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Coordinated regulation of transcription and alternative splicing by the thyroid hormone receptor and its associating coregulators

Tetsurou Satoh [a,*], Akiko Katano-Toki [a], Takuya Tomaru [a], Satoshi Yoshino [a], Takahiro Ishizuka [a], Kazuhiko Horiguchi [a], Yasuyo Nakajima [a], Sumiyasu Ishii [a], Atsushi Ozawa [a], Nobuyuki Shibusawa [a], Koshi Hashimoto [a], Masatomo Mori [b], Masanobu Yamada [a]

[a] Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Maebashi, Japan
[b] Kitakanto Molecular Novel Research Institute for Obesity and Metabolism, Midori, Japan

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ABSTRACT

Emerging evidence has indicated that the transcription and processing of precursor mRNA (pre-mRNA) are functionally coupled to modulate gene expression. In collaboration with coregulators, several steroid hormone receptors have previously been shown to directly affect alternative pre-mRNA splicing coupled to hormone-induced gene transcription; however, the roles of the thyroid hormone receptor (TR) and its coregulators in alternative splicing coordinated with transcription remain unknown. In the present study, we constructed a luciferase reporter and CD44 alternative splicing (AS) minigene driven by a minimal promoter carrying 2 copies of the palindromic thyroid hormone-response element. We then examined whether TR could modulate pre-mRNA processing coupled to triiodothyronine (T3)-induced gene transcription using luciferase reporter and splicing minigene assays in HeLa cells. In the presence of cotransfected TRβ1, T3 increased luciferase activities along with the inclusion of the CD44 variable exons 4 and 5 in a dose- and time-dependent manner. In contrast, cotransfected TRβ1 did not affect the exon-inclusion of the CD44 minigene driven by the cytomegalovirus promoter. T3-induced two-exon inclusion was significantly increased by the cotransfection of the TR-associated protein, 150-kDa, a subunit of the TRAP/Mediator complex that has recently been shown to function as a splicing factor. In contrast, T3-induced two-exon inclusion was significantly decreased by cotransfection of the polypyrimidine tract-binding protein-associated splicing factor, which was previously shown to function as a corepressor of TR. These results demonstrated that liganded TR in cooperation with its associating cofactors could modulate alternative pre-mRNA splicing coupled to gene transcription.

1. Introduction

Gene transcription is orchestrated by the coordinated efforts of ATP-dependent chromatin remodeling, histone modification, transcription initiation, elongation, and termination, and RNA processing [1,2]. Although each of these biochemical reactions is accomplished by diverse protein complexes, communication between transcription factors and RNA splicing factors indicates co-transcriptional RNA splicing, which is performed by one general gene expression machine [1,2]. Alternative pre-mRNA splicing is regulated temporally and spatially and is a major source of protein diversity for higher eukaryotes. More than 90% of genes in humans have been estimated to generate multiple protein isoforms derived from alternative splicing (AS) [3]. Aberrant pre-mRNA splicing caused by mutations in consensus splice regulatory sequences and functional mutations in splicing factors have been reported to play pathogenic roles in various human disorders including endocrine and metabolic diseases, cancers, hematological malignancies, and neurodegenerative diseases [4–6]. Therefore, elucidating the mechanisms underlying pre-mRNA processing in more detail is important for understanding the pathogenesis of human diseases caused by deranged RNA splicing and the development of new treatment strategies.

Nuclear hormone receptors (NRs) are transcription factors that bind hormone response elements located in the responsible genomic regions of target genes and regulate gene transcription in ligand-dependent and -independent manners [7,8]. Previous findings confirmed that NRs dynamically interacted with diverse classes of transcriptional coregulators (TCRs) to regulate target

* Corresponding author. Address: Department of Medicine and Molecular Science Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi 371-8511, Japan. Fax: +81 27 220 8136.
E-mail address: tsato@gunma-u.ac.jp (T. Satoh).

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gene transcription [9–11]. These TCRs possess intrinsic and associated enzymatic activities and modulate the recruitment of RNA polymerase II (pol II) to the transcription start site mainly by the ATP-dependent remodeling of chromatin structures and epigenetic modification of histone tails [9–11]. Emerging evidence has indicated that several NRs including the peroxisome proliferator-activated receptor (PPAR)γ, estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR) may coordinate hormone-induced gene transcription with pre-mRNA processing in collaboration with specific TCRs and/or splicing factors [12–16]. Triiodothyronine (T3) activates the thyroid hormone receptor (TR), which binds to the thyroid hormone-response element (TRE) in both the absence and presence of a ligand [17], and has previously been shown to modulate the AS of beta-amyloid and TRα genes expressed in cultured cells [18,19]. The TR-associated protein, 150-kDa (TRAP150) (also known as TR-associated protein3, THRAP3), was originally isolated as a subunit of the TRAP/Mediator complex, which can be recruited to liganded TR and facilitate the recruitment of pol II to initiate transcription [20], and has recently been shown to play a role in pre-mRNA splicing [21–23]. In addition, the polypyrimidine tract-binding protein (PTB)-associated splicing factor (PSF) (also known as splicing factor proline/glutamine-rich, SFPQ), initially isolated as a protein that interacted with PTB [24] and was recently shown to associate with the DBIRD complex, which integrates AS and pol II transcript elongation [25], has previously been reported to function as a transcriptional corepressor of NRs including TR [26–28]. Taken together, these findings suggest that TR could regulate not only gene transcription, but also pre-mRNA processing in coordination with TRAP150 and/or PSF. However, the co-transcriptional regulation of AS by TR has not yet been examined.

In the present study, we constructed a luciferase reporter vector and CD44 AS minigene driven by the identical minimal promoter carrying the palindromic TRE and examined whether liganded TR could modulate the alternative splicing of CD44 variable exons coupled with gene transcription in collaboration with TRAP150 and/or PSF.

2. Materials and methods

2.1. Cell cultures

HeLa cells were were split 24 h before transfection and cultured in DMEM containing resin–charcoal double stripped 10% fetal bovine serum during the T3 treatment as previously described [29,30].

2.2. Plasmids

The expression vectors of human TRβ1 (pKCR$_2$-hTRβ1), TRAP150 (pSV-SPORT-hTRAP150), and PSF (pCS3+MT-hPSF) were described previously [29–31]. The pGL4.23[*luc2*/minP] vector containing firefly luciferase (*Luc2*) cDNA under the control of a minimal promoter containing a TATAA box was obtained from Promega Corporation (Madison, MI). The DNA fragment containing two copies of palindromic (PAL) TRE (AGGTCATGACCT) was amplified by PCR using a primer pair as described [32] and a 2 × PAL-thymidine kinase luciferase vector [32] as a template. The PCR amplified fragment was ligated into the pGEM-T Easy vector (Promega Corporation) to yield pGEM-T Easy-PAL, and the *Eco*RI digested fragment was then ligated into the *Eco*RI site of pGEM11Zf (Promega Corporation) to yield pGEM11Zf-PAL. The DNA fragment obtained by the *Sac*I digestion of pGEM11Zf-PAL was finally ligated into the *Sac*I site of pGL4.23[*luc2*/minP] (pGL4.23 PAL-Luc). The cytomegalovirus (CMV) promoter-driven CD44 minigene (CMV-CD44) was described previously [13]. The CMV-CD44 minigene contains a genomic DNA fragment including variable exons 4 (v4) and 5 (v5) of the CD44 gene along with their surrounding introns in the intron between exon 1 and exon 2 of the human β globin gene (CD44 minigene cassette) [33]. *Luc2* cDNA in pGL4.23 PAL-Luc or pGL4.23[*luc2*/minP] was excised by *Nco*I and *Xba*I digestion and replaced by the PCR-amplified CD44 minigene cassette to obtain pGL4.23 PAL-CD44 or pGL4.23 minP-CD44, respectively. The proper construction of pGL4.23 PAL-Luc, pGL4.23 PAL-CD44, and pGL4.23 minP-CD44 was verified by nucleotide sequencing.

2.3. Lipofection, RNA isolation, and RT-PCR

Plasmids were transfected into HeLa cells in 60-mm culture dishes using Lipofectamine 2000 reagent (Invitrogen, Life Technology Corporation, Tokyo, Japan). The total amounts of the transfected plasmids were adjusted using empty expression vectors. After incubation with T3 (Sigma Aldrich Japan, Osaka, Japan), total RNA was isolated using Isogen (Nippon Gene Co., Ltd., Tokyo, Japan). AS minigene assays were performed according a previously described protocol [13] with modifications. Briefly, 5 μg of total RNA was treated with RQ1 DNase (Promega Corporation) at 37 °C for 30 min followed by the inactivation of DNase with the addition of the Stop buffer (Promega Corporation) at 65 °C for 10 min. DNase-treated RNA was denatured for 5 min at 65 °C and annealed with an antisense primer complementary to the sequence in exon 2 of the human β globin gene (HBB-AS: 5′-CCATAACAGCATCAGGAGTG-3′). First strand cDNA was synthesized using Superscript III reverse transcriptase (Invitrogen) at 50 °C for 30 min according to the manufacturer's protocol. One microliter of the cDNA sample was subjected to PCR in a total volume of 50 μl using AmpliTaq DNA polymerase (Applied Biosystems by Roche Molecular Systems, Inc., Branchburg, NJ) and a PCR primer pair; sense 5′-ACGTGGATGAAGTTGGTGGT-3′, which was complementary to exon 1 of HBB (HBB-S), and HBB-AS. The PCR conditions used were denaturing at 94 °C for 30 s, annealing at 60 °C for 45 s, and extension at 72 °C for 1 min for 35 cycles. The PCR products were subjected to electrophoresis in agarose gels containing ethidium bromide, and band intensities were quantitated using an image analyzer. The proper amplification of AS products was verified by nucleotide sequencing.

2.4. Luciferase assay

HeLa cells were split into 6-well plates and pGL4.23PAL-Luc along with TR expression vectors or an empty expression vector were transfected using a calcium phosphate precipitation method. The luciferase assay was performed as described [29,30].

2.5. Statistical analysis

Statistical analysis was performed using ANOVA, followed by Turkey's multiple comparison tests. Significance was set at $p < 0.05$.

3. Results

To examine whether TR could modulate transcription-coupled alternative pre-mRNA splicing, we constructed a luciferase reporter vector and CD44 AS minigene driven by the identical minimal promoter carrying PAL-TRE (Fig. 1). Three alternatively spliced RNA products could theoretically be generated at different levels from this CD44 minigene cassette that included two exons (v4 and v5), one exon (v4 or v5), or no exon in the context of the

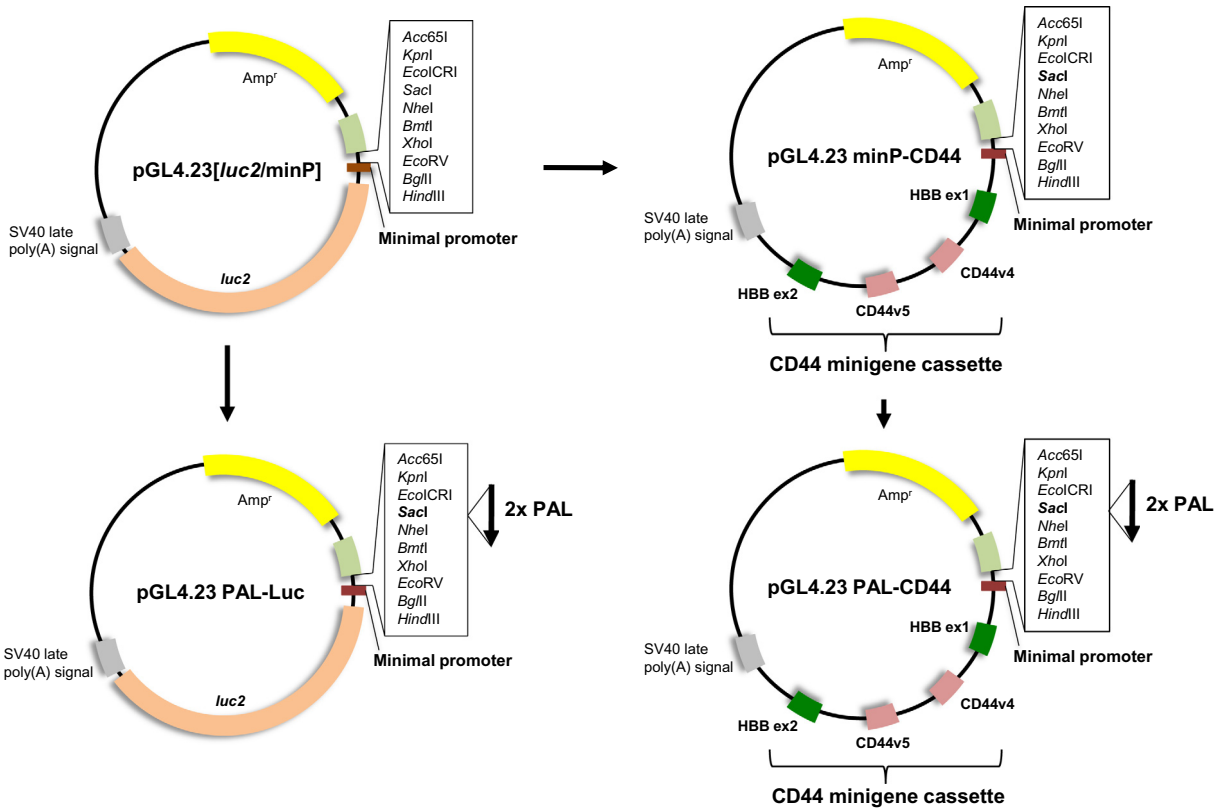

Fig. 1. Construction of a luciferase reporter vector and AS CD44 minigene driven by a minimal promoter carrying the palindromic TRE (PAL). pGL4.23 PAL-Luc, pGL4.23 minP-CD44, and pGL4.23 PAL-CD44 were constructed as described in the Section 2. The positions of multiple cloning sites (an open box), CD44 minigene cassette, the ampicillin-resistant gene (Amp^r), and simian virus (SV) 40 late poly (A) signal are indicated.

driving promoter or transfected cultured cells [13,15,16]. We then cotransfected PAL-Luc or PAL-CD44 with the TRβ1 expression vector into HeLa cells and luciferase and minigene assays were performed in parallel 24 h after incubations with increased concentrations of T3. In the agarose gel electrophoresis of RT-PCR products, only one-exon (v5)-included CD44 RNA was observed in the absence of T3, whereas T3 significantly increased RNA including v4 and v5 in a dose-dependent manner (Fig. 2B). In parallel with the increase of the two-exon inclusion by T3, T3 significantly stimulated the promoter activity of PAL-Luc in a dose-dependent manner (Fig. 2A). T3 also increased the inclusion of two variable exons in a time-dependent manner, and this appeared to be in parallel with the promoter activities of PAL-Luc stimulated by T3 (Fig. 2D and C). These results indicated that T3 could coordinately regulate the transcription of PAL-Luc and AS decision of PAL-CD44 minigene in a dose- and time-dependent manner in the presence of cotransfected TR.

T3 may alter the expression levels of cellular splicing factors, thereby increasing the two-exon included transcript generated from PAL-CD44; therefore, we evaluated whether the AS of the CMV-CD44 minigene lacking functional TREs could be influenced by cotransfected TR. As shown in Supplementary Fig. 1, two-exon and 0-exon included RNA was detected from the CMV-CD44 minigene (the upper panel), whereas cotransfected TRβ1 did not increase the amounts of two-exon included RNA in the presence of T3 (the lower panel). These results suggested that the T3-induced increase in two-exon included CD44 transcripts from PAL-CD44 may be mediated by TRE-bound TR. In addition, different promoters (i.e. PAL vs. CMV) could alter the AS decision of the CD44 minigene.

To evaluate whether these dual-functional TCRs of TR affected T3-induced gene activation as well as AS decisions, the expression vectors for TRAP150 or PSF in the absence or presence of TR was cotransfected with the PAL-Luc or PAL-CD44 minigene, and luciferase activities and splicing reactions were examined in the absence or presence of T3. As shown in Fig. 3A, cotransfected TRAP150 did not stimulate TR-mediated gene transcription in luciferase assays. In contrast, cotransfected TRAP150, but not HELZ2, a DNA/RNA helicase that could interact with TRAP150 [28], significantly increased two-exon inclusion in the presence of liganded TR (Fig. 3B). Consistent with the findings of a previous study [26], the cotransfection of PSF significantly reduced TR-mediated activation of PAL-Luc (Fig. 4A). In addition, cotransfected PSF significantly decreased the two-exon inclusion of the CD44 minigene in the presence of liganded TR (Fig. 4B). In contrast, the two-exon inclusion of the CD44 minigene driven by the CMV promoter was not increased by cotransfected TRAP150, but was paradoxically increased by cotransfected PSF via an unknown mechanism (Supplementary Fig. 2). Taken together, these results indicated that TRAP150 and PSF, two known TCRs of TR, could modulate the co-transcriptional AS of the CD44 minigene mediated by TRE-bound TR.

4. Discussion

It is now increasingly evident that mRNA transcription and processing events are coordinately regulated in the nucleus [1,2]. This coordination was shown to be mediated largely by the C-terminal domain (CTD) of the largest subunit of pol II, which is responsible for the recruitment of splicing factors to transcription sites *in vivo* [1,2]. The initiation form of pol II contains hypophosphorylated CTD (pol IIa), whereas the elongation form of pol II contains a CTD that is hyperphosphorylated (pol IIo) by several kinases [1,2]. This transition of the phosphorylated status from pol IIa to pol IIo is thought to result in the recruitment of some pre-mRNA

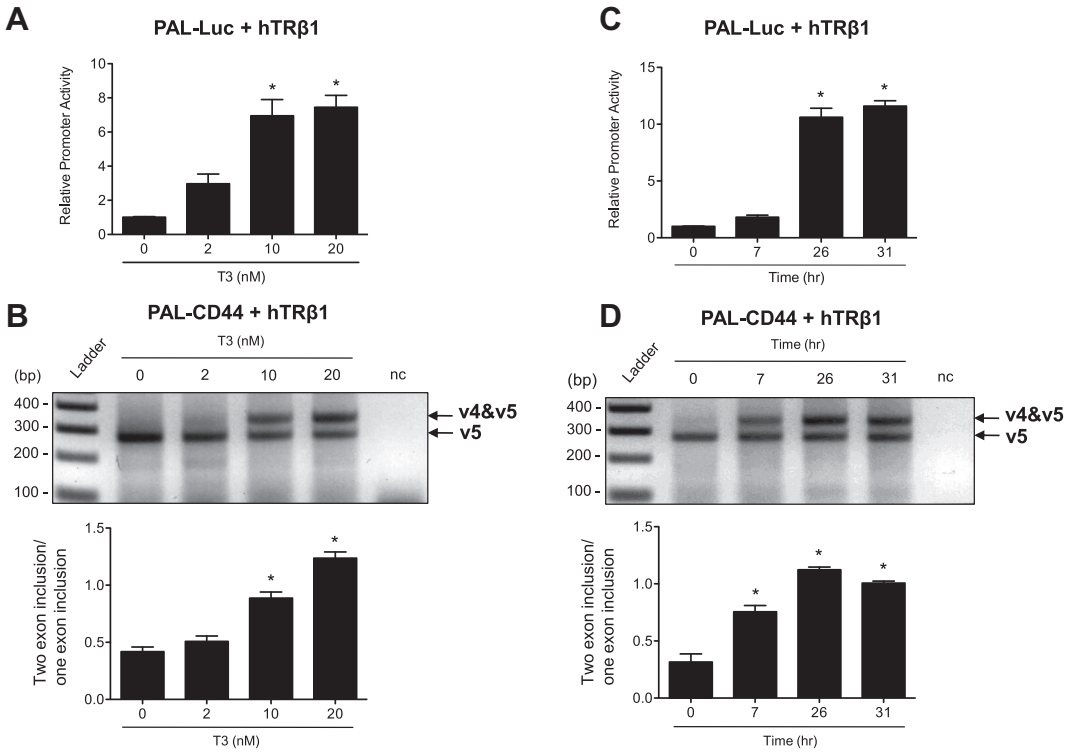

Fig. 2. T3 in the presence of cotransfected TR stimulated the two-exon inclusion of the PAL-CD44 in parallel with the increased transcription of PAL-Luc in a dose- and time-dependent manner. pGL4.23 PAL-Luc or pGL4.23 PAL-CD44 was cotransfected with TRβ1 expression vector, and luciferase assays (Fig. 2A and C) and AS minigene assays (Fig. 2B and D) were performed after treatment with indicated concentrations of T3 during indicated time periods. Luciferase assay data represent the mean ± SEM from triplicate samples. Representative agarose gels are shown (Fig. 2B and D, upper panels). Molecular size markers (Ladder) are indicated as base pairs (bp). Arrows indicate PCR products containing v4 and V5 or v5. Band intensities were quantitated and the ratio of two-exon included RNA to one-exon included RNA was expressed as the mean ± SEM from triplicate PCR samples. Asterisks indicate significant differences from 0. nc represents PCR samples without the cDNA template. Experiments were repeated with similar results.

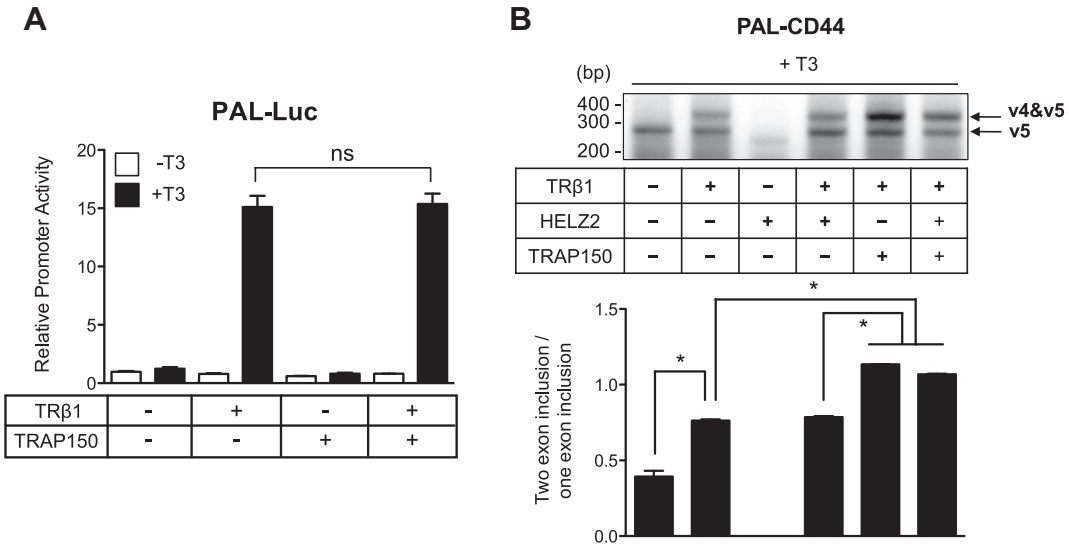

Fig. 3. TRAP150 did not stimulate the transcription of PAL-Luc, but increased the two-exon inclusion of the PAL-CD44 minigene. PAL-Luc or PAL-CD44 was cotransfected in the presence or absence of TRβ1 with or without the TRAP150 expression vector. Luciferase and minigene assays were performed 24 h after the incubation with 10 nM T3(Figs. 3A and 3B). Data are expressed as in Fig. 2. Experiments were repeated twice with similar results. Asterisks indicate significant differences between the indicated groups. ns; not significant.

processing factors to the CTD [1,2]. In addition, certain pre-mRNA processing factors, including PSF, have been shown to associate with pol IIa-containing holoenzyme complexes [34]. Sequence-specific DNA-binding transcription factors and their associating TCRs play important roles in the recruitment of the pol II holoenzyme complex to promoter regions [9], and the types of promoters

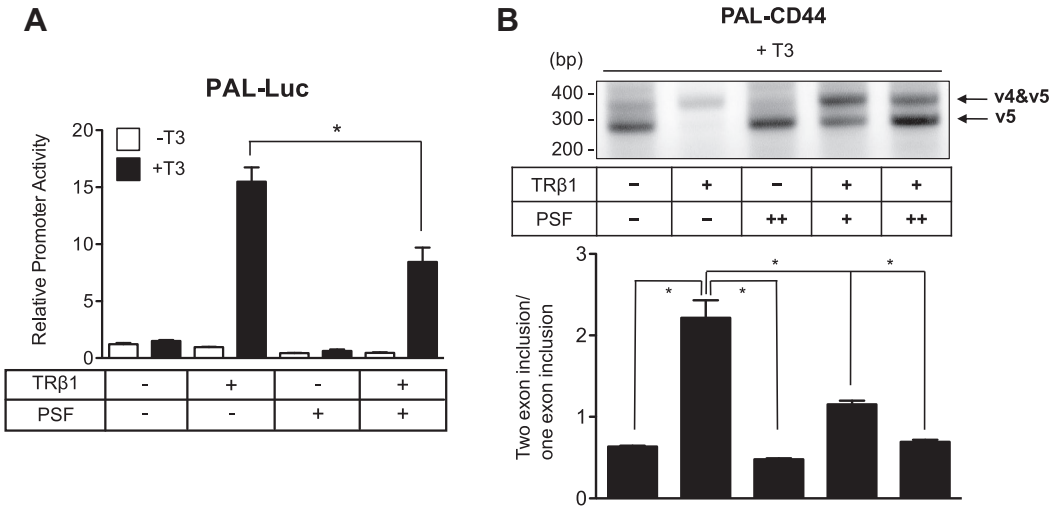

Fig. 4. PSF repressed the transcription of PAL-Luc and two-exon inclusion of the PAL-CD44 minigene. PAL-Luc or PAL-CD44 was cotransfected in the presence or absence of TRβ1 with or without the PSF expression vector. Data from luciferase assays (A) and minigene assays (B) are shown as in Fig. 3. Experiments were repeated twice with similar results.

or promoter-bound activators used to drive transcription can influence the efficiency of pre-mRNA processing steps in corresponding transcribed RNAs [1,2].

In the present study, we showed that liganded TR could stimulate gene transcription in parallel with the two-exon inclusion of the CD44 minigene driven by the minimal promoter under the control of PAL-TRE. However, the present results differed from those reported previously in which a reduction was observed in two-exon inclusion using a CD44 minigene driven by a mouse mammary tumor virus promoter in the presence of liganded PR or a minimal promoter carrying the estrogen responsive element in the presence of liganded ER [13]. Therefore, the types of promoters and recruited NR could affect AS decisions by changing the RNA elongation rate and/or recruitment of different splicing factors, as described previously [1,2]. The AS decision of the CD44 minigene driven by the CMV promoter, which lacks positive TRE, was not affected by the cotransfected TR in the present study, suggesting that TRE-bound TR could co-transcriptionally modulate AS of the CD44 minigene driven by PAL-TRE.

T3-induced two-exon inclusion was significantly increased by the cotransfection of TRAP150 in the present study. TRAP150 was initially identified as a subunit of the TRAP/Mediator multi-protein complex, which has been reported to bridge DNA-bound liganded NRs and the basal transcription machinery [20]. TRAP150 possesses an arginine/serine rich domain, which is an RNA recognition motif that is characteristic of the serine–arginine protein family involved in pre-mRNA splicing [21]. TRAP150 has been shown to associate with spliceosomes in transient and heparin-sensitive manners [35], may be recruited to emerging transcripts via an interaction with pol II-associated splicing factors such as CA150 during transcription [36,37], and activates pre-mRNA splicing *in vivo* [21]. Med23, another subunit of the TRAP/Mediator complex, has recently been shown to regulate AS through an interaction with heterogeneous ribonucleoprotein L and the splicing machinery [38]. The present results provide supportive evidence that specific components of the TRAP/Mediator complex, in addition to other classes of NR coregulators including PPARγ coactivator 1, p72, CoAA, CAPER, and Sam68 [12–16], could play a novel role in coupling transcription with AS in NR-mediated gene regulation.

PSF has previously been shown to function as a transcriptional corepressor of several NRs including TR by recruiting histone deacetylases via direct interactions with Sin3A [26,28]. In contrast to the NR corepressor that dissociates from TR in the presence of T3 [17], PSF could associate with the DNA-binding domain of TR in the absence and presence of T3 [26]. In the present study, the overexpression of PSF significantly reduced the two-exon inclusion of the TRE-driven CD44 minigene in the presence of cotransfected TR. PSF possesses two canonical RNA-recognition motifs [24] and has been suggested to play important roles in RNA processing [39,40]. PSF has subsequently been shown to associate with transcription initiation and elongation complexes and is also capable of directly interacting with the CTD of both pol IIa and IIo [34]. PSF can be co-purified with the activation domain of VP16 and stimulate VP16-dependent pre-mRNA processing via an interaction with the pol II CTD [41]. Heyd et al. recently demonstrated that PSF phosphorylated by glycogen synthase kinase 3 (GSK3) could stably associate with TRAP150 in resting T cells. By reducing GSK3 activity upon T cell activation, the dephosphorylated form of PSF could dissociate from TRAP150 and bind to the exonic splicing silencer element, thereby repressing exon inclusion of the CD45 gene [22]. Taken together, these findings suggest that PSF could play an important role in coupling alternative pre-mRNA splicing with gene transcription. Because the overexpression of PSF significantly attenuated the T3-induced transcription of PAL-Luc by TR, but did not reduce the two-exon inclusion of the CMV-CD44 minigene in the present study, we speculated that the reduction in the two-exon inclusion of the PAL-CD44 minigene by PSF may be mainly caused by its corepressor activity for TR-mediated gene transcription. The present study collectively demonstrated that TR could co-transcriptionally modulate alternative pre-mRNA splicing, similar to other NRs, in collaboration with its associating coregulators [12–16].

Conflict of interest

The authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2014.07.029.

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