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Thyroid hormone receptor and liver X receptor competitively up-regulate human selective Alzheimer's disease indicator-1 gene expression at the transcriptional levels

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ABSTRACT

Selective Alzheimer's disease (AD) indicator-1 (Seladin-1) gene has been identified as a gene, whose expression is down-regulated in the vulnerable region in the brain of AD patients. Thyroid hormone (TH) is important to maintain the function of central nervous system and TH receptor (TR) is known to crosstalk with liver X receptor (LXR) on the lipid metabolism-related gene promoter. Recently, we have demonstrated that TR-β up-regulates the mouse Seladin-1 gene promoter at the transcriptional levels and LXR-α compensates the promoter activation only when the thyroid function is insufficient. In the current study, we have identified that TH and an LXR artificial agonist, TO901317 (TO) activated the human Seladin-1 promoter (−1024/+57 base pair (bp)) including consensus TH response element (TRE) half site (site A: −381 to −375 bp), and the site A mutation deteriorated the activation by TH and TO. Both TR-β and LXR-α heterodimerize with retinoid X receptor (RXR)-α on the site A, and chromatin immunoprecipitation (ChIP) assay revealed that TR-β, LXR-α and RXR-α are recruited to the site A. Moreover, TR-β and LXR-α functionally compete for the promoter activation in CV1 cells. Taken together, we concluded that TR-β and LXR-α competitively up-regulate the human Seladin-1 promoter, sharing the same response element, site A.

1. Introduction

Alzheimer's disease (AD) is the major cause of dementia in the world [1]. In the brain of AD patients, β-amyloid is accumulated in the neurons, typically in the temporal lobe including hippocampus [2]. So far, the pathological cause and curable treatment of AD still remain to be clarified.

Thyroid hormone (TH) is broadly recognized to play a pivotal role in the development and maintenance of central nervous system (CNS) in mammals [3]. Hypothyroidism could be misdiagnosed as dementia especially in elder patients [4], and the TH receptor (TR) β-Δ337T knock-in mouse, which recapitulates resistance to TH, demonstrates severe cerebellar ataxia and cognitive dysfunction [5]. The relationship between thyroid function and AD is still controversial in some basic and large-scale clinical studies [6–8].

Recently, the evidences have been found that intraneuronal cholesterol works as a protector from neuronal degeneration [9,10]. Liver X receptor (LXR) is a key regulator of cholesterol metabolism [11,12], and it has been reported that an artificial agonist of LXR, TO901317 (TO), induces the cholesterol metabolism-related genes in CNS and reduces β-amyloid accumulation in the brain of AD model mice [13,14]. TR and LXR share direct repeat (DR)-4 as a response element, and heterodimerize with Retinoid X receptor (RXR) [11]. Therefore, they crosstalk on the variety of gene promoter such as *Abca1* and *Cyp7a1* [15–17]. Thus, we hypothesized that TR and LXR would co-regulate the lipid metabolism-related and AD-related genes in CNS.

Selective AD indicator 1 (Seladin-1) gene has been identified as a down-regulated gene in the degenerated lesion of AD patient's brain [18] and codes 24-dehydrocholesterol reductase (DHCR24), which catalyzes the final step of *de novo* cholesterol synthesis [19]. Overexpressed Seladin-1 in the neurons increases the amount of cholesterol and avoids β-amyloid accumulation, oxidative stress and apoptosis of neurons [18,20,21]. Seladin-1 gene expression is regulated by estrogen receptor [22], and it has been reported that TR and LXR also involve in the regulation of Seladin-1 gene expression [23,24]. Recently, we have revealed that TR and LXR crosstalk on the mouse Seladin-1 gene promoter [25]. TR and LXR up-regulate Seladin-1 gene expression at the transcriptional levels, however they are recruited on the promoter differently. TR dominantly regulates the mouse Seladin-1 promoter and LXR compensates only in insufficient thyroid status [25].

In the current study, we explored the human Seladin-1 gene promoter and clarified that TR and LXR also up-regulate the pro-

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moter at the transcriptional levels. TR and LXR share the same binding site including DR-4 consensus half site and up-regulate the promoter in a competitive manner. Identification of the human promoter regulation by TR and LXR could push the envelope for the treatment of AD utilizing TH and LXR agonists.

2. Materials and methods

2.1. Plasmids

The human Seladin-1 gene promoter (−1041/+57 base pair (bp)) plasmid, which contains the region from −1041 to +57 bp of the human Seladin-1 gene, was generated by genomic PCR using 5′-GTGTGGTACCGAAGGGGATGGGAAAGGGCA-3′ as a sense primer and 5′-GTGTAAGCTTCTCTGCGCCTGTAGCCCACA-3′ as an anti-sense primer. An *Asp718* or *HindIII* restriction enzyme site was introduced into each primer sequence so that the PCR product could be subcloned between these sites in the pGL4-Luc vector (Promega, Madison, WI). The deletion mutants and a site A point mutant were generated with PCR site-directed mutagenesis [26]. All human TR-β1 and its mutants, RXR-α, and murine LXR-α cDNAs were placed into an SV40 expression construct, pSG5 [26]. We prepared GAL4-LXR-α constructs in the pCMX-GAL4-N vector containing a GAL4 DNA-binding domain by PCR using mouse LXR-α in pSG5 as templates, as we described previously [27].

2.2. Transfections and luciferase assay

We performed the luciferase assay as previously described [25]. We employed CV1 cells and HTB185 cells derived from human medulloblastoma. Ten microgram of the reporter plasmid and 0.25 μg of human TR-β1 or mouse LXR-α in pSG5 (as otherwise indicated) were transfected per plate of a 12-well format into HTB185 cells or a 6-well format into CV1 cells using the calcium-phosphate method. Sixteen hours after transfection, cultures were treated with Dulbecco's modified Eagle's medium (DMEM) containing 10% resin charcoal double-stripped fetal bovine serum (double-stripped FBS) for 8 h in the absence or presence of 10^{-8} M triiodothyronine (T_3) or 10^{-6} M TO901317 (#71810 Cayman, Ann Arbor, MI). Luciferase activity is expressed as arbitrary light units per microgram of cellular protein. Data are presented as fold basal activation in the absence of ligand stimulation ± SEM.

2.3. Western blotting

For analysis of the protein expression of Seladin-1 (DHCR24), 30 μg of whole cell extract from HTB185 cells was subjected to SDS–PAGE. Western blotting was performed using a rabbit anti-DHCR24 polyclonal antibody (#ab40490, Abcam, Cambridge, UK) to detect Seladin-1 protein levels and anti-glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (#ab8245, Abcam, Cambridge, UK) as a control. The Seladin-1 detects a specific band at 55 kDa in tissues and cells. The bands were quantitatively measured using Adobe Photoshop 7.0 and ImageJ as previously described [25]. All Western blotting experiments were repeated at least three times with similar results. Seladin-1 protein levels are normalized by GAPDH.

2.4. RNA preparation and real-time quantitative PCR

Total RNA was extracted from HTB185 cells using ISOGEN (Nippon Gene, Tokyo, Japan). Real-time quantitative PCR assays were performed as previously described [25]. Human Seladin-1 mRNA expression was analyzed using Taqman™ probes (Hs00207388_ml, Applied Biosystems, Carlsbad, CA). The PCR results were normalized to human cyclophilin A expression using a Taqman™ probe (Hs99999904_m1, Applied Biosystems, Carlsbad, CA).

2.5. Electrophoretic mobility-shift assays (EMSAs)

EMSAs were performed as described previously [25]. Mouse LXR-α, human TR-β1, human RXR-α and mouse LXR-α-GAL4 fusion recombinant proteins were *in vitro*-translated from the constructs in the pSG5 expression vector. Six microliter of each of the synthesized nuclear receptors or unprogrammed reticulocyte lysates was employed to binding reactions. Double-stranded oligonucleotides (DR-4 for rat cholesterol 7α-hydroxylase (CYP7A1); 5′-TGTTTGCTTTGGTCACTCAAGTTCAA-3′ and site A probe; 5′- GGCAC-GACCTGCAGAGGTTACCGCCAGGTTTCCA-3′ were labeled with [α-^{32}P] deoxy-CTP using a Klenow fragment of DNA polymerase. For competition experiments, a 1000- or 2500-fold molar excess of cold oligonucleotides was included. For supershift experiments, 3 μl of rabbit anti-TR-β1 polyclonal antibody (06–539, Upstate, Lake Placid, NY) or rabbit anti-GAL4 polyclonal antibody (for DNA binding domain, sc-510, Santa Cruz Biotechnology, CA) was added. All gel-shift assays were repeated at least three times with similar results and a representative result is shown.

2.6. Chromatin-immunoprecipitation (ChIP) assay

ChIP assays were performed using a kit (ChIP-IT™ Express) from Active Motif (Carlsbad, CA) in accordance with the manufacturer's protocol with some modifications as previously described [25]. HTB185 cells were incubated in DMEM containing 10% double-stripped FBS in the absence or presence of 10^{-8} M T_3. After incubation, we prepared the sheared chromatin as described previously. The antibodies used for each ChIP assay were a rabbit anti-TR-β polyclonal antibody (06-539, Upstate, Lake Placid, NY), mouse anti-LXR-α monoclonal antibody (PP-PPZ0412-00, Perseus proteomics, Tokyo, Japan) and rabbit anti-RXR-α polyclonal antibody (sc-774, Santa Cruz Biotechnology, CA). As a negative control, normal mouse IgG (sc-2025, Santa Cruz Biotechnology, CA) was used.

To assess the ChIP result, conventional PCR was performed in 50 μl with Platinum High-fidelity (Invitrogen, Carlsbad, CA) Taq Polymerase for 32 cycles (annealing temperature of 60 °C). The primers used for the region between −586 and −262 bp for conventional PCR were as follows: forward 5′-ATAGCCTTCCA TGCTTCCAA-3′ and reverse 5′-CTTAAGCGGTTTTGCAGTGG -3′. The predicted PCR product was 325 bp long. Conventional PCR signals stained with ethidium bromide in 2% agarose gels were scanned with a Molecular Imager FX (Bio-Rad). All ChIP assays were repeated at least three times with similar results and representative results for conventional PCR are shown.

2.7. Statistical analyses

Statistical analysis was performed using Prism 5 (GraphPad Software, La Jolla, CA) and JMP (SAS Institute Inc., Cary, NC). Values are expressed as the mean ± standard error of the mean (SEM). The significance of differences between the values was evaluated using Welch's *t*-test following ANOVA or Mann–Whitney test where appropriate to assess statistical differences between means.

3. Results

3.1. T_3 up-regulates Seladin-1 gene expression in human meduloblastoma cell line

To evaluate whether TH up-regulates the human Seladin-1 gene expression, we performed real-time PCR assays using total RNA of

HTB185 cells. As shown in Fig. 1A, T_3 up-regulated the expression levels of Seladin-1 gene in a dose-dependent manner. Similar results were obtained in the protein levels (Fig. 1B). We have already demonstrated that an artificial LXR agonist, TO also up-regulated the Seladin-1 mRNA levels in HTB185 cells in the previous report [25].

3.2. Both T_3 and TO up-regulates Seladin-1 gene promoter activity in HTB185 cells

We subcloned human Seladin-1 gene promoter from −1024 to +57 bps (Fig. 1C). When we co-transfected this gene promoter with TR-β1 and RXR-α into HTB185 cells, T_3 increased the promoter activity. Similarly, co-transfected with LXR-α and RXR-α, the Seladin-1 promoter in HTB185 cells were also activated by TO (Fig. 1D).

3.3. Both T_3 and TO activates human Seladin-1 gene promoter via novel positive thyroid hormone response element (TRE)/LXR response element (LXRE), site A

As shown in Fig. 1C, we identified a TRE consensus half site located from −381 to −376 bp in the human Seladin-1 gene promoter. We referred the flanking lesion (from −395 to −362 bp) of this TRE consensus half site to site A. We prepared the deletion constructs of the promoter lacking site A (The −375/+57 and the −132/+57 construct, Fig. 2A), and transfected the wild-type promoter or each deletion mutant constructs with TR-β1 into CV1 cells. As shown in Fig. 2B, T_3 activated the −1041/+57 reporter in CV1 cells, whereas the −375/+57 or the −132/+57 construct was not activated by T_3. In addition, when we introduced mutation to TRE consensus half site in site A as shown in Fig. 2C, the mutant promoter was not activated by T_3 (Fig. 2D). These results indicated that TRE consensus half site in site A is functionally essential in the human Seladin-1 promoter activation by T_3. Likewise, TO activated the promoter which was co-transfected with LXR-α in CV1 cells, and the mutation of the TRE consensus half site diminished the activation by TO (Fig. 2D). It suggested that the TRE consensus half site in site A is indispensable to the human Seladin-1 promoter activation by TO.

3.4. Both RXR-α/TR-β1 heterodimer and RXR-α/LXR-α heterodimer bind to site A

Based on the data in Fig. 2, site A is functionally important to the positive regulation of the human Seladin-1 promoter by both T_3 and TO. Therefore, we hypothesized that TR-β1 and LXR-α share site A for binding. To investigate this, we performed EMSAs using radiolabeled site A probe. As shown in Fig. 3A, RXR-α/TR-β1 (lane 8) or RXR-α/LXR-α (lane 13) heterodimer bound to site A probe. The cold oligonucleotides interfered the binding of both heterodimers (lanes 9,10 and 14,15), and anti-TR-β antibody supershifted the RXR-α/TR-β heterodimer (lane 11).

3.5. Both TR-β and LXR-α are recruited to the site A region in the intrinsic human Seladin-1 gene promoter

To prove the hypothesis that site A plays as a novel positive TRE/LXRE of the human Seladin-1 gene promoter, we performed

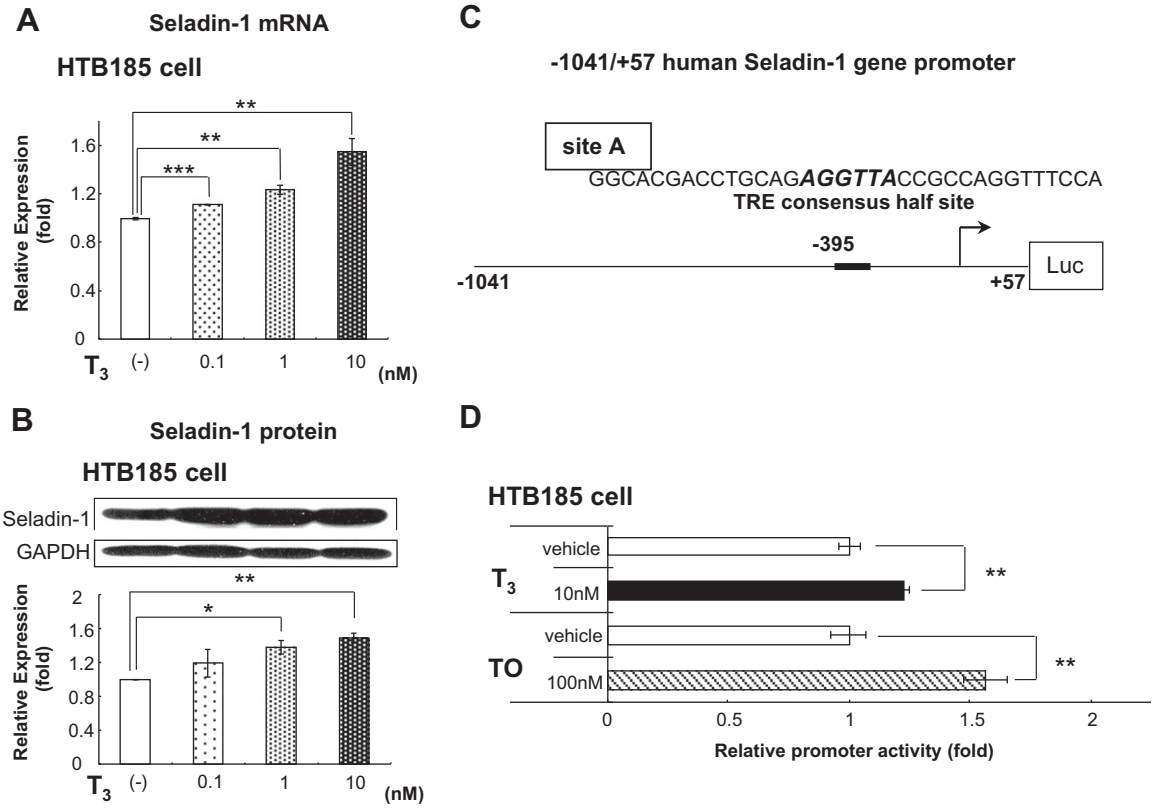

Fig. 1. T_3 up-regulated Seladin-1 gene and protein expression at the transcriptional levels. (A) RT real-time PCR analysis was performed using HTB185 cDNA. Results (mean ± SE, $n = 3$) are normalized by cyclophilin A mRNA levels and shown as fold expression correlated to the level in the absence of T_3. (B) Western blot analysis using whole cell extract in HTB185 cells. Relative O.D. (mean ± SE, $n = 4$) normalized by GAPDH levels compared with the level in the absence of T_3 is shown as relative expression (fold). (C) The structure of the human Seladin-1 gene promoter. The closed box indicates site A. The consensus TRE half-site is highlighted in italics. (D) Both T_3 and TO activated the human Seladin-1 gene promoter in HTB185 cells. Vehicles for T_3 and TO were distilled water buffered with 1 mM HEPES (pH 7.5) and DMSO, respectively. Relative luciferase activities (mean ± SE, $n = 3$) compared with the light units of pGL4 reporter construct in the absence of T_3 or TO are shown as relative promoter activity (fold). An *asterisk* indicates that the difference between the denoted pairs is significant at a confidence level of $p < 0.05$(*), $p < 0.01$(**), $p < 0.001$(***).

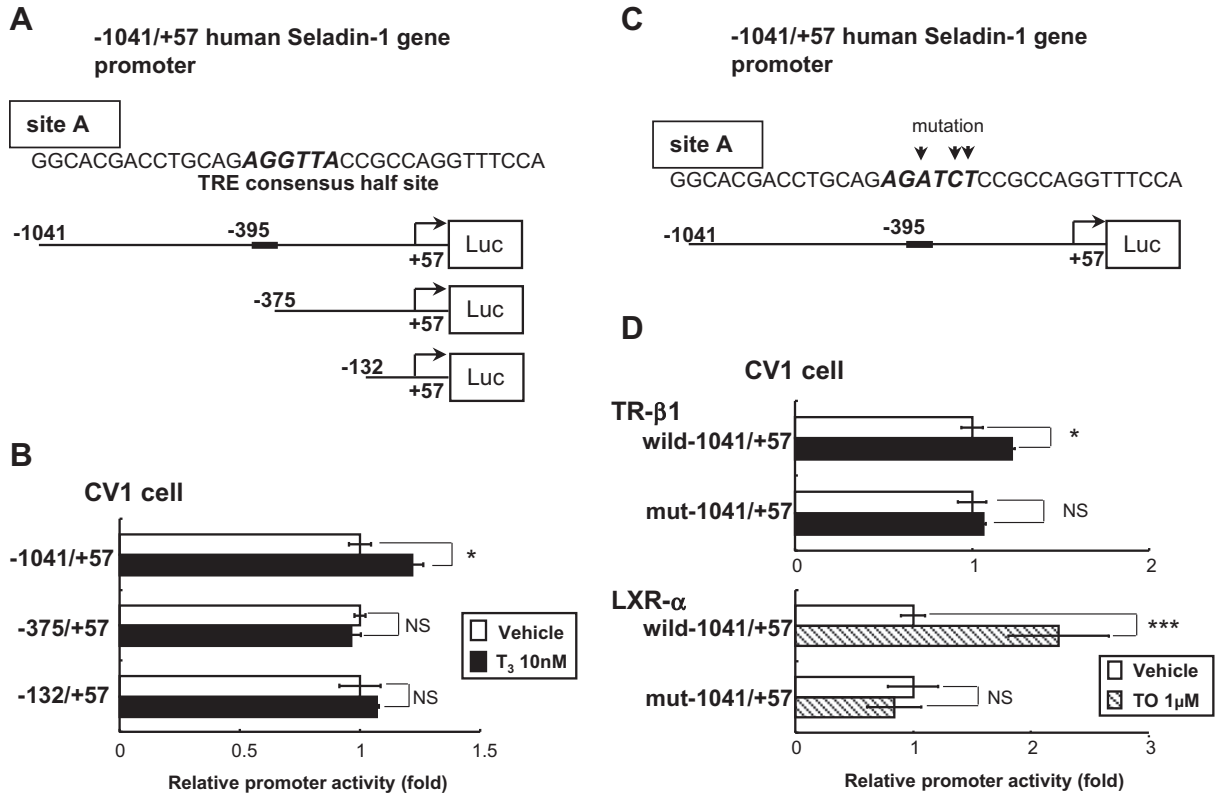

Fig. 2. Both T_3 and TO activated the human Seladin-1 gene promoter via site A. (A) The deletion mutant reporters were co-transfected into CV1 cells with TR-β1 construct. The closed box indicates site A. TRE consensus half-site is highlighted in italics. (B) Relative luciferase activities (mean ± SE, $n = 3$) compared with the light units in the absence of T_3 are shown as relative promoter activity (fold). (C and D) Mutation in site A abolished the promoter activation by either T_3 or TO. In C, arrowheads indicate the mutation in site A. Relative luciferase activities (mean ± S.E., $n = 3$) compared with the light units in the absence of T_3 or TO are shown as relative promoter activity (fold). An *asterisk* indicates that the difference between the denoted pairs is significant at a confidence level of $p < 0.05$(*), $p < 0.001$(***). NS: not significant.

ChIP assays using a set of primers amplifying the −586 to −262 bp region, which includes site A, in HTB185 cells harboring the intrinsic promoter and receptors. As shown in left panel of Fig. 3B, TR-β, LXR-α and RXR-α were recruited in the −586 to −262 bp region of the promoter, and the recruitment of TR-β was increased in a time-dependent manner upon T_3 administration. LXR-α recruitment was not affected by T_3 administration.

On the other hand, TR-β, LXR-α or RXR-α was not recruited to the distinct region from site A (−961 to −692 bp) (Fig. 3B, right panel).

3.6. TR-β1 and LXR-α competitively bind and regulate the human Seladin-1 gene promoter

Since anti-LXR-α antibody, which is commercially available didn't work in EMSAs for the human Seladin-1 promoter analysis (data not shown), we employed the GAL4-tagged LXR-α fusion protein [27]. As shown in Fig. 4A, RXR-α/GAL4-LXR-α also bound to the site A probe, and the anti-GAL4 antibody shifted the heterodimer away from the gel (lane 10). Anti-TR-β antibody separated RXR-α/TR-β1 and RXR-α/GAL4-LXR-α heterodimer (lanes 11–13). The RXR-α/TR-β1 heterodimer seemed to be slightly reduced upon the increase of RXR-α/GAL4-LXR-α heterodimer formation (lanes 12, 13). This result indicates that TR-β and LXR-α might interfere mutually by sharing of binding site.

To prove the functional competition of TR-β and LXR-α, we co-transfected both TR-β and LXR-α with the −1041/+57 reporter in CV1 cells, with the way fixing the amount of one receptor and increasing the other. As shown, T_3 failed to activate the promoter in the presence of LXR-α and the promoter activation by TO was deteriorated upon the increasing amount of TR-β1 (Fig. 4B and C).

4. Discussion

In the current study, we revealed that both TR and LXR up-regulate the human Seladin-1 gene promoter at the transcriptional levels. Both of the receptors share the site A containing TRE/LXRE consensus half site, and regulate the promoter activity competitively. The configuration of the human Seladin-1 gene promoter is similar to the mouse promoter and TREs in both gene promoters contain a half site of consensus DR-4 sequence [25]. Based on the data in Fig. 2D, the TRE half site is essential for the human Seladin-1 promoter activation by T_3 and TO.

The difference between the human and the mouse Seladin-1 promoter is whether TR-β and LXR-α share the DNA binding site. In the human promoter, TR-β and LXR-α utilize the same TRE/LXRE consensus half site, site A. Since TR and LXR basically recognize the DR-4 sequence [11] as a response element, TR and LXR regulate the several gene promoters competitively, such as *Cyp7a1* and *Abca1* [15,16]. In the mouse Seladin-1 promoter, TR-β binds to the region containing a TRE consensus half site, whereas LXR-α does not bind to the region in our previous study [25]. Nonetheless, LXR-α is recruited to a different region, which is located downstream of the TRE consensus half site in the mouse promoter [25]. Furthermore, there are several cases that the crosstalk of TR and LXR in a gene promoter is different among species (ex. CYP7A1 gene in human and mouse [16,28,29]).

In our previous report, we performed ChIP assays and demonstrated that the enrichment of TR-β on the promoter is increased

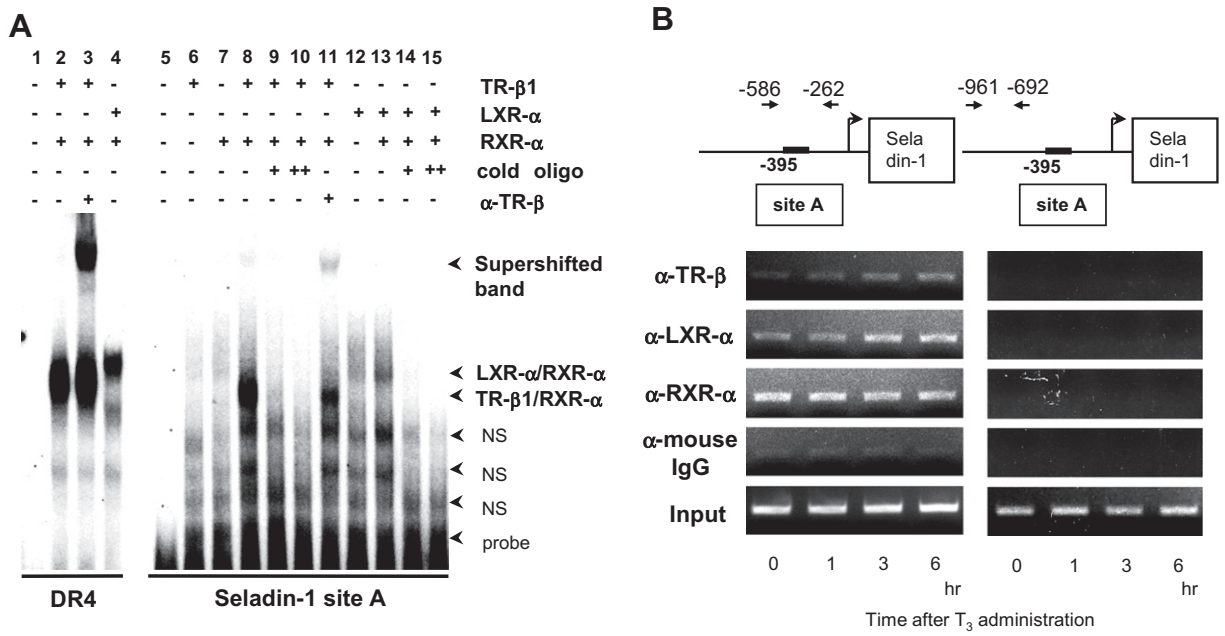

Fig. 3. (A) Both RXR-α/TR-β1 and RXR-α/LXR-α bind to site A. Six microliters (indicated as '+') of *in vitro*-translated human TR-β1 and/or human RXR-α and/or mouse LXR-α protein or unprogrammed rabbit reticulocyte lysates were incubated with radiolabeled DNA probes (DR-4 or site A). For competition experiments, 1000- (+) or 2500-fold (++) molar excess of cold oligonucleotides was included as indicated. α-TR-β: TR-β antibody. NS: non specific band. (B) TR-β is recruited to the region surrounding site A (−586 to −262 bp) in a time-dependent manner upon T_3 administration (left panel) but not to the upstream region at −961 to −692 bp (right panel). The location of the PCR primers is indicated as arrows. Site A is indicated as a closed box. The input was a non-immunoprecipitated sample used as a positive control.

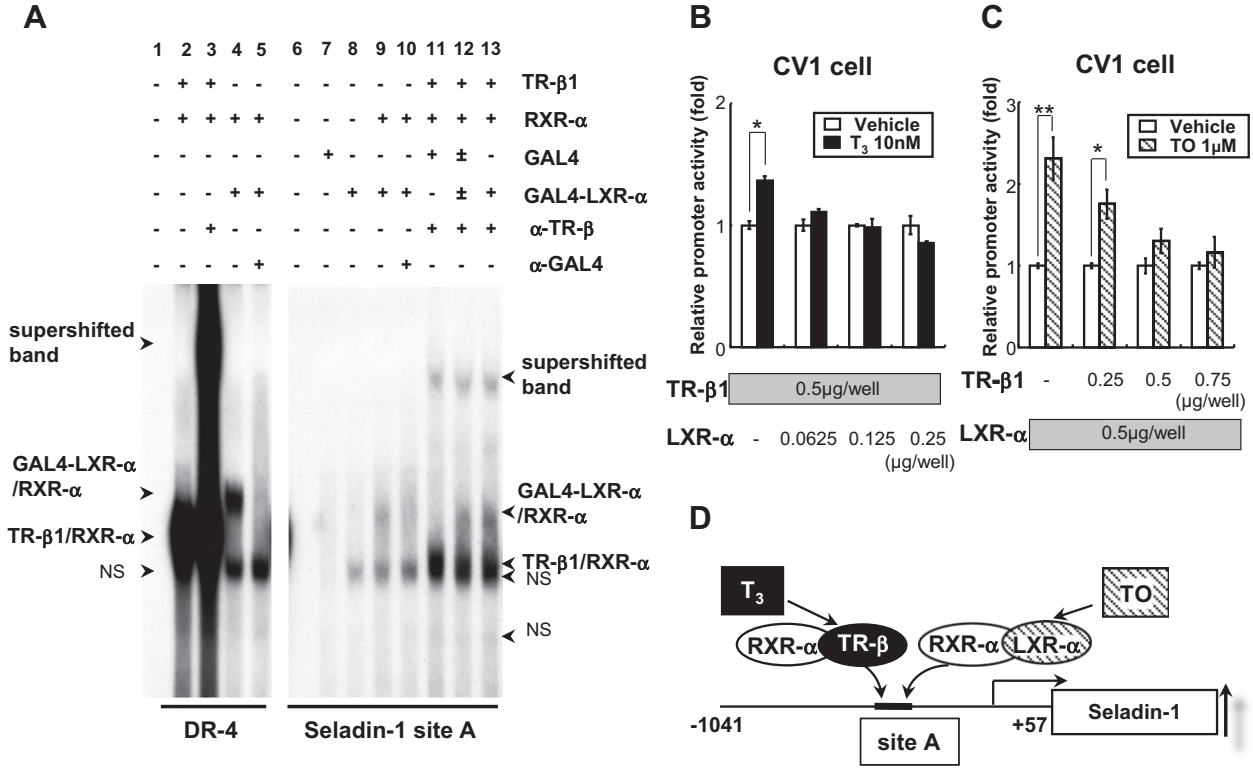

Fig. 4. (A) RXR-α/GAL4-LXR-α and RXR-α/TR-β1 competitively bind to site A. α-TR-β: TR-β antibody, α-GAL4: GAL4 antibody. Six microliters (indicated as '+') of *in vitro*-translated human TR-β1 and/or human RXR-α and/or GAL4-LXR-α protein or unprogrammed rabbit reticulocyte lysates were incubated with radiolabeled DNA probes (DR-4 or site A). '±' indicates 3 μl of GAL4-LXR-α or GAL4. NS: non specific band. (B and C) The human Seladin-1 gene promoter (−1041/+57 bp) coupled to pGL4 was co-transfected into CV1 cells in the presence of an expression vector for TR-β1 or LXR-α as indicated in the figure. Relative luciferase activities (mean ± SE, $n = 3$) compared with the light units in the absence of T_3 (A) or TO (B) are shown as relative promoter activity (fold). An *asterisk* indicates that the difference between the denoted pairs is significant at a confidence level of $p < 0.05$(*), $p < 0.01$(**). (D) Schematic diagram illustrating the hypothetical mechanism of TR/LXR crosstalk on the human Seladin-1 gene promoter.

upon T_3 administration, on the other hand, the recruitment of LXR-α is reduced accordingly. These data suggested that TR-β preferably regulates the mouse Seladin-1 promoter than LXR-α. Therefore, an LXR agonist can activate the Seladin-1 expression in mouse forebrain only in a hypothyroid state or in the presence of TR-β mutant [25]. In contrast, in the human Seladin-1 promoter, LXR-α and TR-β equally heterodimerize with RXR-α and bind to site A. Moreover, functionally, LXR-α and TR-β competitively regulate the human Seladin-1 promoter activity. These results in the current study suggest that in human, TH and LXR agonists equally could exert function to activate the promoter.

In conclusion, we have demonstrated that TR and LXR competitively up-regulate the human Seladin-1 gene promoter at the transcriptional levels and both receptors share the novel positive TRE/LXRE. We also showed the difference in the TR/LXR crosstalk between on the human and the mouse Seladin-1 promoter. On the basis of the data in the current study, since Seladin-1 is favorable to avoid the accumulation of β-amyloid and neuronal death, we speculate that LXR agonists as well as TH and its mimetics could be the targets for the novel molecular treatment against AD.

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