Cofactor of BRCA1: A Novel Transcription Factor Regulator in Upper Gastrointestinal Adenocarcinomas

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Abstract

Cofactor of BRCA1 (COBRA1) is a newly characterized member of the negative elongation factor (NELF) complex. In this work, we show that COBRA1 is overexpressed in the majority of primary upper gastrointestinal adenocarcinomas (UGC), and its overexpression correlates with down-regulation of TFF1. We have detected overexpression of COBRA1 mRNA using quantitative real-time reverse transcription-PCR in 28 (79%) primary UGCs. Immunohistochemical analysis of UGC tissue arrays that contained 70 tumor samples showed moderate-strong staining for COBRA1 in 60 (84%) tumors. Interestingly, the tumor samples showed absent-weak staining for TFF1 in 45 (65%) of the tumors. Simultaneous loss of TFF1 expression and overexpression of COBRA1 was observed in 42 of 70 (60%) tumors. Using small interfering RNA technology with gastric cancer cells, we have shown that COBRA1 inhibition leads to increased TFF1 promoter activity and gene expression. Promoter analysis of TFF1 indicated that regulation of TFF1 by COBRA1 is estrogen independent in contrast to breast cancer. Moreover, COBRA1 regulation of TFF1 in gastric cancer cells was independent of NELF-E. Using several truncated mutants and site mutants of the TFF1 promoter, we have shown that COBRA1 can negatively regulate the activator protein-1 (AP-1) complex at the TFF1 promoter and thus down-regulate TFF1 expression in gastric cancer cell lines. Electrophoretic mobility shift assay showed that COBRA1 attenuates AP-1 binding to DNA. Our results suggest COBRA1 as a novel oncoprotein in UCGs that regulate AP-1 binding and the expression of TFF1 in upper gastric epithelia. (Cancer Res 2006; 66(3): 1346-53)

Introduction

Upper gastrointestinal adenocarcinomas (UGC) are among the most prevalent causes of cancer-related deaths in the world, and the disease frequency is rapidly rising (1, 2). This category of cancers includes adenocarcinomas of the stomach, gastroesophageal junction (GEJ), and lower esophagus. The incidence of Barrett’s related GEJ and lower esophageal adenocarcinomas is rising faster than ever before (3, 4).

The cofactor of BRCA1 (COBRA1) was recently identified as a BRCA1-interacting protein (5) and was found to be a member of the negative elongation factor (NELF) transcription elongation regulatory complex, NELF-B (6). In its role as NELF-B, COBRA1 has been shown to bind directly to the active estrogen receptor (ER) α and recruit the other NELF subunits to stall RNA polymerase II at the promoter proximal region, thereby preventing transcription elongation (7, 8). The polymerase stalling mechanism is used by the NELF complex to inhibit estrogen-induced transcription of TFF1 in breast cancer (7).

TFF1 is one of a family of highly conserved, secreted trefoil peptide proteins (9). TFF1 is normally expressed only in the upper gastrointestinal system, in the upper portion of the glandular pits where it is secreted to become part of the protective mucus layer. Tissue damage leads to up-regulation of TFF1, whereas gastric tumorigenesis is associated with loss of TFF1 expression (10, 11). TFF1 expression is down-regulated in >70% of UCGs (12). Of those, approximately one third shows promoter hypermethylation of TFF1 (13), whereas gene mutation is detected in <5% (10). Other mechanisms that contribute to TFF1 down-regulation remain unclear in UGCs.

In contrast to studies of TFF1 in UGCs, other tumors, such as carcinomas of the breast and liver, often show high levels of expression of TFF1. In the breast cancer model, both ERα and the ligand-independent ERy have been conclusively shown to stimulate TFF1 expression (14). Recent data indicate that estrogen response element is dominant in stimulating TFF1 expression in breast cancer cells (15). Similarly, the importance of estrogen stimulation in induction of TFF1 expression was observed in hepatic cancers (16), although cross-talk between multiple pathways seems to be involved.

In this work, we have identified COBRA1 as a novel oncoprotein in UGCs and showed high expression levels of COBRA1 mRNA and protein in UGCs. We have further examined the regulatory effects of COBRA1 on TFF1 gene expression in gastric adenocarcinoma cell lines.

Materials and Methods

Tissue samples. A total of 70 UGCs and 19 normal stomach paraflin-embedded tissue samples were available for the immunohistochemical analysis. In addition, 28 gastric, GEJ, and lower esophageal tumors and 22 normal gastric epithelial samples were dissected for optimal tumor content (>70%) and used for mRNA extraction, cDNA synthesis, and subsequent quantitative real-time reverse transcription-PCR (RT-PCR) assays. All tissue samples were collected in accordance with institutional review board–approved protocols. Tissues were stained with H&E, and representative regions were selected for inclusion in a tissue array. Tissue cores with a diameter of 0.6 mm were retrieved from the selected regions of the donor blocks and punched to the recipient block using a manual tissue array instrument (Beecher Instruments, Silver Spring, MD); samples were punched in triplicates. Control samples from normal epithelial specimens were punched in each sample row. Sections (5 μm) were transferred to polylysine-coated slides (SuperFrostPlus, Menzel-Glaser, Braunschweig,
Germany) and incubated at 37°C for 2 hours. The resulting tumor tissue array was used for immunohistochemical analysis. All tumors and normal gastric mucosal epithelial tissues were histologically verified. The adenocarcinomas were collected from stomach, GEJ, and lower esophagus and ranged from well differentiated to poorly differentiated, stages I to IV, with a mix of intestinal and diffuse-type tumors.

**Immunohistochemistry.** Immunohistochemical analysis of COBRA1 and TFF1 protein expression was done on a tumor tissue array that contained 70 UGC samples (stomach, GEJ, and lower esophagus) and 19 normal gastric tissues. Adjacent normal gastric and esophageal tissues were available for comparisons. Dewaxing and rehydration by descending concentrations of ethanol was followed by antigen retrieval [20 minutes in a microwave, 450 W, 10 mmol/L EDTA (pH 8.0)]. Blocking was done with 10% goat serum in PBS for 5 minutes. All sections were incubated with either anti-TFF1 mouse monoclonal antibody (anti-pS2, NeoMarkers, Fremont, CA) or anti-COBRA1 rabbit polyclonal antibody (R. Li; ref. 5) followed by washing in PBS and incubation with anti-mouse or anti-rabbit secondary antibody (dilution 1:20; MBL; MoBiTec, Goettingen, Germany) for 1 hour at room temperature and then washed in PBS. For revealing positive immunohistochemical reaction, the Vectastain ABC-AP kit (mouse IgG, Vector, Alexis, Gruenberg, Germany) was used as chromogen substrate, and the specimens were counterstained with hematoxylin and mounted with DEPEX%. Specificity of immunostaining was checked by omitting single steps in the protocol and by replacing the primary antibody with non-immune serum.

Immunohistochemical results were evaluated for intensity and frequency of staining of nuclear and cytoplasmic components and the whole. The intensity of staining was graded as 0 [negative], 1 [weak], 2 [moderate], and 3 [strong]. The frequency was graded from 0 to 4 by percentage of positive cells as follows: grade 0, <3%; grade 1, 3% to 25%; grade 2, 25% to 50%; grade 3, 50% to 75%; and grade 4, >75%. The index score was the product of multiplication of the intensity and frequency grades, which was then binned into a four-point scale: index score 0, product of 0; index score 1, products 1 and 2; index score 2, products 3 and 4; and index score 3, products 6 to 12. Index score 2 or 3 was determined as the overexpression of proteins.

**Real-time RT-PCR.** The mRNA was isolated using RNeasy kit (Qiagen, GmbH, Hilden, Germany). Single-stranded cDNA was synthesized using Advantage RT-for-PCR kit (Clontech, Palo Alto, CA). Quantitative PCR was done using iCycler (Bio-Rad, Hercules, CA) and threshold cycle number was determined using iCycler software version 3.0 (Bio-Rad) with SYBR Green technology (17). Specific primers for COBRA1, TFF1, and HPRT1 were determined using iCycler software version 3.0 (Bio-Rad) with SYBR Green technology. The activator Mutant was detected using anti-COBRA mouse monoclonal antibody (7). Actin was detected using a monoclonal antibody (sc-8432, Santa Cruz Biotechnology, Santa Cruz, CA). Secondary anti-mouse horseradish peroxidase antibody (Pierce, Rockford, IL) was detected using chemiluminescence (Pierce SuperSignal Femto kit).

**TFF1 promoter mutant generation.** In addition, five truncation mutants and three site mutants (graphed in Fig. 3A) were prepared as described below. Electrophoretic mobility shift assay (EMSA) was done using stably transfected AGS cells lines. Stable cell lines were established by transfection (as described) for 48 hours followed by antibiotic selection in 800 ng/mL puromycin (Sigma) for the pSUPER vectors or 600 μg/mL G418 (Sigma) for the pcDNA3.1 vectors. Selection was monitored by incubating untransfected cells in the antibiotic medium and was considered complete when all untransfected cells were dead. Stable cells were then plated at low density for cloning, and colonies were screened by Western blot analysis for total COBRA1 expression.

For generation of promoter fragments and mutants, PCR was used to generate the TFF1 promoter fragments shown in Fig. 3A. The fragments were purified (Qiagen, Valencia, CA), subjected to restriction digest with Mbol and Mf II (Roche), and ligated into pGL3-Luc vector (Promega).

Electrophoretic mobility shift assay. Chemiluminescent EMSA was done on an oligonucleotide containing the AP-1 consensus binding site (Panomics, Redwood City, CA) using the Lightshift EMSA kit (Pierce). Briefly, biotinylated target DNA was incubated with nuclear extract (from COBRA1-transfected or siRNA COBRA1-transfected AGS cells; NE-PER kit, Pierce) and appropriate buffer. The reactions were run on 4% acrylamide gel and transferred to Hybond N+ membrane (Amersham) using semidry electrophoretic transfer (Bio-Rad). Following cross-linking, the membrane was treated according to kit instructions and exposed to Kodak X-ray film (Fisher Scientific, Pittsburgh, PA).

**Results.**

**Overexpression of COBRA1 and loss of expression of TFF1 in UGCs.** The majority (79%) of primary UCG samples showed elevated mRNA expression of COBRA1 and decreased mRNA expression of TFF1 (93%) relative to normal tissue samples. The real-time RT-PCR of mRNA showed that elevated expression of
COBRA1 is associated with attenuated expression of TFF1 in most of the cases (Fig. 1A). Protein levels of COBRA1 and TFF1 paralleled the mRNA levels as confirmed by immunohistochemical staining of UCG tissue arrays (Fig. 1B). The immunohistochemical staining showed that COBRA1 location is primarily nuclear, whereas TFF1 is cytoplasmic or secreted. There was an inverse relationship between the two proteins in adenocarcinoma tissues, with TFF1 immuno-histochemical staining intensity being weak-absent in 45 of 70 (65%) and COBRA1 being moderate-strong in 60 of 70 (84%). Interestingly, tumors with simultaneously elevated COBRA1 and weak-absent TFF1 were 42 of 70 (60%). Our UGC tissue arrays were composed of 7 (10%) female samples and 63 (90%) samples from males, which represent the expected distribution of these tumors in our population. Due to the relatively high frequency of TFF1 and COBRA1 alteration and the small number of cases analyzed, association with a particular tumor site (stomach, GEJ, and lower esophageal), histopathologic subtype, or clinical variables was not possible to ascertain.

**COBRA1 regulates TFF1 Expression in gastric cancer cells.** Activation of the TFF1 promoter was significantly repressed by overexpression of COBRA1 (Fig. 2A), whereas reduction of COBRA1 by siRNA led to a substantial increase in TFF1 promoter activity. AGS, MKN45, and KATO III gastric adenocarcinoma cells and T47D breast cancer cells were transiently transfected with luciferase reporter plasmids as described and treated with 10 nmol/L β-estradiol for 24 hours. In contrast to breast cancer, COBRA1 regulation of TFF1 was not estrogen dependent in gastric adenocarcinoma (Fig. 2A). Addition of estrogen to the cell culture or mutation of the ER-binding site (ERE versus ΔERE, where the binding site sequence is mutated to EcoRI and EcoRV restriction

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**Figure 1.** COBRA1 is overexpressed in UGCs. A, real-time RT-PCR of 28 primary UGCs compared with 22 normal samples to measure expression of COBRA1 and TFF1. The threshold cycle number (Ct) from each sample, run in triplicate, was compared with the average Ct of 22 different normal gastric samples to calculate the fold increase or decrease of gene expression. Bars, SE. Y axis, fold expression relative to normal; shaded area, a range of mRNA expression that is considered normal (0.3-3.0 fold expression). B, immunohistochemical staining of UGCs (left) and normal upper gastrointestinal tissues (right) for COBRA1 and TFF1. Brown, protein expression, nuclear localization of COBRA1, and upper gastric pit and epithelial secretion of TFF1. Results also show loss or reduction of TFF1 coincidental to elevated expression of COBRA1.
sites; ref. 19) in the TFF1 promoter was ineffective in altering COBRA1 regulatory activity (Fig. 2A). Similar results were obtained with MKN45 and KATO III gastric adenocarcinoma cells (data not shown). To verify our technique, this procedure was also done in breast cancer cells (T47D) and resulted in strong TFF1 promoter stimulation as shown previously (Fig. 2B; ref. 7).

In breast cancer, COBRA1 regulation of TFF1 is a function of its role as NELF-B; knockdown of NELF-E has been shown to similarly stimulate TFF1 expression (7). To test the function of NELF-E on the TFF1 promoter in UGC, the stimulatory activity of siRNA NELF-E was tested in AGS cells (Fig. 2C). For this experiment, we transiently transfected cells with the pSUPER-NELF-E vector, which expresses siRNA NELF-E (ref. 7; Fig. 2C). In contrast to knockdown of COBRA1, knockdown of NELF-E had no stimulatory effect on the TFF1 promoter activity. Thus, COBRA1 can act independently from the NELF-E in gastric cancer cells.

Figure 2. COBRA1 regulates TFF1 expression in gastric adenocarcinoma cell lines. A, luciferase reporter assays were used to evaluate TFF1 promoter activity in AGS gastric cancer cells. Cells were transfected with the indicated plasmids (TFF1-Luc, TFF1ERE-Luc, pcDNA3.1 FLAG-COBRA1, pcDNA3.1, or pSUPER-COBRA1) for 24 hours before estrogen treatment (10 nmol/L, 24 hours). Columns, average of three trials; bars, SE.

**B**, luciferase reporter assays show that TFF1 promoter activity in T47D breast carcinoma cells is responsive to estrogen treatment as well as siRNA for COBRA1. Columns, average of two trials; bars, SE.

**C**, luciferase reporter assays show that TFF1 promoter activity is unaffected by siRNA for NELF-E (pSUPER-NELF-E), whereas siRNA for COBRA1 (NELF-B; pSUPER-COBRA1) strongly stimulates promoter activity. Columns, average of three trials; bars, SE.

**D**, real-time RT-PCR of endogenous TFF1 mRNA expression confirms that ectopic expression of FLAG-COBRA1 leads to down-regulation of TFF1, whereas reduction of COBRA1 expression via siRNA leads to elevated levels of TFF1. Columns, fold induction or inhibition relative to vector transfected control cells. Dark columns, reduction of endogenous TFF1 mRNA when COBRA1 is ectopically elevated; light gray columns, elevated levels of TFF1 mRNA relative to controls when COBRA1 is knocked down by transfected siRNA.

**E**, Western blot analysis confirms overexpression of COBRA1 on transient transfection of AGS with pcDNA3.1 FLAG-COBRA1.
The luciferase reporter activity data were verified by examination of the expression of endogenous TFF1 under conditions of COBRA1 overexpression and knockdown. Expression of endogenous TFF1 was measured by real-time RT-PCR in the presence of overexpression and attenuated expression of COBRA1 (Fig. 2D) and Western blot analysis (Fig. 2E). Measurement of COBRA1 expression in these samples verifies transfection efficacy.

COBRA1 regulation of TFF1 occurs at the AP-1-binding sites. Data showed that COBRA1 was not regulating TFF1 at the ER site; therefore, localization of COBRA1 influence was done. Truncation mutants of the COBRA1 promoter were generated by PCR and ligated into the pGL3-Basic luciferase reporter vector (Fig. 3A). The mutants serially eliminated consensus-binding sites of transcription factors that were known to alter TFF1 expression (7, 16, 20, 21). Transient transfection of AGS gastric adenocarcinoma cells was followed by luciferase assays. Figure 3B (data set 3) shows that siRNA COBRA1 stimulated each of the truncated TFF1 promoters until the AP-1 site was lost (P5 versus P6-P8). Loss of the AP-1 site was confirmed by stimulation of the truncation mutants with overexpression of c-Jun (Fig. 3B, data set 4, P5 and P6). These data implied that COBRA1 might regulate the AP-1 complex (Fig. 3B).

Confirmation of COBRA1/AP-1 interactions was achieved in several steps. First, full-length, wild-type TFF1 promoter luciferase reporter was cotransfected with siRNA COBRA1 and c-Jun or c-Fos, representative of AP-1 complex members. These data show a synergistic activation of the TFF1 promoter when AP-1 members were overexpressed and COBRA1 was knocked down by siRNA (Fig. 3C, lanes 2-4 versus lanes 5 and 6; Fig. 4, data set 4). Second, the AP-1 consensus binding sites on the full-length TFF1 promoter at −354 and −710 bp from the 5' untranslated region were each mutated by site-directed mutagenesis. Following sequence verification, luciferase reporter assays confirmed the significance of AP-1 influence on TFF1 expression and COBRA1 regulation (Fig. 4). Cells were cotransfected with the mutant promoter/reporter vector and combinations of siRNA for COBRA1 (lanes 5-8) and c-Fos (lanes 9-12). Both siRNA for COBRA1 and c-Fos activated the wild-type promoter, and the combination had a synergistic effect as seen previously (lane 13). The mutation of the first or primary
AP-1-binding site (−710 bp) had little effect on COBRA1 or c-Fos activation (lanes 6, 10, and 14). However, mutation of the second or secondary AP-1 site (−354 bp) dramatically reduced both COBRA1 and c-Fos effects (lanes 7, 11, and 15), and mutation of both (double ΔAP-1) resulted in further promoter inhibition (lanes 8, 12, and 16), suggesting a small amount of compensation between the two sites when one is mutated. As a control for site-directed mutagenesis, we tested the activity of a second transcription factor-binding site on the mutated promoters. TFF1 expression is inhibited by nuclear factor-κB (21); therefore, IκB superrepressor was used to successfully stimulate the TFF1 promoter activity (data not shown), thus showing that the other transcription factor-binding sites on the TFF1 promoter remained unaltered by mutation of the AP-1 sites.

**COBRA1 regulates AP-1 complex members.** COBRA1 negatively regulates AP-1 binding to DNA. EMSA data (Fig. 5) showed that reduction of COBRA1 by siRNA led to increased DNA shift (lane 4), whereas elevation of COBRA1 expression led to attenuated DNA shift (lane 2). The AP-1 shift was verified by antibody supershift using anti-phospho-c-Jun (lane 6). We chose to use a simple, direct oligonucleotide mobility shift assay to examine COBRA1 interactions with the AP-1 transcription complex because the TFF1 promoter contains numerous transcription factor-binding sites, and our EMSAs using a short fragment of the TFF1 promoter resulted in a complex band pattern (data not shown).

**Discussion**

The current work provides the first evidence for overexpression of COBRA1 and its physiologic role as inhibitor of TFF1 expression in UGCs. First, we showed that the COBRA1 transcriptional cofactor negatively regulates TFF1 expression in vitro and likely in vivo. Second, we showed that, unlike breast cancer, COBRA1 regulation of TFF1 is estrogen independent and NELF-E independent. Finally, we have shown that COBRA1 inhibits AP-1 activation of the TFF1 gene in UGC.

COBRA1 regulation of TFF1 may occur at a variety of different sites on the promoter (Fig. 3A; refs. 7, 20–22). As COBRA1 does not have a DNA-binding domain, it acts solely as a cofactor. In breast cancer, COBRA1 binds to the ER to inhibit hormone-dependent activation of TFF1 (7). However, in gastric cancer cells, we found that TFF1 activation is hormone independent but, nevertheless, inhibited by COBRA1. Therefore, we conducted a search for other transcription factors that may bind COBRA1 and lead to inhibition of TFF1 expression. Our data led to COBRA1 inhibiting AP-1 stimulation of TFF1 expression. Data regarding the interaction of AP-1 with COBRA1 are supported by another recent work (23), where the authors showed direct binding between COBRA1 and c-Fos. Whereas our site-directed mutagenesis of AP-1-binding locations was effective in showing COBRA1/AP-1 regulatory interactions, the results did not show that COBRA1 has absolute control of TFF1 promoter activity. We hypothesize that, because there are many transcription factor-binding sites in the 1,050-bp TFF1 promoter and our experiments only mutated two of these, influence on the expression of this gene is likely to be multifactorial.

Interactions between AP-1 and the ER have been studied for several years. In hepatic carcinoma cells, the AP-1 transcription factor complex [stimulated by the mitogen-activated protein kinase (MAPK) pathway] is known to enhance the estrogen-mediated...
activation of the TFF1 promoter (16). Binding between c-Jun and ERα was shown by mammalian two-hybrid assay and was independent of ER binding to DNA (24), and mutation of a conserved lysine on ERα results in hyperstimulated AP-1 activation of gene promoters (25), further supporting a direct interaction between ER and AP-1. However, the ER/AP-1 pathways described thus far are all ligand dependent. AP-1 and ER are also known to be activated by the MAPK pathway (16, 26), and the possibility remains that ER may bind to AP-1 in response to MAPK influence via protein-protein interactions. COBRA1 regulation of ER in breast cancer was also shown to be ligand dependent (7). The data presented in this article show a ligand-independent regulation of TFF1 (Fig. 2A). DNA microarray data on UCG show a basal level of ER expression, which remains unchanged during carcinogenesis (data not shown), and data presented in this article do not exclude the possibility of ligand-independent interactions between ER and AP-1, nor potential influence of MAPK on either of these proteins.

COBRA1 acts as NELF-B in breast cancer along with other subunits A, C/D, and E. NELF-B (COBRA1) binds to the ER (7), whereas NELF-E is responsible for interactions with RNA (27) and is hypothesized to be critical for the RNA polymerase II "tethering" or transcriptional “pausing” caused by the NELF complex. However, our studies with gastric cancer show that COBRA1 acts independently of NELF-E. Therefore, it is possible that COBRA1 negatively regulates TFF1 expression by preventing AP-1 binding to the TFF1 promoter and thus inhibiting gene transcription, and that COBRA1 does not bind to RNA polymerase II as seen in similar gene regulation involving NELF.

Recent work characterizing the NELF complex in Drosophila melanogaster has shown that the A and E subunits of NELF do not have conserved sequences when compared with mammalian counterparts. However, the C/D and B subunits are uniquely conserved (28), suggesting that COBRA1 is an ancient and important regulator of gene expression. Therefore, COBRA1 may be an important cofactor in regulation of gene expression during tumorigenesis.

Whereas TFF1 expression is lost in UGCs, TFF1 is aberrantly expressed in other cancers around the body. Studies show that TFF1 may be important for tumor metastasis in breast and hepatic cancers, and regulation of this gene has been under investigation for some time (14, 15). Data show that whereas the estrogen response element is dominant in stimulating TFF1 expression in breast cancer cells (7), the binding of the AP-1 complex is mandatory and dominant for estrogen stimulation of this gene in hepatic cancer cell lines (16).

The decline of TFF1 expression during upper gastrointestinal carcinogenesis is well documented (10, 21, 29). Nearly 50% of all UGCs tested showed marked reduction of TFF1 expression (9). The TFF1 knockout mouse develops gastric dysplasia and gastric cancer similar to human (29, 30), leading to the hypothesis that TFF1 is a UGC tumor suppressor. Evidence has shown that less than one third of cases where TFF1 expression is lost can be explained by promoter hypermethylation, gene mutation, or deletion (10, 31). Therefore, the current data suggest that COBRA1 as a novel oncogene that can inhibit TFF1 expression and may account for the loss of TFF1 expression in the majority of tumors where mutations and DNA methylation cannot be found.

In conclusion, we have shown that COBRA1 is a novel transcription cofactor in upper gastrointestinal carcinogenesis. COBRA1 negatively regulates TFF1 in gastric cancer cells by inhibiting AP-1 activation of transcription. As AP-1 affects transcription for multiple genes, the oncogenic potential of COBRA1 could result in widespread effects that require further studies.

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