Biochemical and Biophysical Research Communications 392 (2010) 63–66

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Orphan nuclear receptor Nur77 participates in human apolipoprotein A5 gene expression

Kwang-Hoon Song *

Korea Institute of Oriental Medicine, Daejeon 305-811, Republic of Korea

ARTICLE INFO

Article history:
Received 27 November 2009
Available online 7 January 2010

Keywords:
Orphan nuclear receptor
Nur77
Apolipoprotein
ApoA5
Gene expression

ABSTRACT

The orphan nuclear receptor Nur77 (NR4A1) has been reported to play a crucial role in the modulation of diverse metabolic processes in liver. Here, we reported the identification of human apolipoprotein A5 (ApoA5), which implicated in lowering plasma triglyceride levels, as a novel target gene of Nur77. Nur77 induced the human ApoA5 promoter activity. Using 5′-deletion and mutagenesis of human ApoA5 promoter analysis and chromatin immunoprecipitation assays, it was shown that Nur77 directly regulated human ApoA5 gene expression by binding to a Nur77 response element (AAAGGTCA) located in the proximal human ApoA5 promoter region. In addition, we demonstrated that blocking of Nur77 transcriptional activity via overexpression of dominant negative Nur77 suppressed human ApoA5 promoter activity and mRNA expression in human hepatoma cells, HepG2. Taken together, our results demonstrated that Nur77 is a novel regulator of human ApoA5 gene expression and provide a new insight into the role of this orphan nuclear receptor in lipoprotein metabolism and triglyceride homeostasis.

Introduction

Nuclear receptor Nur77 (NR4A1) belongs to the NR4A family of the nuclear receptors which also includes Nurr1 (NR4A2) and Nor1 (NR4A3) [1]. It has not been identified specific ligands for the NR4A family hitherto and recent studies demonstrated that the ligand-binding domain of these receptors do not contain a ligand-binding pocket suggesting that these receptors are orphan nuclear receptor and their function is regulated by their expression and post-translational modification rather than ligand-binding [1,2]. NR4A receptor family shares a highly conserved DNA-binding domain and recognizes its cognate DNA consensus sequence known as the Nur77 response element (NBRE; AAAGGTCA) as a monomer [3,4]. It has been reported that Nur77 is expressed and modulates diverse metabolic processes including apoptosis, gluconeogenesis and lipogenesis in the liver [5–8]. Although informations regarding Nur77 function have been accumulated, the physiological role of this orphan nuclear receptor largely remains to be elucidated.

Apolipoproteins play an important role in lipid homeostasis and have a major impact on the risk of cardiovascular disease [9,10]. A recently identified apolipoprotein, apolipoprotein A5 (ApoA5), has been shown to be important in the regulation of plasma triglyceride (TG) levels [11,12]. ApoA5 was predominantly expressed in the liver and found in plasma fractions containing the high density lipoprotein (HDL) particles [11,12]. A crucial role of ApoA5 in the regulation of TG was demonstrated using transgenic and knock-out animal models leading to decreased and increased plasma TG concentration, respectively [12,13]. Moreover, overexpression of mouse ApoA5 gene using adenovirus reduced serum levels of TG and cholesterol in mice [14].

It has been reported that human ApoA5 gene expression was directly up-regulated by several nuclear receptors including peroxisome proliferator-activated receptor (PPARα), farnesoid X-activated receptor (FXR), retinoid acid receptor-related orphan receptor (RORα), hepatocyte nuclear factor 4α (HNF4α), and thyroid receptor β (TRβ) [15–19]. Interestingly, these studies revealed an important region for the regulation of human ApoA5 gene expression, direct repeat 1 (DR-1) sequence located at the position from −272 to −260 in the human ApoA5 promoter [15–18]. It is important to identify and characterize transcription factors that bind to the identified DR-1 sequence to understand the regulation mechanism of human ApoA5 gene expression. In contrast, liver X receptor (LXR) down-regulated ApoA5 gene expression via an indirect pathway involving its downstream target gene sterol regulatory element-binding protein 1c (SREBP-1c) which binding to the functional E-box present in human ApoA5 promoter [20].

In this report, we provided evidences that Nur77 directly regulates human ApoA5 gene expression via NBRE sequence in the promoter and highlighted a critical role of Nur77 in the regulation triglyceride homeostasis.

* Fax: +82 42 868 9480.
E-mail address: ksong@kiom.re.kr.

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doi:10.1016/j.bbrc.2009.12.168

Materials and methods

Cell culture. The HepG2 cells were obtained from the American Type Culture Collection (Manassas, VA). The cells were maintained in a 1:1 mixture of Dulbecco's modified Eagle's medium and F-12 (50:50; Invitrogen) supplemented with 100 U/ml penicillin G/streptomycin sulfate (Invitrogen) and 10% heat-inactivated fetal bovine serum (Gibco).

Luciferase reporter constructs and plasmids. The human ApoA5 promoter (−846) was first cloned by PCR using human primary hepatocytes genomic DNA using as template and cloned in pGL3 basic luciferase vector (Promega). The following oligonucleotide primers were used for the PCR: forward primer tailed with a KpnI restriction site, 5′-GGT ACC AGA CCT GTT GGA GGC TAT GAA TGC-3′; reverse primer tailed with a XhoI restriction site, 5′-CTC GAG AAT GCC CTC CCT TAG GAC TGT GAC-3′. A various deletion construct of human ApoA5 promoter (−356 and −147) were obtained by PCR from cloned pGL3 human ApoA5 promoter (−846) as template and cloned in pGL3 basic luciferase vector (Clontech). The following oligonucleotide primers were used for the PCR: forward primer tailed with a KpnI restriction site, 5′-GGT ACC CTC TGG GTA GTT GTG TAA GAG AG-3′ (−356) and 5′-GGT ACC GGT GCC AGG GAA AGG GCA GGA GG-3′ (−147); reverse primer tailed with a XhoI restriction site, 5′-CTC GAG AAT GCC CTC CCT TAG GAC TGT GAC-3′. Site-directed mutagenesis (Stratagene) of the human ApoA5 promoter NBRE site was performed using the oligonucleotide 5′-AGT GGG AAG GTT AAA **AAA** CAT GGG GTT TGG GAG-3′ (mutated bases are indicted in bold) as a mutagenic primer. The expression vectors Nur77 and dominant negative Nur77 (D/N-Nur77), LRH-1 and HNF4α were as described previously [21,22].

Transient transfection and Luciferase reporter assay. For luciferase reporter assay, HepG2 cells were plated in 24-well plates 24 h before transfection with reporter or expression plasmids using Lipofectamine™ 2000 reagent (Invitrogen) according to the manufacturer's instructions. Total DNA used in each transfection was adjusted by adding the appropriate amount of pcDNA3 empty vector. Luciferase activities are expressed as relative luciferase unit (RLU)/β-galactosidase activity as described previously [22]. Assays were performed in triplicates and expressed as means ± SD.

Recombinant adenovirus. RNA isolation and quantitative real-time PCR (Q-PCR). Recombinant adenovirus empty vector (Ad-Mock) and D/N Nur77 (Ad-D/N Nur77) was obtained from Dr. In-Kyu Lee (Kyungpook National University School of Medicine, Daegu, Republic of Korea). Recombinant adenoviruses were amplified in HEK293A cells and purified with Adeno-X virus mini purification kit (BD Biosciences). Virus titer was determined by Adeno-X rapid titer kit (BD Biosciences). HepG2 cells were infected with AD-Mock or Ad-D/N Nur77. Twenty-four hours after infection, total RNA was isolated using Tri-reagent (Sigma, St. Louis, MO) according to the manufacturer's instruction. Reverse-transcription and Q-PCR were performed to detect ApoA5 mRNAs as described previously [23].

Chromatin immunoprecipitation assay (ChIP). ChIP assays were performed using a ChIP Assay kit (Upstate Cell Signaling Solutions) according to the manufacturer's instructions. HepG2 cells were cross-linked in 1% formaldehyde and sonicated. Cell lysate solution (5%) in ChIP dilution buffer was kept aside as "Input". Anti-Nur77 or anti-HNF4α antibody was added to precipitate DNA–protein complexes and non-immune IgG was used as a control. A 351-bp DNA fragment (−400 to −50) containing the NBRE of the human ApoA5 promoter was PCR amplified for 30 cycles using 5 μl of the DNA as template and analyzed on a 1.5% agarose gel. PCR primers for amplification were as follows: forward primer, 5′-GCT GGT AGG TGA ACA CTG TCC ATC-3′, reverse primer, 5′-TGG CAC CAA TTG CTC TGA GTA AAT-3′.

Statistical analysis. All experimental data are shown as the means ± SD. Multiple groups were tested by one-way ANOVA followed by Dunnett's test to determine which groups are significantly different from the control group. A P value <0.05 was considered to be significant. $^{*}P < 0.05$; $^{**}P < 0.001$.

Results and discussion

ApoA5 plays an important physiological role in the regulation of plasma triglyceride homeostasis [12,14]. Previous reports showed that human ApoA5 gene expression is regulated by several nuclear receptors including PPARα, RORα, and HNF4α via DR-1 site present at the position −272 to −260 in the human ApoA5 gene promoter [15–17]. Notably, this DR-1 sequence perfectly matched with the binding site for the orphan nuclear receptor Nur77 led us to explore the potential regulation of human ApoA5 gene expression by Nur77.

Since this DR-1 site sequence contains a potential Nur77 binding site (NBRE, AAAGGTCA), we first evaluated whether this nuclear receptor can modulate human ApoA5 gene expression. To investigate whether Nur77 directly affect human ApoA5 gene promoter transcriptional activity, transient transfection was performed using a luciferase reporter vector driven by human ApoA5 promoter sequence from −846 to +62 together with Nur77, LRH-1, and HNF4α in HepG2 cells. Transfection of Nur77 and HNF4α expression plasmid robustly enhanced human ApoA5 promoter activity (Fig. 1A). In contrast, human ApoA5 promoter activity was not significantly affected by cotransfection of LRH-1 although this receptor also can recognize AGGTCA sequence as a monomer. This result is consistent with recent report that ApoA5 gene expression levels were not modified by shLRH-1, a short hair-

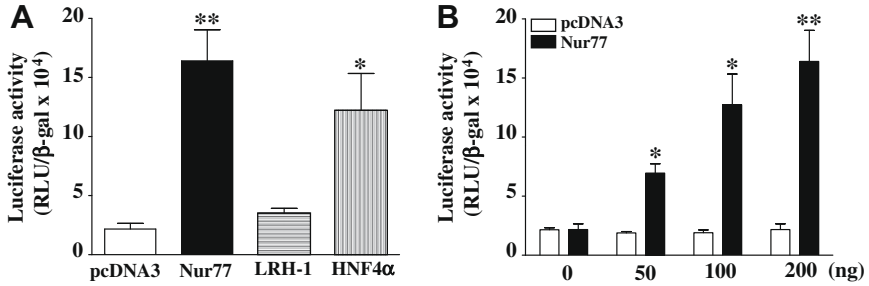

Fig. 1. Induction of the human ApoA5 gene promoter activity by Nur77. (A) HepG2 cells were transient transfected with a luciferase reporter construct driven by the 5′-flanking region (−846/+62) of human ApoA5 gene along with a plasmid expressing Nur77, LRH-1 and HNF4α or the empty plasmid pcDNA3 as control. (B) HepG2 cells were cotransfected with the human ApoA5 promoter (−846/+62) reporter along with increasing amounts of Nur77 plasmid (50, 100 and 200 ng) or empty plasmid pcDNA3 as control. Luciferase activity was normalized to β-galactosidase activity. All experiments were done in triplicates and data represented the means ± SD of three individual experiments. Statically differences from controls are indicated by asterisks ($^{*}P < 0.05$ and $^{**}P < 0.01$).

pin RNA (shRNA) targeting LRH-1, overexpression in HepG2 cells [24].

We also showed that the human ApoA5 promoter activity was strongly increased in a dose-dependent manner by cotransfection of Nur77 expression plasmid (Fig. 1B). Although the degree of activation was variable, human ApoA5 promoter reporter activity was increased by other NR4A family members Nurr1 and NOR1, which also transactivate NBRE-containing promoter [21], in transient transfection experiment (data not shown).

ApoA5 is mainly produced in liver and Nur77 is also expressed in liver and plays an important role in the regulation of diverse metabolic processes [5–8,12]. An understanding of the arrangement of liver-specific transcription factors on the promoter may provide possible mechanisms for regulation of ApoA5 transcription during development and under the physiological conditions. Previous reports that SREBP-1c down regulates ApoA5 gene expression [20] and Nur77 suppresses SREBP-1c activity [8] let us speculate that increasing the expression and transactivity of Nur77 may be beneficial to lower triglyceride accumulation in the liver with regard to its suppressive effect on SREBP-1c expression and subsequent increase in ApoA5 expression. Moreover, after partial hepatectomy and during early stage of liver regeneration, Nur77 are sharply induced [25] and ApoA5 gene expression is also up-regulated [11] suggesting that Nur77 may play an important role in the regulation of ApoA5 expression in hepatocytes during liver injury.

To further investigate the stimulation of human ApoA5 promoter activity by Nur77, we cotransfected a Nur77 expression plasmid with a series of human ApoA5 promoter deletion constructs. As shown Fig. 2, a significant stimulation of human ApoA5 promoter activity was observed with deletion up to −356 which containing NBRE site following coexpression of Nur77. However, a marked decrease in Nur77-mediated stimulation of the human ApoA5 promoter activity was observed upon deletion to −147 which lost NBRE site. These results indicated that Nur77-mediated transactivation of human ApoA5 promoter is directly mediated through NBRE site.

To confirm whether the NBRE site in the human ApoA5 promoter is responsible for Nur77-mediated transactivation of human ApoA4 promoter activity, we mutated AAAGGTCA sequence in the NBRE site to AAAAAACA. In contrast to the native promoter construct (−846), mutated NBRE-containing promoter construct (MT-846) was not stimulated by cotransfection of Nur77 expression plasmid indicating that the NBRE indeed confers Nur77 response to the human ApoA5 promoter (Fig. 2). These results suggested that this NBRE site is required for Nur77-mediated transactivation of human ApoA5 promoter activity.

Subsequently, we performed chromatin immunoprecipitation (ChIP) assay to examine whether Nur77 could bind to the NBRE site *in vivo*. As shown in Fig. 3. PCR amplification of a region, from −400

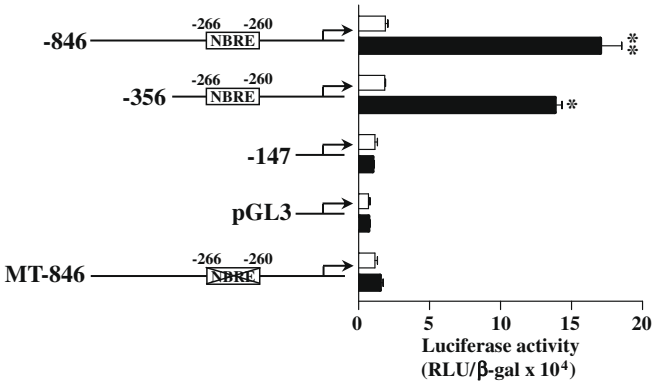

Fig. 2. Identification of the sequence responsive to Nur77 in the human ApoA5 gene promoter. A series of deletion constructs of human ApoA5 luciferase reporters and a construct containing a mutation (cross) of the putative Nur77 binding site (NBRE) were cotransfected with a plasmid expressing Nur77 or the empty plasmid pcDNA3 as control into HepG2 cells. Luciferase activity was normalized to β-galactosidase activity. All experiments were done in triplicates and data represented the means ± SD of three individual experiments. Statically differences from controls are indicated by asterisks ($^{*}P < 0.05$ and $^{**}P < 0.01$).

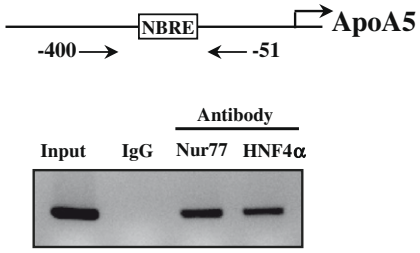

Fig. 3. Recruitment of Nur77 to the human ApoA5 promoter. HepG2 cells were subjected to formaldehyde cross-linking and chromatin fragments were prepared by sonication and immunoprecipitated with indicated specific antibodies. Promoter sequence containing Nur77 binding NBRE sequence was analyzed by PCR using primer sets specific for the human ApoA5 promoter. PCR products were electorphoresed on 1.5% agarose gel. Cell lysate solution (5%) in ChIP dilution buffer was kept aside as "Input". Data represented one of three separate experiments.

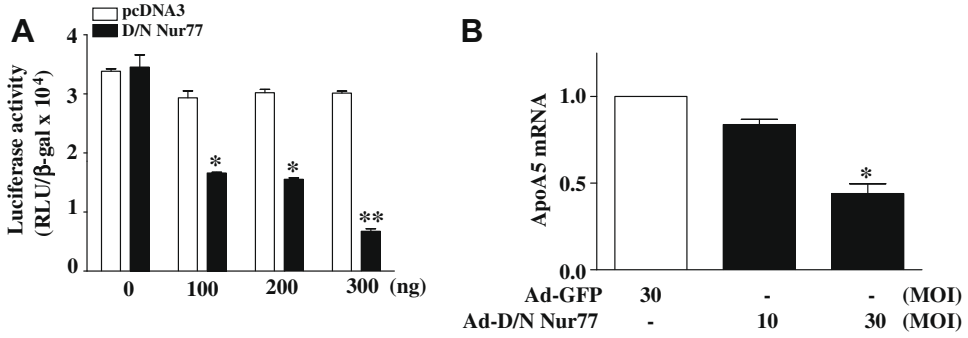

Fig. 4. Effect of dominant negative Nur77 on human ApoA5 promoter activity and mRNA expression. (A and B) HepG2 cells were cotransfected with the human ApoA5 promoter (−846/+62) reporter along with increasing amounts of dominant negative Nur77 (D/N Nur77) plasmid (100, 200 and 300 ng) or empty plasmid pcDNA3 as control. Luciferase activity was normalized to β-galactosidase activity. (B) HepG2 cells were infected with adenoviral vector expression dominant negative Nur77 (Ad-D/N Nur77, 10 and 30 multiplicity of infection, MOI) or control adenovirus (Ad-Mock). Total RNA was isolated for real-time quantitative PCR analysis of human ApoA5 mRNA levels. Numbers above the bars indicated the levels of mRNA relative to controls. All experiments were done in triplicates and data represented the means ± SD of three individual experiments. Statically differences from controls are indicated by asterisks ($^{*}P < 0.05$).

to −50 of the human ApoA5 promoter, containing NBRE site, indicated recruitment of Nur77 to the human ApoA5 promoter region *in vivo*. Similarly, HNF4α was also bound to the NBRE-containing region of the human ApoA5 promoter as expected [18]. Complementary with luciferase reporter assay, our ChIP assay showed a positive signal was obtained from the region from −400 to −50 indicating that a native Nur77 protein complex is formed in the NBRE region *in vivo*.

It has been reported that apparent species differences was observed in the regulation of ApoA5 gene by PPARα and HNF4α between human and mouse [18,26]. We also found that the sequence of NBRE in human ApoA5 promoter is not conserved in murine counterpart (data not shown). To clarify the species-specific regulation of ApoA5 expression, it is necessary to investigate the promoter region of rodent ApoA5.

Finally, we confirmed the involvement of Nur77 in the regulation of human ApoA5 gene expression via blocking of endogenous Nur77 function by overexpression of dominant negative (D/N) Nur77 that prevents transcriptional activity of NR4A receptors [3]. Cotransfection of D/N Nur77 expression plasmid resulted in a dose-dependent decrease of human ApoA5 promoter reporter activity (Fig. 4A). Moreover, quantitative real-time PCR revealed that adenovirus-mediated infection of D/N Nur77 (Ad-D/N Nur77) significantly decreased human ApoA5 mRNA levels compare to the infection of adenovirus empty vector (Ad-Mock) in HepG2 cells (Fig. 4B). Taken together, these results demonstrated that Nur77 plays an important role in the regulation of human ApoA5 gene expression in human hepatoma cells.

In summary, we have identified the human ApoA5 gene as a novel target of the orphan nuclear receptor Nur77. We have demonstrated that Nur77 binds to the specific response element in the human ApoA5 promoter and participates in the regulation of human ApoA5 gene expression in human hepatoma cells.

Acknowledgments

This work was supported by Korea Institute of Oriental Medicine (KIOM) grant funded by the Korea government (K09013) and National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (20090084121).

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