Recent studies have identified the liver X receptors (LXRs and LXRβ) as important regulators of cholesterol and lipid metabolism. Although originally identified as liver-enriched transcription factors, LXRs are also expressed in skeletal muscle, a tissue that accounts for ~40% of human total body weight and is the major site of glucose utilization and fatty acid oxidation. Nevertheless, no studies have yet addressed the functional role of LXRs in muscle. In this work, we utilize a combination of in vivo and in vitro analysis to demonstrate that LXRs can functionally regulate genes involved in cholesterol metabolism in skeletal muscle. Furthermore, we show that treatment of muscle cells in vitro with synthetic agonists of LXR increases the efflux of intracellular cholesterol to extracellular acceptors such as high density lipoprotein, thus identifying this tissue as a potential important regulator of reverse cholesterol transport and high density lipoprotein levels. Additionally, we demonstrate that LXRs and a subset of LXR target genes are induced during myogenesis, suggesting a role for LXR-dependent signaling in the differentiation process.

Disorders of cholesterol and lipid metabolism are associated with cardiovascular disease, obesity, diabetes, and hypertension. Not surprisingly, organisms have developed exquisite regulatory networks that ensure lipid homeostasis is maintained by controlling dietary intake, de novo synthesis, transport, and catabolism. For instance, numerous studies over the past five years have identified members of the nuclear hormone receptor superfamily of ligand-dependent transcription factors as important regulators of the genes involved in cholesterol and lipid metabolism (3). In particular, the peroxisome proliferator-activated receptors (PPARs, β, γ), the farnesoid X receptor, and the liver X receptors (LXRs and LXRβ) are transcription factors whose activity can be controlled by the direct binding of fatty acids (PPARs and LXRs) and cholesterol derivatives (LXRs and farnesoid X receptor). Thus, these transcription factors are poised to sense changes in the intracellular concentrations of lipids and cholesterol and to regulate cellular metabolism accordingly (3, 4).

Recently several studies have demonstrated that the LXRs play a dynamic role in the regulation of genes involved in cholesterol and fatty acid metabolism. LXRs bind to DNA as obligate heterodimers with retinoid X receptors and directly bind cholesterol metabolites and fatty acids (5, 6). Interestingly, cholesterol derivatives and fatty acids have opposing effects on LXR transcriptional activity. Oxy steroids including 24(S), 25-epoxycholesterol, 22(R)-hydroxycholesterol, and 24(S)-hydroxycholesterol are activators of LXR and increase transcription of genes involved in sterol transport including the ATP binding cassette transporters ABCA1, ABCG1, ABCG5, and ABCG8 and the apolipoprotein apoE (7–11). The importance of these LXR target genes to sterol metabolism has recently been highlighted by linkage of ABCA1 to Tangier disease and ABCG5 together with ABCG8 to sitosterolemia, both human genetic syndromes characterized by perturbed cholesterol transport (12–16). Strikingly, mutations in ABCA1 that give rise to Tangier disease result in an almost complete absence of HDL cholesterol and promote accumulation of cholesterol within peripheral tissues. Biochemical analysis of ABCA1 indicates that it mediates the transport of intracellular cholesterol and phospholipids to extracellular acceptors such as HDL, a process termed reverse cholesterol transport (17–19). LXR agonists also increase expression of CYP7a1, the gene encoding cholesterol 7α hydroxylase, which is the rate-limiting enzyme in the metabolic conversion of cholesterol to bile acids (20). Thus, under conditions of elevated cholesterol, LXRs promote the transfer of cholesterol from the periphery to the liver for catabolism and excretion. Furthermore, up-regulation of ABCA1, ABCG5, and ABCG8 in the intestine by LXRs limits the absorption of sterols by promoting efflux from enterocytes to the lumen, resulting in an overall decrease in cholesterol loads (8).

Along with the effects on cholesterol metabolism, LXR agonists also increase expression of genes involved in fatty acid metabolism, including the master transcriptional regulator of fatty acid synthesis, the sterol response element-binding protein 1c (SREBP1c) (1, 21, 22). Additionally, several of the genes encoding the enzymes involved in fatty acid metabolism, including fatty acid synthase (FAS) and stearoyl-CoA desaturase 1 (SCD-1), are regulated directly or indirectly by LXR (1, 20, 21, 23). The coordinate up-regulation of fatty acid synthesis with
reverse cholesterol transport is most likely to provide lipids for the transport and storage of cholesterol. In contrast, however, to the agonist activity of cholesterol metabolites, fatty acids act as antagonists of LXR transcriptional activity, suggesting the possibility of a negative feedback loop whereby the metabolic end product inhibits the inducer (5).

Skeletal muscle accounts for 40% of adult total body weight and relies on the balance of glucose and fatty acid oxidation. Importantly, insulin regulates the balance between glucose and fatty acid utilization in this tissue, and increased fatty acid oxidation in skeletal muscle is a hallmark of type II diabetes. Although LXRs have been shown to be important regulators of hepatic fatty acid metabolism, the function of these transcription factors in muscle has not been well addressed. Nevertheless, given the recent interest in LXR ligands as potential therapeutic agents for the treatment of disorders of cholesterol and lipid metabolism, the contribution of this major mass tissue to LXR action must be defined. In this study we used in vivo analysis in wild type and LXR knockout mice along with the well defined C2C12 skeletal muscle cell culture model to characterize LXR activity in muscle. The results of this work identify skeletal muscle as an important site of LXR activity.

EXPERIMENTAL PROCEDURES

**In Vivo Analysis—** Homozygous LXRβ-double knockout mice (LXRβ−/−) were from a breeding colony established and maintained at X-Ceptor Therapeutics Inc. Mice were fed ad libitum. The LXR agonist T0901317 (1) was administered by daily oral gavage in a sesame oil/ethanol vehicle via a 1-cc syringe fitted with a 20-gauge disposable feeding needle for 7 days. Compound was solubilized in ethanol (5% final volume) and brought up to final volume with sesame oil (Sigma). Plasma triglyceride levels were measured using an enzymatic assay and the supplier’s protocols (Sigma).

**Reporter Plasmids—** Luciferase reporter plasmids were constructed by PCR amplification of the human ABCA1 promoter (−621 to −45) and the mouse SREBP1c promoter (−543 to −39) and cloning into pGL3-basic (Promega, Madison, WI).

**C2C12 Cell Culture and Transient Transfection Assays—** Mouse myogenic C2 cells were grown in Dulbecco’s modified Eagle’s medium supplemented with 20% fetal bovine serum in 5% CO2. Cells were induced to biochemically and morphologically differentiate into multinucleated myotubes by mitogen withdrawal (Dulbecco’s modified Eagle’s medium supplemented with 2% horse serum) as previously described (2). Differentiation was essentially complete within 96 h with respect to the cytoskeletal and contractile isofrom transition. For transient transfections, cells were grown in 24-well dishes to 60–70% confluence and transfected with 0.5–0.8 μg/well of the pGL3b-LUC, SREBP1c-LUC, or ABC1c-LUC reporter constructs using a DOTAP/DOSPER mixture of 16–20 μg of DNA supplemented with 60 μl of DOTAP and 40 μl of DOSPER in 200 μl of 1X HEBS buffer was incubated for 10 min at room temperature and mixed with 14.4 μl of fresh Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum or 2% horse serum. Subsequently, 0.6 ml/well of the DNA/DOTAP/DOSPER mixture was added to the cells and incubated for 16–24 h. Post-transfection, the medium was replaced, and the cells were grown a further 48 h. Cells were harvested and assayed for luciferase activity. The luciferase activity in sample was normalized by determining β-galactosidase activity. Each experiment represented at least two sets of independent triplicates to overcome the variability inherent in transfection experiments.

**Quantitative Reverse Transcription-PCR—** Total RNA from mouse tissues and C2C12 cells was isolated using RNAeasy kits (Qiagen Inc.) according to the supplier’s total RNA isolation procedure. Real-time PCR was performed using a PerkinElmer/ABI 7700 prism. RNA samples were incubated with 1 unit RNase-free DNase (Roche Molecular Biochemicals) per 1.6 μg of RNA at 37 °C for 10 min at 37 °C. Reverse transcription was performed at 75 °C. For each target quadruplicate reactions, each containing 100 ng of total RNA (including one minus reverse transcriptase control), were utilized. RNA was reverse-transcribed using 10 units of Superscript II reverse transcriptase (Invitrogen), 400 nM target-specific reverse primer, 500 μM dNTPs, 10 mM dithiothreitol, and 1X Superscript II buffer. Quantitative PCR of reverse transcriptase reactions was carried out with 1.25 units of Taq polymerase (Invitrogen), 1X Taq buffer, 3 mM MgCl2, 200 μM dNTPs, 400 nM target-specific forward and reverse primers, and 100 nM target-specific fluorogenic probe. All assays were run for 40 cycles (95 °C for 12 s followed by 60 °C for 60 s). Probes and primers were designed using Primer Express (Applied Biosystems, Inc.). Levels of cyclophilin were measured in all in vivo samples, and the results are presented as the number of target transcripts per cyclophilin transcript. GAPDH was used to normalize transcript levels in the experiments using C2C12 cells.

**Cholesterol Efflux—** C2C12 cells were differentiated as described above for 48 h and then labeled with [3H]cholesterol for an additional 48 h. Labeled cells were washed, and efflux was initiated in medium with or without 10 μg/ml apoAI in the absence or presence of receptor-specific ligands. After 24 h, media were removed, cell debris was pelleted, and radioactivity in the media was determined by scintillation counting. To determine the cell-associated radioactivity, cells were lysed in 0.2 M sodium hydroxide, and radioactivity was determined by scintillation counting. Percent efflux was calculated by dividing the radioactivity in the media by the sum of the radioactivity in the media and cell lysate. ApoAI-dependent efflux was determined by subtracting the efflux observed in the absence of added apoAI.

**Statistical Analysis—** Statistical analysis was carried out using a two-tailed unpaired t-test.

**RESULTS**

**Regulation of LXR Target Genes in Muscle—** Treatment of rodents with synthetic LXR agonists has been shown to increase expression of genes involved in cholesterol and lipid metabolism in liver, intestine, and adipose tissue (1, 7–11, 21, 29). To examine the activity of LXR in skeletal muscle, we first quantitated the mRNA levels of LRXα and LRXRβ in the quadriceps of mice and determined that LRXα and LRXRβ are expressed in skeletal muscle at similar levels (Fig. 1A). To further determine functional activity of skeletal muscle, wild type and LRXRβ−/− mice were treated with the synthetic LXR agonist T0901317 (1) for 7 days. After treatment, total RNA was isolated from quadriceps, and LXR-dependent gene expression was measured by quantitative real-time PCR. As shown in Fig. 1, B–F, treatment with LXR agonist increases the mRNAs encoding known LXR target genes including ABCA1 (4.5-fold), SREBP1c (8.3-fold), and apoE (2.3-fold). In contrast to what has been observed in livers of treated mice (1, 8, 21), the mRNAs encoding SCD-1 and FAS are not induced by LXR agonist treatment in muscle. Nevertheless, SCD-1 and FAS are significantly induced by LXR agonist treatment in the livers of these same animals (Fig. 2). LXR agonist-dependent induction of genes involved in fatty acid synthesis in the liver most likely account for the increase plasma triglyceride levels observed in agonist-treated mice (Fig. 2D). As expected, all agonist-dependent effects on gene expression are completely eliminated in LXRβ−/− mice.

The results of Fig. 1 indicate that skeletal muscle is responsive to LXR ligands. Studies in vivo, however, do not rule out the possibility that effects on skeletal muscle gene expression are indirect, arising from the ability of LXR agonists to influence cholesterol and lipid metabolism in other tissues. To confirm that LXR is active in skeletal muscle we turned to the well established mouse C2C12 myoblast cell line as a model. Proliferating C2C12 myoblasts can be induced to biochemically and morphologically differentiate into post-mitotic multinucleated myotubes by serum withdrawal in culture over a 96-h period. This transition from a non-muscle phenotype to contractile phenotype is associated with the repression of non-muscle proteins and the activation of the contractile apparatus and metabolic enzymes. Treatment of differentiated myotubes (72 h after serum withdrawal) with T0901317-induced expression of LXR target genes involved in reverse cholesterol transport including ABCA1, ABCG1, a second ABC transporter impli-
LXR Activity in Skeletal Muscle

Fig. 1. Expression of LXRs and LXR target genes in skeletal muscle. LXRβ+/− and LXRβ−/− mice (n = 4) were treated for 7 days in the absence (white bars) or presence (black bars) of the LXR agonist T0901317 (10 mg/kg), and total RNA was isolated from the quadriceps. Expression of the mRNAs encoding LXRs and LXRα (A), ABCA1 (B), apoE (C), SREBP1c (D), SCD-1 (E), and FAS (F) was determined by real-time quantitative PCR. Levels of cyclophilin were measured in all samples, and the results are presented as the number of target transcripts per cyclophilin transcript. RNA from each individual animal was assayed in quadruplicate. p values indicate statistically significant differences between vehicle- and T0901317-treated animals.

Fig. 2. LXR agonist-dependent induction of SCD-1 and FAS in the liver. LXRα+/+ and LXRα−/− mice (n = 4, the same mice used in Fig. 1) were treated for 7 days in the absence (white bars) or presence (black bars) of the LXR agonist T0901317 (10 mg/kg), and total RNA was isolated from the liver. Expression of the mRNAs encoding SREBP1c (A), SCD-1 (B), and FAS (C) was determined by real-time quantitative PCR. Levels of cyclophilin were measured in all samples, and the results are presented as the number of target transcripts per cyclophilin transcript. RNA from each individual animal was assayed in quadruplicate. Plasma triglyceride levels (D) were determined as described under “Experimental Procedures.” p values indicate statistically significant differences between vehicle- and T0901317-treated animals.

Regulation of Cholesterol Efflux in C2C12 Cells—ABCA1 has been shown to be essential for the transfer of intracellular cholesterol to extracellular acceptors such as HDL, a process termed reverse cholesterol transport (17, 24, 25). The importance of ABCA1 to reverse cholesterol transport is illustrated by the finding that inactivation of ABCA1 in humans results in HDL deficiencies (17–19, 25). Similarly, overexpression of ABCA1 has been shown to elevate HDL by increasing reverse cholesterol transport (26–28). To date, most studies of reverse cholesterol transport have been carried out in fibroblasts and macrophages. Nevertheless, given the ability of LXRs to regulate ABCA1 expression in muscle, promoter-reporter constructs were transfected into proliferating C2C12 myoblasts, and the cells were allowed to differentiate in the absence or presence of LXR agonist. As shown in Fig. 4, there is a dramatic ligand-dependent induction of both promoters, indicating a direct action of endogenous LXRs on SREBP1c and ABCA1 in muscle cells.

Promoter-Reported Gene Activation by LXRs in Myoblasts—To explore the role of LXRs in myoblasts, LXRα and LXRβ promoters were fused to luciferase reporter constructs and transfected into proliferating C2C12 myoblasts, and the cells were allowed to differentiate in the absence or presence of LXR agonist. As shown in Fig. 5, there is a dramatic ligand-dependent induction of both promoters, indicating a direct action of endogenous LXRs on SREBP1c and ABCA1 in muscle cells, promoter-reporter constructs were transfected into proliferating C2C12 myoblasts, and the cells were allowed to differentiate in the absence or presence of LXR agonist. As shown in Fig. 4, there is a dramatic ligand-dependent induction of both promoters, indicating a direct action of endogenous LXRs on SREBP1c and ABCA1 in muscle cells.
differentiation of monocytes to macrophages, indicating an important role for this receptor in macrophage biology (29–31). To examine LXR activity during skeletal myogenesis, expression levels of LXRα/H9251 and LXRβ/H9252 were measured in differentiating C2C12 cells (Fig. 6). LXRα is induced beginning when cells reach confluence (Fig. 6A, CMB) and peaking as myoblasts exit the cell cycle and form differentiated multinucleated cells (Fig. 6A, MT1), suggesting a role for this isotype in the myogenic process. In contrast, LXRβ mRNA is constitutively expressed during myogenic differentiation in culture and is 200-fold more abundant than LXRα in proliferating myoblasts (Fig. 6B). Northern analysis demonstrates the induction of myogenin mRNA (encoding the basic HLH protein), repression of the cytoskeletal non-muscle β/γ-actin mRNAs, and the activation of the sarcomeric α-actins relative to equivalent levels of GAPDH mRNA, confirming that these cells had terminally differentiated (Fig. 6C).

Analysis of LXR targets during myogenesis indicates that genes involved in reverse cholesterol transport (ABCA1, ABCG1, and apoE) are also induced from 4.7- to 29-fold (Fig. 7, A–C) during the differentiation process in the absence of added exogenous LXR ligands. The kinetics of the ABCA1, ABCG1, and apoE lag slightly behind the induction of LXRα and, thus, are consistent with the hypothesis that LXRα plays a role in inducing these genes. The LXR targets involved in lipogenesis (SREBP1c, SCD-1, and FAS), however, are poorly, if at all, induced during differentiation (Fig. 7, D–F). This observation is particularly interesting for SREBP1c and FAS, which have recently been shown to be directly regulated by LXRα (1, 21, 23). Nevertheless, treatment of differentiating C2C12 cells...
with LXR ligands increases the mRNAs for all LXR target genes examined including SREBP1c, SCD-1, and FAS (Fig. 2 and data not shown), indicating that endogenous LXRs are competent to activate these targets during myogenesis if a potent agonist is available. These observations suggest, at least during myogenesis, that the regulation of these two functional classes of LXR targets (cholesterol transport and fatty acid synthesis) can be temporally and mechanistically separated.

**DISCUSSION**

In this study we demonstrate that both LXRα and LXRβ are expressed in skeletal muscle and can be functionally regulated by LXR agonists. The ability of LXRs to induce reverse cholesterol transport in skeletal muscle, most likely via the up-regulation of ABCA1, ABCG1, and apoE, suggests that this major mass tissue can make significant contributions to whole body cholesterol homeostasis. We have not detected LXR agonist-dependent effects on the expression of 3-hydroxy-3-methylglutaryl-CoA reductase in muscle, indicating that increased reverse cholesterol transport is not stimulating de novo cholesterol synthesis (data not shown). Not surprisingly, the ability of LXR agonists to promote reverse cholesterol transport has stimulated great interest in the potential of small molecule activators of LXRs as therapeutic agents for the treatment of cardiovascular disease (3, 4). Previous studies, however, focus on the therapeutic benefit of regulating reverse cholesterol transport...
transport in macrophage foam cells, a cell-type that directly contributes to atherosclerotic lesion development (32). Based on the overall mass of skeletal muscle, our work also identifies this tissue as an important site of action for LXR-based drugs.

LRXs also regulate fatty acid metabolism by controlling expression of SREBP1c, the master transcriptional regulator of fatty acid synthesis, and the enzymes that participate in this metabolic pathway (1, 21, 22). Not surprisingly, treatment of experimental animals with LXR agonists results in significant increases in hepatic and serum triglycerides (1). The ability of LXRs to regulate fatty acid metabolism in skeletal muscle has important consequences for carbohydrate and lipid homeostasis. In response to insulin, skeletal muscle accounts for the majority of glucose uptake in the body. Insulin also induces SREBP1c expression in skeletal muscle, and this regulation is important for carbohydrate and lipid homeostasis (1, 21, 22). Not surprisingly, treatment of these two classes of LXR target genes observed in skeletal muscle and during myogenesis, however, suggests that there are mechanistic differences in the regulation of each target class that can be exploited for drug development. Future studies that define the mechanistic basis for this differential regulation will contribute to our understanding of biological function of LXR and assist in the development of effective LXR-based therapeutic agents.

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