An insulin-inducible transcription factor, SHARP-1, represses transcription of the SIRT1 longevity gene

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\textbf{ABSTRACT}

The rat enhancer of split- and hairy-related protein (SHARP)-1 genes encode insulin-inducible transcriptional repressors. A longevity gene, sirtuin 1 (SIRT1) encodes protein deacetylase. These play an important role in regulating hepatic glucose metabolism. In this study, to evaluate a correlation with these gene expressions, we examined whether SIRT1 effects on expression of the SHARP-1 gene by a treatment with a SIRT1 inhibitor or activator in rat H4IIIE hepatoma cells. Whereas the SIRT1 inhibitor increased the level of SHARP-1 mRNA, the SIRT1 activator decreased it. Next, whether SIRT1 effect on the transcriptional activity of the human SIRT1 gene using luciferase reporter assays was determined. Promoter activity of the SIRT1 gene was specifically repressed by SHARP-1. Further reporter analysis using 5′-deleted or mutated constructs revealed that an E box sequence (5′-CACGTC-3′) of the SIRT1 gene promoter was required for the inhibitory effect of SHARP-1. Thus, we conclude that expressions between the SHARP-1 and the SIRT1 genes show a negative correlation and that SHARP-1 represses transcription of the SIRT1 gene.

\textbf{1. Introduction}

There are two members of the rat enhancer of split- and hairy-related protein (SHARP) family, SHARP-1 (also referred to as the DEC2 and bhlhe41) and SHARP-2 (also referred to as the DECI, Stra13, and bhlhe40). These are basic helix-loop-helix transcriptional repressors and also function as molecular clocks [1]. It has been reported that SHARP-1, SHARP-2, or double knockout mice showed delayed circadian rhythms in glucose metabolism [2,3]. Both SHARP-1 and SHARP-2 form homo- and hetero-dimers and regulate transcription of their target genes via direct binding to the E box sequence (5′-CANNTG-3′) [1]. These genes are ubiquitously expressed and their gene expressions are regulated in a cell type-specific manner by various extracellular stimuli such as growth factors, serum starvation, hypoxia, hormones, nutrient, cytokines, light, and infection [1,3,4]. We reported that both the levels of SHARP-1 and SHARP-2 mRNAs were induced by insulin in the rat liver, primary cultured rat hepatocytes, and highly differentiated H4IIIE rat hepatoma cells [5,6]. Insulin represses transcription of the rat phosphoenolpyruvate carboxykinase (PEPCK) gene. We reported that members of the SHARP family inhibited transcription of the rat PEPCK gene [5,7]. Accordingly, we hypothesize that members of the SHARP family are involved in lowering the blood glucose levels by insulin.

The sirtuin (SIRT) family in mammals has seven isoforms [8]. These function as β-nicotinamide adenine dinucleotide (NAD⁺)-dependent protein deacetylase. SIRT1 deacetylates histones and multiple non-histone target proteins such as p53, FOXO1/3, PGC-1α, and NF-κB [9]. By targeting these proteins, SIRT1 regulates numerous vital signaling pathways, including DNA repair, apoptosis, muscle and fat differentiation, neurogenesis, mitochondrial biogenesis, glucose and insulin homeostasis, hormone secretion, cell stress responses, longevity, and circadian rhythms [9]. It has been reported that an increase of glucose tolerance and a decrease of the levels of blood cholesterol and insulin were observed in transgenic mice overexpressing SIRT1 [10]. On the other hand, SIRT1-knockout mice lost their improved exercise function and prolonged lifespan as confirmed by caloric restriction [11]. These results indicate that SIRT1 is a major factor in these events caused by a caloric restriction. During fasting, glucagon secreted from pancreatic α cells stimulates transcription of the gluconegenic enzyme PEPCK and glucose-6-phosphatase genes via the cyclic AMP (cAMP)/protein kinase A

\textbf{Abbreviations:} SHARP, enhancer of split- and hairy-related protein; PEPCK, phosphoenolpyruvate carboxykinase; NAD⁺, β-nicotinamide adenine dinucleotide; DMEM, Dulbecco’s modified Eagle’s medium; NMN, β-nicotinamide mononucleotide; PCR, polymerase chain reactions; ZHX1, zinc-fingers and homeboxes 1; 36B4, ribosomal protein 36B4

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Fig. 1. A correlation between SHARP-1 and SIRT1 in regulating glucose metabolism in the liver.

signaling pathway. In contrast, after feeding, insulin secreted from pancreatic β cells represses transcription of these genes. In the fasted rat liver, SIRT1 binds to the transcriptional corepressor PGC-1α and deacetylates its lysine residues dependent on NAD⁺, thereby inducing the PEPCk gene expression [12].

Actions of member of the SHARP family and SIRT1 in the expression of the PEPCk gene are reversal. Although they play an important role in regulating glucose metabolism in the liver, the molecular mechanism remains to be determined. The aim of this study was to identify a correlation between the SHARP-1 gene expression and the SIRT1 gene expression (Fig. 1). The findings indicated that the SHARP-1 gene and the SIRT1 gene negatively regulate their expression each other.

2. Materials and methods

2.1. Materials

Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), β-nicotinamide mononucleotide (NMN), GenElute Plasmid Miniprep Kit, and rabbit anti-FLAG antibody (F7425) were purchased from Sigma-Aldrich Co. (Saint Louis, U.S.A.). Streptomyein and penicillin G were purchased from Meijiseika (Tokyo, Japan). Sirtinol was from Sigma-Aldrich Co. (Saint Louis, U.S.A.). Streptomycin and penicillin G were purchased from Meijiseika (Tokyo, Japan). Sirtinol was from Sigma-Aldrich Co. (Saint Louis, U.S.A.).

2.2. Cells and cell culture

Rat H4IIE hepatoma cells were a generous gift from Dr. Daryl K. Granner (Vanderbilt University, U.S.A.). HepG2 cells were purchased from the JCRB Cell Bank (Osaka, Japan). These cells were grown in DMEM supplemented with 10% FBS, 100 μg/ml streptomycin and 100 units/ml penicillin G at 37 °C in a 5% CO₂ incubator. One million H4IIE cells were seeded in a 6-cm dish. After 24 h, the medium was replaced with serum-free DMEM and then cultured for another 24 h. At 2 h after the medium was replaced with the same medium, the cells were treated with the indicated concentrations of sirtinol or NMN for various times.

2.3. Real-time polymerase chain reactions (PCRs)

Preparation of total RNA from various H4IIE cells, reverse transcription, and real-time PCRs were previously described [13-16].

2.4. Construction of plasmids

A BamHI/HindIII fragment containing the nucleotide sequences between −831 and +1 or −809 and +1 of the human SIRT1 gene was synthesized by Life technologies (Carlsbad, USA). Each fragment was subcloned into the BglII/HindIII sites of the pGL4.11 plasmid to produce the phSIRT1/Luc-831 and phSIRT1/Luc-809, respectively. The pCMV-SHARP-1 and pZHX1/Luc-88 plasmids were previously described [16,17]. The pCMV-SIRT1 plasmid which expresses SIRT1 in a mammalian cell was a generous gift from Dr. Youichi Tajima (Tokyo Metropolitan Institute of Medical Science, Tokyo).

The phSIRT1/Luc-831 plasmid was used as the template. PCR was performed in combinations of the following primers, 5′-CGCGGGGTCATGGGGTTTAAATCTCCCGCA-3′ and 5′-CGCGGGTACCTGGGGTTTAAATCTCCCGCA-3′, 5′-GGGGCGGCGATGGGGCGGGTCATGCGATGGGGTTTAAATCTCCCGCA-3′ and 5′-GGGGCGGCGATGGGGCGGGTCATGCGATGGGGTTTAAATCTCCCGCA-3′, respectively. PCR products were digested with BamHI/HindIII, then each fragment was subcloned into the BglII/HindIII sites of the pGL4.11 plasmid to give the phSIRT1/Luc-183 and the phSIRT1/Luc-104, respectively. Site-directed mutagenesis was carried out using the Quik change Lightning Site-Directed Mutagenesis kit. The phSIRT1/Luc-183 plasmid was used as a template for mutagenesis to obtain the phSIRT1/Luc-183 mat with a disrupted E box (GATCCG) (mutated bases are underlined). PCR was performed in a combination of primers, 5′-GGGGGCGGCGATGGGGCGGGTCATGCGATGGGGTTTAAATCTCCCGCA-3′ and 5′-GGGGGCGGCGATGGGGCGGGTCATGCGATGGGGTTTAAATCTCCCGCA-3′, respectively. The pSHARP-1/Luc-1500 plasmid was previously described [18]. The nucleotide sequences of all inserts were confirmed.

2.5. Western blot analysis

H4IIE or HepG2 cells transfected with 0.5 μg or 25 ng of the pCMV-Tag or pCMV-SHARP-1, respectively. Procedures for preparation of whole cell lysates and western blot analysis were previously described [15]. Briefly, whole cell lysates (20 μg) were resolved with 8% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto a PVDF membrane for western blot analysis. The SIRT1 antibody (1:400 dilution), the FLAG antibody (1:500 dilution), and the β-actin (1:1000 dilution) were used as primary antibodies. Horseradish peroxidase conjugate-antibody anti-rabbit IgG antibody (1:4000 or 5000 dilution) or horseradish peroxidase conjugate-antibody anti-mouse IgG antibody (1:4000 dilution) was employed as the secondary antibody. Visualization and analysis of the proteins were also previously described [15].

2.6. Transient DNA transfections and luciferase reporter assays

All plasmids were prepared using the GenoPure Plasmid Maxi kit. A calcium-phosphate method was employed for transfection into H4IIE cells [19]. Briefly, H4IIE cells were co-transfected with 8 μg of a reporter plasmid and 0.1 μg of the phRL-CMV plasmid. After transfection, the medium was replaced with serum-free DMEM and cells were cultured for 16 h.

Fifty thousand HepG2 cells were seeded in a 24 wells plate. Cells
were transfected with 200 ng of a reporter plasmid, the indicated amount of an effector plasmid, and 0.001 ng of the phRL-CMV using the lipofection method. The total amount of plasmid was adjusted by the addition of the pCMV-Tag2 plasmid, if necessary. After 3 h, the medium was replaced with DMEM supplemented with 10% FBS and antibiotics, and cells were cultured for another 48 h.

Firefly and sea pansy luciferase assays were carried out using the Dual Luciferase Reporter Assay System. Procedures were performed according to the manufacturer’s recommended protocol. Luciferase activities were determined by a Berthold Lumat model LB 9507 (Wildbad, Germany). Firefly luciferase activities (relative light units) were normalized by sea pansy luciferase activities.

2.7. Statistical analysis

All experiments were carried out at least three times. Data were represented as the mean and standard error and analyzed by one-way ANOVA followed by Fisher’s protected LSD multiple comparison test.

3. Results

3.1. SIRT1 negatively regulates the SHARP-1 gene expression

SIRT1 stimulates transcription of the PEPCK gene, while member of the SHARP family repress it [5-7,12]. To evaluate a correlation with these gene expressions, we investigated whether SIRT1 affects expression of mRNA of the SHARP-1. Either sirtinol as a SIRT1 inhibitor or NMN as a SIRT1 activator was employed. First, H4IIE cells were treated with various concentrations of sirtinol for 2 h. The level of SHARP-1 mRNA significantly increased in a dose-dependent manner (Fig. 2A).

Next, we determined whether SHARP-1 affects transcriptional activity of the SIRT1 gene. We employed the phSIRT1/Luc-831 plasmid as a reporter plasmid in which the nucleotide sequences between −831 and +1 of the human SIRT1 gene were inserted into a firefly luciferase reporter plasmid. The phRL-CMV plasmid is a cytomegalovirus enhancer/promoter-driven firefly luciferase expression plasmid. The plasmid expressing SHARP-1 was co-transfected with the reporter and the phRL-CMV plasmids into H4IIE cells. When the SHARP-1 expression plasmid was co-transfected, the luciferase activities were dramatically decreased to 50% (Fig. 3A). We confirmed the production of SHARP-1 protein in H4IIE cells by western blot analysis using the antibody against FLAG (Fig. 3B).

Then, to confirm whether SHARP-1 specifically affects the human SIRT1 gene promoter, we used another hepatic cell line, HepG2 cells. HepG2 cells are easier transfected with plasmids than H4IIE cells. The pZHX1/Luc-88 plasmid in which the nucleotide sequences between −88 and +1 of the mouse zinc-fingers and homeoboxes 1 (ZHX1) transcriptional repressor gene were inserted into the reporter plasmid was also employed as a negative control reporter plasmid. The luciferase activities of the phSIRT1/Luc-831 decreased by a co-transfection with the SHARP-1 as well as H4IIE cells (Fig. 3C). In contrast, promoter activity from the pZHX1/Luc-88 plasmid was not changed by co-transfection with these plasmids (Fig. 3C). We confirmed the production of SHARP-1 protein in HepG2 cells by western blot analysis using the antibody against FLAG (Fig. 3D).

These results indicate that SHARP-1 specifically represses the transcriptional activity of the human SIRT1 gene.

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3.3. SHARP-1 represses promoter activity of the SIRT1 gene via an E box

In order to map a SHARP-1 responsive region of the SIRT1 gene, we prepared three 5′-deletion constructs. The phSIRT1/Luc-809, the phSIRT1/Luc-183, and the phSIRT1/Luc-104 plasmids contained nucleotide sequences between −809 and +1, −183 and +1, and −104 and +1 of the human SIRT1 gene, respectively. When the SHARP-1 expression plasmid was co-transfected with these reporter plasmids, promoter activities of the phSIRT1/Luc-809 and the phSIRT1/Luc-183 were decreased (Fig. 4A). However, promoter activity of the phSIRT1/Luc-104 was not affected (Fig. 4A). In contrast, SHARP-1 had no change

**Fig. 2. Effect of sirtinol or NMN on the level of SHARP-1 mRNA.** Total RNA was prepared from H4IIE cells under various conditions. The levels of SHARP-1 and 36B4 mRNAs were determined. Each column and bar represents the mean and standard error of the ratio of the levels of SHARP-1 and 36B4 mRNAs of three or four independent experiments. The value of the ratio in the absence of inhibitor or activator was set to 1. (A) H4IIE cells were treated for 2 h with the concentrations of sirtinol indicated on the bottom. (B) Cells were cultured in the absence or presence of 100 μM sirtinol for the times indicated on the bottom. (C) H4IIE cells were treated for 4 h with the concentrations of NMN indicated on the bottom. (D) Cells were cultured in the absence or presence of 50 μM NMN for the times indicated on the bottom. (E) Whole cell lysates were prepared from H4IIE cells treated with the concentrations of NMN indicated on the upper for 4 h. Whole cell lysates (20 μg/lane) were resolved using an 8% SDS-PAGE gel and transferred onto a PVDF membrane for western blot analysis. Rabbit anti-SIRT1 antibody (SIRT1), or mouse anti-rat β-actin antibody (β-actin) were used as primary antibody. *P < 0.05; **P < 0.01; ***P < 0.001.
the promoter activity of the empty vector, the pGL4.11 plasmid (Fig. 4A).

These results indicate that the region of −183 to −105 of the SIRT1 gene contains an important region responding to SHARP-1.

SHARP-1 binds to the E box sequence of the target genes and represses their transcription [1]. In the region from −831 to +1 of the SIRT1 gene, there are eight E box sequences, two of which are CACGCTG. An CACGTG E box sequence existed in the region from −183 to −105 of the SIRT1 gene. We then investigated whether the E box sequence is involved in a decrease of promoter activity by SHARP-1. The phSIRT1/Luc-183 was mutated in its E box sequence to produce the phSIRT1/Luc-183 mut. The inhibitory effect on promoter activity by SHARP-1 disappeared in phSIRT1/Luc-183 mut (Fig. 4B).

This result indicates that SHARP-1 represses promoter activity of the SIRT1 gene via an E box 5′-CACGTG-3′ locating from −110 to −105 of the gene.

3.4. Effect of SIRT1 on promoter activity of the SHARP-1 gene

SIRT1 acts as a protein deacetylase [8]. It is known that deacetylation of histone proteins decreases transcriptional activities. We determined whether SIRT1 affects promoter activity of the rat SHARP-1 gene. A SIRT1 expression plasmid was co-transfected with several reporter plasmids into HepG2 cells. The nucleotide sequences between −1500 and −1 of the rat SHARP-1 gene was inserted into a luciferase reporter plasmid to obtain the pSHARP-1/Luc-1500 plasmid. When the reporter plasmid was co-transfected with the SIRT1 expression plasmid, SIRT1 had no effect on the promoter activity within the investigated condition (Fig. 5A). We confirmed the production of SIRT1 protein in HepG2 cells by western blot analysis using the antibody against SIRT1 (Fig. 5B).

This result suggests that a SIRT1-responsive element does not exist in the nucleotide sequences between −1500 and −1 of the rat SHARP-1 gene.

4. Discussion

A correlation of expressions between the SHARP-1 gene and SIRT1 gene was examined. Expression of the SHARP-1 gene was elevated by a SIRT1 inhibitor and down-regulated by a SIRT1 activator (Fig. 2). Promoter activity of the SIRT1 gene was specifically inhibited by SHARP-1 (Fig. 3). Further analysis using 5′-deleted or mutated constructs showed that a CACGCTG E box sequence of the SIRT1 gene promoter was required for the inhibitory effect of SHARP-1 (Fig. 4). Therefore, these findings suggest that expression between the SHARP-1 gene and the SIRT1 gene was a negative correlation.

We have found that the SIRT1 gene is a novel target gene of SHARP-1. There are no reports involving in transcription factors directly acting on the promoter region of the SIRT1 gene. SHARP-1 acted on a CACGCTG E box existing from −110 to −105 in the promoter region. It has been reported that SHARP-1 has strong affinity with CACGCTG but not CACCTG and CAGCTG [20]. In addition, SHARP-1 represses transcription...
of the clock, *Per* 1 through a binding to a CACGTG sequence in the promoter region [21]. Therefore, it seems to be true that SIRT-1 binds to the CACGTG sequence of the SIRT1 gene.

Promoter activity from the phSIRT1/Luc-183 plasmid which is mutated in the E box sequence was higher than that from the phSIRT1/Luc-104 plasmid but lower than that from the phSIRT1/Luc-183 plasmid (data not shown). This suggests that this E box sequence is necessary for the basal level of the SIRT1 gene expression and that other positive elements should exist in the region of −183 to −105.

We elucidated that SIRT1 may inhibit the SIRT-1 gene expression (Fig. 2). We then examined whether SIRT1 affects the promoter activity of the rat SIRT-1 gene using a luciferase reporter gene assay. The nucleotide sequences between −1501 and −1 of the rat SIRT-1 gene contain some transcriptional regulatory elements essential for basal expression and regulation by hypoxia [22]. However, this region did not respond to the SIRT1 expression (Fig. 5). Therefore, the response elements should exist in a region other than between −1501 and −1 of the rat SIRT-1 gene.

In this study, our results showed that SIRT1 repressed the SIRT-1 gene expression, SIRT-1 inhibited promoter activity of the SIRT1 gene, and SIRT1 and SHARP-1 inhibited the expressions of their genes each other. These findings suggest that SIRT1 and SHARP-1 regulate hepatic glucose metabolism by mutually exclusive gene expressions. This interrelationship of expressions between these genes in rat hepatoma cells should provide new insight into molecular mechanism by which gene expression in glucose homeostasis is regulated in the liver.

Further studies will be needed to clarify whether SIRT-1 actually binds to the SIRT1 gene promoter via a protein-DNA interaction, which is a cis-acting element of the rat SIRT-1 gene respond to SIRT1, and which signal transduction pathways are involved in expression of both genes.

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CRediT authorship contribution statement
Kouke Asano: Investigation, Formal analysis, Writing - original draft. Akiko Tsukada: Investigation, Formal analysis. Katsunori Takagi: Resources, Data curation. Kazuya Yamada: Conceptualization, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest
K. Asano, A. Tsukada, K. Takagi, and K. Yamada have no conflicts of interest.

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