Biochemical and Biophysical Research Communications 400 (2010) 175–180

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

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

Transcriptional regulation of a brown adipocyte-specific gene, UCP1, by KLF11 and KLF15

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ARTICLE INFO

Article history:
Received 10 August 2010
Available online 13 August 2010

Keywords:
Brown adipocyte
UCP1
Promoter
KLF11
KLF15

ABSTRACT

Several growth factors and transcription factors have been reported to play important roles in brown adipocyte differentiation and modulation of thermogenic gene expression, especially the expression of UCP1. In this study, we focused on KLF11 and KLF15, which were expressed highly in brown adipose tissue. Our data demonstrated that KLF11 and KLF15 interacted directly with the UCP1 promoter using GC-box and GT-boxes, respectively. Co-transfection of KLF11 and KLF15 in the mesenchymal stem cell line muBM3.1 during brown adipocyte differentiation enhanced the expression level of UCP1. KLF11, but not KLF15, was essential for UCP1 expression during brown adipocyte differentiation of muBM3.1.

1. Introduction

Brown adipocytes are multilocular lipid-storage cells that play a crucial role in non-shivering thermogenesis [1]. The cells are characterized by their high content of large mitochondria packed with cristae that contain uncoupling protein 1 (UCP1). UCP1 uncouples oxidation of fuel substances from ATP production, resulting in the generation of heat. Expression of UCP1 and thereby non-shivering thermogenesis are regulated by various factors, including cold, diet, leptin, corticosterone and obesity.

Several growth factors and transcription factors have been reported to play important roles in the final stage of brown adipose tissue development and modulation of thermogenic gene expression, especially the expression of UCP1 [2,3]. Among these, BMP-7 [4], PRDM16 [5] and PGC-1α [6] have been suggested to have central roles in brown adipocyte differentiation and UCP1 regulation. Studies have also been performed with UCP1 promoters, and CRE, TRE/RARE and PPRE have been reported to control UCP1 gene expression [7]. However, little is known about the molecular basis of UCP1 promoter system.

Recent studies have revealed that key transcription factors regulate cell lineage and their fate [8,9]. Surprisingly, pluripotent stem cells were even induced from differentiated cells by induction of several transcription factors including one of the KLF family proteins, KLF4 [10]. Krüppel-like factors (KLFs) are a subclass of the zinc-finger family of transcriptional regulators homologous to the Drosophila gap gene Kruppel, a critical regulator of fly body patterning via its function as a transcriptional repressor [11]. Members of this family can function as activators or repressors depending on which promoter they bind to and the coregulators with which they interact. They bind to GC-rich sequences including GC-boxes (CGCCC or GCGGG) and GT-boxes (CACCC or GTGGG).

We recently examined series of recombinant KLF proteins to identify transcription factors that bind to the p21 promoter [12]. We preliminary applied these series of KLFs to the UCP1 promoter. KLF11 and KLF15 were identified as candidates of activator of the UCP1 promoter. In the present study, we demonstrated that KLF11 and KLF15 enhanced UCP1 expression level during brown adipocyte differentiation through their direct interaction with specific binding domains of the UCP1 promoter.

2. Materials and methods

2.1. Cell culture

A human embryo kidney cell line, HEK293, was obtained from RIKEN CELL BANK (Tsukuba, Japan) and maintained in Dulbecco's

Abbreviations: UCP, uncoupling protein; KLF, Krüppel-like factor; EMSA, electrophoretic mobility shift assay; siRNA, small interfering RNA.

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doi:10.1016/j.bbrc.2010.08.039

modified MEM (DMEM) supplemented with a nutrient mixture of Hum's F-12 (Invitrogen, Carlsbad, CA) and 10% fetal bovine serum (FBS). A mouse bone marrow-derived mesenchymal stem cell line, muBM3.1, was established and maintained as previously described [13]. To induce differentiation into white adipocytes, muBM3.1 cells were cultured in DMEM supplemented with 10% FBS, 500 μM isobutyl metylxanthine (MP Biomedicals, Irvine, CA), 1 μM dexamethasone (Merk Banyu Pharmaceutical, Tokyo, Japan), and 1× insulin-transferrin-selenium-A containing sodium pyruvate (Invitrogen). For differentiation into brown adipocytes, the cells were cultured with 1 μM troglitazone (Cayman Chemical Company, Ann Arbor, MI) in DMEM supplemented with 10% FBS.

2.2. Western blot analysis

Liver, white-adipose and brown-adipose tissues were isolated from 6-week-old BALB/c male mice. Western blot analysis was performed under conventional conditions [12] using 10 μg of protein extracts. The antibodies used were as follows: rabbit anti-UCP1, mouse anti-KLF11 and goat anti-KLF15 antibodies (Abcam, Cambridge, MA); mouse anti-tubulin antibody (Sigma–Aldrich, St. Louis, MO); HRP-linked anti-mouse and anti-rabbit IgG antibodies (Cell Signaling Technologies, Beverly, MA); and HRP-linked anti-goat IgG antibody (MBL, Nagoya, Japan). Intensity of bands was quantified by ImageJ software (National Institute of Health; freeware from http://rsb.info.nih.gov/ij/).

2.3. Expression constructs and luciferase reporter assay

Mammalian expression constructs carrying KLF family genes were prepared as described previously [12]. The mouse UCP1 promoter covering a region from −3162 to −122 (3051 bp) was amplified from mouse genomic DNA by PCR and ligated into pGL4.14 luciferase reporter vector (Promega, Madison, WI). Putative KLF binding sites, cis-acting Sp1 response elements (Sp1REs), were identified by MOTIF Search (Kyoto University Bioinfomatics Center; http://motif.genome.jp/). Based on the results of MOTIF Search (Supplementary Fig. S1), a series of 5′ deletion constructs of the mouse UCP1 promoter (−1666 to −122 (1555 bp), −1226 to −122 (1115 bp), −874 to −122 (763 bp), and −522 to −122 (411 bp)) was prepared. The nucleotide sequence of each construct was confirmed by DNA sequencing. The partial promoter fragments were conjugated to luciferase to make reporter plasmids. HEK293 cells were transfected with the reporter plasmids and pTracer-EF/lacZ vector (Invitrogen) carrying each KLF expression construct using FuGENE-HD Transfection Reagent (Roche, Basel, Switzerland). Luciferase activity of transfected cells was measured using a Luciferase Repoter Assay System (LucLite; Packard Bioscience, Groningen, Netherlands). The luciferase activity was normalized to co-transfected β-galactosidase activity.

2.4. Electrophoretic mobility shift assay (EMSA)

EMSA was performed as described previously (12). We used putative KLF binding sites of the mouse UCP1 promoter, Sp1REs, which were searched in silico as described above (Supplementary Fig. S1). The probes used were as follows: Sp1RE-1, 5′-cctgcccctgcccctctt-3′; Sp1RE-2, 5′-ttctccc**cgccc**cccattc-3′; Sp1RE-3, 5′agtttcccagcccccagg-3′; Sp1RE-4, 5′-gaaa**cacccc**ccccccacacac-3′; Sp1RE-5, 5′-tcatccc**cacccc**catcc-3′; and Sp1RE-6, 5′-agggaaccagcccctgct-3′(bold letters indicate GC- or GT-boxes).

2.5. DNA pull-down assay

Biotinylated Sp1REs-1 to -6 of the mouse UCP-1 promoter were purchased from Hokkaido System Science (Sapporo, Japan). They were bound to streptavidine agarose (Invitrogen) and then incubated with nuclear extracts pretreated with excess of streptavidin agarose in a buffer (0.1% TritonX-100, 60 mM KCl, 5 mM $MgCl_2$, 0.1 mM EDTA, 50 mg/ml poly (dI-dC), 1 mM dithiothreitol (DTT), 5% glycerol, 10 μg/ml leupeptin, 10 μg/ml aprotinin, 200 μg/ml phenylmethanesulfonyl fluoride and 20 mM Hepes/pH 7.4) at 4 °C for 120 min. After washing the agarose beads, bound proteins were fractionated by SDS–PAGE.

2.6. Overexpression of KLF11 and KLF15

muBM3.1 cells were transfected with KLF11- and KLF15-expression vectors (pDNR-CMV-KLF11 and pDNR-CMV-KLF15) using a mixture of lipofectamine LTX and PLUS reagent (Invitrogen). Twenty-four hours after transfection, the culture medium was changed to a medium to induce differentiation either into brown adipocytes or white adipocytes.

2.7. siRNAs

siRNAs against mouse KLF11 (Stealh siRNA: 3′-UGCAUGUGG ACCUUUCGCUGUCAUG-5′), mouse KLF15 (mixture of three Stealth select siRNAs: 3′-UUUGAGGGCAGGUUCAAGUUGGAGG-5′, 3′-AUU UCUUCUCGCACACGGGACACUG-5′, UUCAGGGAAGCAGAAAUGUUC CUCC-5′) and control siRNA (Stealth RNAi Negative Control High GC Duplex) were purchased from Invitrogen. The siRNAs were transfected using Lipofectamine RNAiMAX regent (Invitrogen).

3. Results

3.1. Expression of KLF11 and KLF15 in adipose tissues and adipogenic cells

At first we screened for KLF proteins that are potentially involved in regulation of the UCP1 gene. HEK293 cells were transfected with a reporter construct (UCP1-luc) and each KLF expression construct (KLF2–16), and then luciferase activity was determined (Supplementary Fig. S2). KLF11 and KLF15 among the 15 KLF family members were shown to significantly increase the luciferase activity.

Next we examined whether these potential regulators of the UCP1 promoter, KLF11 and KLF15 are expressed in adipose tissues. KLF11 and KLF15 were detected in both white and brown-adipose tissues (Fig. 1A). As expected, UCP1 was strongly expressed only in the brown adipose tissue. We used muBM3.1 cells for analyzing roles of KLF11 and KLF15 in regulation of the UCP1 gene. The cell line was established from mouse bone marrow under conditions similar to those described previously [13]. Immunocytochemical and biological characterization showed that muBM3.1 cells are categorized into mesenchymal stem cells (Supplementary Figs. S3 and 4). KLF11 and KLF15 are expressed at low levels in muBM3.1 cells (Fig. 1B). When the cells were induced to differentiate, levels of KLF11 and KLF15 were enhanced in brown adipogenic lineages.

3.2. Activation of the UCP1 promoter via direct binding of KLF11 and KLF15 to defined Sp1REs

To identify potential binding sites of the UCP1 promoter to KLF11 and/or KLF15, a sequence of 3051 bp in size was analyzed using MOTIF Search and 6 Sp1REs (Sp1RE–Sp1RE-6) were identified (Supplementary Fig. S1). Based on the data, we made deletion fragments of the UCP1 promoter and inserted each of them into a reporter plasmid (Fig. 2A). A luciferase reporter assay using a plasmid expressing KLF11 resulted in a high level of induction of

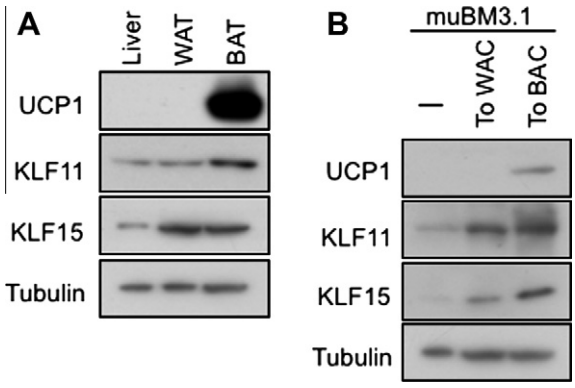

Fig. 1. Expression of UCP1, KLF11 and KLF15 in mouse tissues (A) and in muBM3.1 cells (B) determined by Western blot analysis. WAT, white adipose tissue; BAT, brown adipose tissue. muBM3.1 cells were induced to differentiate into white adipocytes (To WAC) or into brown adipocytes (To BAC) under the conditions described in Section 2 Tubulin was used as a control for applied amounts of protein.

luciferase activity when co-transfected with the reporter plasmids containing Sp1RE-1–Sp1RE-3 but not with those lacking Sp1RE-1–Sp1RE-3, indicating that Sp1RE-1–Sp1RE-3 are potential responsive elements. In accordance with this, an EMSA DNA probes corresponding to each Sp1RE and nuclear extract of KLF11-transfected HEK293 cells revealed that transfection of KLF11 resulted in a gel shift of Sp1RE-2 (Fig. 2B). In case of KLF15, moderate induction of luciferase activity was observed when co-transfected with the plasmids at least one of the Sp1REs and positions of Sp1RE-4 and Sp1RE-5 were shifted in the gel. Thus the functional binding elements for KLF15 remain obscure.

To examine whether KLF11 and KLF15 directly bind to the UCP1 promoter, we performed a DNA pull-down assay using the same nuclear extracts as those used in the EMSA after confirming expression of transfected KLA11 and KLF15 (Fig. 3A). KLF11 was pulled down with Sp1RE-2 and KLF15 was pulled down with Sp1RE-4 and Sp1RE-5 (Fig. 3B), indicating that KLF11 and KLF15 directly bind to the corresponding Sp1 responsive elements.

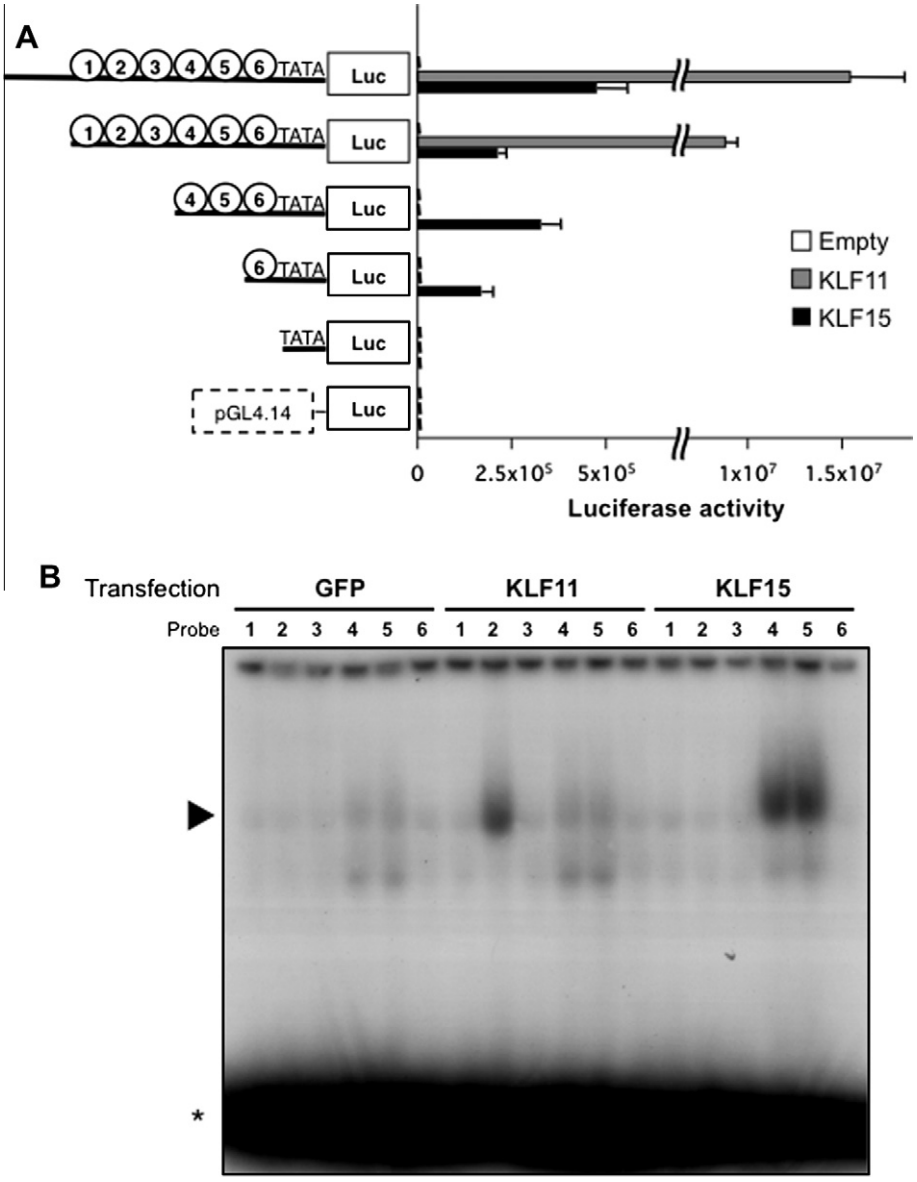

Fig. 2. A luciferase reporter assay (A) and EMSA (B) to determine regions of the UCP1 promoter responsive to KLF11 and KLF15. (A) Serial deletion constructs of the mouse UCP1 promoter and either KLF11 or KLF15 were transfected into HEK293 cells. Circled numbers indicated putative KLF binding sites (Sp1RE-1, -2, -3, -4, -5, and -6). (B) The EMSA was performed using the putative KLF binding sequences as probes and nuclear extracts from HEK293 cells pre-transfected with GFP, KLF11 or KLF15. Arrowhead indicates the position of shifted bands.

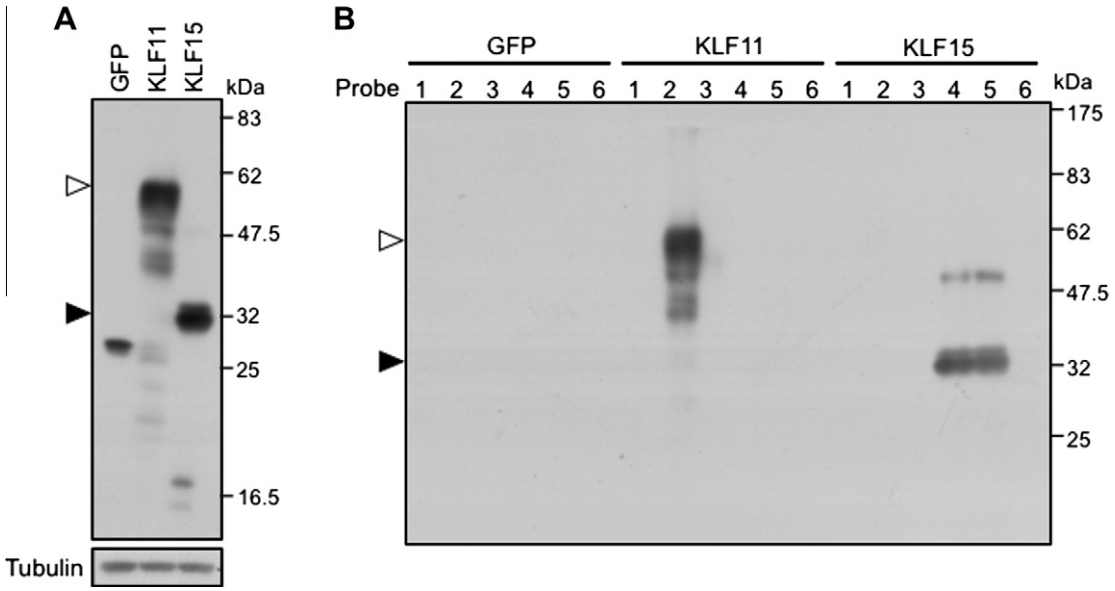

Fig. 3. Direct binding of KLF11 and KLF15 to Sp1REs of the UCP1 promoter *in vitro*. (A) Expression of genes transfected into HEK293 cells. Western blot analysis was performed using a mixture of antibodies against GFP, KLF11 and KLF15.(B) A DNA pull-down assay using biotinylated fragments of putative KLF binding sites (Sp1RE-1, -2, -3, -4, -5, and -6) incubated with nuclear extracts prepared as described in the legend for Fig. 2. Open and closed arrowheads indicate KLF11 and KLF15, respectively.

3.3. Crucial role of KLF11 and KLF15 in the induction of UCP1 during brown adipogenic differentiation of muBM3.1 cells

To determine whether KLF11 and KLF15 play a role in regulation of the endogenous UCP1 gene in cells, we examined the expression of UCP1 after transfecting KLF11 and/or KLF15 into muBM3.1 cells during differentiation processes into white and brown adipocytes (Fig. 4). When induced to differentiate into brown adipocytes, the cells expressed UCP1 at an appreciable level, which was clearly enhanced upon forced expression of KLF11 (Fig. 4A). Overexpression of KLF15 did not affect UCP1 expression but greatly enhanced the expression level of UCP1 when co-transfected with KLF11. The quantitated data are shown in Fig. 4B. Expression level of UCP1 in the differentiating muBM3.1 cells to brown adipocytes was much lower than that in brown adipose tissue, but transfection of KLF11 and KLF15 enhanced the expression level to about 40% of the level observed in brown adipose tissue (Fig. 4C and D).

To know whether KLF11 and/or KLF15 are essential for muBM3.1 cells to differentiate into brown adipocytes, differentiating muBM3.1 cells were transfected with siRNAs for KLF11 and/or KLF15. UCP1 protein expression was completely suppressed by KLF11 siRNA, whereas the inhibitory effect of KLF15 siRNA was partial (Fig. 4E).

4. Discussion

The main function of brown adipose tissue is to generate heat by non-shivering thermogenesis. This function depends on UCP-1, a BAT-specific protein present only in the inner mitochondorial membrane of brown adipocytes [14]. Being involved in brown adipocyte differentiation, PPARγ was reported to regulate UCP1 expression in cooperation with PCG-1α [2] or PRDM16 [5]. In our preliminary study on the KLF family, we identified several candidates of UCP1 activator (Supplementary Fig. S2). One of them, KLF5, was already known to be a key regulator of adipocyte differentiation and to bind to the PPARγ promoter [15]. Expression of the other candidates, KLF11 and KLF15, was moderately enhanced in brown adipose tissue and differentiating bone marrow-derived mesenchymal stem cells into brown adipocytes (Fig. 1).

KLF11 has been shown to be mainly expressed in pancreatic β cells and to be associated with type 2 diabetes [16]. In pancreatic β cells, a GC-box of the insulin gene promoter is a binding target of KLF11. Our results revealed that KLF11 also bound to a GC-box of the UCP1 promoter and that the binding was essential for UCP1 expression during brown adipocyte differentiation (Figs. 2 and 3). KLF15 is expressed in multiple tissues with strong expression in the liver and kidney. KLF15 was reported to play an important role in the regulation of gluconeogenesis [17]. Recently, KLF15 was shown to regulate white adipogenesis through its regulation of PPARγ expression, but potential binding sites of the PPARγ promoter were not identified [18]. Our data showed that KLF15 bound to GT-boxes of the UCP1 promoter to increase its expression, but the binding was not essential for differentiation (Figs. 2–4). During brown adipocyte differentiation of muBM3.1 cells, expression of KLF11 and that of KLF15 were rapidly induced and remained at high levels (Supplementary Fig. S5). On the other hand, expression of UCP1 was first induced on the second day and increased gradually. These findings indicated the importance of the KLF proteins, but KLF11 and/or KLF15 could not initiate brown adipocyte differentiation (Fig. 4A). Thus, activation of KLF11 and/or KLF15 was necessary but not sufficient to induce brown adipocyte differentiation.

Recently, several KLF family proteins have been reported to control white adipocyte differentiation. KLF2 inhibits differentiation of adipocyte progenitor cells by acting as a repressor for the PPARγ promoter [19]. KLF4 and KLF5 function as early activators of white adipocyte differentiation [15,20] and KLF15 regulates the late stage of white adipocyte differentiation [18]. Such a cascade interaction of KLF family proteins is thought to play a critical role during white adipocyte differentiation. Some of those KLF family proteins, e.g., KLF15, may be shared by the brown adipocyte differentiation, and the others, e.g., KLF11, may be specific to brown adipocytes. These KLF family proteins may coorperate to regulate brown adipocyte differentiation. Further studies are needed to understand the functional regulation of UCP1 expression and brown adipocyte differentiation by KLF family proteins.

In conclusion, we identified binding sites for KLF11 and KLF15 in the UCP1 promoter. Cooperative action of KLF11 and KLF15 on the UCP1 promoter was essential for induction of UCP1 in the process of brown adipocyte differentiation of mesenchymal stem cells.

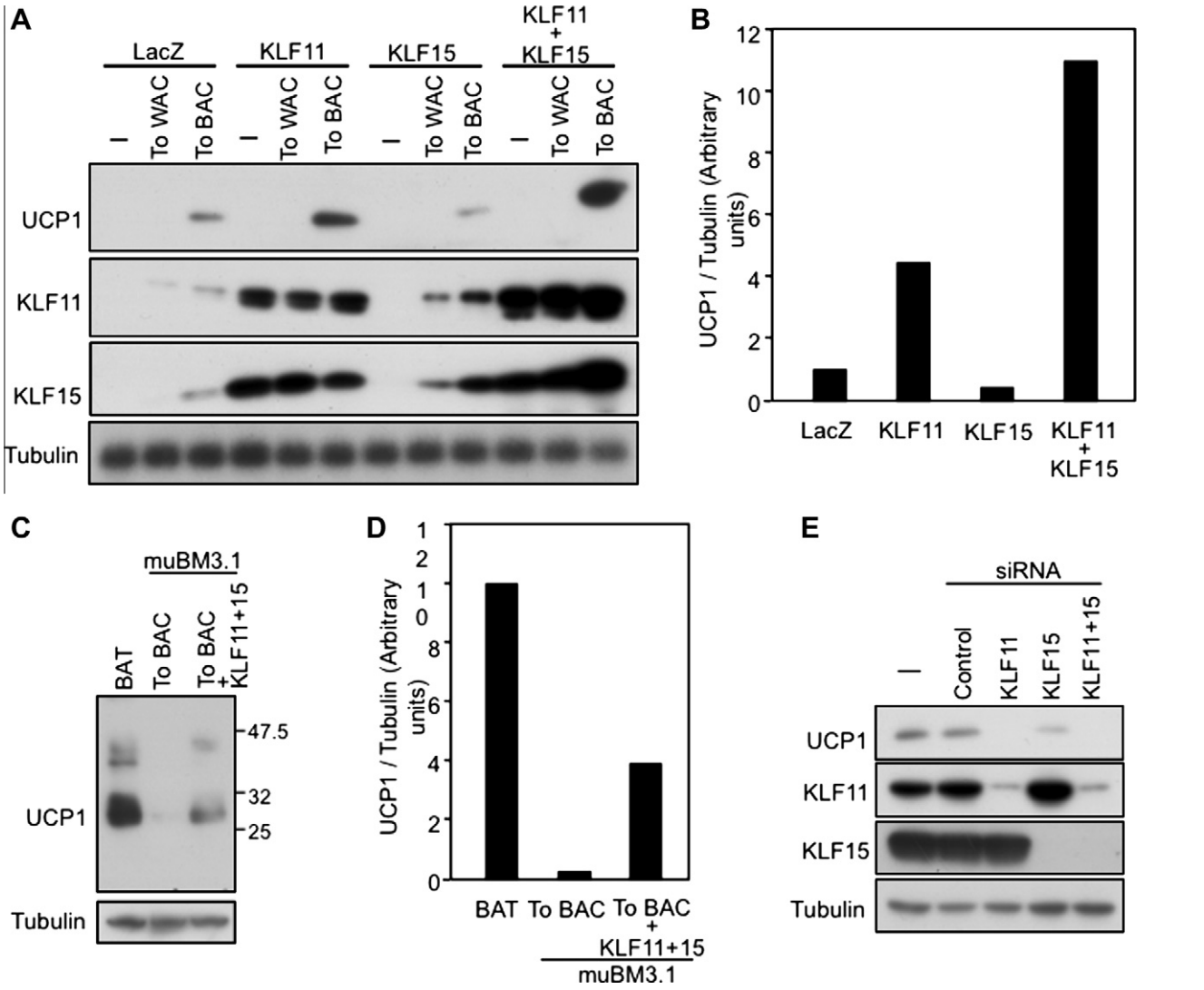

Fig. 4. Crucial role of KLF11 and KLF15 in the induction of UCP1 during brown adipogenic differentiation of muBM3.1 cells. (A–D) Induction of UCP1 by forced expression of KLF11 and KLF15. muBM3.1 cells were transfected with KLF11 and KLF15 48 h prior to the induction of differentiation into white adipocytes (To WAC) or into brown adipocytes (To BAC) for 7 days (A). Western blot analysis was performed for UCP1, KLF11 and KLF15. UCP1 expression level in muBM3.1 cells after brown adipocyte differentiation was quantified (B). Comparison of UCP1 protein level in brown adipose tissue (BAT) with that in muBM3.1 cells in the process to differentiate into brown adipocytes (C). Quantitated levels of UCP1 (D). Reduction of UCP1 by siRNAs against KLF11 and KLF15 (E). Immediately after transfection of siRNAs against KLF11 and KLF15, muBM3.1 cells were induced to differentiate into brown adipocytes for 6 days. On the third day, application of siRNA was repeated.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2010.08.039.

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