# Cell type-dependent regulation of human DNA topoisomerase IIIα gene expression by upstream stimulatory factor 2

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**Abstract Here, we report that an E-box element located within the human topoisomerase IIIα (h*TOP3α*) gene promoter acts as a cell type-specific enhancer. The upstream stimulatory factor (USF) was shown to specifically recognize the mutationally sensitive E-box element. When assayed by transient transfection with h*TOP3α* promoter-dependent reporter genes, USF is transcriptionally active in HeLa cells but lacks transcriptional activity in Saos-2 cells. The h*TOP3α* mRNA level in Saos-2 cells was reduced to about 30% of the level observed for HeLa cells, suggesting that the inactivity of USF in h*TOP3α* promoter activity may be the cause of the marked reduction of h*TOP3α* mRNA levels in Saos-2 cells. Using transient transfection assays in HeLa cells, we demonstrated that ectopically expressed USF2, but not USF1, was capable of activating h*TOP3α* transcription through the E-box element. However, USF2 did not stimulate h*TOP3α* promoter activity in Saos-2 cells. This cell type-specific regulation of promoter activity by USF2 may provide a mechanism for the differential expression of h*TOP3α* in various tissues and during developmental stages.** 

*Key words:* E-box; Promoter; Topoisomerase IIIα; Transcription; Upstream stimulatory factor; YY1

## 1. Introduction

DNA topoisomerases are ubiquitous nuclear enzymes that are able to catalyze changes in the topological state of DNA [1–4]. Type I topoisomerases catalyze the removal of positive and negative supercoils by transiently breaking one strand of the DNA double helix [5]. These enzymes are further divided into two subfamilies, IA and IB, based on differences in their reaction mechanisms [6,7]. The type IA subfamily contains archaebacterial reverse gyrase, bacterial topoisomerase I and III, and eukaryotic topoisomerase III, and all enzymes link covalently to the 5′-end of the cleaved DNA strand via a phosphotyrosine bond. This mechanism clearly distinguishes the type IA from type IB enzymes, which bind at the 3′-end of the cleaved DNA.

A cDNA encoding human topoisomerase IIIα (hTOP3α) was cloned in 1996, and its gene locus was mapped to chromosome 17p11.2–12 [8]. Overexpression of a truncated form or an antisense construct of h*TOP3α* was found to inhibit spontaneous and radiation-induced apoptosis upon transfection into ataxia-telangiectasia (A-T) fibroblasts, whereas a full-length sense construct failed to suppress apoptosis [9]. These results suggested that the hTOP3α may be deregulated in A-T cells and involved in maintaining genomic stability, perhaps in concert with Bloom's or Werner's syndrome DNA helicases [10,11]. Targeted disruption of the mouse *TOP3α* gene revealed that this gene is essential in early embryogenesis [12]. The requirement of TOP3α for viability might be due to its plausible roles in DNA replication and its interaction with the RecQ/SGS1 family of DNA helicases.

Although endogenous expression of the h*TOP3α* gene was found in multiple somatic tissues [9], the transcriptional mechanisms involved in h*TOP3α* gene expression remain poorly understood. Previously, we have shown that the h*TOP3α* gene promoter region from −326 to +82 (+1 is transcription initiation site) was sufficient to support the promoter activity [13]. On the basis of gel mobility shift and supershift assays, we have defined a mutationally sensitive E-box element within the h*TOP3α* gene promoter. This E-box element is capable of binding in vitro to the upstream stimulatory factor (USF), which functions as an activator of h*TOP3α* transcription. Here, we demonstrate that USF2, but not USF1, in HeLa cells is capable of stimulating h*TOP3α* transcription activity through the E-box. However, cotransfection of USF2 with h*TOP3α* promoter–reporter gene in Saos-2 cells did not alter reporter gene activity from the level observed in the absence of ectopically expressed USF. Therefore, we propose that the mutationally sensitive E-box element functions as a cell type-specific enhancer of h*TOP3α* promoter activity.

## 2. Materials and methods

### 2.1. DNA constructs

The chimeric construct (wild-type −326LUC) containing the 5′-flanking region of the h*TOP3α* gene was constructed by inserting DNA fragments between the *Kpn*I and *Bgl*II sites of the pGL2 vector (Promega) as described previously [13]. Site-directed E-box mutant construct (E-box mut −326LUC) was generated by polymerase chain reaction (PCR) using wild-type −326LUC as a template and the primers, 5′-CGGGGTACCGGATCCTGCTACCGCGGCGCCGCCATCTTGAC*AGGTA*ATGACTCC-3′ (bases −326 to −280 from the transcription initiation site) and 5′-GAAGATCTTCACTGAGCCTTTCCCGTGCCGC-3′ (bases +60 to +82). PCR products were digested with *Kpn*I and *Bgl*II to release the −326/+82 mutated fragment and ligated into pGL2.

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*Abbreviations:* EMSA, electrophoretic mobility shift assay; hTOP3α, human topoisomerase IIIα; PCR, polymerase chain reaction; USF, upstream stimulatory factor; USR, USF-specific region

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*2.2. Transfection and luciferase expression assays*

Cells plated onto six-well plates were grown to 70% confluence prior to transfection. 2 μg of test constructs were cotransfected with 2 μg of β-galactosidase expression plasmid, pCH110 (Amersham Pharmacia Biotech) using LipofectAMINE (Life Technologies) according to the manufacturer's protocol. Luciferase and β-galactosidase assays were performed exactly as described [13]. The luciferase activities were normalized with the β-galactosidase activities.

*2.3. Northern hybridization analysis*

Total cellular RNA was isolated from exponentially growing cells using Tri reagent (Molecular Research Center). RNA samples (10 μg/lane) were separated on a 1% formaldehyde–agarose gel and vacuum transferred to Hybond $N^+$ membrane (Amersham-Pharmacia Biotech). A probe consisting of a full-length h*TOP3α* cDNA was labeled with [α-$^{32}$P]dCTP (Amersham Pharmacia Biotech) to a specific activity of $1\times10^8$ cpm/μg using a random-primed DNA labeling system (Amersham Pharmacia Biotech). Control hybridization was carried out using a labeled glyceraldehyde-3-phosphate dehydrogenase probe.

*2.4. Nuclear extracts and electrophoretic mobility shift assays*

Nuclear extracts were prepared according to the method of Dignam et al. [14]. For electrophoretic mobility shift assay, duplex probes were end-labeled by filling in with Klenow DNA polymerase and [α-$^{32}$P]dCTP. Approximately 1 ng of the labeled probe was mixed with 2.4 μg of nuclear proteins. After incubation on ice for 20 min, the reaction mixture was separated on a 6% non-denaturing polyacrylamide gel. The gel was dried and subjected to autoradiography. For supershift experiments, 0.2 μg of antibody (Santa Cruz Biotechnology) was added to the mixture 20 min prior to the addition of labeled probe, and the mixture was further incubated for 20 min at room temperature.

## 3. Results

*3.1. USF transactivation of the hTOP3α promoter is active in HeLa cells, but not in Saos-2 cells*

Recently, Qyang et al. reported the cell type-dependent activity of USF in cellular proliferation and transcriptional activation [15]. The USF proteins are transcriptionally active in HeLa cells but do not function in Saos-2 cells as transcriptional effectors. Our previous work has shown that an E-box element located within the h*TOP3α* gene promoter serves as a binding site for USF in vitro [13]. This initial observation prompted us to examine whether USF function on the activation of h*TOP3α* gene transcription is cell type-dependent. We mutated the h*TOP3α* promoter by site-directed mutagenesis at the E-box (Fig. 1A). Wild-type (−326LUC) or mutant (E-box mut −326LUC) plasmid was transfected into HeLa cells, and luciferase activity was measured from the cell lysates. The mutation at the E-box reduced the luciferase gene expression by about 40% when compared with wild-type promoter, indicating that the E-box functions as a positive regulatory element for the expression of the h*TOP3α* gene (Fig. 1C). In contrast, when the promoter activity of the E-box mutant construct was examined by transient transfection into Saos-2 cells, no reduction of luciferase activity was observed as compared to the basal level obtained with wild-type promoter (Fig. 1D). These results suggest that endogenous

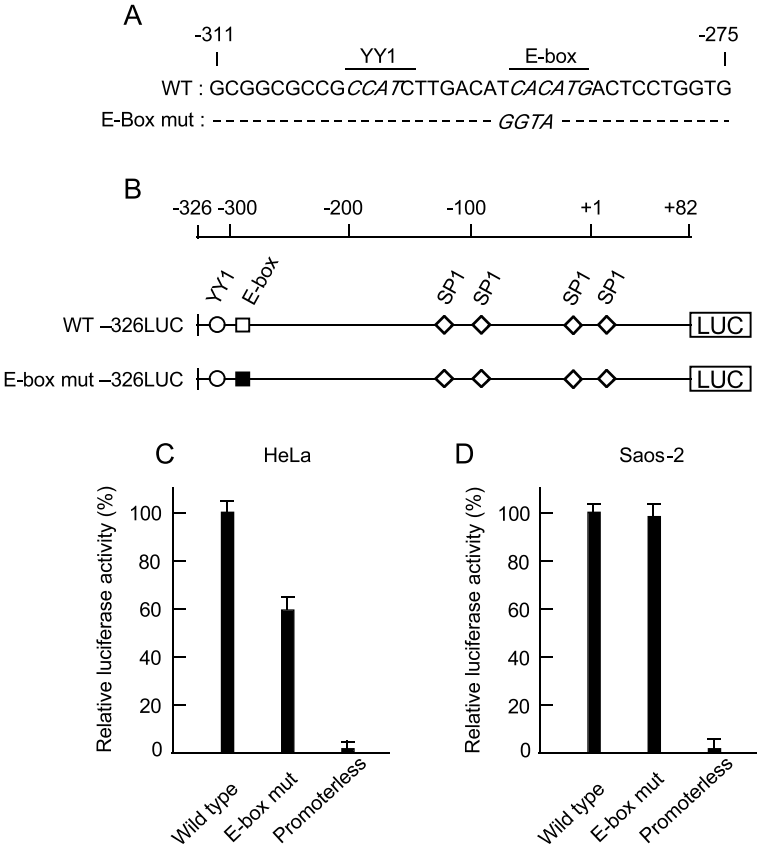


Fig. 1. The E-box element in the h*TOP3α* promoter is active in HeLa cells but inactive in Saos-2 cells. A: DNA sequences of the wild-type and mutant E-box. B: Wild-type (WT −326LUC) and E-box mutant (E-box mut −326LUC) h*TOP3α* reporter constructs are shown with selected regulatory motifs indicated. YY1 and four SP1-binding sites are also shown. HeLa (C) and Saos-2 cells (D) were transfected with the indicated h*TOP3α* reporter constructs, and the promoter function was assessed. The amount of the cell lysate employed for each luciferase activity assay was normalized to the β-galactosidase activity, and the relative luciferase activity of each construct was expressed as a percentage of that of wild-type construct. The data represent the average of four independent experiments.

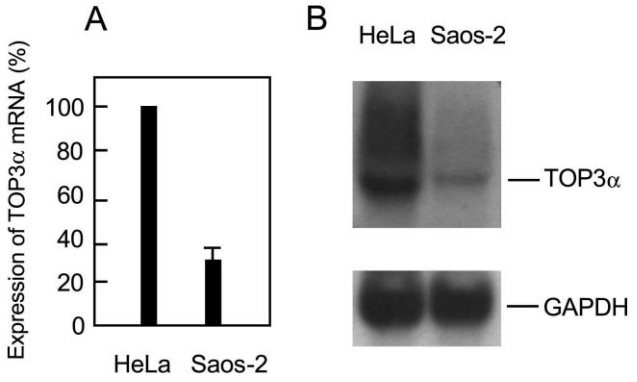


Fig. 2. Northern analysis of h*TOP3α* mRNA levels in HeLa and Saos-2 cells. A: Relative expression of h*TOP3α* mRNA. Data shown are averages of three separate experiments. The relative band intensities on Northern blots were determined with a phosphoimaging analyzer. B: Representative Northern blot showing expression of h*TOP3α*. RNA samples were separated on 1% formaldehyde–agarose gel, transferred to membrane, and probed with a full-length h*TOP3α* cDNA. A human glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) cDNA probe was used for normalization of gel loading.

USF can activate the E-box of the h*TOP3α* promoter in HeLa cells but is completely inactive in the h*TOP3α* promoter of Saos-2 cells.

### 3.2. Endogenous level of hTOP3α mRNA is reduced in Saos-2 cells

Since the E-box element acts as a cell type-specific enhancer of h*TOP3α* promoter activity, we reasoned that endogenous h*TOP3α* mRNA levels would be lower in Saos-2 cells as compared to HeLa cells. To test this possibility, we performed Northern blot analysis with total RNA prepared from the two cell lines. Northern blots were hybridized with a probe consisting of a full-length h*TOP3α* cDNA. One distinct h*TOP3α* transcript of about 3.8 kb and a smear of larger transcripts were detected, and the level of h*TOP3α* mRNA in Saos-2 cells was reduced to about 30% of that observed for HeLa cells (Fig. 2). This result suggests that the inability of USF to activate the h*TOP3α* promoter in Saos-2 cells may directly account for the marked reduction in h*TOP3α* mRNA level in these cells.

### 3.3. Expression and DNA binding activity of the endogenous USF proteins in HeLa and Saos-2 cells

The above-mentioned findings suggest that the cell type-dependent transcription activity of h*TOP3α* gene between HeLa

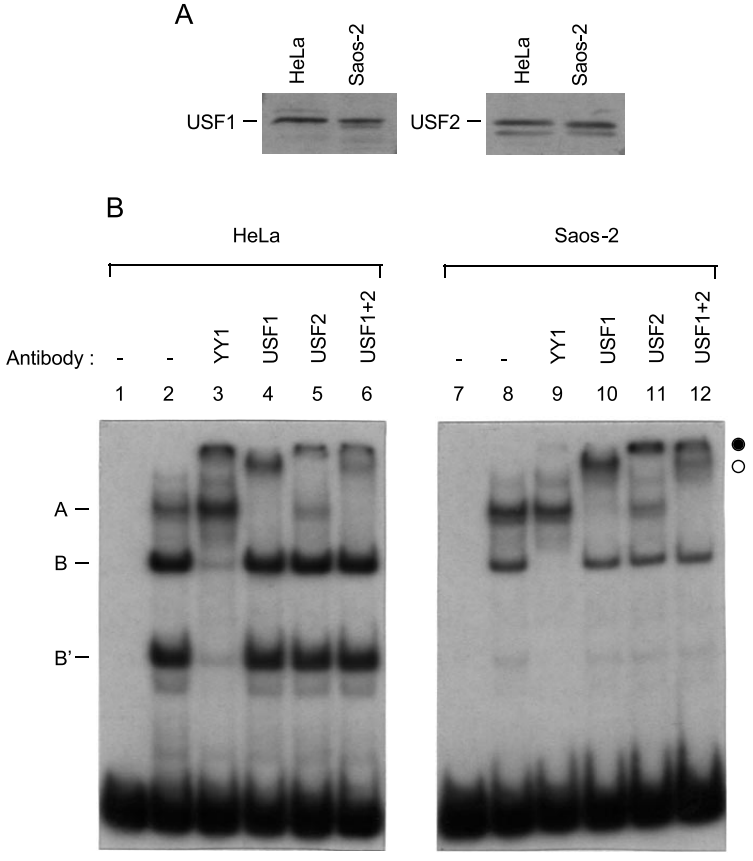


Fig. 3. Expression and DNA-binding activity of endogenous USF1 and USF2 in HeLa and Saos-2 cells. A: Western blot analysis was performed with nuclear extracts prepared from HeLa and Saos-2 cells to compare the endogenous levels of USF1 and USF2 present in both cells. B: The 52-bp radiolabeled duplex probe (1 ng) extending from −275 to −326 was incubated with 2.4 μg of HeLa or Saos-2 cell nuclear extracts (lanes 2 and 8) in the binding mixture containing antibody against YY1 (lanes 3 and 9), USF1 (lanes 4 and 10), USF2 (lanes 5 and 11), or USF1 plus USF2 (lanes 6 and 12). Lanes 1 and 7 contained probe alone. Bands A, B, and B′ represent specific protein–DNA complexes. Anti-USF1 antibody generated the rapidly migrating supershifted complex (indicated by the open circle), and anti-USF2 antibody generated the slower-migrating supershifted complex (indicated by the closed circle).

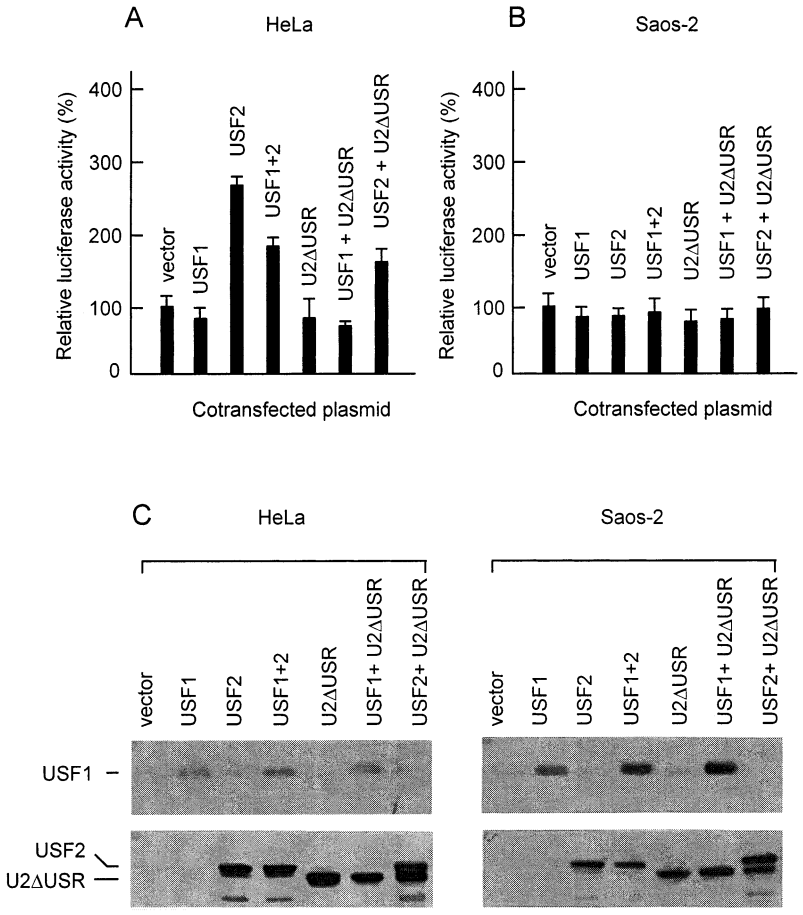


Fig. 4. Ectopically expressed USF2 enhances h*TOP3α* transcription activity in HeLa cells but not in Saos-2 cells. HeLa (A) or Saos-2 cells (B) were transfected with the −326LUC reporter plasmid and the indicated USF expression vectors. The amount of the cell lysate employed for each luciferase activity assay was normalized to the β-galactosidase activity, and the relative luciferase activity of each construct was expressed as a percentage of that of the corresponding empty vector. The data represent the average of four independent experiments. C: The levels of expression of the various USF proteins were measured by Western blot analysis with the same extracts used in luciferase assays.

and Saos-2 cells may be due to differences in the expression and DNA-binding activity of the USF proteins. To address this possibility, we measured the amounts of the endogenous USF proteins in nuclear extracts from HeLa and Saos-2 cells prepared under identical conditions. Western blot analysis of the USF protein contents of the two cell lines revealed that both contain similar amounts of USF1 and USF2 (Fig. 3A). We next determined USF DNA-binding activities in the two cell lines by electrophoretic mobility shift assay (EMSA) using the extended E-box, consisting of the 52-bp region extending from −275 to −326 upstream of transcription initiation in the h*TOP3α* promoter, as a probe. This 52-bp region was shown to serve as the binding sites for both YY1 and USF [13]. As shown in Fig. 3B, nuclear extracts derived from HeLa and Saos-2 cells formed three major DNA–protein complexes (lanes 2 and 8). The specificity of these complexes for the probe was shown by supershift analysis. Preincubation with the anti-YY1 antibody selectively reduced the level of complex B, but had no effect on complex A (lanes 3 and 9). The complex B′ most likely contained proteolytic degradation products of YY1, as it was also supershifted by the anti-YY1 antibody. YY1 has been previously reported to be susceptible to proteolytic degradation [16]. Conversely, preincubation with the anti-USF1 antibody completely inhibited the formation of complex A and generated a distinct supershifted complex in both cell lines, but did not affect the formation of complexes B and B′ (lanes 4 and 10). This result suggests that complex A contained USF1 homodimers and USF1-USF2 heterodimers in the two cell lines. When anti-USF2 antibody was preincubated with nuclear extracts, the formation of complex A was partially inhibited and a further supershifted complex was generated (lanes 5 and 11). Complex A did not completely disappear even when excess amounts of anti-USF2 antibody were added to the reactions (data not shown). The addition of both USF1 and USF2 antibodies together completely eliminated USF-containing complexes and generated two distinct supershifted complexes (lanes 6 and 12). Taken together, these data indicate that similar USF DNA-binding activities are present in the two cell lines. From these results, we conclude that the inability of the USF proteins to activate h*TOP3α* transcription in Saos-2 cells is not due to a lack of expression or DNA-binding activity of the USF proteins.

### *3.4. Expression of USF2 enhances hTOP3α transcription activity in HeLa cells but not in Saos-2 cells*

HeLa and Saos-2 cells were cotransfected with h*TOP3α* promoter–reporter constructs (−326LUC), together with either a USF1 or USF2 expression vector or both. When

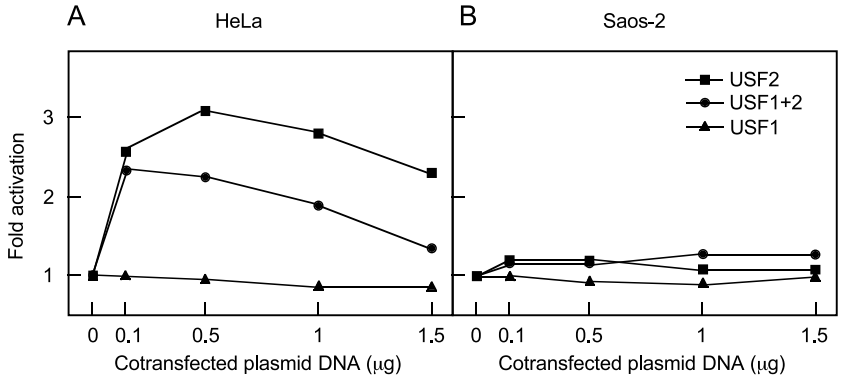


Fig. 5. Transactivating effects of the USF expression vectors. HeLa (A) and Saos-2 cells (B) were transfected with the −326LUC reporter plasmid and various amounts of either USF1, or USF2, or USF1 plus USF2 expression vectors, as indicated. Luciferase activity was measured as described in the legend to Fig. 4. The results of the luciferase assay are expressed as fold activation over the basal level observed in the absence of a USF expression vector. The data represent the average of four independent experiments.

USF1 was ectopically expressed in HeLa cells, transcription activity of the −326LUC reporter was not enhanced over the basal level obtained in the absence of exogenous USF (Fig. 4A). In marked contrast, ectopically expressed USF2 activated the −326LUC reporter about 2.7-fold. This activation was mediated through the E-box since the h*TOP3α* promoter with a mutated E-box (E-box mut −326LUC) was unresponsive to exogenous USF2 (data not shown). Furthermore, transcription activation of the −326LUC reporter in the presence of USF2 was decreased by cotransfecting USF1. Such reduction would be induced because overexpressed USF1 is shifting the equilibrium of USF dimer compositions and competing off the USF2 homodimers. When the same experiments were performed in Saos-2 cells, cotransfection of either a USF1 or USF2 expression vector or both with the −326LUC reporter did not enhance h*TOP3α* promoter activity over the basal level (Fig. 4B). These results suggest that the exogenous USF proteins were completely inactive and were incapable of activating h*TOP3α* transcription in Saos-2 cells.

The highly conserved USF-specific region (USR) of USF2 acts as an autonomous transcriptional activation domain at promoters containing an initiator element [15,17]. Since the sequence surrounding the transcription initiation site of the h*TOP3α* promoter is homologous to the initiator consensus sequence [13], we examined the role of the USR in the activation of the h*TOP3α* promoter by USF2. HeLa cells were cotransfected with the −326LUC reporter, together with a USF2 mutant construct lacking only the USR (U2ΔUSR). Overexpression of U2ΔUSR did not alter −326LUC transcription from the level observed in the absence of ectopically expressed USF, indicating that the USR of USF2 is required to activate the h*TOP3α* promoter in HeLa cells (Fig. 4A). Furthermore, cotransfection of U2ΔUSR reduced transcriptional activation by USF2 to about 60% of the activity observed with USF2 alone. These experiments suggest that U2ΔUSR functions as a dominant-negative regulator of E-box-dependent enhancer activity in h*TOP3α* promoter. In Saos-2 cells, cotransfection of U2ΔUSR did not significantly alter −326LUC transcription activity from the level observed in the presence of either USF1 or USF2 alone (Fig. 4B). The overexpression levels of exogenous USF variants produced by transient transfection were examined by Western blot analysis. As shown in Fig. 4C, the levels of USF expression were found to be similar between the two cell lines. These data further confirmed that the inability of exogenous USF proteins in Saos-2 cells was not due to a lack of expression in transfected cells.

### 3.5. *Transactivating effects of increasing amounts of the USF expression vectors*

When the transcription activators are expressed at very high levels, trans-activation could be diminished due to the self-squelching effect through which inhibitory protein interactions can occur [18–20]. Thus, it would be possible that the inability of the USF proteins in Saos-2 cells could be due to the self-squelching effect when overexpressed. To address this point, the −326LUC reporter construct was cotransfected into HeLa and Saos-2 cells with increasing amounts of USF expression vectors. In HeLa cells, reporter gene expression activity increased with increasing amounts of USF2 concentrations (up to 0.5 μg of expression vectors), while increasing the concentration of USF1 did not activate reporter activity (Fig. 5A). Consistent with the results shown in Fig. 4, transactivation by USF2 was decreased by cotransfecting increasing concentrations of USF1. A squelching phenomenon was observed at elevated concentrations of USF proteins. However, increasing the concentration of overexpressed USF2 in Saos-2 cells had no effect on the activity of the cotransfected reporter (Fig. 5B). The overexpression levels of the exogenous USF proteins were examined by Western blot analysis and were found to be similar (data not shown).

## 4. Discussion

Although endogenous expression of mammalian *TOP3α* gene is differentially regulated in different tissues and during developmental stages [21,22], very little is known about the molecular mechanisms involved in the transcriptional regulation of the *TOP3α* gene. Recently though, we demonstrated that both YY1 and USF transcription factors bind to the *TOP3α* promoter and function as transcriptional activators [13,23]. Since the USF proteins have been recognized as important players in the regulation of tissue-specific genes [24] and in the specific response of genes to external modulators [25], it seems of interest to examine whether the USF proteins functionally regulate the transcription activity of h*TOP3α* gene in a cell type-specific manner. Mutation of a consensus binding site for USF was shown to markedly decrease

h*TOP3α* promoter activity in HeLa cells, indicating that USF is transcriptionally active and essential for the high level expression of the h*TOP3α* gene. In contrast, USF lacks transcriptional activity in Saos-2 cells. These data demonstrate that USF functionally regulates the expression of the h*TOP3α* gene and acts as a cell type-specific regulator of h*TOP3α* promoter activity.

Using transient transfection assays, we demonstrated that USF2 in HeLa cells was able to activate transcription of the reporter gene driven by the h*TOP3α* promoter through the E-box element. In contrast, USF1 overexpression had no effect on h*TOP3α* promoter activity. Furthermore, coexpression of ectopic USF1 and USF2 is less potent than overexpression of USF2 alone. The USF1 and USF2 proteins are ubiquitously expressed in many cell types. However, relative ratios of USF homo- and heterodimers are known to vary among different cell types [26]. Although the effect of the different compositions of endogenous USF dimers on h*TOP3α* promoter activity has not been extensively examined, it appears more likely that USF2 homodimers are more potent transactivator than other USF species in HeLa cells.

Cotransfection of USF2 with h*TOP3α* promoter–reporter construct in Saos-2 cells did not enhance h*TOP3α* promoter activity over the basal level. Thus, the critical question that remains to be answered is why USF2 was completely inactive and failed to activate transcription of the h*TOP3α* gene in Saos-2 cells. Recently, Qyang et al. reported a cell type-dependent activity of the USF proteins in cellular proliferation and transcriptional activation [15]. Consistent with our findings, they demonstrated that the USF proteins in HeLa cells function as transcriptional effectors and their overexpression causes marked growth inhibition, but the USF proteins in Saos-2 cells are transcriptionally inactive. The inactivity of the USF proteins in Saos-2 cells on the promoters examined was not due to a deficiency of transcription factors since USF and other transcription factors were present in both Saos-2 and HeLa cells. The coactivator model was proposed to account for the complete inactivity of USF in Saos-2 cells [15]. In this model, the transcription activity of USF is controlled by interaction of a specific coactivator that could not be expressed in Saos-2 cells. Although this cellular activator has not been identified yet, transcriptional activation of the h*TOP3α* gene through the E-box element is consistent with the coactivator model for cell type-dependent activity of USF.

In summary, the present study suggests that USF2 is capable of enhancing promoter activity of the h*TOP3α* gene through the upstream E-box element in a cell type-specific manner. USF2 functions as a transactivator of the h*TOP3α* promoter in HeLa cells but are completely inactive in Saos-2 cells. This cell type-specific regulation by USF2 may, at least in part, provide a mechanism for the differential expression of h*TOP3α* gene in various tissues and during developmental stages.

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