of a family of ABC sterol transporters in the liver and intestine.

EXPERIMENTAL PROCEDURES

Materials

Nuclear receptor agonists were obtained from the following sources. Fenofibrate, pregnenolone α-carbonitrile, and chenodeoxycholic acid were purchased from Sigma; troglitazone was a generous gift from Roger Unger (University of Texas Southwestern Medical Center at Dallas); LC268 and GW4064 were provided by Richard Heyman and Rajan Mohan (X-Ceptor Therapeutics, Inc., San Diego, CA); and T9091317 was supplied by Bei Shan (Tularik, South San Francisco, CA). Sodium mevalonate, sodium compactin, and delipidated fetal calf serum were prepared as described previously (24, 25).

Animal Studies

Lxr-knockout mice (6, 12) were maintained on a mixed-strain background (C57BL/6J;129Sv) and housed in a temperature-controlled environment with 12-h light/dark cycles. Mice were fed ad libitum a cereal-based mouse/rat diet (No. 7001, Harlan Teklad, Madison WI) that contained 0.02% cholesterol and 4% total lipid. Diets were supplemented with cholesterol (ICN Biomedicals), vehicle (0.9% carboxymethylcellulose, 9.85% polyethylene glycol, 0.05% Tween 80) added at 3.3 ml/100 g of diet, and/or nuclear receptor agonist. Nuclear receptor agonists were added to diets to provide the appropriate dose (mg/kg of body weight, mpk) on consumption of 5 g of diet by a 25-g mouse per day. There were no changes in food consumption observed by animals fed the various synthetic agonists. Following dietary treatment, mice were anesthetized with Nembutal and exsanguinated prior to organ harvest. The small intestine was removed, flushed with ice-cold saline, and opened lengthwise, and the mucosa were gently scraped and transferred to tubes for flash freezing in liquid nitrogen. In some studies the small intestine was divided into three segments of equal length designated duodenum (proximal), jejunum (medial), and ileum (distal). All experiments were approved by the Institutional Animal Care and Research Advisory Committee.

Northern Analysis

Total RNA was extracted from tissues of individual mice or from cultured cells using RNA STAT-60 (Tel-Test, Inc.) according to the manufacturer’s instructions. Equal amounts of total RNA from the four to six animals per treatment were pooled, and mRNA was isolated using oligo-dT cellulose columns (Pharmacia). 5 μg of poly(A) RNA or 10 μg of total RNA were size-fractionated on 1% agarose, formaldehyde gels for 18794 h and transferred to nylon membranes (Zetaprobe, BioRad). Hybridizations were performed using 32P-labeled cDNA probes for mouse or rat ABCG5 and ABCG8 (21), mouse SREBP-1 (26), and β-actin or glyceraldehyde-3-phosphate dehydrogenase. The amount of radioactivity in each band was quantitated by phosphorimaging and normalized to the signal of β-actin or glyceraldehyde-3-phosphate dehydrogenase.

Real-time PCR Analysis

Total RNA was prepared from FTO2B hepatoma cells using RNA STAT-60 (Tel-Test, Inc.), treated with DNase I (RNase-free, Roche Molecular Biochemicals), and reverse-transcribed with random hexamers using the SuperScript II First-Strand Synthesis System (Invitrogen) to generate cDNA. Primers for each gene were designed using Primer Express Software (PerkinElmer Life Sciences) based on sequence data available through GenBank (accession numbers in parentheses): rat glyceroldehyde-3-phosphate dehydrogenase (AF106860): forward 5′-GAGGTTGAGCCGATCTCTTTG, reverse 5′-CCGACCTTCACATCTGTGC; rat ABCG5 (AF132174): forward 5′-CCGGTTGCTAAAGCTTCCA, reverse 5′-GGAACGACATTTGGAATACC. The real-time PCR contained, in a final volume of 10 μl, 25 ng of reverse-transcribed total RNA, a 150 nm concentration of each primer, and 5 μl of 2× SYBR Green PCR Master Mix (Applied Biosystems). All PCRs were performed in triplicate on an Applied Biosystems Prism 7900HT Sequence Detection System, and relative mRNA levels were calculated using the comparative C(T) method.3 Primers were validated by analysis of a standard curve and dissociation curve for each primer pair in a template titration assay. In addition, real-time PCR results were confirmed by comparison to a Northern analysis for a single experiment.

In situ Hybridization

Probes—cDNA fragments encompassing the 3′-untranslated regions of mouse ABCG5 and ABCG8 were amplified by PCR and subcloned into pGEM in both orientations to allow the synthesis of RNA riboprobes using the T7 promoter. PCR primers for mouse ABCG5 were 5′-ATCCAAACCTCTGATGTTAAC (forward) and 5′-TACATT-TGGACCAGTGTCGGC (reverse) to generate a 411-bp fragment. Primers for mouse ABCG8 were 5′-ACAGGCTCACAGCAGTCTCTCA (forward) and 5′-TATAATGTGGTTCCTTCCACTGACT (reverse) to produce a 212-bp cDNA. A 413-bp cDNA fragment of mouse ABCA1 containing nucleotides 390–892 (GenBank accession number NM 013454) and flanked by BamHI and XhoI sites was generated by PCR using the primers 5′-CGGATCTCTGTCATGCTAC (forward) and 5′-CCGCTCGAGAGACCTAGTTCCAGATGCC (reverse). Ligating this fragment into pBSK (1) allowed production of both antisense (T3/BamHI) and sense (T7/XhoI) in situ probes. RNA riboprobes were generated by in vitro transcription with the Ambion Megascript kit (Austin, TX) in the presence of [γ-32P]UTP (Amersham Biosciences, >1000 Ci/mmol). Probes were purified over G50 spin columns and evaluated by diagnostic polyacrylamide gel electrophoresis.

Tissues—Tissues were harvested from A129 strain male mice following a 16-h dietary treatment (see “Animal Studies” for diet information). Organs were removed from anesthetized mice after transcardial perfusion with cold heparinized diphosphoryl glycerol-saline solution followed by chilled 4% paraformaldehyde, diethyl pyrocarbonate-phosphate-buffered saline. Tissues were fixed for 16 h in paraformaldehyde, transferred to diethyl pyrocarbonate-saline, then dehydrated, paraffin-embedded, and sectioned.

In situ hybridization was performed as described previously (27). Optimal autoradiographic exposure of the slides was achieved at 14 days for ABCG5 and ABCG8 probes and 21 days for the ABCA1 antisense riboprobe. Control slides using sense riboprobes were evaluated at those times and gave no significant signals.

Cell Culture

The rat hepatoma cell line FTO2B (28) was maintained in Dulbecco’s modified Eagle’s medium/F12 containing glutamine and 5% fetal calf serum at 37 °C in an 8% CO2 incubator. Cells were plated at 700,000/10-cm dish and allowed to adhere overnight. The following morning, the cells were washed, and the sterol depletion medium was as described by DeBose-Boyd et al. (29) (Dulbecco’s modified Eagle’s medium/F12 + 5% delipidated fetal calf serum + 50 μM mevalonate) for 6 h before the addition of 10 μM T0901317, 10 μM GW4064, 100 μM chenodeoxycholic acid, and/or 500 μM cycloheximide. Cells were harvested at various times later, and RNA was extracted for Northern analysis. Similar results were observed with the rat hepa-

3 User Bulletin No. 2, PerkinElmer Life Sciences.
A reproducible increase in expression of these genes was also maintained in the \( \text{lxr}\beta \)-knockout mice demonstrating that sterol up-regulation of \( \text{ABCG5/8} \) requires \( \text{LXR}\). The apparent \( \text{LXR}\)-specific response may be due to the greater abundance of \( \text{LXR}\alpha \) than \( \text{LXR}\beta \) in the liver (31). Alternatively \( \text{LXR}\alpha \) may exhibit a higher activity than \( \text{LXR}\beta \) in activating these genes (10). Similar trends in hepatic gene expression have been observed for other \( \text{LXR} \) target genes such as cholesterol 7a-hydroxylase, which is dependent on \( \text{LXR}\alpha \), but not \( \text{LXR}\beta \), expression (10).

An \( \text{LXR}\)-dependent increase in \( \text{ABCG5} \) and \( \text{ABCG8} \) mRNA expression was also observed in the duodenum, jejunum, and ileum of cholesterol-fed wild-type mice (Fig. 2). Interestingly the expression levels of \( \text{ABCG5} \) and \( \text{ABCG8} \) were higher in tissues of \( \text{lxra}\beta^{−/−} \) mice than wild-type mice fed control diets (Figs. 1 and 2). This increase in expression in \( \text{lxra}\beta^{−/−} \)-knockout mice has also been observed for other \( \text{ABC} \) transporters identified as \( \text{LXR} \) target genes such as \( \text{ABCA1} \) and \( \text{ABCG1} \) (6, 15).

The dietary cholesterol-induced increase in \( \text{ABCG5} \) and \( \text{ABCG8} \) expression observed only in mice harboring \( \text{LXR}\alpha \) identified as \( \text{LXR} \) target genes such as \( \text{ABCA1} \) and \( \text{ABCG1} \) (6, 15). The dietary cholesterol-induced increase in \( \text{ABCG5} \) and \( \text{ABCG8} \) expression observed only in mice harboring \( \text{LXR}\alpha \) suggested these genes were primary targets of the \( \text{RXR/\text{LXR}} \) heterodimer. To determine the specificity of this effect, wild-type mice were treated for 12 days with a series of synthetic agonists for a variety of nuclear hormone receptors (Fig. 3). This treatment protocol was previously shown to elicit increases in RNA levels of target genes for each of these nuclear receptors (6). Both the \( \text{RXR}\)-specific agonist LG268 (32) and the \( \text{LXR}\)-specific agonist T0901317 (7) caused coordinate up-regulation of \( \text{ABCG5} \) and \( \text{ABCG8} \) mRNA expression in liver and intestine (Figs. 3 and 4).

A reproducible increase in expression of these genes was also
LXR Regulation of ABCG5 and ABCG8

FIG. 3. ABCG5 and ABCG8 mRNA levels in liver and duodenum of mice fed synthetic agonists of various nuclear hormone receptors. Male A129 strain mice were fed diets containing 0.2% cholesterol plus vehicle or the following agonists for 12 h: 30 mpk LG268 (RXR), 1000 mpk fenofibrate (PPARα), 150 mpk troglitazone (PPARγ), 100 mpk pregnenolone α-carbonitrile (FXR), 1000 mpk chenodeoxycholic acid (LXR), or 50 mpk T0901317 (LXR). Northern analyses were performed on 5 μg of mRNA/lane prepared from pooled RNA of four mice per group. RNA was quantified by phosphorimaging and standardized against β-actin (results for the lower bands of ABCG5 and ABCG8 are shown; upper bands gave very similar relative expression changes).
Under conditions of cellular sterol loading or LXR/RXR agonist administration, liver cells exhibit an LXR-dependent increase in the transcription of ABCG5/G8 mRNA. Furthermore we show that ABCG5/G8 genes are direct targets of LXR action since transcriptional up-regulation of these genes does not require new protein synthesis. The ABCG5 and -G8 genes sit adjacent to one another, and both genes are transcribed in opposite directions from independent transcription start sites that are separated by only ~150 bp of intergenic sequence that does not contain an LXR response element (21). Similar to other paired genes, it is likely that the regulatory elements for these two genes are in adjacent introns or are located far from the coding regions of the genes (37–39). Alternatively it is possible that LXR may be affecting transcription in a novel manner through protein-protein interactions with another transcription factor. Future studies will be required to characterize these regulatory regions and possibly identify an LXR response element.

Our studies show that other nuclear receptors are also capable of regulating liver-specific expression of ABCG5/G8. Of notable interest is the apparent up-regulation by the bile acid receptor FXR. However, in contrast to the LXR response, the transcriptional response mediated by FXR is indirect, indicating a secondary mechanism that requires synthesis of other regulatory factors. This bile acid-mediated response was observed only in the liver and not in the intestine, although FXR is present in both tissues. This suggests that the factor induced by FXR is produced or functional only in hepatocytes.

The inclusion of ABCG5 and ABCG8 to the growing list of LXR target genes provides further evidence that the RXR/LXR heterodimer is an intracellular sterol sensor that up-regulates the expression of genes involved in cholesterol elimination and reverse cholesterol transport. In peripheral cells, particularly macrophages, LXR-mediated up-regulation of ABCA1, ABCG1, and apolipoprotein E promotes the efflux of free cholesterol and phospholipids to produce high density lipoprotein particles. High density lipoprotein cholesterol is then delivered to the liver where an LXR-dependent increase in cholesterol 7α-hydroxylase expression results in enhanced bile acid synthesis and elimination. Increased biliary excretion and decreased in-
FIG. 5. Localization of ABCG5, ABCG8, and ABCA1 mRNA in the mouse liver and small intestine by in situ hybridization. Male A129 strain mice were fed for 16 h diets containing vehicle or the LXR agonist T0901317 (50 mpk). The expression patterns of ABCG5, ABCG8, and ABCA1 mRNA were visualized by dark field microscopy following hybridization with antisense 35S-labeled riboprobes. The right panels display the hematoxylin staining, revealed by bright field microscopy, of the LXR agonist-treated samples shown in adjacent panels. All tissues were negative with the corresponding sense riboprobes (data not shown). LP, lamina propria. Solid arrows indicate red blood cells that refract light by dark field illumination but do not show silver grains indicative of specific riboprobe hybridization. Magnification of view is ×10 for jejunum and ×20 for liver.
Although the relative roles of ABCA1 and ABCG5/G8 in cholesterol efflux from the gut have yet to be clearly defined, our work provides unequivocal data that demonstrate ABCA1, -G5, and -G8 are expressed in enterocytes and are strongly up-regulated by LXR agonists. Under basal conditions (i.e., in the absence of dietary cholesterol or RXR/LXR agonists) ABCA1 expression is relatively weak in the absorptive cells of mice (Fig. 5) and primates (34). An initial report showing increased cholesterol absorption efficiency by abca1−/− mice (20) has recently been contradicted by analysis of a second abca1-knockout mouse strain fed a low cholesterol diet (41), leaving the question open on the role of ABCA1 in regulating cholesterol absorption in chow-fed animals. However, the strong up-regulation of ABCA1 in enterocytes, accompanied by a decrease in the efficiency of cholesterol absorption in the cholesterol-fed and/or RXR/LXR agonist-treated mice, suggests that ABCA1 may play a role in cholesterol absorption under high cholesterol or pharmacologic conditions (Fig. 5 and Ref. 6). Further studies will be required in abcg5/8-knockout mice and abca1-knockout mice treated with LXR agonists to firmly establish the relative roles of these three ABC transporters in cholesterol absorption.

The recent identification of genes in which mutations result in human disorders involving cholesterol homeostasis has opened the exciting opportunity to study the mechanisms of these gene products and their modes of regulation in normal, pathologic, and pharmacologic states. Concurrent up-regulation of ABCG5 and ABCG8 promotes biliary sterol secretion, and in the intestine the LXR-mediated up-regulation of ABCA1, ABCG5, and ABCG8 prohibits the absorption of luminal cholesterol thereby resulting in net cholesterol loss from the body. These actions point to the therapeutic potential of LXR agonists in the treatment of atherosclerosis and other disorders of hypercholesterolemia.

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