PERGAMON

Journal of Steroid Biochemistry & Molecular Biology 87 (2003) 57–63

The Journal of Steroid Biochemistry & Molecular Biology

www.elsevier.com/locate/jsbmb

p33^{ING1b} stimulates the transcriptional activity of the estrogen receptor α via its activation function (AF) 2 domain

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Received 29 January 2003; accepted 16 June 2003

Abstract

The ING1 gene was originally cloned as a candidate tumor suppressor of human breast cancer, and recent studies suggest that ING1 proteins are involved in chromatin remodeling functions via physical association with both histone acetyltransferases (HATs) and histone deacetylases (HDACs). In this study, we investigated whether p33^{ING1b}, one of the major ING1 isoforms, modulated the transcriptional activity of estrogen receptor (ER) α. In Cos-7 cells transfected with increasing concentrations of a mammalian expression vector encoding for p33^{ING1b}, estrogen-induced ERα transcriptional activity was found to increase in a dose-dependent manner. As p33^{ING1b} expression levels increased, transcription of an ER-responsive reporter gene by either estrogen-inducible full-length ERα or activation function (AF) 1 deletion mutant was enhanced, while the AF2 deletion mutant was unaffected by the presence of p33^{ING1b}. These results showed that p33^{ING1b} enhanced estrogen-induced ERα activity through the AF2 domain. Our data also demonstrated that the antiestrogens inhibited the transcriptional activity of ERα as stimulated by p33^{ING1b}. Furthermore, a weak physical association was observed between in vitro translated p33^{ING1b} and ERα. Our data presented here demonstrate that p33^{ING1b} acts like a coactivator for ERα and stimulates estrogen-induced ERα transcriptional activity consistent with a function for p33^{ING1b} in chromatin remodeling.

Keywords: p33^{ING1b}; ING1b; Estrogen receptor α; Cofactor

1. Introduction

Estrogens play an important role in the growth of most ERα-positive mammary carcinomas [1]. Considerable data indicate that many of the growth-promoting characteristics of estrogens are mediated through their mitogenic effects on breast cancer cells. The ability of antiestrogens to inhibit the growth of ERα-positive breast tumors is consistent with this basic model, but the detailed molecular events involved in this process are not understood. During estrogen-induced transactivation, current evidence indicates that a cofactor complex is recruited, forming a higher complex with ERα to achieve activation and repression of transcription. Several coactivators have been identified which directly interact in an estrogen-dependent manner with the activation function (AF) 2 domain of ERα [2–7].

The ING1 candidate tumor suppressor was cloned by subtractive hybridization of human breast cancer cell line-derived cDNA with cDNA from normal human epithelial cells [8]. Suppression of p33^{ING1} expression promotes focus formation and cell growth in vitro and tumor formation in vivo, whereas ectopic overexpression of this protein blocks cell cycle progression by arresting transfected cells at the G_1 phase of the cell cycle [8]. Reduced levels of p33^{ING1} have been found in breast cancer-derived cell lines and in a proportion of primary breast cancers [9], as well as a variety of other tumor types [10]. Recently, several ING1 splicing variants and ING1-like proteins have been reported [11]. p33^{ING1} was the first ING1 sequence cloned [8], followed by the isoforms ING1a and ING1b [12], which encode for the p47^{ING1a} and p33^{ING1b} proteins, respectively. These isoforms contain a plant homeodomain (PHD) form of zinc finger that is commonly found in chromatin-associated protein [13]. Recent studies suggest that human ING1 proteins might be involved in chromatin remodeling functions via physical association with both histone acetyltransferases

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doi:10.1016/S0960-0760(03)00388-1

(HATs) and histone deacetylases (HDACs) [14,15]. Since both ERα and ING1 proteins have been linked to HAT complexes, in this study, we investigated whether $p33^{ING1b}$ was involved in ERα-mediated transcriptional activation.

2. Materials and methods

2.1. Chemicals, cells and cell culture

Tamoxifen (TAM) was purchased from Sigma (Tokyo, Japan). ICI182,780 (ICI) and the raloxifene analog LY117018 (RALa) were kindly provided by AstraZeneca (Macclesfield, UK), and Eli Lilly & Co. (Indianapolis, IN, USA), respectively. African green monkey kidney cell line (Cos-7), human hepatocellular carcinoma (HepG2) and human cervical carcinoma (HeLa) cells were purchased from the American Type Culture Collection (Rockvill, MD, USA) and maintained in either DMEM (Invitrogen Life Technologies, Tokyo, Japan) or RPMI1640 (Invitrogen Life Technologies), containing 10% fetal bovine serum (FBS) (Sigma), penicillin, and streptomycin. These cell lines require expression of exogenous ERα to activate ER response element (ERE)-mediated transcription.

2.2. Plasmids

The mammalian expression vectors for $p33^{ING1b}$ was constructed by introducing the cDNA into pCI-neo vector (Promega, Tokyo, Japan) [16]. Hemagglutinin antigen epitope (HA)-tagged $p33^{ING1b}$ (HA-$p33^{ING1b}$), as well as human full-length (HEG0) and deletion mutants (HE15 and HEG19) of ERα, have been described previously [17,18]. c-Myc-tagged full-length ERα expression vector (c-Myc-ERα) was constructed by subcloning an *Eco*RI fragment of HEG0 into the *Eco*RI site of pGBKT7 (BD Biosciences Clontech, Tokyo, Japan). c-Myc-tagged-luciferase expression vector (c-Myc-luc) was constructed by subcloning an *Nco*I–*Bam*HI fragment of pGL3-promoter vector (Promega) into the *Nco*I and *Bam*HI sites of pGBKT7 (BD Biosciences Clontech).

2.3. Transient transfection and transcriptional activation assays

For transfection assays, cells were maintained in DMEM or RPMI1640 (devoid of phenol red) and supplemented with 10% charcoal dextran-treated FBS (HyClone, Logan, UT, USA). Approximately 18 h prior to transfection, 2×10^5 cells were seeded into each well of six-well dishes. Cells were transiently transfected using Fugene-6 transfection reagent (Roche Diagnostics, Tokyo, Japan) according to the manufacturer's instructions. A total amount of 2.0 μg plasmid DNA per well was used, including 500 ng of estrogen-responsive reporter gene construct (ERE-TATA-luciferase) [19], and 4 ng of pRL-TK vector (Promega), which contains cDNA encoding for Renilla luciferase so as to provide an internal control for transfection efficiency. Twenty-four hours later, the cells were lysed in 1 × passive lysis buffer (Promega). Luciferase activity was measured using the Dual-luciferase assay system (Promega).

2.4. In vitro coimmunoprecipitation

HA-$p33^{ING1b}$, c-Myc-ERα, and c-Myc-luc fusion proteins were synthesized in vitro by T7 promoter-based combined transcription/translation using the TNT reticulocyte lysate system (Promega) in the presence of [^{35}S]methionine. In vitro translated HA-$p33^{ING1b}$ and/or c-Myc-ERα proteins were incubated at room temperature for 1 h in the presence of 10^{-8} M 17β-estradiol. Following this, one microliter of anti-c-Myc monoclonal antibody (BD Biosciences Clontech) or anti-HA polyclonal antibody (BD Biosciences Clontech) was added and the mixture was incubated at room temperature for 1 h. Protein G plus-agarose (Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA) was added, followed by incubation at room temperature for 1 h. Samples were washed eight times in 1 × PBS (Sigma), resuspended in 2 × SDS sample buffer (Bio-Rad Laboratories, Tokyo, Japan), and heated at 80 °C for 5 min. The proteins were resolved by SDS–PAGE and visualized by autoradiography. c-Myc-luc was used as a negative control of c-Myc-ERα.

3. Results

3.1. $p33^{ING1b}$ increased ERα transcriptional activity stimulated by estrogen

Human ING1 immunoprecipitates contain HAT activity, and overexpression of $p33^{ING1b}$ induces hyperacetylation of histones H3 and H4 [15]. $p33^{ING1b}$ was also found to be functionally and physically linked to HDAC1 [20,21]. Therefore, we examined the ability of $p33^{ING1b}$ to modulate estrogen-induced transcriptional activation by ERα. Cos-7 cells were transiently cotransfected with an expression plasmid encoding human full-length ERα and increasing concentrations of an expression plasmid encoding for $p33^{ING1b}$, together with an ERE-TATA-luciferase expression vector. In Cos-7 cells transfected with increasing concentrations of $p33^{ING1b}$ expression vector (0–1 μg), estrogen-induced ERα transcriptional activity was found to increase in a dose-dependent manner up to ∼40-fold (Fig. 1).

3.2. $p33^{ING1b}$ stimulated the transcriptional activity of ERα through the AF2 domain

The ERα protein contains several important functional domains (Fig. 2A). The hormone binding domain within the E region of ERα also contains an estrogen-inducible transcriptional activation function called AF2. A second, constitutive activation function (AF1) is located within the A/B

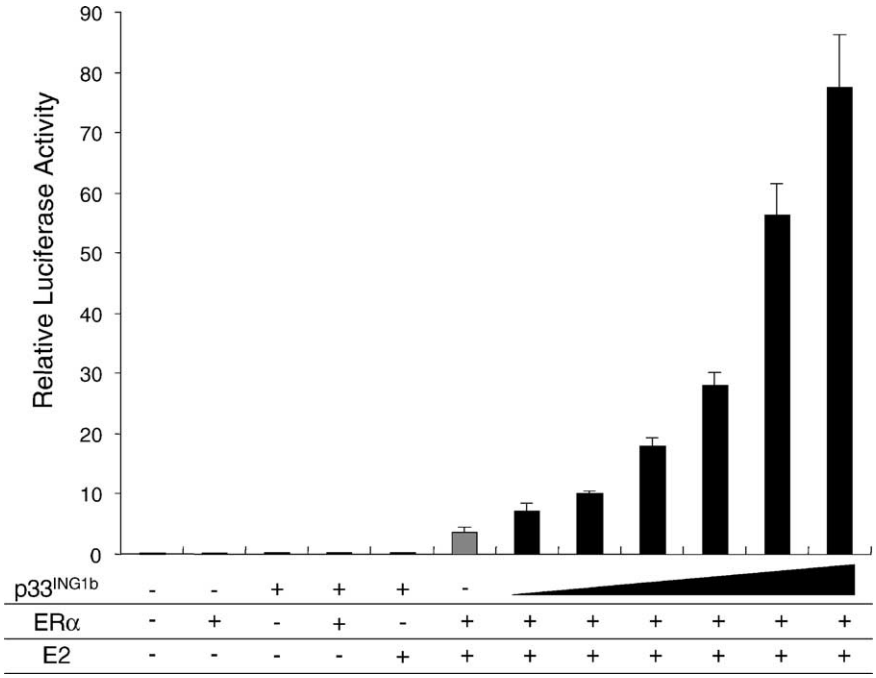

Fig. 1. p33^{ING1b} increased ERα transcriptional activity stimulated by 17β-estradiol: Cos-7 cells were transiently transfected with 30 ng of full-length ERα (HEG0), 500 ng of ERE-TATA-luciferase expression vector and 4 ng of pRL-TK vector (as an internal control of transfection efficiency) in the absence or presence of 1 μg of p33^{ING1b} expression vector or increasing concentrations (0, 10, 25, 100, 250, 500 ng, or 1 μg) of p33^{ING1b}. Cells were treated with or without 10^{-8} M 17β-estradiol (E2). E2-stimulated gene expression was increased in a dose-dependent manner by up to ∼40-fold. Data are presented as the average of four experiments.

region of the receptor [18]. To investigate which domain of ERα was involved in the enhancement of ERα transcriptional activity by p33^{ING1b}, we measured the transcriptional activity of ERα using full-length (HEG0) and ERα deletion mutants (HE15 and HEG19) as shown in Fig. 2A. Cos-7 cells were transiently cotransfected with either HEG0, AF2 deletion mutant (HE15) or AF1 deletion mutant (HEG19) of ERα along with ERE-TATA-luciferase expression vector in the absence and presence of p33^{ING1b} expression vector. When p33^{ING1b} expression levels were increased, transcription of the target gene by estrogen-activated full-length ERα or AF1 deletion mutant was enhanced in Cos-7 cells, while AF2 deletion mutant was not stimulated by expression of p33^{ING1b} (Fig. 2B). These results suggested that the AF1 domain might not be required for ERα transcriptional activity as stimulated by p33^{ING1b}. To assess the ability of p33^{ING1b} to contribute to ERα transcriptional activity in different tissues, experiments were performed under the same conditions using HepG2 and HeLa cells (Fig. 2C and D). These results showed that p33^{ING1b} enhanced estrogen-induced ERα activity through the AF2 domain in a cell type-independent manner.

3.3. Antiestrogens inhibited the estrogen-induced transcriptional activity of ERα enhanced by p33^{ING1b}

TAM and RALa are classified as selective estrogen receptor modulators (SERMs) as these compounds have both estrogenic and antiestrogenic activities at different sites in the body. On the other hand, ICI completely attenuates ERα-mediated transcription as this agent inactivates both AF1 and AF2, leading to complete suppression of estrogen–ERα-dependent gene expression [22]. To test whether antiestrogens function as antagonists against estrogen when estrogen-induced transcriptional activity for ERα was stimulated by p33^{ING1b}, Cos-7 cells were cotransfected with HEG0 and ERE-TATA-luciferase expression vector in the presence or absence of p33^{ING1b} expression vector (100 ng) and, subsequently, were treated with 10^{-8} M 17β-estradiol. Different concentrations of antiestrogens, ranging from 10^{-12} to 10^{-5} M, were added. As shown in Fig. 3, the addition of antiestrogens reduced the transcriptional activity of ERα enhanced by p33^{ING1b}. Furthermore, the data obtained with coexpression of p33^{ING1b} was very similar to those without coexpression of p33^{ING1b}. Therefore, our data demonstrated that p33^{ING1b} did not influence the action of antiestrogens on ERα.

3.4. Interaction of in vitro synthesized p33^{ING1b} with ERα

The ability of ERα and p33^{ING1b} to physically interact was assessed in vitro by a coimmunoprecipitation assay. HA-p33^{ING1b}, c-Myc-ERα, and c-Myc-luc were synthesized in vitro in the presence of [^{35}S]methionine. In vitro

synthesized c-Myc-ERα, and/or HA-p33^{ING1b} were coimmunoprecipitated with antibodies against c-Myc or HA in the presence of 10^{-8} M 17β-estradiol. As shown in Fig. 4, a weak but reproducible band of ERα or p33^{ING1b} was detected in the lane 5 or 6, respectively. c-Myc-luc was added as a negative control of c-Myc-ERα in the lane 4 in Fig. 4. The results obtained suggested that p33^{ING1b} physically interacted with ERα.

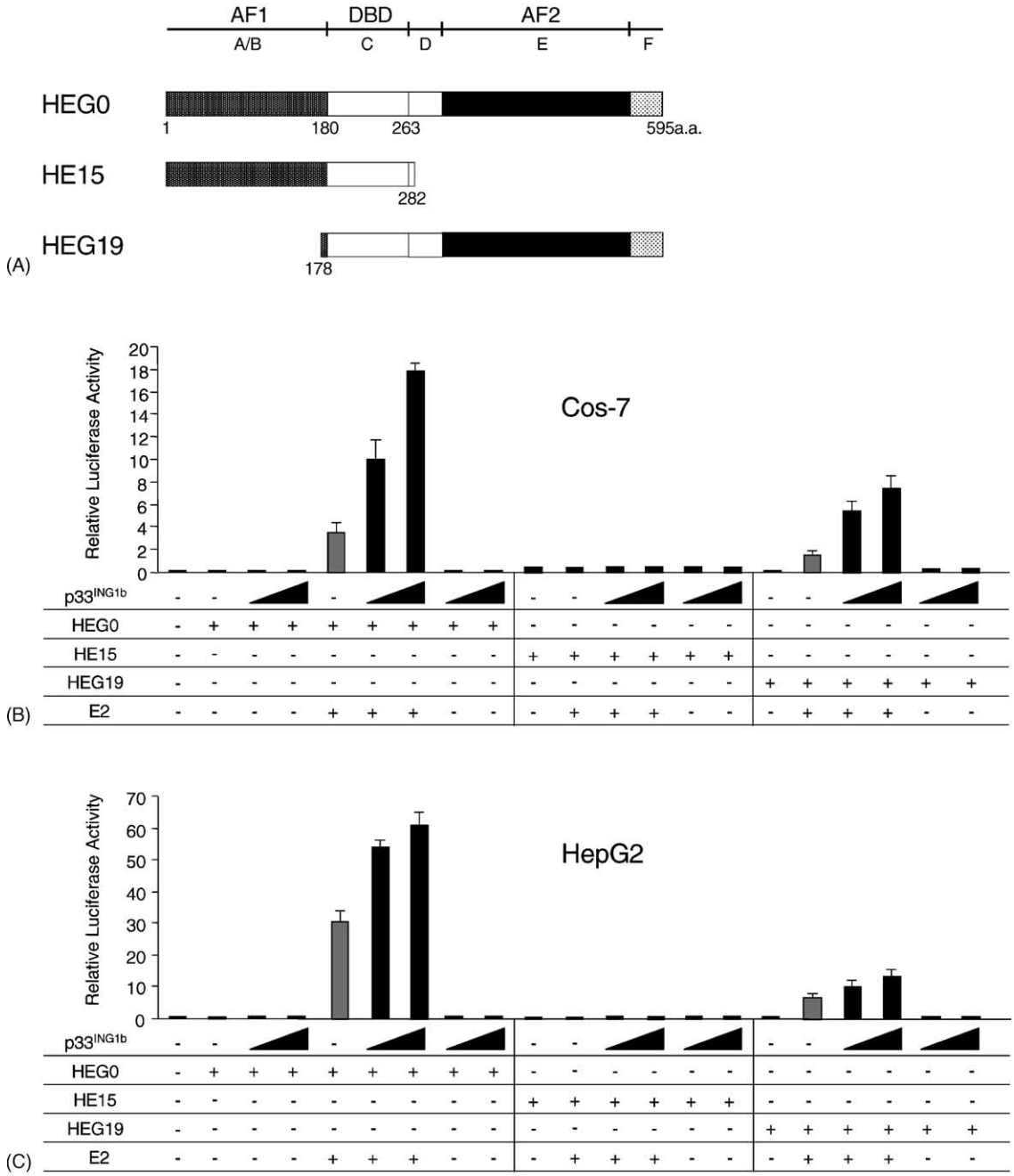

Fig. 2. (A) Full-length and deletion mutants of human ERα. Human full-length: ERα (HEG0) is schematically represented, with the positions of the functional domains, AF1and AF2, as well as the DNA binding domain (DBD), being shown [18]. Deletion mutant ERα proteins lacking AF2 (HE15) or AF1 (HEG19), which were used in this study, are also indicated [18]. (B) p33^{ING1b} stimulated the transcriptional activity of ERα through the AF2 domain. Cos-7 cells, HepG2 cells (C); or HeLa cells (D) were transiently transfected with 30 ng of HEG0, HE15, or HEG19, and 500 ng of ERE-TATA-luciferase expression vector and 4 ng of pRL-TK vector in the absence or presence of an expression vector for p33^{ING1b} (25, 100 ng). Cells were treated with or without 10^{-8} M 17β-estradiol (E2). Data are presented as the average of four experiments. Transcription of the target gene by estrogen-activated full-length or AF1 deletion mutant was enhanced, while the transcriptional activity of the AF2 deletion mutant was not stimulated in these cell lines.

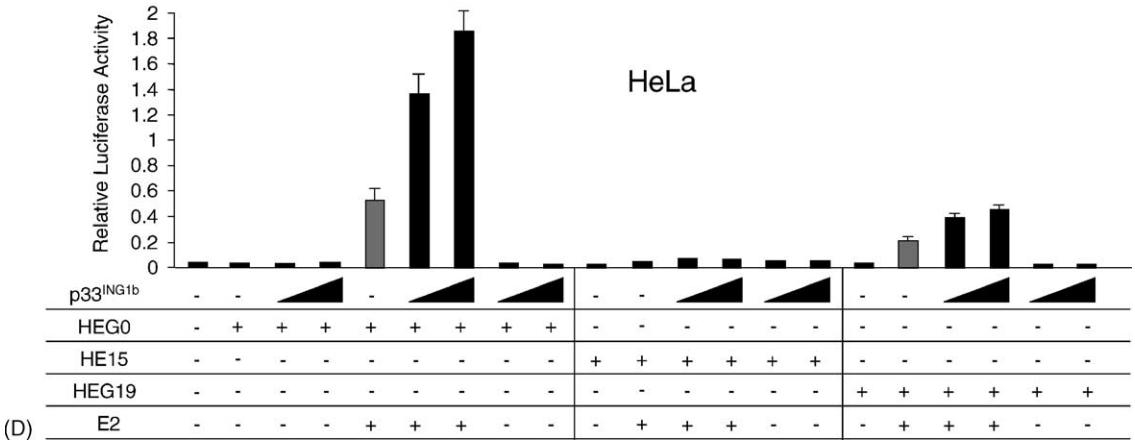

Fig. 2. (*Continued*).

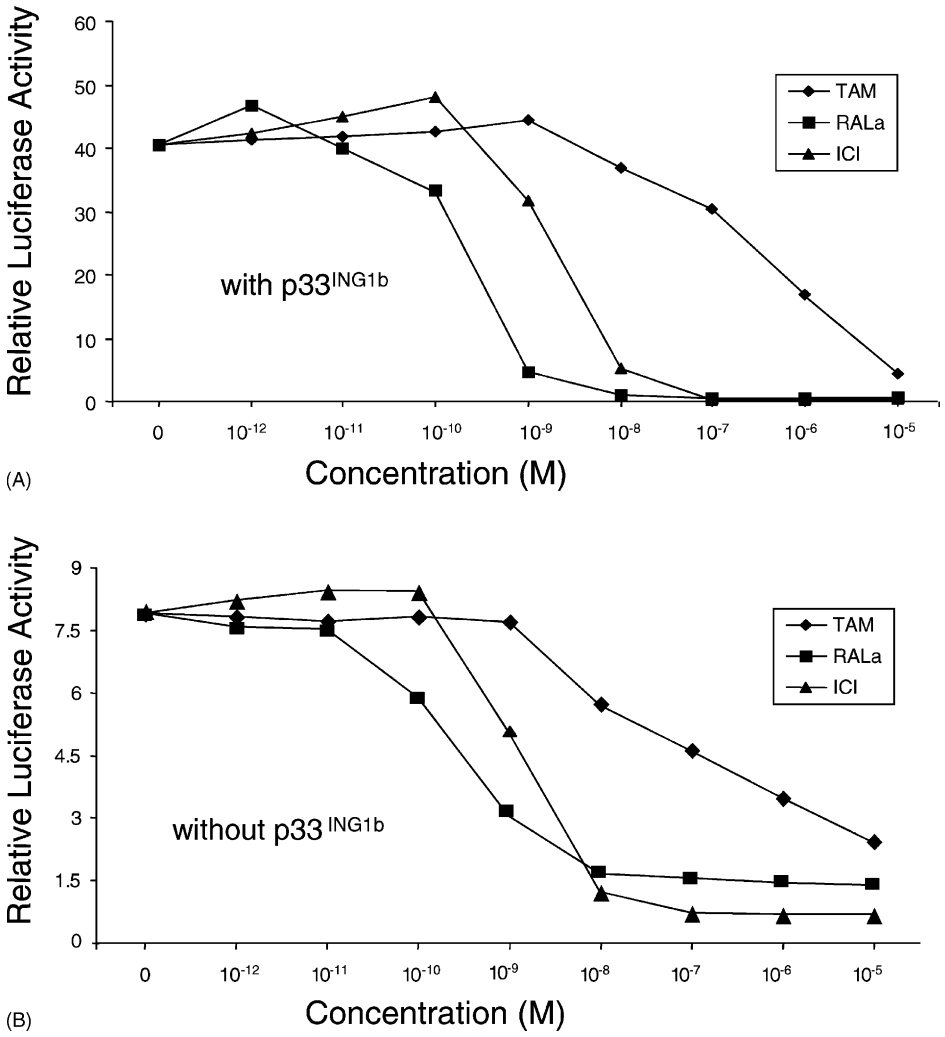

Fig. 3. Antiestrogens inhibited the estrogen-induced transcriptional activity of ERα enhanced by $p33^{ING1b}$: Cos-7 cells were transiently transfected with (A) or without (B) $p33^{ING1b}$ (100 ng) and ERα expression vectors, along with ERE-TATA-luciferase expression vector and 10^{-8} M 17β-estradiol in the medium. After transfection, cells were treated with increasing concentrations (ranging from 10^{-12} to 10^{-5} M) of tamoxifen (TAM), raloxifene analog LY117018 (RALa), and ICI182,780 (ICI). The addition of antiestrogens reduced the transcriptional activity of ERα stimulated by $p33^{ING1b}$. Similar results were obtained when the transcriptional activity of ERα was not stimulated by $p33^{ING1b}$. Data are presented as the average of three experiments.

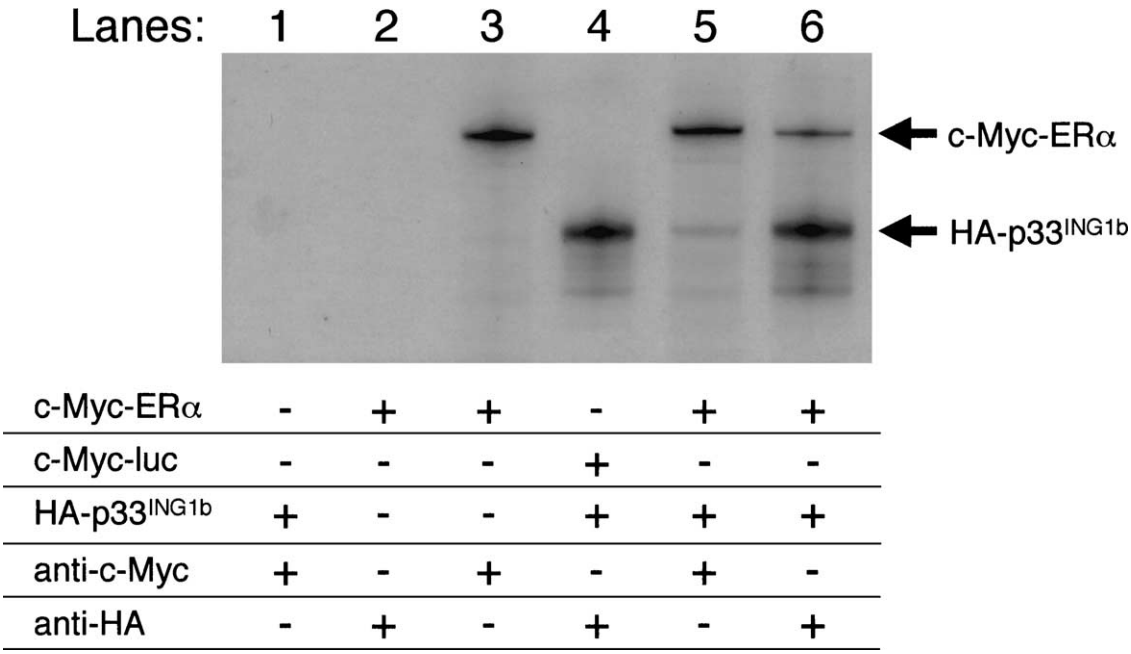

Fig. 4. Interaction of in vitro synthesized p33^{ING1b} with ERα. HA-p33^{ING1b}, c-Myc-ERα, and c-Myc-luc fusion proteins were synthesized in vitro in the presence of [^{35}S]methionine. In vitro synthesized c-Myc-ERα and/or HA-p33^{ING1b} were coimmunoprecipitated with antibodies against c-Myc or HA in the presence of 10^{-8} M 17β-estradiol. c-Myc-luc was added as a negative control of c-Myc-ERα in the lane 4. A weak but reproducible band of ERα or p33^{ING1b} was detected in the lane 5 or 6, respectively.

4. Discussion

Breast cancer growth is regulated by estrogen, whose effect is mediated by binding to the ERα. The presence of ERα in breast cancers has thus been used to identify those patients who may respond to endocrine agents such as TAM. However, one-half of the patients with ERα-positive tumors fail to respond favorably to antiestrogen treatment [23]. Several cofactors have been reported to interact with ERα and the basal transcriptional machinery; these cofactors activate or repress ERα-mediated transcription [24,25]. It has been postulated that these cofactors may be involved in the response to antiestrogen therapy. There have been some reports suggesting a possible relationship between the expression levels of a coactivator, SRC-1, and clinical responses to TAM [26], between the expression levels of another coactivator, AIB1, and ERα expression levels [27,28], and between the development of TAM resistance and the expression levels of a corepressor, N-CoR, in breast cancer [29].

ING1 was isolated as a candidate tumor suppressor [8]. The ING1 isoforms, p47^{ING1a} and p33^{ING1b}, both contain a similar nuclear localization signal, as well as the evolutionarily conserved PHD finger domain, which is commonly found in transcription factors and proteins involved in chromatin-mediated transcriptional regulation [13]. Recent studies demonstrated that human ING1 proteins were involved in chromatin remodeling functions via physical interaction with both HATs and HDACs [14,15]. Human ING1 proteins has been reported to interact with proteins associated with HAT activity, such as TRRAP, PCAF, CBP, and p300 [15]. Human ING1 immunocomplexes contain HAT activity, and overexpression of p33^{ING1b}, but not of p47^{ING1a}, induces hyperacetylation of histones H3 and H4 in vitro and in vivo [15]. p47^{ING1a} inhibits histone acetylation in vitro and in vivo and binds HDAC1 [15]. This study showed that p33^{ING1b} stimulated estrogen-induced ERα transcriptional activity in a dose-dependent manner, and that this activation was enhanced through the AF2 domain of ERα. Therefore, it is suggested that the transcription of ERα-responsive target genes in ERα-positive breast cancers might be enhanced when p33^{ING1b} is expressed at a high levels, and that p33^{ING1b} might be involved in the carcinogenesis of some human breast tumors as *ING1b* mRNA expression was previously shown to be relatively high in some early stage breast cancers [9].

The presented data also demonstrated that the antiestrogens, TAM, RALa, and ICI inhibited the transcriptional activity of ERα stimulated by p33^{ING1b} in Cos-7 cells. Moreover, it was shown that p33^{ING1b} did not influence the action of antiestrogens on ERα. Generally, ICI182,780 is found to facilitate more inhibition of ER-dependent transcription than SERMs such as TAM and RALa. However, our results showed that RALa demonstrated more inhibitory activity against ERα than ICI182,780. In Cos-7 cells, some corepressors might be involved in the inhibition by RALa of ERα-dependent transcription. p33^{ING1b} has been reported to bind nuclear receptor coactivators on the basis of co-immunoprecipitation analysis [15]. Our results revealed a weak physical association between in vitro translated p33^{ING1b} and ERα, although the binding site of p33^{ING1b}

to ERα was not clarified. It was observed that $p33^{ING1b}$, ERα and coactivators bound each other, and suggested that ERα might activate target genes by making a stable complex of $p33^{ING1b}$, coactivators and components of the transcriptional machinery.

The results in this study suggested that $p33^{ING1b}$, which was originally cloned as a candidate tumor suppressor for human breast cancer, acted like a coactivator for ERα.

Acknowledgements

We thank Dr. P. Chambon for the expression constructs of HEG0, HE15, and HEG19, Dr. M.G. Parker for the estrogen-responsive reporter gene construct ERE-TATA-luciferase, and Mrs. M. Nishio for the technical assistance. This work was supported in part by a grant from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (to T.T.).

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