Cholesterol is an essential component of eukaryotic cells; at the same time, however, hyperaccumulation of cholesterol is harmful. Therefore, the ABCA1 gene, the product of which mediates secretion of cholesterol, is highly regulated at both the transcriptional and post-transcriptional levels. The transcription of ABCA1 is regulated by intracellular oxysterol concentrations via the nuclear liver X receptor (LXR)/retinoid X receptor (RXR); once synthesized, ABCA1 protein turns over rapidly with a half-life of 1–2 h. Here, we show that the LXRβ/RXR complex binds directly to ABCA1 on the plasma membrane of macrophages and modulates cholesterol secretion. When cholesterol does not accumulate, ABCA1-LXRβ/RXR localizes on the plasma membrane, but is inert. When cholesterol accumulates, oxysterols bind to LXRβ, and the LXRβ/RXR complex dissociates from ABCA1, restoring ABCA1 activity and allowing apoA-I-dependent cholesterol secretion. LXRβ can exert an immediate post-translational response, as well as a rather slow transcriptional response, to changes in cellular cholesterol accumulation. Thus, we provide the first demonstration that protein-protein interaction suppresses ABCA1 function. Furthermore, we show that LXRβ is involved in both the transcriptional and post-transcriptional regulation of the ABCA1 transporter.

Maintenance of cellular cholesterol homeostasis is important for normal human physiology. Disruption of cellular cholesterol homeostasis leads to a variety of pathological conditions, including cardiovascular disease (1). ABCA1 (ATP-binding cassette protein A1), one of the key proteins in cholesterol homeostasis, mediates secretion of cellular free cholesterol and phospholipids to an extracellular acceptor in the plasma, apoA-I, to form high density lipoprotein (HDL) (2, 3). HDL formation is the only known pathway that can eliminate excess cholesterol from peripheral cells. Defects in ABCA1 cause Tangier disease (4–6), in which patients have a near absence of circulating HDL, prominent cholesterol ester accumulation in tissue macrophages, and premature atherosclerotic vascular disease (1, 7).

ABCA1-mediated cholesterol efflux is highly regulated at both the transcriptional and post-transcriptional levels. When cholesterol accumulates in cells, intracellular concentrations of oxysterols increase; subsequently, the liver X receptor (LXR), activated via binding of oxysterols, stimulates the transcription of ABCA1 (8–10). ABCA1 protein eliminates excess cellular cholesterol and turns over rapidly with a half-life of 1–2 h (11–15). Several proteins, including apoA-I, α-syntrophin, and β1-syntrophin, have been reported to interact with ABCA1 and reduce the rate of ABCA1 protein degradation (13–16). Syntrophins play critical roles in regulating the apoA-I-dependent cholesterol efflux (and thus in lipid homeostasis) by suppressing protein degradation in brain (14) and liver (15). Because cholesterol is an essential component of cells, however, excessive elimination of cholesterol could result in cell death. Consequently, the ability to rapidly degrade ABCA1, to prevent cholesterol efflux, is also important.

We performed a yeast two-hybrid screen to search for additional proteins associated with the C-terminal region of ABCA1. The screen identified a nuclear receptor, LXRβ, as a candidate that associates with the C-terminal 120 amino acids of human ABCA1. In WI-38 and THP-1 cells, endogenous LXRβ interacts with ABCA1 under conditions in which cholesterol does not accumulate, i.e. when cholesterol is not in excess. LXRβ suppresses ABCA1-mediated cholesterol efflux and thereby blocks HDL formation. This study is the first to show that protein-protein interaction suppresses the function of ABCA1 and that LXRβ is involved not only in the transcriptional regulation but also in the post-translational regulation of ABCA1.

**EXPERIMENTAL PROCEDURES**

**Plasmids—cDNAs encoding human LXRα (NCBI Database accession number NM_005693) and human LXRβ (accession...**
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number NM_007121) were inserted into the p401 vector or pGEX-4T1 (Amersham Biosciences).

Antibodies—The linker region (amino acids 1134–1345) of human ABCA1 was fused with glutathione S-transferase, and the fusion protein was expressed in Escherichia coli strain BL21. The fusion protein was purified and used to raise rabbit polyclonal antibodies. Anti-LXRα (PP-K8607-00), anti-LXRβ (PP-K8917-00), and anti-retinoid X receptor (RXR; PP-K8508-00) monoclonal antibodies were purchased from Perseus Proteomics.

Cell Culture and Transfection—THP-1 cells were maintained in RPMI 1640 medium (Sigma) containing 10% fetal bovine serum under a humidified atmosphere of 5% CO₂ and 95% air at 37 °C. Differentiation into macrophages was achieved by exposing cells to 50 ng/ml phorbol 12-myristate 13-acetate for 18 h of incubation, cells were transfected with ABCA1 and LXRα, or LXRβ. Cells were lysed with phosphate-buffered saline containing 1% Tween 20 and protease inhibitors at 4 °C for 15 min. The nucleus was precipitated by centrifugation (2800 × g), and the supernatant were collected as the cytosolic fraction. The pellet was disrupted in the presence of 1% SDS using a sonicator.

RNA Interference—Small interfering RNAs (siRNAs) specific for LXRα (siNR1H3, GAGGCUCGAGCAGCAUAUGUG-GAA (sense)), LXRβ (siNR1H3, GCUCAACACCAGAGCA-GAGUGUAA (sense)), and a scrambled control were obtained from Invitrogen. WI-38 cells were transfected for 72 h with 120 nm siRNAs using RNAiMAX (Invitrogen).

RESULTS

ABCA1 Interacts with Nuclear LXRα and LXRβ—Using yeast two-hybrid screening, we searched for proteins that are associated with the C-terminal 120 amino acids of human ABCA1. We identified a nuclear receptor, LXRβ, as a candidate and then examined the interaction between ABCA1 and LXRβs by co-immunoprecipitation (Fig. 1). ABCA1 and LXRα or LXRβ were transiently expressed in HEK293 cells, and a membrane fraction was prepared as described under “Experimental Procedures.” Under these conditions, LXRα or LXRβ was detected in the lysate of the membrane fraction (Fig. 1, lanes 1 and 5). When either LXRα or LXRβ was precipitated with an appropriate antibody, ABCA1 was co-precipitated (lanes 3 and 7). Conversely, LXRα were also co-precipitated with ABCA1 when we used an antibody against ABCA1 (data not shown). The addition of an LXR agonist, TO901317, to the lysate impaired the co-precipitation of ABCA1 with LXRα by the anti-LXR antibodies, although the immunoprecipitation of LXRαs themselves was not affected (lanes 4 and 8), suggesting that conformational changes caused by agonists impair the interaction. To confirm
that this interaction is direct, the C-terminal 298 amino acids of ABCA1 fused with maltose-binding protein and LXRα or LXRβ fused with glutathione-S-transferase were purified from E. coli. The maltose-binding protein-fused C-terminal 298 amino acids of ABCA1 were pulled down by glutathione-S-transferase-fused LXRαs (supplemental Fig. 1).

Because the addition of TO901317 to the lysate impaired the co-precipitation, it was not likely that the co-precipitation was due merely to the aggregation of these proteins. However, it was still possible that the localization of LXR in the membrane fraction and the co-precipitation were due to the overexpression of these proteins in the heterologous expression system.

Interaction of Endogenous LXRαs with ABCA1 in WI-38 Cells—Therefore, we next examined whether the endogenously expressed LXRαs interact with ABCA1. WI-38 human lung fibroblasts were incubated with retinoic acid for 24 h to induce the expression of ABCA1 and LXRαs. LXRα and LXRβ were detected in the lysate of the membrane fraction of WI-38 cells (Fig. 2, a and b, lane 1). When LXRα or LXRβ was precipitated with a suitable antibody, ABCA1 was co-precipitated (lane 5). Following knockdown of each LXR with siRNA, the corresponding band (LXRα or LXRβ) disappeared from the lysate (lanes 2 and 3), as did the band corresponding to co-precipitated ABCA1 (lanes 6 and 7). Both LXRα and LXRβ co-precipitated with ABCA1 by the antibody against ABCA1 (Fig. 2, c and d, lane 5). Neither LXRα nor LXRβ was co-precipitated when they were knocked down with siRNA (lanes 6 and 7). These results suggest that the antibodies used in this study against LXRα and LXRβ indeed react with endogenous LXRα and LXRβ, respectively, and that endogenous LXRα and LXRβ interact with ABCA1.

The expression of ABCA1 was greatly reduced when LXRβ was knocked down with siRNA (Fig. 2, a–d, lane 3), but not when LXRα was knocked down (lane 2). These results suggest that LXRβ plays a major role in the expression of ABCA1 in WI-38 fibroblasts under these conditions. This is consistent with the report that the expression of LXRβ does not change during cholesterol accumulation and that LXRβ plays a role in resting macrophages, whereas LXRα plays a prominent role in macrophages in the context of cellular cholesterol loading (20, 21).

Interaction of LXRβ with ABCA1 in THP-1 Cells—To confirm further that endogenous LXRβs interact with ABCA1, THP-1 human monocytic leukemia cells were induced to differentiate into macrophage-like cells by treatment with phorbol ester, and a membrane fraction was prepared. Because LXR agonists cause the dissociation of LXRαs from ABCA1 (Fig. 1), THP-1 cells were not incubated with LXR agonists but with a minimum dose (10 nM) of retinoic acid. Under these conditions, LXRβ was detected in the lysate of the membrane fraction (Fig. 3, a and b, lane 1), but LXRα was not (data not shown). When ABCA1 was immunoprecipitated, LXRβ was co-precipitated (Fig. 3a, lane 3) and vice versa (Fig. 3b, lane 3). RXR was also co-precipitated with ABCA1 and LXRβ (Fig. 3, a and b, lane 3). The co-precipitation of LXRβ and RXR with ABCA1 was impaired when an LXR agonist, TO901317 (lane 4) or 25-hy-
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Differentiated THP-1 cells were treated with or without 100 nM TO901317 for 2 h. Cells were lysed with 1% Tween 20, and nuclear (Nuc.) and cytoplasmic (Cyto.) fractions were prepared. a, LXRβ and c-Myc were detected by anti-LXRβ monoclonal antibody or anti-c-Myc antibody. b, the Western blot was analyzed using the LAS-3000 imaging system. Error bars represent the means ± S.E. of three measurements. *p < 0.05 (significantly different from the control). c and d, differentiated THP-1 cells were treated with or without 100 nM TO901317 for 2 h. Cells were fixed and immunostained using anti-LXRβ monoclonal antibody. The nucleus was visualized with propidium iodide (Pi).

droxycholesterol (lane 5), was added to the lysate; in contrast, the addition of an RXR agonist, retinoic acid, did not affect the co-precipitation (lane 6). These results suggest that LXRβ/RXR interacts with ABCA1 in THP-1 cells under conditions in which cholesterol does not accumulate in the cells and that the heterodimer dissociates from ABCA1 when LXR agonists accumulate.

Subcellular Localization of LXRβ in THP-1 Cells—LXRs are thought to be located in the nucleus even in the absence of agonists. We analyzed the subcellular distribution of LXRβ in THP-1 cells in the absence of exogenously added agonists (Fig. 4, a and b). Cells were lysed with 1% Tween 20 and fractionated as described under “Experimental Procedures.” Under the experimental conditions, ~40% of LXRβ was recovered in the cytosolic fraction, although no c-Myc protein was detected in this fraction. When TO901317 was added to the cells, only ~20% of LXRβ was recovered from the cytosolic fraction (Fig. 4, a and b).

Next, the subcellular distribution of LXRβ in THP-1 cells was observed under an immunofluorescence microscope. In the absence of added agonists, a significant amount of LXRβ was observed outside of the nucleus (Fig. 4c). When TO901317 was added, most of the LXRβ translocated into the nucleus (Fig. 4d). When LXRβ was knocked down by siRNA, no signal for LXRβ was observed, confirming the specificity of the antibody (supplemental Fig. 2). These results strongly suggest that a significant amount of LXRβ exists outside of the nucleus under conditions in which cholesterol does not accumulate in the cell but that the protein translocates into the nucleus when LXR ligands accumulate. Because LXRs are abundantly expressed in tissues important for cholesterol homeostasis, such as liver, kidney, spleen, intestine, and macrophages, and because LXRα plays a major role in reverse cholesterol transport from cholesterol-loaded cells, the dynamics of LXRβ cytosolic localization might have been overlooked in previous studies.

LXRβ Modulates Turnover of ABCA1 and Increases Surface Expression—While investigating the consequence of ABCA1-LXRβ interaction, we noticed that the amount of ABCA1 was significantly increased when it was coexpressed with LXRβ (data not shown). We expected the interaction with LXRβ to retard the degradation of ABCA1. We measured the half-life of ABCA1, obtaining a value 1.5–2 h (Fig. 5, a–d), consistent with previous reports (13, 14), when ABCA1 was expressed alone in HEK293 cells. When ABCA1 was coexpressed with LXRβ (Fig. 5, a and b), however, its degradation was retarded, and its half-life became longer than 5 h as α1-syntrophin was coexpressed. When TO901317, which causes dissociation of the ABCA1-LXRβ/RXR complex, was added, the coexpression of LXRβ did not retard the degradation of ABCA1, whereas the coexpression of α1-syntrophin still did (Fig. 5, c and d).

Next, we examined the surface expression of ABCA1 by conducting biotinylation experiments (Fig. 5e). When ABCA1 was transiently coexpressed with LXRβ in HEK293 cells, the amount of ABCA1 in the lysate increased, and 51 ± 7.0% of ABCA1 was precipitated with avidin-agarose compared with 33 ± 3.4% when expressed alone. These results suggest that interaction with LXRβ not only retards the degradation of ABCA1 but also increases the surface expression of ABCA1.

Interaction with LXRβ Suppresses ABCA1-mediated Cholesterol Efflux—To analyze the functional consequences of the formation of ABCA1-LXRβ/RXR αpoA1-dependent cholesterol efflux was examined in HEK293 cells transiently cotransfected with ABCA1 and LXRβ (Fig. 6a, open bars).
ApoA-I-dependent efflux was reduced with increasing amounts of transfected LXRβ DNA and with increased expression of LXRβ, even though the amount of ABCA1 was increased compared with that without cotransfection with LXRβ (Fig. 6, a and b). With the addition of TO901317, which impairs ABCA1-LXR interaction, apoA-I-dependent cholesterol efflux was greatly enhanced (>100%) when LXRβ was cotransfected (Fig. 6a, filled bars). TO901317 neither induced endogenous ABCA1 expression (data not shown) nor affected apoA-I-dependent cholesterol efflux when LXRβ was not cotransfected (Fig. 6a). Western blot analysis of ABCA1 after the efflux experiment showed that, when LXRβ (5 μg) was cotransfected, treatment with TO901317 for 2 h reduced the amount of ABCA1 to the level obtained without LXR expression (Fig. 6b).

ABCA1-LXR Interaction Modulates ApoA-I-dependent Cholesterol Efflux from THP-1 Cells—The above results suggested that ABCA1-mediated cholesterol efflux might be suppressed by the interaction with the LXRβ/RXR heterodimer when cholesterol does not accumulate in cells. Therefore, we carefully analyzed the apoA-I-dependent efflux of cholesterol from THP-1 cells. When differentiated THP-1 cells were incubated with a minimum dose (10 nM) of retinoic acid, no apoA-I-dependent efflux was detected (Fig. 7a), although a significant amount of ABCA1 was expressed (Fig. 7b). However, when 100 nM TO901317 was added to the medium for 2 h, apoA-I-dependent cholesterol efflux was clearly observed. Under these conditions, no increase in ABCA1 mRNA (Fig. 7c) or ABCA1 protein (Fig. 7d) was observed. Even after a 4-h incubation with TO901317, only a slight increase in ABCA1 mRNA and protein (1.34 ± 0.13-fold and 1.05 ± 0.04-fold, respectively) was observed. After a 6-h incubation, mRNA and protein were markedly increased (2.33 ± 0.21-fold and 1.72 ± 0.04-fold, respectively) (data not shown).

**DISCUSSION**

When cholesterol accumulates in cells, intracellular concentrations of oxysterols increase, and LXR, activated via the binding of oxysterols, stimulates the gene expression of ABCA1, ABCG1, and other proteins that remove cholesterol from cells. The synthesized ABCA1 protein is distributed on the plasma membrane as well as in intracellular compartments and turns over rapidly with a half-life of 1–2 h (11–13). Therefore, after excess cholesterol is eliminated, ABCA1 would be degraded rapidly, and cells would have little ABCA1 on the plasma membrane. Because the transcription, splicing, translation, and maturation of ABCA1, at >2000 amino acid residues, takes several hours after transcriptional activation, cells would not be able to cope with an acute accumulation of cholesterol for several hours before the vigorous transcriptional activation of ABCA1 via the LXRα autoregulatory loop.

We propose a novel regulatory mechanism of ABCA1 based on the results presented in this study as follows (Fig. 8). (i) When the intracellular concentration of oxysterols is low, the LXRβ/RXR complex binds to ABCA1, and the ABCA1-LXRβ/RXR complex distributes on the plasma membrane but is inert in terms of cholesterol efflux, which prevents the excessive elimination of cholesterol from cells. (ii) When cholesterol accumulates and the intracellular concentration of oxysterols increases, oxysterols bind to LXRβ, and the LXRβ/RXR complex dissociates from ABCA1. (iii) Once free from LXRβ/RXR, ABCA1 is now active in the formation of HDL and decreases the local cholesterol concentration immediately. (iv) Upon binding oxysterols in the cytosol, LXRβ/RXR is translocated to the nucleus and activates the transcription of ABCA1 and other genes. Consequently, LXRβ can exert an immediate post-translational response, as well as a rather slow transcriptional response, to
changes in cellular cholesterol accumulation to maintain cholesterol homeostasis. This novel mechanism would be important for macrophages because macrophages must cope with rapid increases in intracellular cholesterol when they phagocytose apoptotic cells.

α1-Syntrophin (14) and β1-syntrophin (15) are involved in the post-translational regulation of ABCA1. Both proteins interact directly with ABCA1 via the C-terminal three amino acids SYV (a PDZ (PSD95-Discs large-ZO1) protein-binding motif). These interactions retard the degradation of ABCA1, increase the surface expression of ABCA1, and consequently increase the apoA-I-mediated release of cholesterol (14). The mechanisms of ABCA1 degradation and of its retardation by syntrophins have not yet been clarified. Interaction with LXRβ also retards the degradation of ABCA1 and increases the surface expression of ABCA1. In contrast to the interaction with syntrophins, this interaction suppresses the formation of HDL; hence, the mechanism of the LXRβ interaction is likely different from that of the syntrophin interaction. We found that the site of interaction of ABCA1 with LXRβ is different from that with syntrophins. The replacement of Leu2247 of ABCA1 with alanine abolished the co-precipitation with LXRβ (supplemental Fig. 3a). The coexpression of LXRβ did not retard the degradation of ABCA1(L2247A), whereas the coexpression of α1-syntrophin retarded the degradation of ABCA1(L2247A) (supplemental Fig. 3b and c). These results suggest that the amino acid substitution L2247A does not alter total protein conformation but rather specifically affects the interaction with LXRβ. ABCA1(L2247A) showed significant apoA-I-dependent cholesterol efflux, and the addition of TO901317 did not affect it even when LXRβ was coexpressed (supplemental Fig. 3d). Leu2247 is in a sequence (2247LTSFL2251) that resembles the sequences (ϕXXϕϕ) (22) of co-activators and co-repressors interacting with nuclear receptors. Therefore, we speculate that the co-activator/co-repressor interaction site of LXRβ could be involved in the interaction with ABCA1.

These results suggest that LXRβ regulates the efflux of cholesterol not only by modulating ABCA1 gene expression as nuclear receptors but also by directly modulating the efflux activity of ABCA1. This study is the first to show that protein-protein interaction suppresses ABCA1 function. This is also the first example of mutual regulation between a nuclear receptor and a membrane protein that is also an end product of transcriptional regulation by the same nuclear receptor. This unusual situation possibly came about through the co-evolution of these proteins, resulting in a sophisticated network devoted to the maintenance of homeostasis.

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