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Induction of ABCA1 by overexpression of hormone-sensitive lipase in macrophages

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ABSTRACT

Initial step toward the reverse-cholesterol transport is cholesterol efflux that is mediated by the ATP-binding cassette transporter A1 (ABCA1). However, it is unknown how the cholesteryl ester (CE) hydrolysis induces the expression of the ABCA1 gene. Overexpression of hormone-sensitive lipase (HSL) increased the hydrolysis of CE and stimulated the expression of ABCA1 gene at the transcriptional level in RAW 264.7 macrophages. The stimulatory effects of the HSL overexpression and cholesterol loading on the ABCA1 promoter activity were additive. Mutational analyses of the promoter of ABCA1 identified the responsible element as the direct repeat-4 (DR-4) that binds LXR/RXR heterodimers. In conclusion, stimulation of hydrolysis of CE in macrophages induces the expression of ABCA1 gene primarily via the LXR-dependent pathway and can be useful for the prevention of atherosclerosis.

Introduction

The initial step for the elimination of cholesterol from foam cells, a hallmark of atherosclerosis, is mediated by two pathways: passive efflux from the cell membrane to HDL and energy-dependent efflux mediated by apolipoproteins [1]. The latter pathway has been reported to be defective in Tangier disease or familial HDL deficiency [2] which is caused by inherited mutations in the gene for ATP-binding cassette (ABC) A1 [3–9], a member of ABC transporter superfamily whose members are characterized by two nucleotide binding folds (NBF) with conserved Walker A and B motifs and two transmembrane domains, each consisting of six membrane spanning helices [10]. The human ABCA1 gene on chromosome 9q31 [6] encodes a protein with 2231 amino acids and is ubiquitously expressed particularly in placenta, fetal tissues, liver, lung, and adrenal glands [11,12].

The mRNA expression of ABCA1 is induced by cholesterol loading of macrophages through incubation with acetylated LDL (acetyl-LDL) [11]. This sterol-dependent transactivation is mediated by nuclear hormone receptors of the liver X receptor (LXR) and retinoid X receptor (RXR) family [13–15]. The cytosolic CE is in turn hydrolyzed by neutral CE hydrolase (NCEH) to generate FC and fatty acids [16]. Several investigators [17–19] have attributed the NCEH activity to hormone-sensitive lipase (HSL), a cytosolic enzyme that hydrolyzes intracellular triacylglycerol (TG), diacyl glycerol (DG), CE, and retinyl ester in various organs including adipose tissue, adrenal gland and testes [20,21]. Previously, we have shown that the adenovirus-mediated overexpression of HSL in THP-1 macrophages stimulates the efflux of cholesterol from foam cell macrophages with a concomitant increase in ABCA1 mRNA, resulting in nearly complete elimination of the intracellular CE [22]. However, it is unclear how the increased hydrolysis of CE up-regulates the ABCA1 gene expression. Here, we show that the transactivation of human ABCA1 promoter by increased hydrolysis of CE depends on the binding of LXR/RXR to a DR4 element.

Materials and methods

General procedures. Immunoblot analysis and measurements of cellular lipids were performed essentially as described [22].

Lipoproteins. Ultracentrifugation was used to isolate β-migrating VLDL (β-VLDL) from plasma of Japanese white rabbits (3 kg male) that were fed a chow diet supplemented with 1% (w/w) cholesterol.

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Plasmid constructs. The HSL cDNA was subcloned into the polylinker region of pCI to obtain the plasmid vector expressing HSL cDNA under the promoter of CMV [23]. The promoter region of ABCA1 gene (from −928 to +101 bp) was amplified from human genomic DNA (CLONTECH) by PCR using Platinum Pfx DNA polymerase (Invitrogen Life Technologies, Inc.) and the following primers: forward primer, 5′-GATCGATCAGATCTTAAGTTGGAGGTCT GGAGTG-3′; reverse primer, 5′-GATCGATCAAGCTTGCTCTGTTGGT GCGCGGA-3′, which were designed based on the reported DNA sequence [24] and contained restriction sites for BglII and HindIII at the 5′ end of the forward and reverse primers, respectively. ABCA1 promoters with various deletion mutations were generated by PCR using TaKaRa LA TaqTM (TaKaRa) and the following primers: forward primer1 (−406 to +928), 5′-GATCGATCAGATCTAGCAGGA TTTAGAGGAAGCA-3′; forward primer2 (−106 to +928), 5′-GATCGA TCAGATCTCGGGCCCCGGCTCCACGTG-3′; forward primer3 (−100 to +928), 5′-GATCGATCAGATCTAGGGGGCGGGGAGGAGGGA-3′; forward primer4 (−36 to +928), 5′-GATCGATCAGATCTGAATCTAT AAAAGGAACTA-3′; reverse primer, 5′-TAGATCGCAGATCTCGAGCCC G-3′. Primers used for generation of the mutated LXR/DR4 element were as follows: forward primer, 5′-GATCGATCctgcaGATAGTAA CCTCTGCGCTCGG-3′; reverse primer, 5′-GATCGATCtgcagAAGCCTG TGCTGTGCTCTCCCTCCTC-3′ [13,14]. The amplified fragments were digested with BglII and HindIII and subcloned into the site of the polylinker region of pGL3-basic vector (Promega) by using DNA Ligation Kit Ver. 2 (TaKaRa).

Recombinant adenovirus. A fragment of ABCA1 promoter region (−926 to +101) and luciferase gene were subcloned into Gateway® entry vector pENTR4 (Invitrogen). pAd-ABCA1-luc was obtained by Vira Power Adenoviral Expression system (Invitrogen). Briefly, the plasmid was generated by performing an LR recombination reaction between pENTR-ABCA1 and pAd/PL-DEST. pAd-ABCA1-luc was transfected into 293A cells and the recombinant adenoviruses were produced according to the manufacturer's instructions. In our experiments, 1 multiplicity of infection (m.o.i.) corresponded to 183 particles of adenovirus of ABCA-luc (Ad-ABCA1-luc) and 25 particles of adenovirus LacZ (Ad-LacZ) used as a control per cell. Cells were infected at m.o.i. indicated in figures.

Cell culture. RAW264.7, THP-1 cells and mouse peritoneal macrophages (MPM) prepared from 8- to 9-month-old C57BL/6J mice were cultured as described [22,23].

NCEH assay. Protein for the NCEH assay was prepared as described previously [22,23].

Northern blot analysis. Total RNA was prepared from RAW264.7 cells with TRIzol reagent (Invitrogen Life Technologies, Inc.). RNA (30 μg) was electrophoresed through formalin-denatured agarose gels and transferred to Hybond-N+ membranes (GE Healthcare). Probes for ABCA1 were constructed from cDNA fragments amplified by RT-PCR using cDNA obtained from mouse liver as a template. Primer sequences forward primer: 5′-TAGGCTTGTTGGCCT CAGCT-3′, reverse primer: 5′-TTGCGCATGTCCTTCATGCT-3′. Probes were labeled with [α-^{32}P]dCTP (∼6000 Ci/mmol; Perkin Elmer) using Megaprime DNA Labeling System (GE Healthcare). Membranes were hybridized with the radiolabeled probes in Rapid-hyb Buffer (GE Healthcare), washed in 0.1× SSC, 0.1% SDS at 65 °C, and exposed to BAS2000 phosphoimager (Fuji Film, Tokyo).

Luciferase reporter assay. Twenty-four hours after culturing of 4.0×10^4 cells/well in 96-well plates, the cells were transfected with 0.5 μg of total DNA mixture of pGL3-ABCA1 promoter with or without pCI-HSL by Superfect® Transfection Reagent (QIAGEN). After incubation in DMEM containing 5 mg/ml BSA for 12 h, the cells were incubated in DMEM containing 5 mg/ml BSA and various concentrations of β-VLDL for 12 h. Luciferase activities were measured by Steady-Glo Luciferase Assay System (Promega) and TR717 Microplate Luminometer (Applied Biosystems).

Electrophoretic mobility shift assay. A fragment containing His(HHHHHH)-HA(YPYDVPDYA)-FLAG(DYKDDDDK) was subcloned into HindIII/BamHI of the polylinker region of pcDNA3.1(+) (Invitrogen) to obtain pcDNA3.1/HisHAFLAG/N. Mouse cDNA for LXRα or RXRα amplified by RT-PCR was then ligated into BamHI/XhoI site in the pcDNA3.1/HisHAFLAG/N to obtain pcDNA3.1/HisHAFLAG/N-mLXRα or pcDNA3.1/HisHAFLAG/N-mRXRα, respectively. A fragment containing cDNA for mouse LXRβ, which was obtained from pCMV7-mLXRβ (a gift from Dr. David Russell) by digestion with SalI and NotI, was blunt ended with Klenow fragment and subcloned into EcoRV site of pcDNA3.1/myc-HisB to get pcDNA3.1/myc-HisB-mLXRβ.

mLXRα, mLXRβ and mRXRα proteins were translated by a TNT Quick Coupled Transcription/Translation System (Promega) using pcDNA3.1/HisHAFLAG/N-mLXRα, pcDNA3.1/myc-HisB-mLXRβ or pcDNA3.1/HisHAFLAG/N-mRXRα as templates.

Oligonucleotide containing LXR/DR4 (5′-TTTGACCGGTAGTAG TAACCCCGGCGC-3′) was labeled with [γ^{32}P]ATP (Perkin Elmer).by T4 polynucleotide kinase (TaKaRa), and was mixed with the proteins synthesized by IVTT and incubated in binding buffer containing 10 mM Hepes, 50 mM KCl, 1 mM $MgCl_2$, 10% glycerol, 1 mM DTT, 0.4 μg of poly(dI–dC), and 10 μg of BSA on ice for 30 min and reacted with or without antibodies against LXRα, LXRβ, or RXRα for 30 min, and subjected to electrophoresis in 4% polyacrylamide gel. The binding was competed by the unlabeled oligonucleotides containing LXR/DR4 or mutated LXR/DR4 (5′-TTCTGCAGGTAGTAACCCCGGCG C-3′). The gels was dried and exposed to BAS2000 phosphoimager (Fuji Film, Tokyo).

Statistical analyses. All values are stated as means ± SD, and differences between groups were evaluated with ANOVA, unless otherwise stated. All calculations were performed with STAT view version 5.0 for Macintosh (SAS Institute).

Results and discussion

Transfection of pCI-HSL resulted in a dose-dependent increase in the expression of HSL protein, whose molecular weight is identical to that expressed in white adipose tissue (WAT), in RAW264.7 cells (Fig. 1A). In parallel, it increased the NCEH activity by 1.8-fold compared to that expressed endogenously in RAW264.7 cells (Fig. 1B). The levels of expression were much lower than those which we reported in our previous study, in which we used adenovirus-mediated gene transfer in THP-1 cells [22].

Incubation with β-VLDL increased the cellular contents of CE by 9-fold at the concentration of 10 μg/ml. The overexpression of HSL significantly decreased the cellular CE contents by 11%, while it increased the FC contents by 50% at the concentration of 10 μg/ml of β-VLDL (data not shown).

To examine whether the overexpression of HSL affects the mRNA expression of endogenous ABCA1gene, we performed Northern blot analyses (Fig. 1C). Incubation with β-VLDL or transfection with pCI-HSL alone did not affect the mRNA expression of ABCA1. However, the overexpression of HSL in the presence of β-VLDL increased the mRNA expression of ABCA1 gene by 2-fold.

To investigate the mechanism behind the increased expression of ABCA1 gene in RAW264.7 cells, we have generated a firefly luciferase reporter gene construct containing nucleotides −928 to +101 of the ABCA1 gene (pGL3-ABCA1) and co-transfected both pCI-HSL and pGL3-ABCA1 to RAW264.7 cells which were subsequently incubated with increasing concentrations of β-VLDL (Fig. 1D). Incubation with 2.5 μg/ml of β-VLDL per se stimulated the ABCA1 promoter activities by 1.8-fold. Further increases in the concentration of β-VLDL did not cause additional increase in the ABCA1 promoter activity. At every concentration of β-VLDL, the overexpression of HSL further stimulated the ABCA1 promoter activities

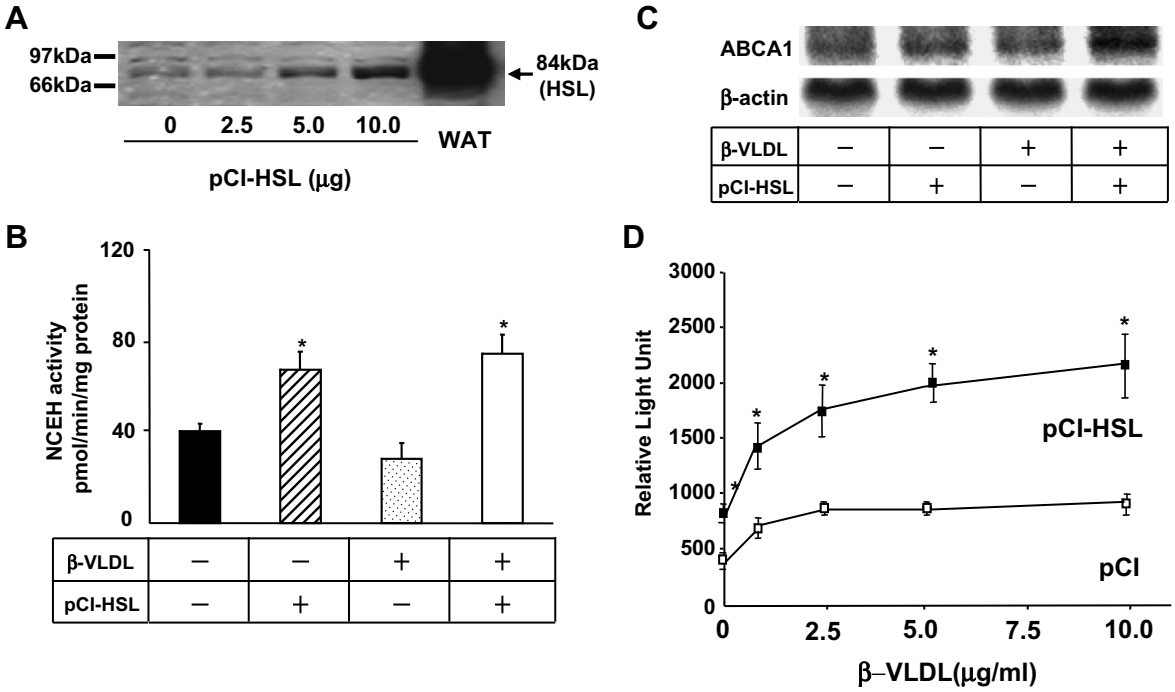

Fig. 1. HSL protein expression (A) and NCEH activities (B) in RAW 264.7 cells overexpressing HSL. Stimulation of mRNA expression (C) and promoter activities (D) of ABCA1 gene by the overexpression of HSL. RAW 264.7 cells were plated in 10-cm dishes and transiently transfected with the indicated amounts of pCI-HSL and total cell lysates were subjected to Western blot analysis using an epididymal fat pad as a control. White adipose tissue, WAT (A). RAW 264.7 cells were grown in 12-well (B) or 6-well plates (C) and transiently transfected with 0.75 or 1.0 μg of pCI-HSL or pCI, respectively, followed by incubation with or without 2.5 μg/ml of β-VLDL. Cell lysates were used for the measurements of NCEH activities (B) and total RNA was subjected to Northern blot analyses for ABCA1 or β-actin (C). RAW 264.7 cells were grown in 96-well plates and transiently transfected with 0.25 μg of pCI-HSL (closed square) or pCI (open square) and 0.25 μg of pGL3-ABCA1-luc in RAW 264.7 cells, and incubated with the indicated concentrations of β-VLDL (D). Bars indicate means ± S.D. $^{*}P < 0.001$, HSL(−)β-VLDL(−) vs HSL(+)β-VLDL(−); HSL(−)β-VLDL(+) vs HSL(+)β-VLDL(+) (B). pCI-HSL vs pCI (D).

by ~2.6-fold. Similar results were obtained in an independent experiment using the fixed concentration of β-VLDL (data not shown).

It is known that activation of peroxisome proliferator-activated receptor (PPAR)α or PPARγ up-regulates ABCA1 gene expression via increasing the expression of LXRα [25,26]. Furthermore, hydrolysis of CE by the overexpressed HSL may provide fatty acids, which may function as a ligand for PPARs, by hydrolyzing CE, TG and retinyl ester. Therefore, it is important to know whether agonists for PPARs transactivate the expression of ABCA1gene in various macrophage-like cell lines. To compare the stimulatory activities of ligands for PPARs with that of ligands for LXRs, we treated three different macrophage-like cells with bezafibrate, a PPARα agonist, pioglitazone, a PPARγ agonist, T0901317, 22(R)-hydroxycholesterol and 24(*S*),25-epoxycholesterol, LXR agonists, and 9-*cis*-retinoic acid, a RXRα agonist (Supplementary figure). With regards to LXR agonists, all of the three significantly transactivated the ABCA1 gene in all of the three lines of cells. 9-cis-retinoic acid transactivated the ABCA1 gene in THP-1 and RAW264.7 cells, but not in MPM. However, neither pioglitazone nor bezafibrate significantly transactivated the ABCA1 gene at least in RAW264.7 cells. In THP-1 cells and MPM, pioglitazone transactivated the gene marginally, but bezafibrate did not. Thus, liberation of cholesterol for conversion to oxysterols might be the most plausible explanation at present.

To define the element in the promoter of ABCA1 that mediated the stimulation of the transcription of the gene, we performed electrophoretic mobility shift assays using recombinant LXRα, LXRβ and RXRα (Fig. 2A). When the ABCA1 wild-type DR4 element was used alone, a single major shift in activity was detected for both LXRα/RXRα and LXRβ/RXRα (Fig. 2A, lanes 2 and 8), which disappeared with excess of cold wild-type competitor (Fig. 2A, lanes 3 and 9) but not with excess of cold mutant competitor (Fig. 2A, lanes 4 and 10). Inclusion of an antibody against LXRα or LXRβ in the binding reaction resulted in a supershift in the LXRα/RXRα or LXRβ/RXRα, respectively (Fig. 2A, lanes 5 and 11, while inclusion of an antibody against RXRα resulted in a supershift in both reactions (Fig. 2A, lanes 6 and 12).

To map the response element which mediates the HSL-stimulated ABCA1 transcription, we generated several promoter constructs with various length of deletion (Fig. 2B). The response was clearly preserved when the promoter insert was sequentially deleted down to position −100, and subsequently lost when sequences −100 to −36 were removed. However the latter deletion mutant lacked promoter activity, presumably because it no longer contained the element for basic transcription factors such as Sp1. The relative induction by β-VLDL was the lowest in the construct with the sequences from −160 to +101 of the promoter, while it was the highest in the construct with the sequences from −100 to +101 of the promoter. Similarly, the relative induction by the overexpression of HSL was the lowest in the construct with the sequences from −160 to +101 of the promoter, while it was the highest in the construct with the sequences from −100 to +101 of the promoter. These results indicate that a negative regulatory element is present between −160 and −100 bp of the promoter. It is of note that the promoter region between −100 and −36 bp is required for the induction of the transcription both by β-VLDL and by the overexpression of HSL. Since this region contains DR4 element, an established binding site for LXR/RXR, we presume that this element mediates the HSL-induced stimulation of the transcription of the ABCA1 gene. To test this hypothesis, we have mutated the DR4 element in the promoter sequences from −928 to +101 bp (Fig. 2C). The promoter with the mutated DR4 element had negligible basal transcription activity. Furthermore, it did not respond either to β-VLDL or to the overexpression of HSL, supporting the critical role of this element in the stimulation of the transcription of ABCA1 gene by the increased hydrolysis of CE. This pattern of

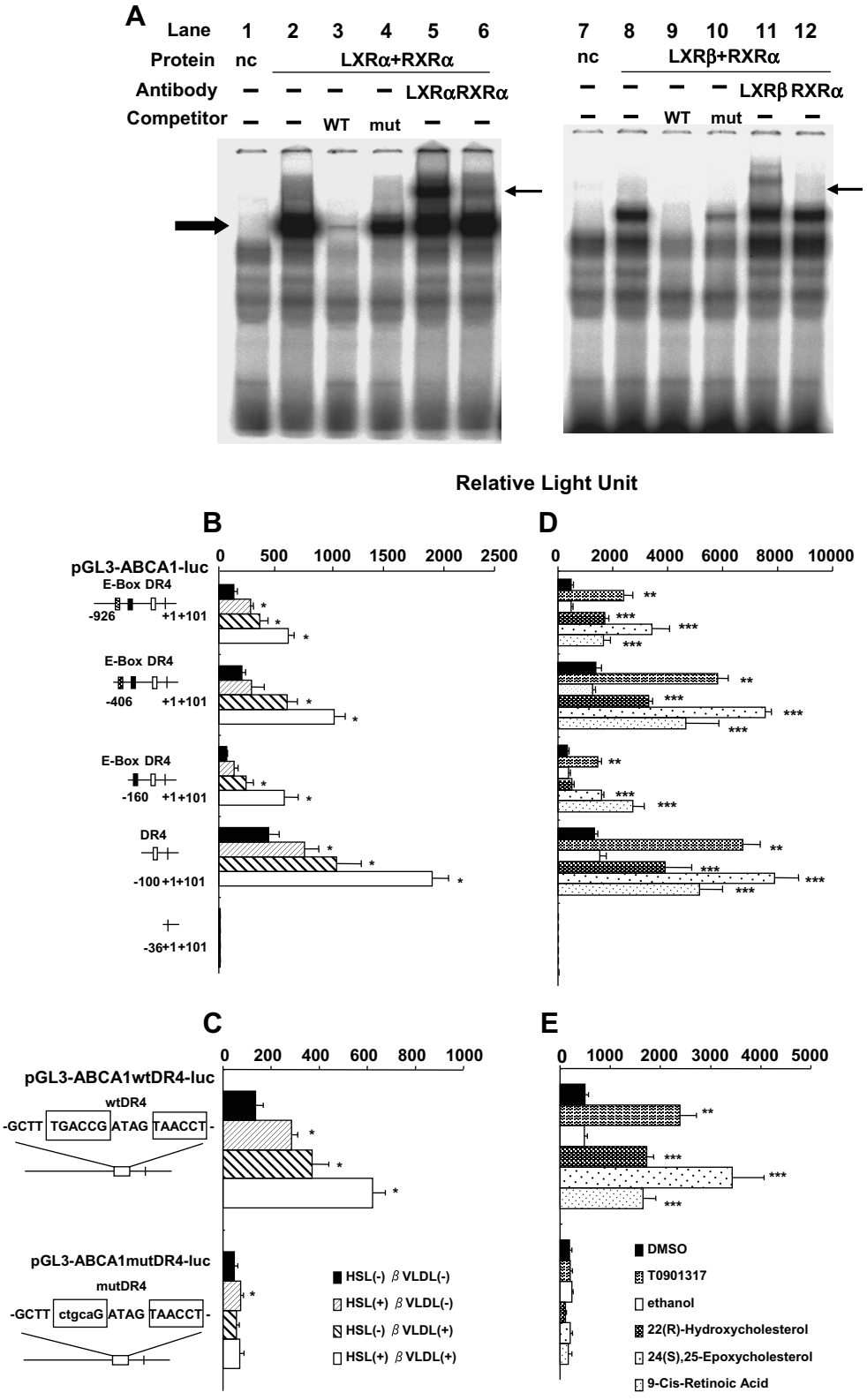

Fig. 2. Electrophoretic mobility shift assay of human ABCA1 promoter fragment (A) and mutational analysis of ABCA1 promoter (B, C, D, and E). Oligonucleotides containing the DR4 element were ^{32}P-radiolabeled and incubated with recombinant LXRα/RXRα (lanes 1–6) or LXRβ/RXRα without or with cold wild-type (lanes 3 and 9) or mutated (lanes 4 and 10) competitor oligonucleotides. Antibody against LXRα (lane 5), LXRβ (lane 11) or RXRα (lanes 6 and 12) was included in the reaction mixture. Position of bands corresponding to the ABCA1 promoter fragment that was bound to LXRα/RXRα or LXRβ/RXRα is indicated by a big arrow. Position of supershift bands is indicated by a small arrow (A). RAW 264.7 cells were grown in 96-well plates and transiently transfected with 0.25 μg of the plasmids containing the indicated hABCA1 promoter with deletions (B,D) or mutated DR4 (C,E). (B,C) The cells were co-transfected with 0.25 μg of pCI-HSL or pCI followed by incubation with or without 2.5 μg/ml of β-VLDL. (D,E) The cells were incubated with 10^{-5} M of various compounds indicated in (E). Bars indicate means ± SD. $^{*}P < 0.05$, HSL(−) β-VLDL(−) vs HSL(−) β-VLDL(−); HSL(−) β-VLDL(−) vs HSL(−) β-VLDL(+); HSL(−) β-VLDL(+) vs HSL(+) β-VLDL(+); $^{**}P < 0.01$ vs DMSO; $^{***}P < 0.01$ vs ethanol.

transactivation of ABCA1 gene was recapitulated by agonists for LXR/RXRα, T0901317, 22(*R*)-hydroxycholesterol, 24(*S*),25-epoxyxholesterol and 9-*cis*-retionoic acid as shown in Fig. 2D and E.

In conclusion, overexpression of HSL increases the supply of free cholesterol as a ligand for LXR, thereby stimulates the expression of ABCA1 gene in macrophages. This pathway can be used as a therapeutic target for the treatment of atherosclerosis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2008.08.101.

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