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XBP-1 increases ERα transcriptional activity through regulation of large-scale chromatin unfolding

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Abstract

Human X box binding protein 1 (XBP-1) is a transcription factor essential for hepatocyte growth, the differentiation of plasma cells, and the unfolded protein response. Recently, we have demonstrated that two forms of XBP-1, XBP-1S, and XBP-1U, enhance estrogen receptor α (ERα)-dependent transcriptional activity in a ligand-independent manner. However, how XBP-1S and XBP-1U regulate ERα transcriptional activity remains unknown. Here, we report that XBP-1S and XBP-1U induce large-scale chromatin unfolding by targeting the XBP-1 proteins to an amplified, lac operator-containing chromosome region in mammalian cells. This unfolding activity maps to the transactivation domains of XBP-1S and XBP-1U. Wild-type XBP-1S and XBP-1U, but not the mutants that completely abolished the ERα transcriptional activation, increased the chromatin unfolding activity of ERα. These data identify a novel function of XBP-1 and suggest that regulation of large-scale chromatin unfolding by XBP-1 may be responsible for the enhancement of ERα transcriptional activity.

Keywords: XBP-1; ERα; Large-scale chromatin unfolding; Transcription

Chromatin structure is thought to play critical roles in many nuclear processes in eukaryotes, including DNA replication, transcription, and DNA repair, and consequently affect proper cell function [1–4]. Chromatin structure has several levels of organization: nucleosome, the 30 nm chromatin fiber, and large-scale structure above the level of the 30 nm chromatin fiber. The basic subunit of chromatin in almost all eukaryotic cells is the nucleosome, which consists of DNA wrapped twice around a histone octamer comprising the core histones H2A, H2B, H3, and H4. A number of studies have identified two distinct systems capable of remodeling the nucleosome structure for transcriptional activation. Histone modifying enzymes, including histone acetyltransferases (HATs) and histone deacetylases (HDACs), are involved in the posttranslational modifications of the amino- and carboxy-terminal ends of histones, such as acetylation, phosphorylation, and methylation. The functional consequences of covalently modifying the histones are to alter nucleosome structure and gene expression. The second class consists of ATP-dependent chromatin remodeling complexes, including the SWI/SNF, NURF, RSC, CHRAC, and ACF complexes. The ATP-dependent chromatin remodeling complexes use the energy of ATP hydrolysis to locally disrupt the association of histones with DNA. Although

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small-scale chromatin structure, from the level of the nucleosome to the 30 nm fiber, is remodeled or modified to enable or repress transcription, functional connections between higher-order levels of chromatin organization and regulation of transcription remain to be established.

Human X box binding protein 1 (XBP-1) is a basic region-leucine zipper (bZIP) transcription factor that recognizes the *cis*-acting X box present in the promoter regions of target genes [5]. XBP-1 is essential for hepatocyte growth as well as for plasma cell differentiation [6,7]. XBP-1 mRNA expression is highly upregulated in a subset of breast cancers, and highly correlated with estrogen receptor α (ERα), a member of a superfamily of nuclear receptors that act as ligand-activated transcription factors [8–13]. Since the cloning of the XBP-1 over 10 years ago [5], there has been general acceptance that only one XBP-1 existed. More recently, however, the XBP-1 mRNA was shown to be unconventionally spliced by IRE1 in response to endoplasmic reticulum stress [14,15]. Translation of the spliced XBP-1 mRNA produces a protein, XBP-1S, and the unspliced form of XBP-1 is then designated XBP-1U. Using a transient transfection reporter assay, we recently showed that XBP-1S and XBP-1U enhance ERα-mediated transcriptional activity in a ligand-independent manner [16]. XBP-1S and XBP-1U interact with the ERα both in vitro and in vivo in a ligand-independent fashion. However, the mechanism by which XBP-1 enhances ERα transcriptional activity remains to be determined.

The role of XBP-1 in transcription has raised the possibility that the protein may regulate various chromosomal events, such as large-scale chromatin remodeling. Using the lac operator/repressor system, Belmont and colleagues [17] developed a system to visualize large-scale chromatin dynamics in mammalian cells. By fusing proteins or protein domains to the lac repressor, this system was used to demonstrate large-scale chromatin decondensation induced by several transcription-related proteins, such as VP16 acidic activation domain [17], ERα [18], BRCA1 [19], and Smad4 [20]. Here, we show that both XBP-1S and XBP-1U induce large-scale chromatin unfolding by targeting the XBP-1 proteins to an amplified, lac operator-containing chromosome region in mammalian cells. This unfolding activity is conferred by the transactivation domains of XBP-1S and XBP-1U. Intriguingly, wild-type XBP-1S and XBP-1U, but not the mutants that abolish ERα transcriptional activation, increase ERα-mediated large-scale chromatin unfolding.

Materials and methods

Plasmids. The following plasmids have been described previously: pcDNA3-FLAG-XBP-1S and pcDNA3-FLAG-XBP-1U (human XBP-1 expression vector) [16]; pcDNA3-FLAG-XBP-1SΔ82 and pcDNA3-FLAG-XBP-1UΔ82 (human XBP-1 deletion mutant expression vector) [16]; pcDNA3-ERα (human ERα expression vector) [16]; pERE-LUC (estrogen-responsive element-containing luciferase reporter) [16]; and plac op-LUC (eight lac operator repeats-containing luciferase reporter) [20]. To construct recombinant plasmids for chromatin unfolding assay, the pRC-lac vector was used [20]. pRC-lac-XBP-1S and pRC-lac-XBP-1U were made by cloning the PCR-generated full-length XBP-1S and XBP-1U cDNAs from pcDNA3-FLAG-XBP-1S and pcDNA3-FLAG-XBP-1S into the *Asc*I site of the pRC-lac vector. Deletion mutants of XBP-1S and XBP-1U were constructed by inserting PCR-generated fragments from the corresponding cDNAs into the pRC-lac vector. pRC-lac-ERα was made by cloning the PCR-generated full-length ERα from pcDNA3-ERα into the *Asc*I site of the pRC-lac vector. All of the constructs were confirmed by DNA sequencing.

Transfections and luciferase assays. Human 293T and AO3_1 cells were grown in Dulbecco's modified Eagle's medium (DMEM) (Invitrogen) containing 10% fetal bovine serum (FBS) at 37 °C in a 5% CO_2 incubator. For transfection, cells were plated onto 12-well plates. Twenty-four hours later, the cells were transfected with plasmid constructs using Lipofectamine 2000 according to the manufacturer's instructions (Invitrogen). Transfections were performed using 0.2 μg plac op-Luc or pERE-LUC reporter, 50 ng of expression vector for XBP-1 or its mutants, or ERα, and 0.1 μg of expression vector for β-galactosidase. The transfected cells were harvested 24 h after the transfection. Luciferase and β-galactosidase activities were determined as described previously [16]. The data were normalized to the β-galactosidase activity.

Immunoblotting. Cells were washed with cold phosphate-buffered saline and lysed on ice in RIPA buffer supplemented with protease inhibitors (Sigma). Following removal of insoluble debris by centrifugation, supernatant was used to determine protein concentration by the Bradford procedure (Pierce). Protein samples were separated by SDS–polyacrylamide gel electrophoresis and blotted to a nitrocellulose membrane. Blotted membranes were blocked overnight at 4 °C in TBST containing 5% nonfat milk. Blots were probed with primary antibodies diluted in TBST containing 5% nonfat milk for 1 h at room temperature. After washing extensively with TBST, membranes were incubated with the appropriate horseradish peroxidase-conjugated secondary antibody (Santa Cruz), followed by chemiluminescent detection according to the manufacturer's instructions (Pierce).

Chromatin unfolding assay. Chromatin unfolding assay was performed as previously described [21]. Briefly, AO3_1 cells were transiently transfected with the lac expression vectors using the FuGENE 6 transfection reagent according to the manufacturer's instructions (Roche). Media were changed 24 h after transfection and cells were stained 48 h after transfection. Cells grown on glass coverslips were fixed in PBS with 1.6% paraformaldehyde for 30 min, permeabilized with 0.2% Triton X-100 in PBS for 5 min, and blocked in 1% normal goat serum in PBS for 1 h. The coverslips were then incubated with primary antibodies at room temperature for 1 h, followed by incubation with the appropriate secondary antibodies for 1 h. A rabbit polyclonal anti-lac repressor antibody (Stratagene) and mouse monoclonal anti-FLAG antibody (Sigma–Aldrich) were applied at 1:2000 dilution. The secondary antibodies were goat anti-rabbit IgG conjugated with rhodamine (Santa Cruz Biotechnology) and goat anti-mouse IgG conjugated with fluorescein isothiocyanate (FITC; Santa Cruz Biotechnology). Nuclei were counterstained with 0.2 μg/ml 4,6-diamidino-2-phenylindole (DAPI) for 5 min before mounting. Fluorescent images were acquired by a charged-coupled device camera that was mounted on an Olympus LX70 microscope and equipped with Spot Advanced software. Confocal images were collected on a Radiance2100 confocal microscope (Bio-Rad).

Results

Large-scale chromatin unfolding induced by XBP-1S and XBP-1U

To determine the effects of XBP-1S and XBP-1U on large-scale chromatin structure in mammalian cells, we took advantage of a Chinese hamster ovary (CHO) cell line, AO3_1, in which lac operator repeats and co-amplified genomic DNA form a ~90-Mb heterochromatic region of the genome. In vivo binding of lac repressor or its derivatives to this chromosomal site allows direct visualization of large-scale chromatin fibers. As shown in Fig. 1A, expression of lac repressor fused with the full-length XBP-1S (lac rep-XBP-1S) and XBP-1U (lac rep-XBP-1U) induced an irregularly shaped subnuclear structure in approximately 36% and 34%, respectively, of transfected cells, whereas expression of lac repressor (lac rep) alone showed a compact nuclear dot (Fig. 1A). Although the extent of unfolding by XBP-1S and XBP-1U approached that observed with the lac rep-VP16 positive control [17], a lower percentage of lac rep-XBP-1-transfected cells exhibited this unfolding compared with the control (36% for XBP-1S or 34% for XBP-1U vs 62% for VP16). These results indicate that XBP-1S and XBP-1U can induce large-scale chromatin decondensation in mammalian cells.

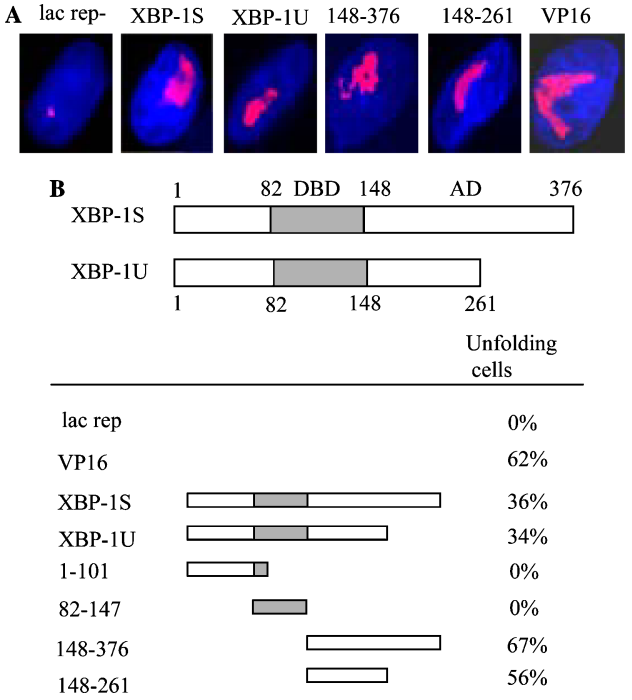

Fig. 1. XBP-1S and XBP-1U induce large-scale chromatin unfolding. (A) AO3_1cells which contain a heterochromatic lac operator array were transfected with expression vectors for the lac repressor fusion proteins as indicated, immunostained for lac repressor (red), and counterstained for DNA with DAPI (blue). (B) The ability of various XBP-1 fragments to unfold chromatin was measured by the percentage of transfected cells that displayed enlarged lac staining. Over 200 transfected cells were surveyed for each construct. Also shown are schematic diagrams of the constructs used in this study. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

Mapping of the XBP-1-induced large-scale chromatin unfolding domains

XBP-1S and XBP-1U are proteins of 376 and 261 amino acids, respectively, with an identical N-terminus (amino acids 1–164). To determine the domains in the XBP-1S and XBP-1U that mediate large-scale chromatin unfolding, a set of XBP-1 deletion mutants was used in chromatin unfolding experiments (Fig. 1B). Chromatin-unfolding activity was conferred by either the last 229 amino acids of XBP-1S (aa 148–376) or the last 114 amino acids of XBP-1U (aa 148–261) because the identical N-terminal XBP-1S and XBP-1U fragments (aa 1–101 and aa 82–147) upstream of these regions did not display chromatin unfolding activity (Fig. 1). These regions of XBP-1S and XBP-1U were shown to act as transactivation domains. It is of note that deletion of the identical N-terminus of XBP-1S and XBP-1U led to a higher percentage of cells showing unfolding. The degree of unfolding by these deletion mutants approached that observed with the VP16 control, with around 60% of cells showing this response. Thus, the N-terminal 147 amino acids have inhibitory effect on chromatin unfolding.

The transcriptional activity of XBP-1 fusion proteins in the lac system

To examine the correlation between transcriptional activity and large-scale chromatin decondensation, XBP-1S and XBP-1U, and their mutants were tested for transcriptional activity in the lac system. Human embryonic kidney 293T cells were transfected with the lac operator repeats-containing reporter lac op-LUC, and lac rep-XBP-1S or lac rep-XBP-1U or their mutants. As shown in Fig. 2A, full-length XBP-1S and XBP-1U induced the transcriptional activity 3.1- and 60-fold, respectively, whereas deletion of the identical N-terminal 147 amino acids enhanced the activation capacity of XBP-1S and XBP-1U. This is consistent with the results of chromatin unfolding. The two fragments (aa 1–101 and aa 82–147), which do not have chromatin unfolding activity, did not display transcriptional activity. All of the full-length and mutant proteins were expressed at a comparable level (Fig. 2B). These results suggest that the N-terminal region of XBP-1S and XBP-1U has repressive effect on transactivation and that the transcriptional activation capability of XBP-1S and XBP-1U correlates with large-scale chromatin unfolding.

A

	Relative transactivation
lac	1.0
XBP-1S	3.1
XBP-1U	60
1-101	0.91
82-147	1.3
148-376	21
148-261	79

B

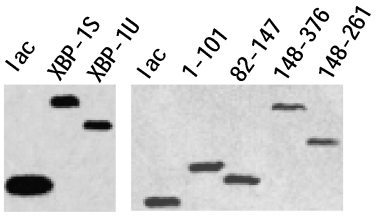

Fig. 2. The transcriptional activity of XBP-1 and its mutants in the lac system. (A) 293T cells were co-transfected with 0.2 μg lac op-LUC, 50 ng of the expression vectors for either lac rep-XBP-1 or lac rep-XBP-1 mutants. The LUC activity obtained on transfection of lac op-LUC and lac rep was set as 1. (B) Western blotting showing expression of the lac rep derivatives. Cells were transfected as in (A). Whole-cell extracts were prepared, and equivalent amounts of each extract were probed with anti-lac repressor antibody (Stratagene).

Wild-type XBP-1 but not mutant XBP-1 increases ERα-mediated large-scale chromatin unfolding in AO3_1 cells

Using the lac operator/repressor tethering system, Belmont and colleagues [18] observed ERα-induced decondensation of large-scale chromatin structure in the absence of estradiol. The degree of decondensation approached that observed with the VP16 control. However, ERα-induced chromatin unfolding is partially reversed by estradiol. To determine the mechanism by which XBP-1S and XBP-1U enhance ERα-mediated transcriptional activity in a ligand-independent manner [16], we examined if XBP-1S and XBP-1U increase ERα-mediated large-scale chromatin unfolding. As expected, ERα did not show chromatin unfolding activity in the estradiol-producing medium (Fig. 3, column c). Interestingly, wild-type XBP-1S and XBP-1U increase ERα-mediated large-scale chromatin unfolding (Fig. 3, columns d and e), whereas the deletion mutants, XBP-1SΔ82 (the N-terminal region from amino acids 1 to 82 was deleted) and XBP-1UΔ82 (the N-terminal region from amino acids 1 to 82 was deleted), which completely abolished the ERα transcriptional activation, were inactive (Fig. 3, columns f and g). As a negative control, wild-type XBP-1S and XBP-1U did not change lac-mediated large-scale chromatin structure (Fig. 3, columns a and b).

Wild-type XBP-1 but not mutant XBP-1 increases ERα-mediated transcriptional activity in AO3_1 cells

XBP-1S and XBP-1U have been shown to enhance ERα-dependent transcriptional activity in a ligand-independent manner in human breast cancer MDA-MB-435 cells. To confirm if XBP-1S and XBP-1U increase the transcriptional activity of ERα in AO3_1cells, which were used for chromatin unfolding assay, AO3_1 cells were co-transfected with the estrogen response element-containing reporter ERE-LUC, ERα, and either XBP-1S, XBP-1U, XBP-1SΔ82 or XBP-1UΔ82. As expected, both XBP-1S and XBP-1U increased ERα tran-

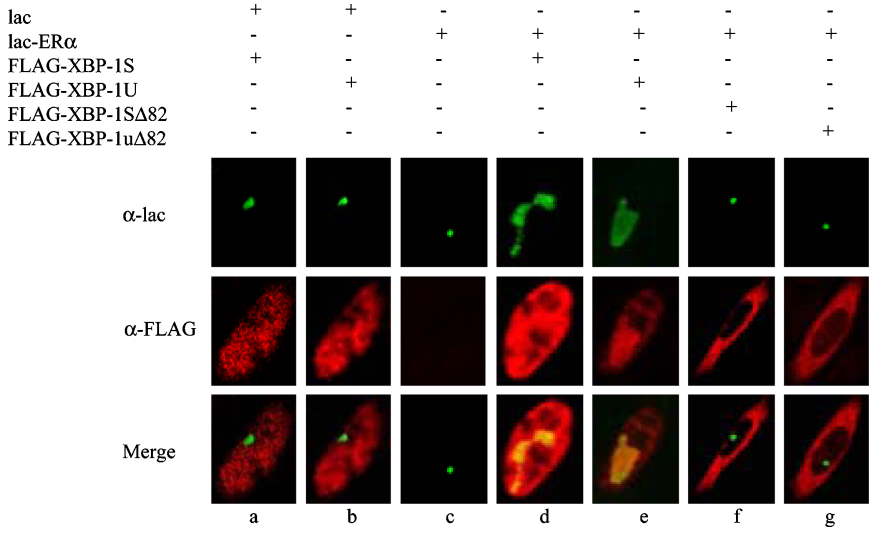

Fig. 3. Enhancement of ERα-dependent chromatin unfolding by XBP-1S and XBP-1U. AO3_1cells were co-transfected with the expression vector for lac repressor alone (lac) or lac-ERα, and the expression vector for FLAG-tagged XBP-1S, XBP-1U, XBP-1SΔ82 or XBP-1UΔ82, as indicated. The cells were double stained with a rabbit anti-lac antibody (Stratagene) and a mouse anti-FLAG antibody (Sigma–Aldrich). The images were captured by confocal immunofluorescence microscopy.

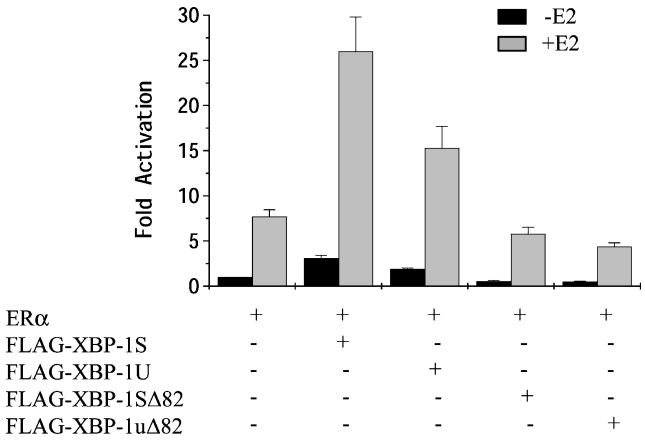

Fig. 4. Potentiation of ERα transcriptional activity by wild-type XBP-1S and XBP-1U but not by XBP-1S and XBP-1U mutants. AO3_1cells were cotransfected with 0.2 μg ERE-LUC, 50 ng of the expression vector for ERα, and 0.5 μg of the expression vector for FLAG-tagged XBP-1S, XBP-1U, XBP-1SΔ82 or XBP-1UΔ82 as indicated. Cells were then treated with control (0.1% ethanol) vehicle or 10 nM 17-βestradiol (E2) for 24 h before luciferase assay. The LUC activity obtained on transfection of ERE-LUC and ERα without exogenous XBP-1 and its derivatives in the absence of E2 was set as 1. Results are shown as means ± SE.

scriptional activation, whereas XBP-1SΔ82 and XBP-1UΔ82 completely abolished the ERα transcriptional activation (Fig. 4). Taken together, these data suggest that transcriptional activation of ERα by XBP-1S and XBP-1U correlates with the chromatin unfolding capacity of XBP-1S and XBP-1U.

Discussion

It has been well accepted that chromatin structure plays a critical role in regulation of gene transcription. Although it is now clear that large-scale chromatin structure is present in many eukaryotic species, the functional connections between large-scale chromatin organization and regulation of transcription are poorly understood. Recently, several transcription-related proteins have been shown to possess large-scale chromatin unfolding activity: BRCA1 [19], p53 [19], Smad4 [20], ER [18], GR [21], VP16 [17], and E2F1 [19]. Based on the relationship between large-scale chromatin unfolding and transcriptional activity, these proteins can be divided into two categories. The first category, which includes p53, E2F1, and VP16, supports a direct correlation, especially a qualitative correlation between chromatin unfolding and transcriptional activity, whereas the second category, which includes Smad4, BRCA1, and ER, fails to support such correlation. Based on the results of chromatin unfolding, XBP-1 belongs to the first category. Explanation for the second category is that large-scale chromatin decondensation may be insufficient for transcriptional activation or involved in transcriptional repression.

Although there is no significant identity at the amino acid level between the transactivation domains of XBP-1S and XBP-1U (data not shown), both of the transactivation domains display similar strong large-scale chromatin unfolding activity. To date, all of the chromatin unfolding domains examined have been shown to be equal to or smaller than the transactivation domains. For the proteins in the first category, the chromatin unfolding domain is usually equal to that of the transactivation domain, whereas for the proteins in the second category, the chromatin domain is often smaller than that of the transactivation domain. These data suggest that transactivation domains play an important role in large-scale chromatin unfolding. Since many transcriptional activators have multiple activation domains, it is not surprising that many transcriptional activators have multiple large-scale chromatin unfolding domains. For example, BRCA1 has two transactivation domains, and the chromatin unfolding activity of BRCA1 maps to three subdomains within the transactivation domain of BRCA1. For XBP-1, which has one transactivation domain, the transcriptional activation and large-scale chromatin unfolding activities map to the same amino acid motifs.

XBP-1 has been shown to function as a co-activator of ERα in a ligand-independent manner [16]. However, the detailed mechanisms of ERα activation by XBP-1 remain unclear. To date, many co-activators for ERα have been identified and characterized [22–25]. Different ERα co-activators regulate ERα transcriptional activity through a variety of mechanisms, including formation of multiprotein complexes that act at several functional levels, such as local chromatin remodeling, enzymatic modification of histone tails, or modulation of the pre-initiation complex via interactions with RNA polymerase II and general transcription factors (GTFs). Other mechanisms include increase of binding of the ERα DNA binding domain to the estrogen response element and ERα homodimerization, alteration of ERα stability, and effects on RNA processing. The present work demonstrated for the first time that XBP-1 increases ERα transcriptional activity possibly by regulation of large scale chromatin unfolding. However, we cannot exclude other possible mechanisms because most ERα co-activators have been shown to control the transcriptional activity of ER through more than one mechanism. It is possible that the synergy between different pathways cooperates to fully activate ERα transcriptional activity. How ERα induces unfolding by recruiting XBP-1 with large-scale chromatin unfolding activity remains to be elucidated. Now that XBP-1-mediated chromatin unfolding domain has been mapped, it would be interesting to identify the interacting proteins required for this activity.

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