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ORIGINAL ARTICLE

Basic Study

Overexpression of Csk-binding protein decreases growth, invasion, and migration of esophageal carcinoma cells by controlling Src activation

Dong Zhou, Peng Dong, Yu-Min Li, Fa-Cai Guo, An-Ping Zhang, Run-Ze Song, Ya-Min Zhang, Zhi-Yong Li, Dong Yuan, Chuan Yang

Dong Zhou, Yu-Min Li, Gansu Provincial Key Laboratory of Digestive System Tumors, Lanzhou University Second Hospital, Lanzhou 730030, Gansu Province, China
Peng Dong, Department of Cardiology, Aviation General Hospital, Beijing 100012, China
Fa-Cai Guo, An-Ping Zhang, Run-Ze Song, Ya-Min Zhang, Zhi-Yong Li, Dong Yuan, Chuan Yang, Department of Vascular Surgery, Lanzhou University Second Hospital, Lanzhou 730030, Gansu Province, China
Author contributions: Zhou D and Dong P contributed to the work equally and should be regarded as co-first authors; Zhou D and Li YM designed the research; Zhou D, Dong P, Guo FC and Zhang AP performed the research; Zhang YM, Li ZY, Yuan D and Yang C analyzed data; Zhou D and Dong P wrote the paper.
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Correspondence to: Yu-Min Li, PhD, Professor, Gansu Provincial Key Laboratory of Digestive System Tumors, Lanzhou University Second Hospital, 82 Cuiyingmen, Lanzhou 730030, Gansu Province, China. 13919951166@139.com
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Abstract

AIM: To investigate the mechanisms by which Csk-binding protein (CBP) inhibits tumor progression in esophageal carcinoma.

METHODS: A CBP overexpressing esophageal carcinoma cell line (TE-1) was established. The growth, invasion, and migration of CBP-TE-1 cells, as well as the expression of Src were then determined and compared with those in normal TE-1 cells.

RESULTS: The expression of Src was decreased by the overexpression of CBP in TE-1 cells. The growth, invasion, and migration of TE-1 cells were decreased by the overexpression of CBP.

CONCLUSION: This study indicates that CBP may decrease the metastasis of esophageal carcinoma by inhibiting the activation of Src. CBP may be a potential tumor suppressor and targeting the *CBP* gene may be an alternative strategy for the development of therapies for esophageal carcinoma.

Key words: Csk-binding protein; Esophageal carcinoma; Cell growth; Invasion; Migration

Core tip: Csk-binding protein (CBP) is a ubiquitously expressed transmembrane protein and functions as a suppressor of Src-mediated tumor progression by promoting the inactivation of Src. Here, we established a CBP overexpressing esophageal carcinoma cell line

(TE-1) and found that the overexpression of CBP significantly decreased the proliferation, invasion, and migration of TE-1 cells, accompanied by decreased activation of Src. These results indicate that CBP may decrease the metastasis of esophageal carcinoma by inhibiting the activation of Src. Targeting the *CBP* gene may be an alternative strategy for the development of therapies for esophageal carcinoma.

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INTRODUCTION

Csk-binding protein (CBP), a ubiquitously expressed transmembrane protein, functions as a suppressor of Src-mediated tumor progression by promoting the inactivation of Src[1,2]. CBP is widely reported to act as a scaffold in the Csk-mediated negative regulation of Src family kinases (SFKs)[3,4]. First, CBP is phosphorylated by SFKs, then it associates with C-terminal Src kinase (Csk) through a specific site (Tyr-317 in humans) and brings it into proximity with membrane-associated SFKs. After that, Csk phosphorylates the C-terminal negative regulatory tyrosine residue of SFKs, which suppresses their activation[1]. SFKs are membrane-associated non-receptor protein tyrosine kinases that play pivotal roles in regulating various cellular processes including proliferation, differentiation, adhesion, migration, and survival[5]. Thus, CBP plays the opposite role in various Csk-mediated cellular processes and might be a significant target for Csk-mediated tumors.

Recent studies have shown that CBP is expressed at low levels in various human cancer cells[6-8], suggesting that CBP may be an important suppressor in the progression of various human cancers. We have previously reported that the expression of CBP is markedly down-regulated in esophageal carcinoma[9]; however, the mechanisms by which the down-regulation of CBP affects the progression of esophageal carcinoma remain unknown. Therefore, we established an esophageal carcinoma cell line stably overexpressing CBP (TE-1). We found that overexpression of CBP decreased the growth, invasion, and migration of esophageal carcinoma cells.

MATERIALS AND METHODS

Cell culture

The human esophageal carcinoma cell line TE-1 was provided by the Cell Bank of the Chinese Academy of Sciences, Shanghai, China. Cells were cultured in RPM1640 medium supplemented with 10% fetal bovine serum.

Lentiviral vector constructs and preparation

A lentiviral-delivered CBP vector was constructed and prepared by Shanghai qcbio Science & Technologies Co., Ltd. (Shanghai, China), as described by Lois *et al*[10]. Briefly, primers were designed according to the CBP sequence (Genbank Accession Number NC_000008.10). The primer sequences were: CBP-F, 5′-GGAATTCCCTGCCATGGGGCCCGCG-3′; CBP-R, 5′-GGAATTCGAGCCTGGT AATATCTCTGCCT-3′. The target gene was obtained by polymerase chain reaction and was inserted into the pUC57 vector. Subsequently, both pLenO-DCE and pUC57-CBP were digested by EcoRI and NotI. After ligation, the pLenO-DCE-CBP vector was constructed. After sequencing, the pLenO-DCE-CBP vector was transfected into 293T cells and the lentiviral-delivered CBP vector was prepared.

Cell transfection

Briefly, 1 × 10^6 TE-1 cells were seeded in each well of a 6-well plate in 500 μL of complete medium at 37 ℃ in a 5% CO_2 incubator for 24 h, and then transduced by lentiviral vectors at a multiplicity of infection of 10:1[11]. Transduction was carried out in the presence of polybrene (8 μg/mL). After washing three times with PBS, 1 mL of RPMI1640 was added in each well. Cells were seeded at 37 ℃ in a 5% CO_2 incubator for 48 h. Fluorescence microscopy was used to observe the transduction. G418 (400 μg/mL) was used for screening. Transduced cells were passaged and seeded for further experiments. Also, the pLenO-DCE-(-) vector was transduced into TE-1 cell as a blank transfection control.

MTT assay

Cells (5 × 10^3) were seeded in a 96-well plate (BD Biosciences, United States) and harvested for the MTT assay at different time points from days 1-6. Cell samples were incubated with 20 μL of MTT (5 mg/mL; Sigma, United States) for 6 h. Following the removal of the MTT solution, formazan crystals were dissolved in 150 μL of dimethyl sulfoxide (DMSO, Sigma, United States). The absorption of the solution was measured at 570 nm[12].

Transwell invasion assay

Invasion chambers coated with Matrigel were purchased from BD Biosciences. Assays were conducted as described by Seton-Rogers *et al*[13]. Briefly, cells (1 × 10^5) were added to the top chambers (in 300 μL of RPMI1640) of 24-well Transwell plates (BD Biosciences; 8 μm pore size). After 24 h, the top (non-migrated) cells were removed, and the bottom (migrated) cells were fixed with 70% methanol and stained with trypan

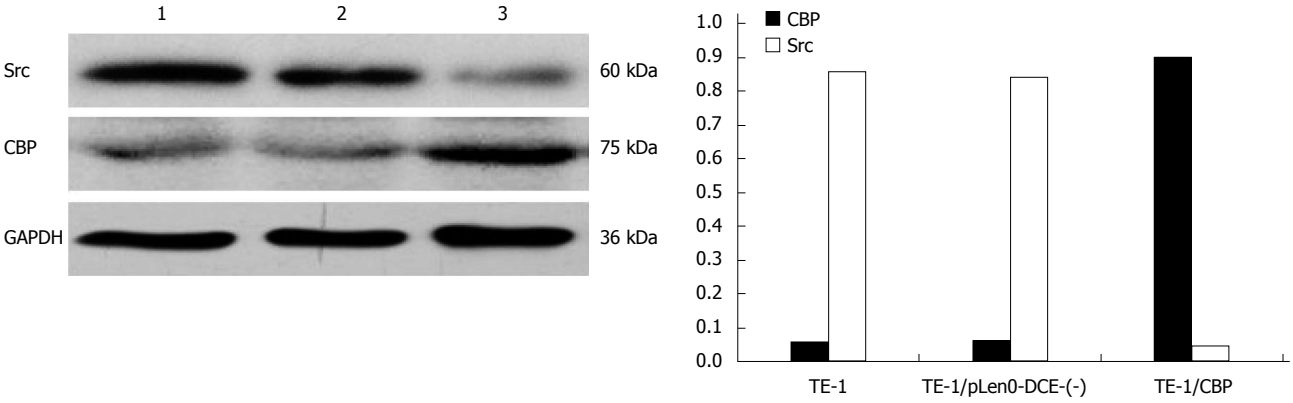

Figure 1 Overexpression of Csk-binding protein decreases the expression of Src in TE-1 cells. Western blot analysis of the expression of Csk-binding protein (CBP) and Src in TE-1 cells before and after transduction with CBP lentiviral vectors. GAPDH was used as a protein loading control. The expression of CBP was much higher in transduced TE-1 cells than in normal TE-1 and TE-1/pLenO-DCE cells ($P < 0.05$), and expression of Src was much lower in transduced TE-1 cells than in normal TE-1 and TE-1/pLenO-DCE cells ($P < 0.05$). 1 = normal TE-1 cells; 2 = TE-1 cells after transfection with pLenO-DCE-(-); 3 = TE-1 cells after overexpression CBP.

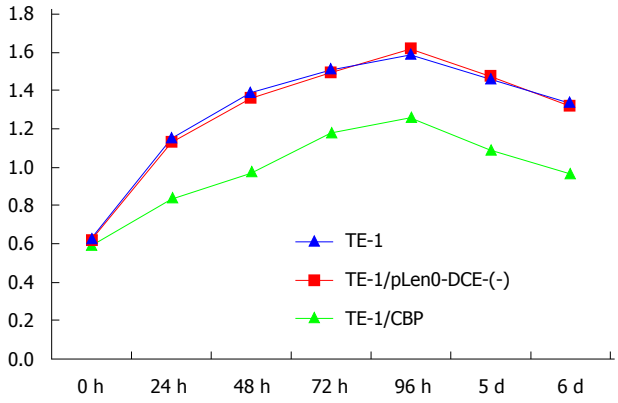

Figure 2 Cell growth of TE-1, TE-1/pLenO-DCE-(-) and TE-1/Csk-binding protein cells. The growth of TE-1/CBP cells was slower than that of TE-1 and TE-1/pLenO-DCE-(-) cells ($P < 0.05$).

blue to visualize nuclei. The number of migrating cells in five fields was counted at 100× magnification, and the mean for each chamber was determined with ImageJ (version 1.38, National Institutes of Health). Experiments were repeated a minimum of three times.

Scratch assay

Scratch assay was used for the detection of cell migration as described by Gough *et al*[14]. Briefly, cells (1×10^6) were seeded in a 6-well plate (BD Biosciences, United States) until cells reached 100% confluence. A p200 pipette tip was then used to create a scratch of the cell monolayer. After washing the plate once with PBS and replacing with the new medium, the cells were incubated at 37 ℃ in a 5% CO_2 incubator. After 24 h, the number of cells that had migrated into the scratch was calculated at 100× magnification.

Western blot analysis

Cells were lysed on ice in RIPA buffer (50 mmol/L Tris-HCl, 150 mmol/L NaCl, 1% NP-40, 0.1% SDS, 0.5% sodium deoxycholate, 2 mmol/L sodium fluoride, 2 mmol/L Na_3VO_4, 1 mmol/L EDTA, and 1 mmol/L EGTA). Total protein extracts were analyzed by Western blot, as described previously[15]. Proteins (20 μg) were separated by SDS-PAGE (Invitrogen) and transferred to PVDF membranes. The membranes were blotted for 1 h with 5% milk. Membranes were incubated with a primary antibody (1:500 dilution) against CBP or Src (Santa Cruz Biotechnology, Inc., United States) at 4 ℃ overnight. After incubation with a horseradish peroxidase-conjugated secondary antibody (1:1000 dilution) for 3 h at 37 ℃, signals were detected by ECL chemiluminescence for 5 min. The films were analyzed by densitometry with image software.

Statistics analysis

Data are expressed as mean ± SE and were statistically evaluated by one-way ANOVA followed by a Newman-Keuls test. $P < 0.05$ was considered statistically significant.

RESULTS

CBP overexpression decreases the expression of Src in TE-1 esophageal carcinoma cells

To check the overexpression of CBP in our stably transfected cells and to determine if overexpression of CBP leads to decreased expression of Src, we assessed the expression of Src in our TE-1 esophageal carcinoma cells that had been transduced with lentiviral constructs to overexpress CBP. As illustrated in Figure 1, our stably transduced cells overexpressed CBP, and CBP overexpression significantly decreased the protein levels of Src ($P < 0.05$) (Figure 1), supporting the previous finding that CBP down-regulates the activity

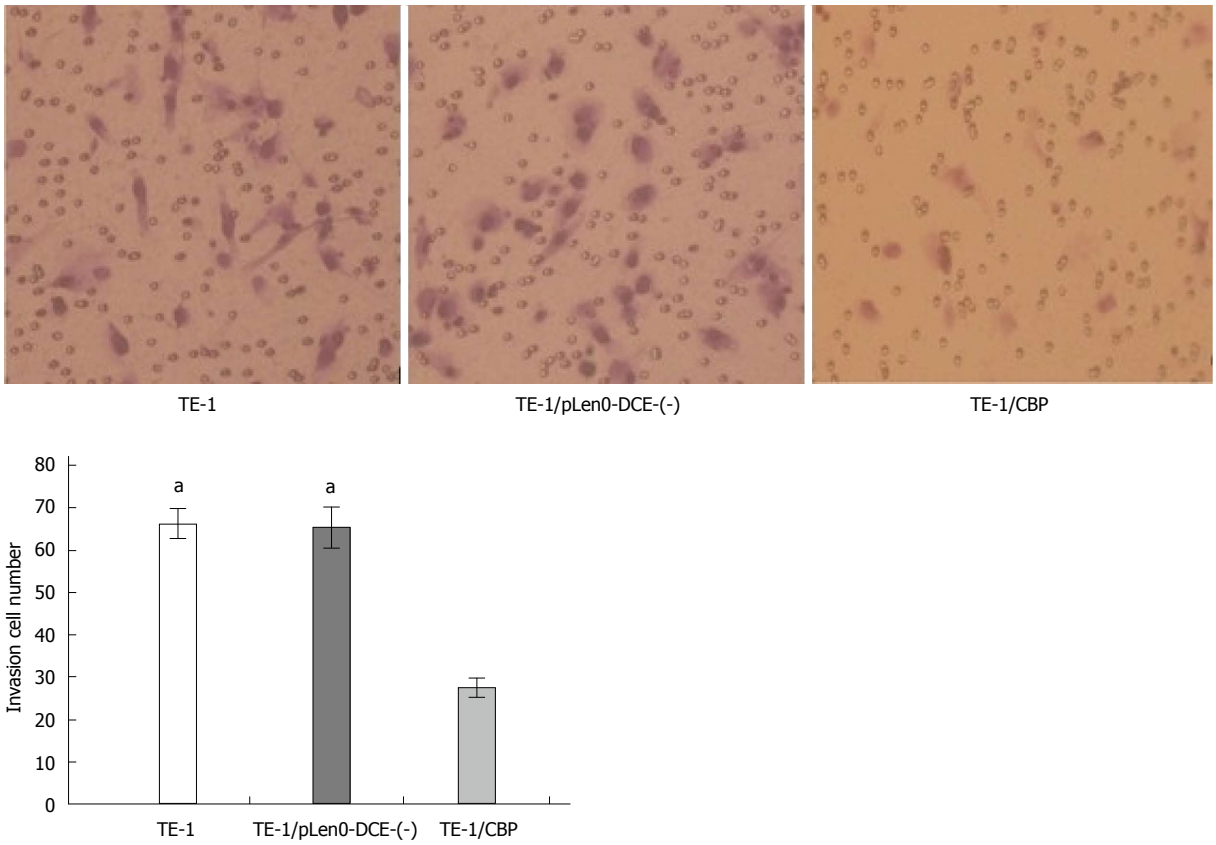

Figure 3 Invasion of TE-1, TE-1/pLenO-DCE-(-) and TE-1/Csk-binding protein cells. Trypan blue staining showed that TE-1, TE-1/pLenO-DCE-(-) and TE-1/CBP cells passed through the Matrigel (200×). [a]*P* < 0.05 *vs* TE-1/CBP cells, no significant difference compared with TE-1/pLenO-DCE-(-) cells.

of Src[1,2].

Overexpression of CBP inhibits the growth of TE-1 esophageal carcinoma cells

We assessed the cell growth of TE-1, pLenO-DCE-(-) vector transfected TE-1 (TE-1/pLenO-DCE) and CBP overexpressing TE-1 (TE-1/CBP) cells. As illustrated in Figure 2, compared with TE-1 and TE-1/pLenO-DCE cells, the cell growth of TE-1/CBP cells decreased significantly ($P < 0.05$) (Figure 2).

Overexpression of CBP decreases the invasion of TE-1 esophageal carcinoma cells

As illustrated in Figure 3, Transwell analysis showed that the numbers of TE-1 cells (62.2 ± 3.6) and TE-1/pLenO-DCE cells (65.4 ± 4.8) passing through the Matrigel were markedly higher than that of TE-1/CBP cells (27.6 ± 2.2) ($P < 0.05$) (Figure 3).

Overexpression of CBP decreases the migration of TE-1 esophageal carcinoma cells

As illustrated in Figure 4, scratch analysis showed that the distance of TE-1 cells (116.2 ± 6.4 μm) and TE-1/pLenO-DCE cells (122.4 ± 8.8 μm) migrating into the scratch was markedly greater than that of TE-1/CBP cells (66.6 ± 6.2 μm) ($P < 0.05$) (Figure 3).

DISCUSSION

CBP is weakly expressed in many types of human cancers, including non-small cell lung cancer[7], esophageal cancer[9], and head and neck squamous cell cancer[16], suggesting that CBP may play an important suppressive role in the progression, development, and invasion of cancers. Recently, we reported that the expression of CBP is down-regulated in esophageal carcinoma[9], but the functions of CBP in esophageal carcinoma remain undetermined. To investigate the role of CBP in esophageal carcinoma, we examined the alteration of cell growth, invasion and migration of esophageal carcinoma cells after overexpressing CBP.

We up-regulated the expression of CBP by transfection of TE-1 esophageal carcinoma cells with CBP constructs. Our data demonstrate that CBP overexpression resulted in a decrease in the growth, invasion, and migration of TE-1 cells. These findings indicate that CBP plays an important role in the suppression of tumor progression. Since tumor progression inhibition is a prerequisite for efficient tumor therapy[17,18], CBP might be a promising target for tumor therapy. Our data also indicate that controlling the activation of the Src pathway may be one of the underlying mechanisms by which CBP up-regulates

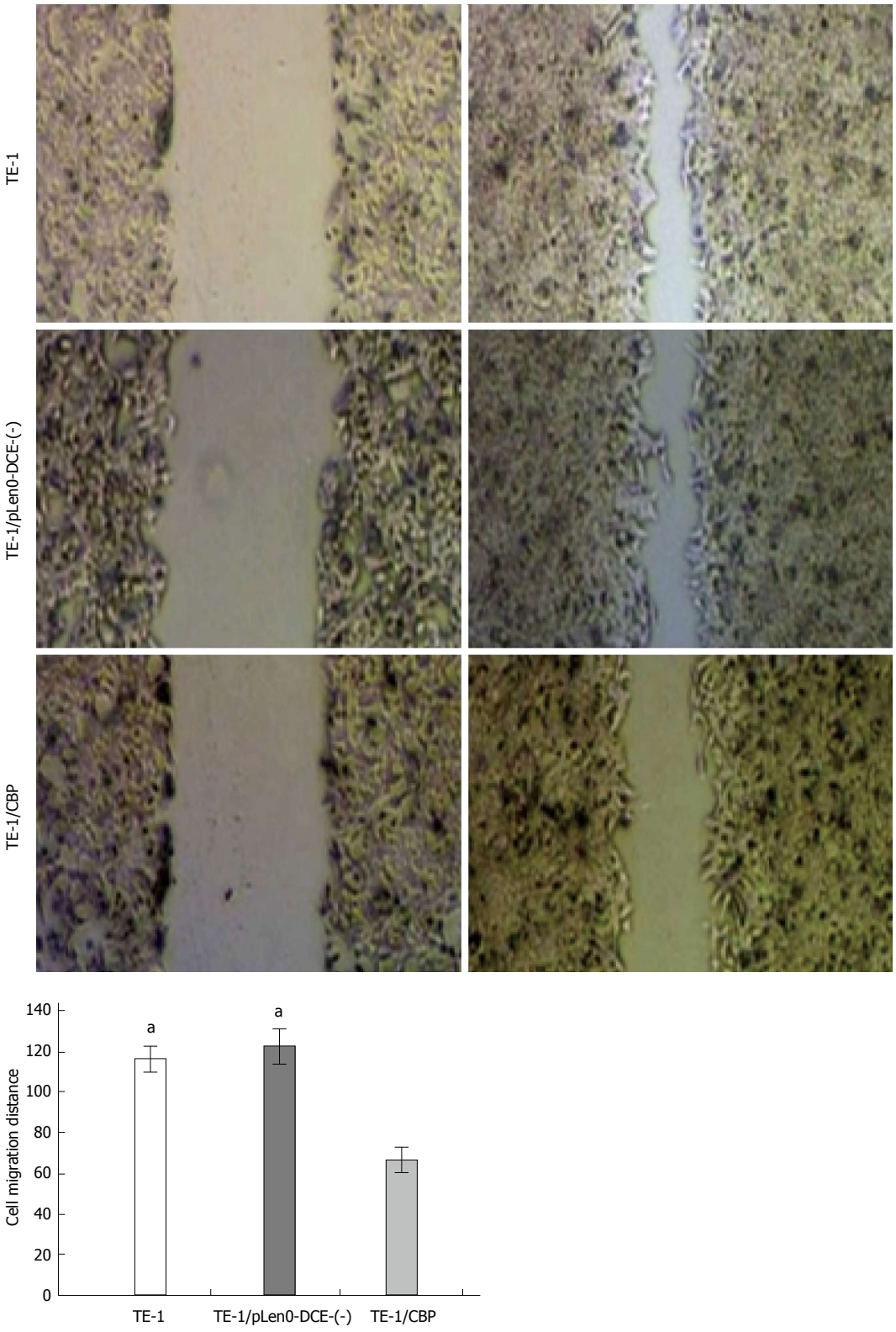

Figure 4 Migration of TE-1, TE-1/pLenO-DCE-(-) and TE-1/ Csk-binding protein cells. The scratch assay showed that TE-1, TE-1/pLenO-DCE-(-) and TE-1/CBP cells moved into the scratch (200×). The distance of cell migration was assessed. $^{a}P < 0.05$ *vs* TE-1/CBP cells, no significant difference compared with TE-1/pLenO-DCE-(-) cells.

the growth, invasion and migration of esophageal carcinoma cells.

Src signaling, a prominent cancer cell growth-promoting and invasion-promoting pathway[19,20], can be activated by receptor tyrosine kinases and integrins to promote the growth, migration, and invasion of tumor cells. Although many studies have demonstrated the role of CBP in promoting the inactivation of Src

signaling[1,2], we sought to investigate whether the up-regulation of CBP is able to decrease the growth, invasion, and migration of esophageal carcinoma cells through the inactivation of Src signaling. We found that CBP overexpression decreased the activity of Src in TE-1 esophageal carcinoma cells, and reduced esophageal carcinoma cell growth, invasion, and migration. Thus, we propose that CBP up-regulation decreases esophageal carcinoma progression, at least partially, through the inactivation of Src signaling. Further studies are needed to determine the molecular mechanism(s) by which CBP regulates Src signaling.

In summary, we demonstrated that CBP inhibits the growth, invasion, and migration of esophageal carcinoma cells by inactivating Src signaling, suggesting that CBP plays an important role in the inhibition of tumor progression and development of esophageal carcinoma. CBP as an effective target aiming to modulate Src signaling may be a reasonable approach to treating esophageal carcinoma.

COMMENTS

Background

Csk-binding protein (CBP) is a ubiquitously expressed transmembrane protein and functions as a suppressor of Src-mediated tumor progression by promoting the inactivation of Src. The authors previously reported that expression of CBP is markedly down-regulated in esophageal carcinoma; however, the mechanisms by which the down-regulation of CBP affects the progression of esophageal carcinoma remain unknown.

Research frontiers

Previous studies have suggested that CBP has an opposing role in various Csk-mediated cellular processes and might be a significant target in Csk-mediated tumors. CBP is weakly expressed in many types of human cancers, including non-small cell lung cancer, esophageal cancer, and head and neck squamous cell cancer, suggesting that CBP may play an important suppressive role in the progression, development, and invasion of cancers.

Innovations and breakthroughs

The authors have reported that the expression of CBP is down-regulated in esophageal carcinoma, but the functions of CBP in esophageal carcinoma remain to be determined. To investigate the role of CBP in esophageal carcinoma, the authors examined the alterations in the growth, invasion, and migration of esophageal carcinoma cells overexpressing CBP. The data demonstrate that CBP overexpression resulted in a decrease in the growth, invasion, and migration of TE-1 cells. These findings indicate that CBP plays an important role in suppressing tumor progression.

Applications

This study indicates that CBP plays an important role in the inhibition of tumor progression and the development of esophageal carcinoma. CBP as an effective target aiming to modulate Src signaling may be a reasonable approach to treating esophageal carcinoma.

Peer-review

This study indicates that CBP overexpression resulted in decreased growth, invasion, and migration of TE-1 cells. These findings indicate that CBP plays an important role in suppressing tumor progression. These findings are interesting, and overall the writing is good.

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