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ERBP, a novel estrogen receptor binding protein enhancing the activity of estrogen receptor

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Abstract

To understand the mechanism by which estrogen receptor (ER) activates transcription in a tissue specific fashion, we isolated ERα binding protein (ERBP) by performing yeast two-hybrid screening with human mammary gland cDNA library. ERBP is a nuclear protein and its mRNA is ubiquitously expressed. The in vitro interaction of ERBP with ERα was demonstrated by GST pull-down assay and this interaction was enhanced by estrogen. In addition, ERBP also bound to PPARγ, RXRα, and ERβ. ERBP interacted with the DNA binding domain and the hinge region of ERα. There are two ERα binding regions on ERBP. The binding of ERBP region at C-terminus to ERα is increased by estrogen while the binding of ERBP region at N-terminus is not affected by estrogen. The interaction of ERBP with ERα was further confirmed in vivo by immunoprecipitation. Transient transfection experiment demonstrated that ERBP enhanced the transcriptional activity of ERα.

Keywords: Estrogen receptor binding protein; Coactivator; Estrogen receptor α

Estrogen is a critical regulator of normal mammary gland and breast cancer development [1,2]. It also plays an important role in numerous human diseases including endometrial cancers, cardiovascular disease, osteoporosis, and Alzheimer's disease [3–5]. The biological action of estrogen is mediated by the products of two genes, estrogen receptor (ER) α and β [6,7]. ERα and ERβ have similar affinity for estrogen but exhibit distinct tissue distribution and physiological function. ERα is the receptor responsible for estrogen-induced growth of mammary gland and of the reproductive tract [8].

ER is a hormone-dependent transcription factor that belongs to the nuclear receptor superfamily [6,9]. ER binds estrogen response element which is a 13-bp inverted repeat through its conserved DNA binding domain. Like other nuclear receptors, ER contains two transcriptional activation function domains: the autonomous transcriptional activation function domain AF-1 located at the N-terminus and the ligand-dependent AF-2 located in the C-terminus [10]. The abilities of AF-1 and AF-2 to activate transcription vary according to the promoter context and the cell type [11].

Identifying the ER interacting proteins sheds light on the mechanism by which ER modulates transcription [12,13]. The three members of SRC-1 family and CBP/p300 which interact with the AF-2 domain of ER in a ligand-dependent manner harbor histone acetyltransferase activities [14–16]. ER interacts with protein arginine methyltransferases including CARM1, PRMT1, and PRMT2 directly or indirectly [17–19]. CARM1 and PRMT1 can methylate histone H3 and H4, respectively. The covalent modification of histone alters the state of chromatin organization at the promoter of target genes. On the other hand, ER recruits DRIP/TRAP complex through PBP [20–22]. This complex interacts with basal transcription machinery to facilitate the formation of transcription initiation complex.

Here, we report the identification of ERBP as a novel ERα binding protein through yeast two-hybrid screening. Unlike most of ERα binding proteins identified so far which interact with ERα through its hormone

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binding domain, ERBP binds to the DNA binding domain and hinge region. We demonstrate that ERBP enhances ERα transcription activity.

Materials and methods

Plasmids. pGBKT7-ERα, PcDNA3.1-ERα, ERE-TK-LUC, GST-ERα, GST-ERα (AA 1–184), GST-ERα (AA 185–250), GST-ERα (AA 251–301), and GST-ERα (AA 302–595) expression vectors were described elsewhere [19]. PCMV-SPORT6-ERBP was obtained as an Image clone from Invitrogen and confirmed by sequencing. PcDNA3.1-ERBP was constructed by inserting ERBP encoding region into the *Kpn*I/*Not*I site of PcDNA3.1 vector. GST-ERBP P12 (1–443), P34 (444–756), P1 (1–202), P2 (203–443), P3 (444–624), and P4 (625–756) were constructed by inserting the corresponding ERBP fragment into the *Sal*I/*Not*I site of PGEX-5X vector. pFlag-ERBP and pGal4-ERBP were constructed by inserting coding region of ERBP into *Hin*dIII/*Bam*HI site of pFlag-CMV (Sigma) and PM (Clontech), respectively.

Yeast two-hybrid screening. The Matchmaker two-hybrid system kit (Clontech) was used for detecting specific protein factors interacting with ERα bait protein as described by manufacturer. Briefly, the yeast strain HF7C competent cells were cotransformed with a mixture of a human matchmaker mammary gland cDNA expression library and pGBKT7-ERα. The yeast was then selected in medium lacking histidine. Five days later, the clones expected to contain ER interacting proteins emerged. These clones were further confirmed by its expression of β-galactosidase.

GST pull-down assay. The GST alone and GST fusion proteins were expressed in *Escherichia coli* BL21 and bound to glutathione–Sepharose 4B beads according to the manufacturer's instructions (Amersham–Pharmacia Biosciences). [^{35}S]Methionine-labeled proteins were synthesized in the TNT T7 quick-coupled In vitro transcription and translation system with rabbit reticulocyte lysate (Promega). In GST pull-down reactions, a 10-μl aliquot of a 50% slurry of GST fusion protein bound to glutathione–Sepharose beads was incubated with 5 μl ^{35}S-labeled proteins for 2 h in 500 μl NETN buffer (20 mM Tris–HCl, pH 7.5, 100 mM KCl, 0.7 mM EDTA, 0.05% Nonidet P-40, and 1 mM phenylmethylsulfonyl fluoride) at room temperature. The binding was assayed in the presence or absence of specific ligands: 17β-estradiol (1×10^{-6} M) for ER; BRL49653 (1×10^{-5} M) for PPARγ; and 9-*cis*-retinoic acid (1×10^{-6} M) for RXRα. The beads were precipitated, washed five times with binding buffer, and eluted by boiling for 5 min in 20 μl SDS loading buffer. The eluted proteins were separated by SDS–PAGE. The gels were fixed, dried, and autoradiographed.

Cell lines, tissue culture, transfection, and luciferase assay. CV-1 cells (3×10^5) were split into 6-well plates and cultured in Dulbecco's modified Eagle's medium containing 10% fetal calf serum for 24 h before transfection. Cells were transfected using lipofectAMINE 2000 regent (Invitrogen) with 1.5 μg luciferase reporter DNA, 20 ng plasmid expressing ER receptor, 2.0 μg of appropriate expression plasmid, and 0.1 μg of β-galactosidase expression vector pCMVβ (Clontech) as an internal control. Cell extracts were prepared 24 h after transfection. The luciferase and β-galactosidase activities were assayed by a chemiluminescent protocol (Tropix). At least three independent transfections were performed for each assay.

Antibody development. GST-ERBP (AA 457–756) fusion protein was expressed and purified according to the manufacturer's protocol (Pharmacia). The ERBP protein was released from GST by digestion with 1 mg/ml bovine factor Xa for 30 min at RT. The purified protein was sent to Spring Valley Laboratories to make the antibody in rabbit by standard protocol. The antibody specificity was verified by its reaction with in vitro translated 82 kDa protein through Western blotting.

Immunofluorescent staining. HeLa cells on chamber slides (Nalge Nunc International) were transfected with 1 μg pCDNA3.1-ERα and 1 μg pCMV-SPORT$_6$-ERBP using lipofectAMINE 2000 regent (Invitrogen). Fourty-eight hours after transfection, the cells were fixed with 4% of formaldehyde for 10 min and washed three times with TBS, pH7.5 (100 mM Tris, 1.5 M NaCl). The cells were blocked with 5% milk powder in TBS and incubated with monoclonal anti-ERα and rabbit anti-ERBP, followed by incubation with Rhodamine-conjugated anti-rabbit IgG and FITC-conjugated sheep anti-mouse IgG (Sigma). The cells were mounted with a Prolong anti-fade kit and visualized on a fluorescent microscopy.

Immunoprecipitation. MCF-7 cells were grown in the presence or absence of 1 μM of 17β-estradiol. The cells were lysed and harvested in ice-cold lysis buffer (50 mM Tris–Cl, pH8.0, 150 mM NaCl, 1% NP40, 1 mM EDTA, and 1 mM DTT) with proteinase inhibitors (1 mM phenylmethylsulfonyl fluoride, 1 mg/ml leupeptin, and 1 mg/ml aprotinin). After centrifugation, the supernatants were incubated with anti-ERBP or control serum. After extensive washing with the lysis buffer, the immunoprecipitates were resolved by SDS–PAGE, transferred onto a nitrocellulose membrane, and subjected to Western blot analysis using anti-ERα.

Results and discussion

Identification of ERBP as an ERα binding protein by two-hybrid screening

To isolate the interacting proteins for ERα, yeast two-hybrid screening was performed with human mammary gland cDNA library and full-length ERα as a bait. We isolated a partial cDNA encoding a novel ERα binding protein, designated ERBP. To obtain the full-length cDNA, the sequence of the partial ERBP was searched in

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MVVTRSARAKASIQAASAESSGQKSFAANGIQAHPESSTGSDARTTDESQTTGKQSLIPR   60
TPKARKSKSRTTGSLPKGTEPSTDGETSEAESNYSVSEHHDTILRVTRRRQILIACSPVS  120
SVRKKPKVTPTKESYTEEIVSEAESHVSGISRIVLPTEKTTGARRSKAKSLTDPSQESHT  180
EAISDAETSSSDISFSGIATRRTRSMQRKLKAQTEKKDSKIVPGNEKQIVGTPVNSEDSD  240
TRQTSHLQARSLSEINKPNFYNNDFDDDFSHRSSENILTVHEQANVESLKETKQNCKDLD  300
EDANGITDEGKEINEKSSQLKNLSELQDTSLQQLVSQRHSTPQNKNAVSVHSNLNSEAVM  360
KSLTQTFATVEVGRWNNNKKSPIKASDLTKFGDCGGSDDEEESTVISVSEDMNSEGNVDF  420
ECDTKLYTSAPNTSQGKDNSVLLVLSSDESQQSENSENEEDTLCFVENSGQRESLSGDTG  480
SLSCDNALFVIDTTPGMSADKNFYLEEEDKASEVAIEEEKEEEEDEKSEEDSSDHDENED  540
EFSDEEDFLNSTKAKLLKLTSSSIDPGLSIKQLGGLYINFNADKLQSNKRTLTQIKEKKK  600
NELLQKAVITPDFEKNHCVPPYSESKYQLQKKRRKERQKTAGDGWFGMKAPEMTNELKND  660
LKALKMRASMDPKRFYKKNDRDGFPKYFQIGTIVDNPADFYHSRIPKKQRKRTIVEELLA  720
DSEFRRYNRRKYSEIMAEKAANAAGKKFRKKKKFRN                           756
```

Fig. 1. The amino acid sequence of human ERBP (GenBank Accession No. AY394925). The cDNA encoding the amino acid 400–756 was isolated by yeast two-hybrid screening. The 216-amino acid region at C-terminus is highly conserved among different organisms.

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Human:          541 EFSDEEDFLNSTKAKLLKLTSSSIDPGLSIKQLG**GLYINFNADKL  585
Mouse:          543 -S-----L-++—S---------------+-----**-------V---  587
C.Elegans:       51                             RAV+EEA**PKEGA-E-VD-   68
D.melanogaster:79  VAKQL--LCEKV++A+ENS+KPK+V-RKR+T+-NHDAP+++LRQ+N-  125
Yeast:            2  DQ-V-+L-GALRD-SASLEVKN-AKEQ+-++-ED**V-Q-GN-D-++   47

Human:          586 Q*SN*KRTLTQIKEKKKNELLQKAVITPDFEKNHCVPPYSESKYQLQ  630
Mouse:          588 -*P+*-E-----------------------K----------++--  632
C.Elegans:       69  L*GT*SYLEPYEM+-DLQ---+-+-+G-K—G+-QPQNRLLG+NAAA  113
D.melanogaster:126 +*--M---***************-Q-+N-GL-+A-A+P**+VG-R-QP  155
Yeast:           48 +IE+*-FQEI+TNL—-LP+-ETGFDALA+K+-KKN-L-SV-+****+   88

Human:          631 KKRRKERQKTAGDGWFGMKAPE**MTNELKNDLKALKMRASMDPKRF  675
Mouse:          633 -+----------+---------**+-+------+------G------  677
C.Elegans:      114 +L++S--+--K -SA—N+P-T-**+-+-H-R--+F-+--++++--LAH  158
D.melanogaster:156 IIN-A—-S—-K-K---N+P-T-**+-+-++-+--I+++--V+---+-  200
Yeast:           89 D--+PN+SDKND+D—-T+PK-+DN-RR-++R—-LL+-H--++----H  135

Human:          676 YKKNDRDGFPKYFQIGTIVDNPADFYHSRIPKKQRKRTIVEELLA    720
Mouse:          678 --------------+---------------------+--------   722
C.Elegans:      159 -++---AVL-----+-R+--A-E---S--+V+-+--+-+-+-+-H    203
D.melanogaster:201 -----LKSL--+-----++**-+HLD-Y+EK-S++-+++-N---E    243
Yeast:          136 ---Q*-WEV-+R-A----+++K+++-S--+N+-+--S--+-T-+G    179

Human:          721 DSEFRRYNRRKYSEIMAEKAANAAG**KKFRKKKKFRN           756
Mouse:          723 ------+----------------E-**---+-------           758
C.Elegans:      204 +E-SLSKA++--+--RQ++Q+KRR-AF+--GN+-SH+Q           241
D.melanogaster:244 -ES-+++-+--++-++KRTDKY-YRKNL-KM—-L-KNK           259
Yeast:          180 -EASN+-F+---+--QE+ST+GRKAHY-—M+EM+—K-R           217
```

Fig. 2. Homology of the conserved region at C-terminus among human ERBP, mouse ERBP, *C. elegans* Y49F6B (GenBank Accession No. AAF60729), *D. melanogaster* CG1142 (GenBank Accession No. AAO41511), and yeast YLR051 (GenBank Accession No. S61625). Dashes represent the same amino acid as in human ERBP. Pluses represent similar amino acid to that in human ERBP. Asterisks represent space inserted for optimum alignment.

GenBank. As a result, three Image clones were found in GenBank and were acquired from Invitrogen. After sequencing, one of the Image clones turned out to contain full-length cDNA. The full-length ERBP cDNA has an open reading frame of 2368 nucleotides that encodes a protein of 756 amino acids (Fig. 1) with an estimated molecular mass of ~82 kDa. The ERBP cDNA fragment directly recovered by yeast two-hybrid screening encodes amino acids 460–756. When the amino acid sequence of ERBP was searched in GenBank, the 216 amino acid fragment at C-terminus showed homology to Y49F6B protein from *Caenorhabditis elegans*, CG1142 protein from *Drosophila melanogaster*, and YLR051C protein from yeast (Fig. 2). Although the function of this protein has not been defined in these organisms, it was determined to be required for cell viability in yeast by Yeast Genome Deletion Project, indicating that this well-conserved protein possesses critical unknown function.

To determine the cellular localization of ERBP protein, a plasmid expressing ERBP protein was transfected into HeLa cells. Just as ERα, immunofluorescent staining with anti-ERBP revealed that ERBP was localized in the nuclear compartment in a fraction of cells while the nuclei of all cells were stained blue with DAPI (Fig. 3A). To confirm the nuclear localization of ERBP protein, COS-7 cells were transfected with a plasmid expressing Flag-tagged ERBP. Transfected cells were probed with anti-Flag followed by a fluorescein-conjugated secondary antibody and stained with DAPI to identify the nuclei. Flag-ERBP was found in the nuclei in a fraction of cells (Fig. 3B).

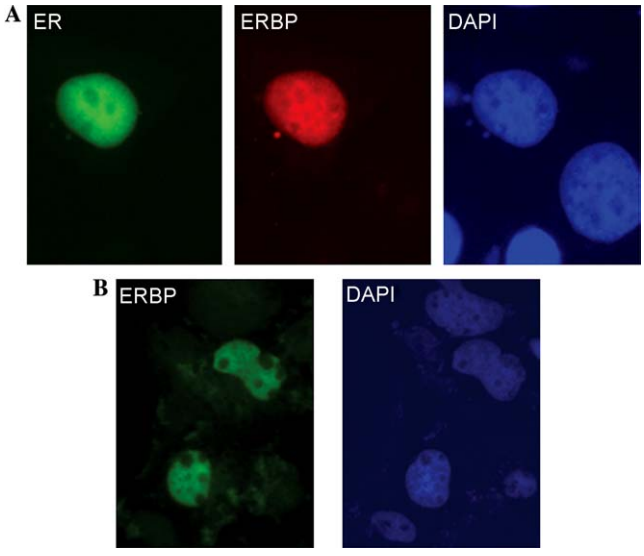

Fig. 3. ERBP was localized to nucleus. (A) Plasmids pCMV-SPORT6-ERBP and pcDNA3.1-ERα were cotransfected into HeLa cells. The cells were stained with rabbit anti-ERBP and monoclonal anti-ERα, which were then detected by second antibody Rhodamine-conjugated anti-rabbit IgG and FITC-labeled anti-mouse IgG, respectively. Nuclei were stained with DAPI. (B) Plasmid pCMV-Flag-ERBP was transfected into COS-7 cells, which were fixed and stained with monoclonal anti-Flag followed by FITC-labeled anti-mouse IgG. Nuclei were stained with DAPI.

The tissue distribution of ERBP expression was determined by Northern blot. ERBP is expressed as a 2.4-kb transcript in all tissues examined, with high levels of expression in testis (Fig. 4).

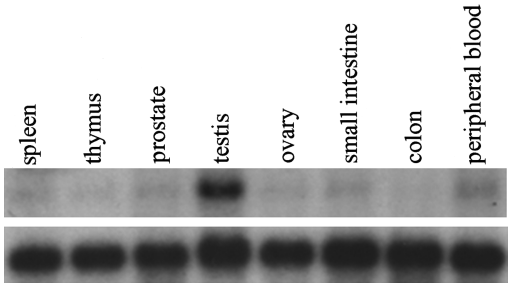

Fig. 4. ERBP mRNA expression in human tissues. A blot (Clontech) containing 2 μg of mRNA from each tissue was hybridized with P^{32}-labeled ERBP probe and exposed to film for 24 h. The transcript size of ERBP is 2.4 kb. The blot was then stripped and hybridized with control probe β-actin.

Interaction of ERBP with ERα and other nuclear receptors in vitro

The direct interaction between ERBP and ERα was further tested by in vitro GST pull-down assay, which was performed with bacterially generated GST-ERα fusion protein and in vitro translated ERBP. The immobilized GST-ERα, but not GST alone, retained [^{35}S]methionine-labeled ERBP both in the presence and absence of estrogen, but the presence of estrogen increased the physical interaction (Fig. 5A). ERBP also showed interaction with PPARγ and RXRα and the interaction was enhanced by the presence of the corresponding ligand.

To determine which region of ERα binds to ERBP, a GST pull-down assay was performed using fusion proteins between GST and different regions of ERα. As shown in Fig. 5B, ERBP bound to the DNA binding domain and the hinge region of ERα in a ligand-independent fashion. The binding to ERα DNA binding domain was much stronger than that to the hinge region.

To define the regions of ERBP which interact with ERα, GST fusion proteins with different ERBP fragments were generated. When ERBP were divided into two fragments, both fragments were found to bind ERα (Fig. 5C). Each of the fragments was further divided into two fragments. GST pull-down assays revealed that ERBP fragment (AA 1–202) and fragment (AA 625–756) bound to ERα. The binding of fragment (AA 625–756) was enhanced by the presence of estrogen (Fig. 5C).

To ascertain whether ERBP protein binds ERβ and which region of ERBP binds ERβ, GST pull-down assays were carried out with GST-ERBP fragments and [^{35}S]methionine-labeled ERβ. Similar to ERα, ERβ was found to bind to the same fragments of ERBP (Fig. 5C). The difference was that the interaction between ERBP and ERβ was not affected by estrogen.

ERBP interacts with ERα in vivo

The potential interaction between ERBP and ERα in the intact cell was examined in MCF-7 cells. The lysate from MCF-7 cells was precipitated with control serum or anti-ERBP. The precipitates were subjected to Western blot analysis with anti-ERα. Only precipitates with anti-ERBP exhibited ERα band (Fig. 6), indicating that ERBP interacted with ERα in vivo. Unlike the interaction in vitro, the interaction in vivo was not affected by estrogen, which could be due to the fact that the ligand-independent interaction between the N-terminal region and ERα is so strong in vivo that the ligand-dependent interaction between the C-terminal region and ERα was obscured.

ERBP enhances the transcriptional activity of ERα

Having firmly established that ERBP is an ERα binding protein, we investigated the effect of

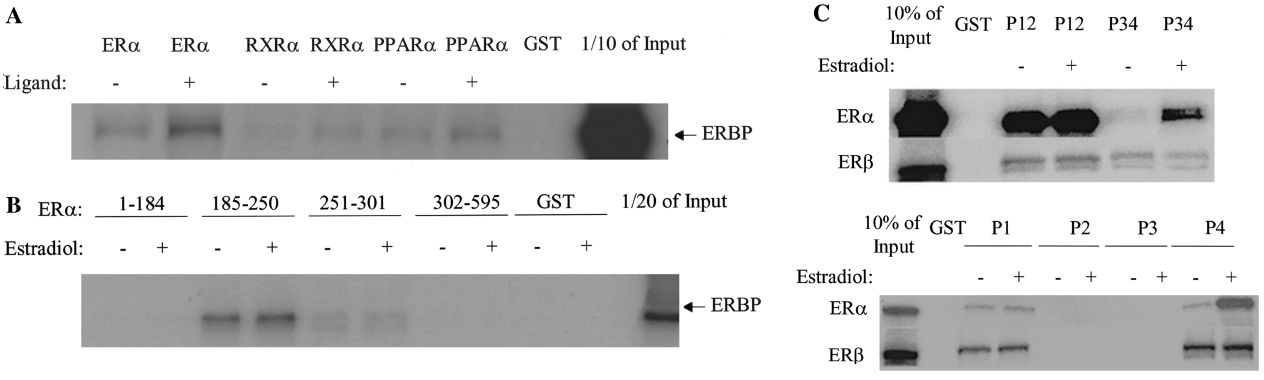

Fig. 5. (A) In vitro interaction of ERBP with ERα, RXRα, and PPARγ. [^{35}S]Methionine-labeled ERBP was incubated with GST-PPARγ, GST-RXRα, and GST-ERα or with GST in the presence (+) or absence (−) of ligand. The bound proteins were eluted, resolved using 12% SDS–PAGE, and autoradiographed. (B) GST pull-down assay with ^{35}S-labeled ERBP and GST-ERα (AA 1–184) GST-ERα (AA 185–250), GST-ERα (AA 251–301), and GST-ERα (AA 302–595) or GST in the presence (+) or absence (−) of estrogen. (C) In vitro interaction of ERα and ERβ with ERBP fragments. GST pull-down assay was performed with ^{35}S-labeled ERα or ERβ and GST-ERBP fragments. The ERBP fragments included P12 (AA 1–443), P34 (AA 444–756), P1 (AA 1–202), P2 (AA 203–443), P3 (AA 444–624), and P4 (AA 625–756).

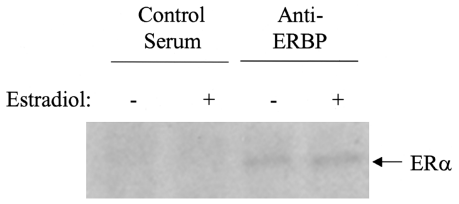

Fig. 6. Interaction of ERα with ERBP in vivo. Cell extracts were made from MCF-7 cells growing in the presence or absence of 17β-estradiol. The cell extracts were immunoprecipitated with either anti-ERBP serum or pre-immune control serum. The precipitates were analyzed by Western blot using anti-ERα.

overexpression of ERBP upon ERα-mediated transcription with ERα-dependent reporter in CV-1 cells. The reporter is the luciferase gene under control of one copy of ERE and basal HSV-TK promoter. ERα increased the expression of luciferase gene by 7-fold in the presence of estrogen (Fig. 7). ERBP alone without ERα did not activate the expression of luciferase. Coexpression of ERBP resulted in a further increase of luciferase gene activity in the presence of estrogen while no significant change was observed in the absence of estrogen, suggesting that ERBP acts as a coactivator for ERα. Expression of 0.5, 1, and 2 μg ERBP expression vector led to about 1, 1.5, and 2-fold increment of luciferase activity, respectively, indicating that the enhancement of

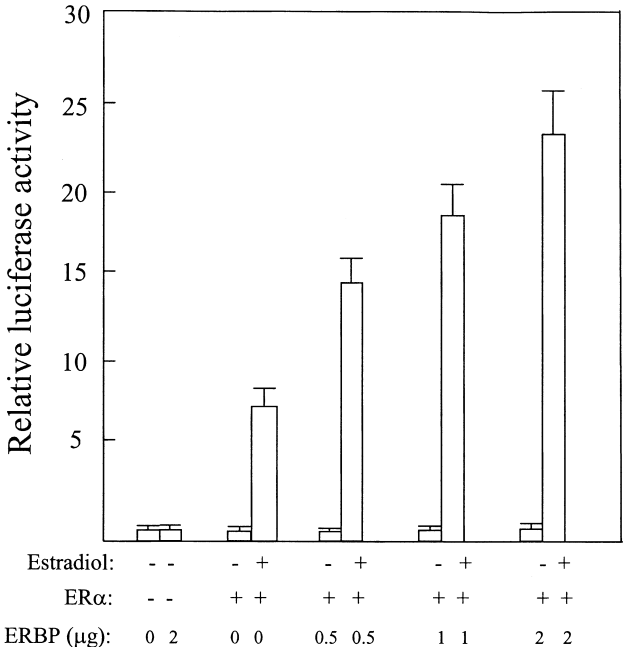

Fig. 7. ERBP enhances ERα-mediated transactivation. CV-1 cells were transfected with 1.5 μg of reporter ERE-LUC, 0.1 μg PCMVβ, plus PCMV-ERα (20 ng), and PCDNA3.1-ERBP as indicated in the absence (−) or presence (+) of 1 μM estrogen. PCDA3.1 was added to make sure that equal amount of DNA was used for each transfection. The luciferase and β-galactosidase activities were measured. The results represent the average of three independent transfections normalized with the internal control β-galactosidase activity.

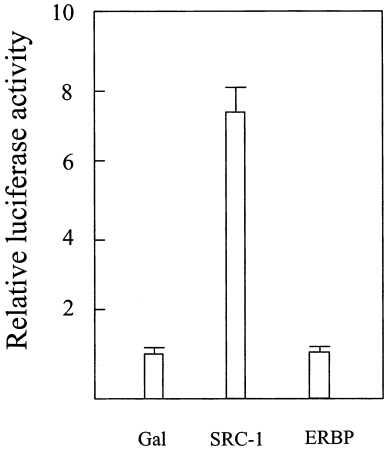

Fig. 8. ERBP possesses no intrinsic transcriptional activity. CV-1 cells were transfected with 2 μg GAL-TK-LUC, 0.1 μg PCMVβ, plus 1 μg Gal4-DBD, Gal4-DBD-SRC-1, or Gal4-DBD-ERBP. The activity of luciferase from transfection of Gal4-DBD was taken as 1.

ERα activity by ERBP was dose-dependent. Although ERBP binds to ERα in the absence of estrogen in vivo, it cannot increase ERα activity without estrogen, suggesting that the binding of ERBP alone does not result in the transcriptional activation and other ligand-dependent factors are also most likely required for the transactivation.

ERBP has no intrinsic transcriptional activity

Coactivators such as SRC-1 contain intrinsic transcriptional activity. To find if ERBP has this property, ERBP was fused to the Gal4 DNA binding domain and transfected into CV-1 cells with Gal4 responsive element-directed reporter gene luciferase. As a positive control, Gal4-SRC-1 fusion protein increased the luciferase activity by about 7-fold as compared to Gal4 DNA binding domain alone (Fig. 8). Gal4-ERBP fusion protein did not increase the luciferase activity, indicating that ERBP contains no intrinsic transcriptional activity.

Acknowledgments

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