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Modulation of immediate early gene expression by tristetraprolin in the differentiation of 3T3-L1 cells

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Abstract

Tristetraprolin (TTP) is a zinc-finger-containing AU-rich elements (ARE)-binding protein. AREs presented in the 3′untranslated region (UTR) of mRNAs from many proto-oncogenes, cytokines, and growth factors may be targets for regulation of messenger RNA stability. In this study, we observed that many immediate early genes (IEGs) were induced during the early differentiation of 3T3-L1 preadipocytes and their ARE-containing transcripts were degraded rapidly. Immunoprecipitation followed by RT-PCR analysis showed that two of IEG mRNAs, COX-2 (cyclooxygenase-2) and MKP-1 (mitogen-activated protein kinase phosphatase), were the target of TTP. Biotinylated MKP-1 AREs also could bring down TTP and the other ARE-binding protein HuR. RNA EMSA and competition assays showed that each of three AREs located in 3′UTR of MKP-1 mRNA has differential binding affinity to TTP. Sequence analysis of 3′UTR of IEG mRNAs suggested that TTP may prefer binding to UUAUUUAUU sequence. Taken together, our results implied that TTP may target specific ARE-containing IEGs' mRNAs such as COX-2 and MKP-1 mRNAs to modulate their expression post-transcriptionally.
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Keywords: Immediate early gene; Tristetraprolin; 3T3-L1; AU-rich element; MKP-1

The established preadipocyte cell line 3T3-L1 has been used in examining the process of adipogenesis in vitro. When treated with an empirically-derived prodifferentiative regimen that includes cAMP, insulin, and glucocorticoids in the presence of fetal bovine serum, they undergo differentiation to mature fat cells over a period of 4–6 days. The first step in the process of adipogenesis is the re-entry of growth-arrested preadipocytes into the cell cycle and the completion of several rounds of clonal expansion [1–3]. Several transcriptional factors are expressed coordinately to exert the terminal differentiation. Many immediate early genes (IEGs) such as *c-jun, c-fos, egr-1, egr-2, nur77, cox-2, cyr61, pip92, btg2, ttp*, and *mkp-1*, which expressed briefly in the trigger of differentiation hormones, have been observed [4].

Most IEGs contain adenylate/uridylate-rich elements (AREs) in the 3′UTR of their mRNAs to control their RNA turnover [5]. AREs can range in size and generally contain one or more copies of the pentameric sequence AUUUA, and have been divided into three classes [6]. Several ARE-binding proteins have been identified to regulate mRNA turnover [7]. HuR can respond to certain extracellular stimuli to mediate specific mRNAs stabilization [8]. Knockdown of HuR could attenuate the differentiation process in 3T3-L1 cells [9]. In contrast, TTP is important for the destabilization of tumor necrosis factor and GM-CSF mRNAs, as shown in knockout mice [10,11] and in

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tissue culture by ectopic-overexpression studies [12]. It binds AREs of target mRNAs and induces deadenylation [13,14], or directs them to the exosome [15–17], or associates with RISC-microRNA complexes [18] for rapid degradation of target mRNAs. Recent reports showed that TTP could interact with mRNA decapping enzymes and nucleate processing body (PB) formation to deliver ARE-mRNAs to PBs [19,20]. Our study showed that TTP could be induced as an IEG during 3T3-L1 differentiation and its expression was controlled by negative autoregulation [21].

In this study, we detected the expression and half-lives of IEG mRNAs during early differentiation of 3T3-L1 cells by using real-time PCR analysis. A novel TTP target-mRNA, MKP-1 mRNA, was identified. Sequence analysis of 3′UTR of IEG mRNAs and RNA EMSA using MKP-1 AREs as probes suggested that TTP may prefer binding to UUAUUUAUU sequence.

Materials and methods

Cell culture. 3T3-L1 cells are grown in Dulbecco's modified Eagle's medium (DMEM, Gibco-BRL) containing 1.5 g/l $NaHCO_3$ and supplemented with 10% Bovine serum (BS, Gibco-BRL), 100 U/ml penicillin, and 100 mg/ml streptomycin (Gibco-BRL) in 5% CO_2 humidified atmosphere (37 °C). Two-day postconfluent cells (day 0) are stimulated to differentiation by change fresh medium containing 10% fetal bovine serum (FBS, Hyclone-Characterized) and addition of hormone cocktail (5 μM dexamethasone (Sigma–Aldrich), 1.7 μM insulin (Sigma–Aldrich, from bovine), and 0.5 mM 1-methyl-3-isobutylmethylxanthine (MIX, Sigma–Aldrich).

Plasmid constructs. The 3′UTR of MKP-1 (from cDNA 1254–1887 nt) was PCR cloned by using primers 5′-AGGTGTGGAGTTTCACTTGCC-3′ and 5′-CCCAGTAACAAAATGTCTTCAC-3′, and the cDNAs from 1 h differentiation-triggered 3T3-L1 as templates. The PCR fragment was cloned into pCRII-TOPO vector (Invitrogen) and sequence confirmed to prepare riboprobe.

RNA isolation and reverse trasncription-PCR. Total RNAs were extracted from the cell cultures by using Blue extract reagent (LTK, Inc., Taiwan) following the procedures recommended by the manufacturer. Five micrograms of total RNAs extracted from 3T3-L1 cells treated with differentiation inducers for different time intervals was reverse-transcribed to produce cDNA using reverse transcriptase and oligo dT (Promega) as a primer.

Real-time PCR. Real-time PCR was performed with the Applied Biosystems 7300 Real-Time PCR System (Applied Biosystems) in a total volume of 20 μl. Expression of IEGs was analyzed using SYBR Green PCR Master Mix (Applied Biosystems) containing 50 ng of cDNAs and 160 nM of each specific primers showed in Table 1. The real-time PCR amplification conditions were 40 cycles of 95 °C for 15 s and 60 °C for 1 min. The real-time PCR data were analyzed using the $2^{-\Delta\Delta CT}$ relative quantitation method, according to the manufacturer's directions.

RNA-Immunopreciptation assays. One milligram cytoplasmic extracts from 3T3-L1 cells were incubated with pre-immune serum or anti-HuR (Santa Cruz), or anti-TTP antibody to precipitate the associated RNAs as described previously [21]. RNAs were extracted for RT-PCR analysis. The specific cDNA of IEGs was amplified using 5% of the RT reaction in 20 μl containing 10 pmol of forward and reverse primer as shown in Table 1, and lypholized Taq DNA polymerase, buffer and dNTPs (LTK, Inc.). PCR was performed in a Robocycler gradient 96 PCR thermal machine (Stratagene) using the following conditions: 94 °C (3 min) for one cycle, 94 °C (40 s), 55 °C (40 s), 72 °C (depending on the product length, 1 min/1 kb) for 25–30 cycles, and a final incubation at 72 °C for 3 min. The PCR products were separated in 2% agarose gel.

RNA pull-down assay. Cytoplasmic extracts from 10^7 3T3-L1 cells were isolated and pre-treated as described previously [21]. Four micrograms of in vitro transcribed biotinylated MKP-1 ARE or control RNA (T7-MEGA shortscript™, Ambion) was added to the extract and the mixture was incubated for 1 h at 4 °C. The protein and biotinylated RNA complexes were recovered by addition of 12 μl Streptavidin Sepharose at 4 °C for 2 h with rotation. After extensive washes, the brought-down complexes were analyzed by Western blotting with anti-HuR and anti-TTP antibodies.

REMSA (RNA electrophoretic mobility shift assay). Three MKP-1 AREs were PCR cloned in pCRII-TOPO (Invitrogen) by using following primers: F1: 5′-AGGTGTGGAGTTTCACTTGCC-3′ and R1: 5′-T TGGTCCCGAATGTGCCGAG-3′ for ARE1; F2: 5′- GATGACAT GCGCGTATGAGAG-3′ and R2: 5′-CCTGCTCTGGGTCTATTTAC-3′ for ARE2; F3: 5′-GTAAATAGACCCAGAGCAGG-3′ and R3: 5′-CC CAGTAACAAAATGTCTTCTC-3′ for ARE3. The plasmids were linearized with restriction enzyme and in vitro transcribed by T7 or SP6 RNA polymerase in the presence of (α-^{32}P)-UTP for REMSA. One picomole of radiolabeled probe was incubated with recombinant GST-TTP proteins at room temperature for 40 min in a final volume of 10 μl containing 15 mM Hepes (pH 7.9), 10 mM KCl, 5 mM $MgCl_2$, 10% glycerol, 0.2 mM DTT, 0.5 μg heparine sulfate, and 5 μg of yeast total RNA. Binding mixtures were then loaded onto native 5% polyacryamide gel (acryl:bis = 40:1) containing 2.5% glycerol in 0.25× Tris–borate–EDTA buffer. After electrophoresis at 15 V/cm for 60 min, gel was dried and exposed to Kodak XAR film at −70 °C for appropriate time.

Table 1
Primers used to characterize the IEGs expression in differentiation of 3T3-L1 cells by real-time PCR

IEGs	Primers
c-jun	F: 5′-GCAGAGAGGAAGCGCATGAG-3′ R: 5′-AGCATGTTGGCCGTGGAT-3′
c-fos	F: 5′-CTTCTTGTTTCCGGCATCATC-3′ R: 5′-GCTCCCAGTCTGCTGCATAGA-3′
egr-1	F:5′-ACTCCCAACACTGACATTTTTCCT-3′ R: 5′-GGGAACCTGGAAACCACCTT-3′
egr-2	F: 5′-ACGGGACCAGGAGCAAGTG-3′ R: 5′-CGTTTTGCTGGGCCTGTTAG-3′
nur77	F: 5′-CCTGGGACGGCTCATTTG-3′ R: 5′-GTGGGAGGACTGAAGGAGAAGA-3′
cox-2	F: 5′-TGGAGGCGAAGTGGGTTTTA-3′ R: 5′-GTTTTGGTAGGCTGTGGATCTTG-3′
cyr61	F: 5′-GCTCCACCGCTCTGAAAGG-3′ R: 5′-CGGCGCCATCAATACATGT-3′
pip92	F: 5′-GCGATTTGAGCGACAGTAGTGA-3′ R: 5′-AGACTGGAGAAGCGCCTTTG-3′
btg2	F: 5′-TGTGGGTTGATCCCTATGAAGTG-3′ R: 5′-CAGGTGAGGAGCCCATAGGA-3′
ttp	F: 5′-GGATCTCTCTGCCATCTACGA-3′ R: 5′-CAGTCAGGCGAGAGGTGAC-3′
mkp-1	F: 5′-TAGACTCCATCAAGGATGCTGG-3′ R: 5′-GCAGCTTGGAGAGGTGGTGAT-3′

Result and discussion

mRNA Expression profiles and half-life analysis of IEGs during early differentiation of 3T3-L1 cells

To verify the induction of IEGs during the differentiation of preadipocytes, confluent 3T3-L1 cells were treated

with a cocktail of fetal bovine serum, MIX, dexamethasone, and insulin (MDI) to induce their differentiation. RNAs were isolated for real-time PCR by using specific primers for IEGs including *c-jun, c-fos, egr-1, egr-2, nur77, cox2, cyr61, pip 92, btg2, ttp, and mkp-1.* Fig. 1A shows their mRNA expression profiles from 0 to 16 h after the trigger of differentiation. All IEG mRNAs presented the similar expression kinetics, they rapidly increased to the highest level at 1-h induction that resulted in activation ranging from 3.2 folds (for *c-jun*) to 135 folds (for *nur77*), and then decreased dramatically. This observation was consistent with the result of previous report by using Northern blotting analysis [4]. The transient expression may imply that post-transcriptional regulation was involved in the control of IEG mRNAs.

The half-lives of these IEG mRNAs were determined after hormone induction for 1 h (Fig. 1B). The results showed that all detected half-lives were shorter than 20 min, raging from 6.6 min (TTP) to 18.6 min (Egr-1). The short half-lives may reflect some specific sequences or structures in their mRNAs. c-Jun, c-Fos, TTP and COX-2 mRNAs have been reported having AREs located

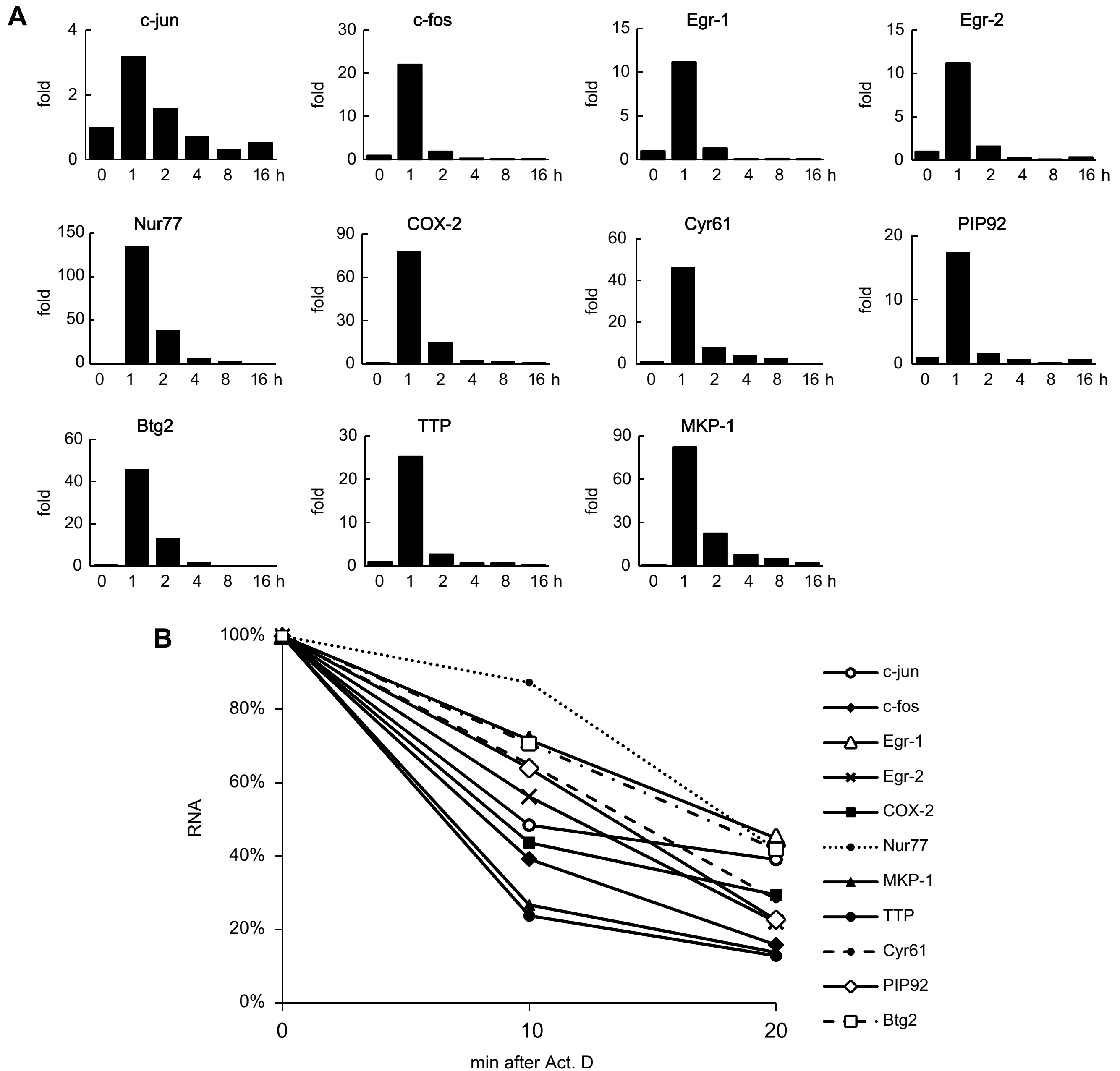

Fig. 1. mRNA metabolism of the IEGs during the early differentiation of 3T3-L1 cells. (A) mRNA expression profiling. Two-day postconfluent 3T3-L1 preadipocytes were induced to differentiation with MDI and 10% FBS for 0, 1, 2, 4, 8, and 16 h, and RNAs were isolated and reverse-transcribed to produce cDNAs for real-time PCR with specific primers for IEGs. Two independent experiments were performed and consistent results were gotten. (B) mRNA half-life of IEGs. Two-day postconfluent 3T3-L1 preadipocytes were induced to differentiation for 1 h. Transcription was then stopped by adding 10 μg/ml of actinomycin D (Act.D) for 0, 10, and 20 min. The following experiments were as described in (A).

Table 2
Characteristics of IEG's AREs

Gene name (Accession No.)	Length of 3′UTR (b)	No. of UUAUUUAUU	No. of UAUUUAU	No. of AUUUA	ARE class[a]	mRNA half-life (min)
mkp-1 (NM_013642)	633	2	1	1	II	6.8
cox-2 (M64291)	2047	1	4	6	II	8.9
ttp (NM_011756)	773	1	2	0	II	6.6
nur77 (J04113)	539	0	0	2	I	18.4
c-jun (NM_010591)	1214	0	0	4	I	9.8
c-fos (V00727)	846	0	1	1	I	8.3
egr-1 (M20157)	1208	0	0	2	I	18.6
egr-2 (NM_010118)	1200	0	0	2	I	11.9
cyr61 (NM_010516)	689	0	2	3	II	14.4
pip92 (L26490)	966	0	0	0	III	13.5
btg2 (M64292)	2040	0	0	4	I	17.7

[a] According to the rule of Chen and Shyu [6].

in their 3′UTR [7,21–23]. Analysis of 3′UTR of all these IEG mRNAs showed that most of them were ARE-containing mRNAs (Table 2). Frevel et al. provided evidence that the number of the overlapping pentamer AUUUA may contribute to the mRNA half-life, and the mRNA half-lives in the class II category (overlapping AUUUA) were significantly shorter than those of class I (separated AUUUA) [24]. Our analysis showed the class II mRNAs such as TTP and MKP-1 had the shortest half-life, and this result seemed to partially correlate with previous description.

c-jun, c-fos, egr-1, and *egr-2* encode transcription factors. Egr-2 has been identified to be acting early in the adipogenic program and appearing to contribute to induction of C/EBPβ expression [25,26]. Orphan nuclear receptor Nur77 has the effect to promote mitotic clonal expansion [27]. COX-2 is required for conversion of arachidonic acid to prostaglandins which may serve as a ligand for PPARγ (the key regulator of adipogenesis) [28]. Cyr61 could promote cell proliferation [29]. A cofactor of transcription, BTG2, is known to have antiproliferative effect [30]. MKP-1 (also named Dusp1) is a mitogen-activated protein kinase phosphatase. It has been reported that MKP-1 plays an essential role in adipocyte differentiation through down-regulation of ERKs activity [31]. *ttp* encodes a zinc-finger containing ARE-binding protein. The tight expression control of these IEG transcripts may implicate their critical function in early differentiation of 3T3-L1 cells.

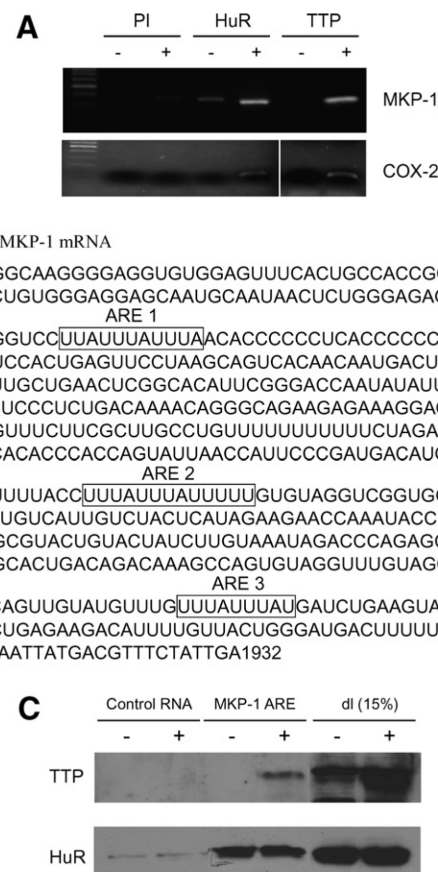

Fig. 2. TTP could interact with MKP-1 mRNA. (A) RNA immunoprecipitation analysis. The cytoplasmic extracts from MDI and FBS treated (+) or non-treated (−) 3T3-L1 cells were immunoprecipitated using pre-immune serum, or anti-TTP or anti-HuR antibody. After extensive washes, the protein-associated RNAs were extracted for RT-PCR with IEGs specific primers. (B) Nucleotide sequences of 3′UTR of MKP-1mRNA. The predicted AREs were rectangled and indicated as ARE1, ARE2, and ARE3. (C) RNA pull-down assay. The biotinylated full-length MKP-1 ARE or control 18S RNA was incubated with cytoplasmic extracts from 3T3-L1 cells treated (+) or non-treated (−) with MDI and FBS. The RNA-proteins complexes were brought-down by Streptavidin sepharose and subjected to SDS–PAGE for Western blotting. Anti-TTP and anti-HuR antibody were used. The protein amount in the lanes of direct loading was 15% of the pull-down assay used.

MKP-1 and COX-2 mRNAs interact with TTP protein

Our previous report showed that ARE-binding protein TTP could bind to its own mRNA and cause its mRNA destabilized [21]. To elucidate whether TTP could target other IEG mRNAs, immunoprecipitation (IP) reactions were performed to isolate mRNA subsets bound to TTP using anti-TTP antibody. RNAs present in IP reactions were reverse transcribed and PCR was performed with IEGs specific primers. Fig. 2A showed that COX-2 and MKP-1mRNA could interact with TTP, whereas the other IEG mRNAs were not detectable in TTP brought-down com-

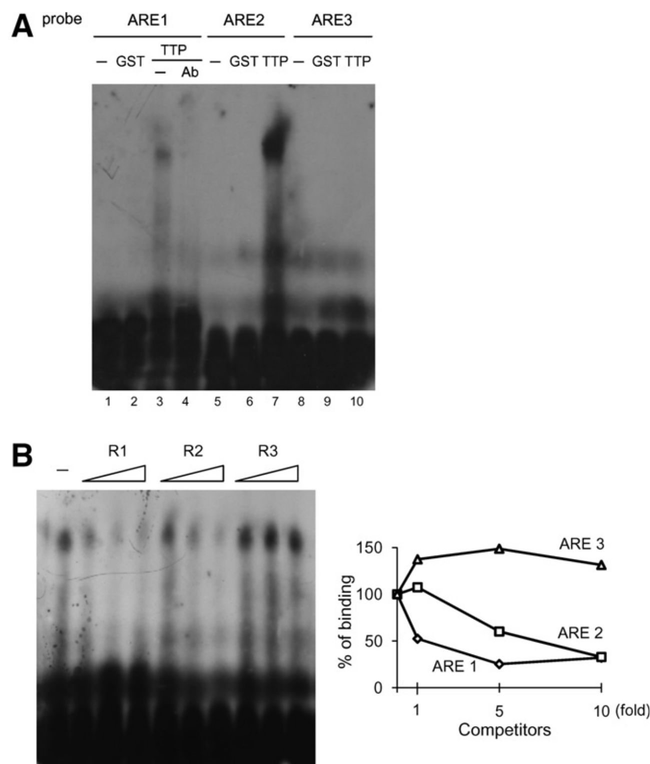

Fig. 3. Analysis of interaction of recombinant TTP with three AREs in MKP-1 mRNA by EMSA. (A) Each radiolabeled ARE probe was incubated with recombinant GST-TTP (lanes 3-4, 7, and 10) or control GST protein (lanes 2, 6, and 9) as indicated. Anti-TTP antibody was added in lane 4. (B) Radiolabeled ARE2 probe was incubated with GST-TTP in the presence of increasing amount (1-, 5-, and 10-fold the hot probe used) of cold ARE1, or ARE2, or ARE3 as indicated. The quantitative results were shown in right panel.

plexes (data not shown). On the other hand, HuR antibody could precipitate all our demonstrated IEG mRNAs (Fig. 2A and data not shown). COX-2 mRNA has been reported to be TTP-associated and it also belongs to class II ARE [32,33]. MKP-1 mRNA is a novel target of TTP, which has not been identified before. There are three AREs scattered in 633 base of MKP-1 mRNA 3′UTR (NM_013642), and one belongs to class II ARE and contains two overlapping copies of AUUUA motifs (Fig. 2B). Moreover, to verify the interaction between MKP-1 mRNA and TTP proteins, the RNA pull-down analysis was performed. The 3′UTR of MKP-1 mRNA was biotin-labeled and then incubated with 3T3-L1 cell lysates. The pulled down RNA–protein complexes could be detected by anti-TTP and anti-HuR antibodies (Fig. 2C).

ARE is a very heterogeneous element. In a previous report, immobilized TTP protein was used to select its optimal binding site by RNA SELEX and revealed a strong preference for the extended sequence UUAUUUAUU, rather than UAUUUAU and a simple AUUUA motif [34]. In the analysis of IEG AREs, we found that UUAUUUAUU motif was present in our identified TTP interacting mRNAs including that of TTP itself, COX-2 and MKP-1 (Table 2). Although most IEG mRNAs could not be detected in anti-TTP antibody precipitation complexes, they also were short-lived. It may be possible that other ARE-binding proteins such as KSRP and AUF1 involve in the stability regulation of other IEG mRNAs [7,35].

Analysis of interaction of TTP with three MKP-1 AREs

To demonstrate TTP-binding affinity on each of three MKP-1 AREs, RNA EMSA was performed by using ARE1, ARE2, and ARE3 probes and recombinant GST-TTP. Fig. 3A showed that two of MKP-1 AREs could be bound with TTP proteins, and the anti-TTP antibody could block the RNA–protein complex formation (Lane 4). Moreover, the competition experiments represented that their binding affinity to TTP seemed to be ARE1≧ARE2>ARE3 (Fig. 3B). ARE1 contains two overlapping AUUUA pentamers and forms one UUAUUUAUU. ARE2 has one UUAUUUAUU, and ARE3 contains one UAUUUAU. This result reflects the above description that TTP prefers to recognize the UUAUUUAUU sequence.

In conclusion, we showed that differentiation inducer could stimulate the transient expression of a panel of IEGs in 3T3-L1 cells. These IEG mRNAs were short-lived and belonged to different ARE classes. The RNA destabilizing protein, TTP, could interact with class II and UUAUUUAUU-containing mRNAs. The expression and functional activity of both MKP-1 and TTP was controlled by MAPKs [36–40], and MKP-1 was a negative regulator of MAPK pathways [41,42]. We first identified that MKP-1 mRNA was one of TTP targets. This finding suggested that TTP may involve in the complex net work of MAPKs to control the signal duration and strength through regulation of MKP-1 mRNA stability.

Acknowledgments

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