Overexpression of splicing factor poly(rC)-binding protein 1 elicits cycle arrest, apoptosis induction, and p73 splicing in human cervical carcinoma cells

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Abstract
Purpose Splicing factor poly(rC)-binding protein 1 (PCBP1) is a novel tumor suppressor that is downregulated in several cancers thereby regulating tumor formation and metastasis. However, the involvement of PCBP1 in apoptosis of cancer cells and the molecular mechanism remains elusive. On this basis, we sought to investigate the role of splicing factor PCBP1 in the apoptosis in human cervical cancer cells.

Methods To investigate PCBP1 functions in vitro, we overexpressed PCBP1 in human cervical cancer cells. A series of cytological function assays were employed to study the role of PCBP1 in cell proliferation, cell cycle arrest and apoptosis.

Results Overexpression of PCBP1 was found to greatly repress proliferation of HeLa cells in a time-dependent manner. It also induced a significant increase in G2/M phase arrest and apoptosis. Furthermore, overexpressed PCBP1 favored the production of long isoforms of p73, thereby inducing upregulated ratio of Bax/Bcl-2, the release of cytochrome c and the expression of caspase-3.

Conclusion Our results revealed that PCBP1 played a vital role in p73 splicing, cycle arrest and apoptosis induction in human cervical carcinoma cells. Targeting PCBP1 may be a potential therapeutic strategy for cervical cancer therapy.

Keywords PCBP1 · p73 · Splicing · Apoptosis · Cancer · Therapy

Abbreviations
PCBP1 Poly(rC)-binding protein 1
DNp73 N-terminally truncated p73
TAp73 Transactivating p73
EMT Epithelial-mesenchymal transition
CD44 Cluster differentiation-44
Bax Bcl-2-Associated X
Bcl-2 B-cell CLL/lymphoma 2

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Introduction

Cervical cancer ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women (Bray et al. 2018; Lu et al. 2019). Therefore, research on the pathogenesis and novel therapeutic target of Cervical cancer is crucial. PCBP1, a member of the poly-cytosine binding proteins (PCBPs) family, was firstly cloned from human lymphocyte cDNA library in 1994 (Aasheim et al. 1994). With the deepening of research in recent years, PCBP1 has been found to be ubiquitously expressed in many tissues and plays a multifunction role in various life activities, especially intracellular transcription and post-transcriptional regulation, including alternative splicing of pre-mRNA, mRNA stability and translation (Chaudhury et al. 2010; Choi et al. 2007). In recent years, an increasing body of researches focused on the relationship between PCBP1 and tumorigenesis (Silipo et al. 2015). Studies have found that PCBP1 could act as a tumor suppressor and its expression is significantly downregulated in various tumor types including gastric cancer (Ji et al. 2017), acute myeloid leukemia (Zhou and Tong 2015), non-small-cell lung cancer (Liu et al. 2015), cervical cancer (Pillai et al. 2003) et al. In general, PCBP1 plays a multifunctional role in tumor progress. For instance, overexpressed PCBP1 has been reported to induce cell apoptosis mediated by caspase-3 and caspase-8, and the level of activated caspase3 and PARP-1 in PCBP1-deficient cells were significantly lower than those in wild-type cells when treated with hydrogen peroxide (Zhang et al. 2016; Ishii et al. 2018a). Moreover, PCBP1 also involved in the alternative splicing regulation of multiple pre-mRNA, which dysregulation is usually implicated in genesis and development of multiple human diseases, especially cancers (Zhang et al. 2010; Jiang et al. 2017). Furthermore, PCBP1 negatively regulated the tumor hypoxic microenvironment and inhibited autophagy to further affect the tumor formation and development (Zhang et al. 2016; Nandal et al. 2011; Wang et al. 2010). In addition, it was reported that highly expressed PCBP1 might play an important role in preventing the process of EMT and metastasis in NSCLC (Liu et al. 2015). The above cases all turn out that PCBP1 is involved in the development of tumors as a tumor suppressor, but little information has been available on the molecular mechanisms by which PCBP1 causes cervical cancer apoptosis. In the present study, we present some preliminary data which might help to illustrate the mechanisms of PCBP1 on cervical cancer cells apoptosis and its roles in p73 alternative splicing regulation. In general terms, these results suggested that PCBP1 may be an attractive novel target for cervical cancer therapy.

Results

The expression of PCBP1 and its spatial distribution

To explore the underlying biological function of PCBP1, we initially transfected HeLa cells with pEGFP-N1 or pEGFP-N1-PCBP1, and then the test of qRT-PCR and immunofluorescence experiments were performed to verify a successful establishment of PCBP1 overexpressed model in Hela cells. In contrast with mock group, the mRNA expression of PCBP1 was significantly increased in Hela cells transfected with pEGFP-N1-PCBP1 (Fig. 1A). More importantly, there was no significant difference in mRNA expression between mock and vector group (Fig. 1A). In addition, immunofluorescence experiments results showed that the fluorescent intensity of PCBP1 in pEGFP-N1-PCBP1 group was higher than mock and vector group. PCBP1 is distributed in both the cytoplasm and the nucleus (Fig. 1B), indicating its multiple functions in the regulation of cell life activities (Fig. 1B).

The effect of overexpressed PCBP1 on human cervical carcinoma cells viability

To understand the effects of overexpressed PCBP1, the proliferation of HeLa cells in different time points after transfection was examined. MTS analysis proved that elevated PCBP1 significantly reduced the cell viability of HeLa cells and examined whether the reduction of PCBP1 could affect cell viability (Fig. S1A, B). It is showed that downregulation of PCBP1 had no significant effect in cell viability compared to control (Fig. S1C), which is contrary to the conclusion of overexpression of PCBP1.

PCBP1 induces cell cycle arrest and apoptosis

To elucidate the mechanism of the effect of overexpressed PCBP1, the nuclei were stained and the morphology were observed after transfection. The nuclear morphology of pEGFP-N1-PCBP1 group showed remarkable nuclear shrinkage and fragmentation as well as increased apoptotic bodies, which all represented the typical features of cells that undergoing apoptosis (Fig. 3A).

To elucidate the mechanism of PCBP1 in inhibiting the growth of HeLa cells, we used flow cytometry to detect the cell cycle progression and apoptosis. The results showed that overexpressed PCBP1 could cause a significant increase in the ratio of G2/M phase (Fig. 3B, D), which might contribute...
to the decreased cell viability in HeLa cells. Subsequently, flow cytometry was performed to prove that whether the decreased viability of PCBP1-overexpressed HeLa cells was caused by apoptosis. As shown in Fig. 3C, cells transfected with pEGFP-N1-PCBP1 for 48 h performed more apoptosis than the mock and vector group. The results were statistically analyzed and were further verified (Fig. 3E). However, we found that HeLa cells with decreased PCBP1 expression displayed no changes in cell apoptosis rate compared to controls (Fig. S2A).

**PCBP1 favors TAp73 splicing and induces the increase of TAp73/ΔNp73 ratio**

TAp73 has been reported play a vital role in the apoptosis of p53 impaired cervical cancer cells (Liu et al. 2006). The correlation analysis was limited to the number of clinical samples, and showed that increased positive cells of PCBP1 is probable a positive correlation with positive cells of TAp73 in different cancers especially in patients with CESC (Fig. 4A, B). To further demonstrate whether p73 is involved in PCBP1 induced cell cycle arrest and apoptosis in human cervical carcinoma cells, western blot and immunofluorescence were used to detect the level of TAp73 and ΔNp73 proteins. Contrast with the mock group, level of ΔNp73 was significantly reduced in pEGFP-N1-PCBP1 group at 24 h after transfection. Conversely, the level of TAp73 was increased compared with the mock group (Fig. 4C). Quantitative results showed that PCBP1 induced a significant increase in the ratio of TAp73/ΔNp73 (Fig. 4D). Furthermore, immunofluorescent was used to verify the spatiotemporal distribution of p73 splicing isoforms in Hela cells (Fig. 4E). As shown in Fig. 4E, the expression of ΔNp73 was clearly reduced but TAp73 expression obviously upregulated. Notably, TAp73 was mainly detected in the cytoplasm, however, ΔNp73 was mainly detected in the nucleus. Furthermore, the expression of anti-apoptotic isoforms ΔNp73 had significantly increased in the PCBP1 knockdown group at 48 h after transfection (Fig. S2B). Overall, these findings suggested that the switching of p73 splicing isoforms might involve in the cell cycle arrest and apoptosis of HeLa cells induced by PCBP1.

**PCBP1 regulates apoptosis through the intrinsic mitochondrial pathway**

We next examined the correlation between PCBP1 with some mitochondrial apoptosis pathway related genes across cancers. PCBP1 expression was shown to be favorably linked with apoptosis gene expression levels in a variety of tumor types, including CESC (Fig. 5A, B), indicating that overexpression of PCBP1 in patients with CESC might contribute to increased cell apoptosis. To further verify whether apoptosis induced by PCBP1 is associated with mitochondrial apoptosis pathway, western blot was used to examine the key proteins in the intrinsic apoptotic pathway.
As shown in Fig. 5, overexpression of PCBP1 upregulated the ratio of Bax/Bcl-2 to promote cell apoptosis (Fig. 5C, D). In addition, there was a substantial increase in the expression of cytochrome c at 24 h after transfected with pEGFP-N1-PCBP1 (Fig. 5A, E). Furthermore, decreased procaspase-3 and increased cleaved caspase-3 both indicated the occurrence of apoptosis (Fig. 5A, F). These data reveal that overexpression of PCBP1 could upregulate Bax/Bcl-2 ratio, promote cytochrome c release and activate caspase-3 expression, thereby inducing mitochondrial apoptosis.

**Discussion**

Cervical cancer is one of the foremost common cancers threatening women's health, however, the underlying pathogenesis of cervical cancer is still poorly understood. It is imminent to further study its pathogenesis (Shafabakhsh et al. 2019). PCBP1 is an evolutionarily conserved RNA-binding protein and is proven to regulate transcription, translation, and alternative splicing of genes (Chaudhury et al. 2010; Dejgaard and Leffers 1996; Chkheidze and Liebhaber 2003). Increasing evidence revealed that PCBP1 is significantly downregulated in gastric cancer (Ji et al. 2017), acute myeloid leukemia (Zhou and Tong 2015), non-small-cell lung cancer (Liu et al. 2015), cervical cancer et al (Pillai et al. 2003). Notably, recent studies have suggested that PCBP1 might act as a tumor suppressor in various tumors (Lu and Gao 2016; Barboro et al. 2014). For instance, Zhang et al. (2016) reported that overexpression of PCBP1 decreased the Bcl-2 expression and caused apoptosis of cancer cells. In addition, Shi et al. confirmed that PCBP1 could increase p27 expression via stabilizing its mRNA to facilitate cell apoptosis (Shi et al. 2018). Moreover, Ishii et al. reported that PCBP1 activated apoptosis through interacting with more severely oxidized RNA (Ishii et al. 2018b). Intriguingly, although PCBP1 has gained more and more attention due to its multiple functions in tumor progression, the mechanism still needs further exploration. Here, we transfected PCBP1 into HeLa cells and verified...
that overexpressed PCBP1 could greatly repress proliferation of HeLa cells in a time-dependent manner (Fig. 2). It also induced G2/M phase arrest and significant increase of the number of apoptotic cells (Fig. 3). In conclusion, these results indicated that elevated PCBP1 is an efficient way to inhibit tumor cell progression, which provides a reference for further understanding of the pathogenesis of cervical cancer.

Alternative splicing of pre-mRNA is a key step that contributes to proteomic and functional diversity of eukaryotes. A growing body of evidence have shown that aberrant splicing events were frequently found in human cancers and act as contributors of hallmarks of tumorigenesis including proliferation, metastasis and apoptosis evade (Guo and Jia 2019; Di et al. 2019; Baralle and Buratti 2017; Jin et al. 2020). To date, PCBP1 has been reported to be involved in alternative splicing regulation of multiple genes. In pancreatic cancer, upregulated PCBP1 could reduce tumor metastasis by interacting with integrin β1 to regulate its splicing (Jiang et al. 2017). Moreover, overexpression of PCBP1 inhibited the tumor invasion and metastasis in HepG2 cells via regulating exon inclusion of CD44 (Zhang et al. 2010). In the present study, we transfected PCBP1 into HeLa cells and indicated that overexpressed PCBP1 obviously enhanced the expression of TAp73 and decreased ΔNp73 expression (Fig. 4). TAp73 and ΔNp73 are two variants encoded by p73, which is a structural homolog of p53 and acts as a tumor suppressor (Lunghi et al. 2009; Holtkamp et al. 2007). This gene often encodes two opposing variants: the transcriptionally active TAp73 and the dominant-negative ΔNp73 (Melino et al. 2002). ΔNp73 overexpressed in a variety of cancers was reported to be correlated with poor prognosis (Prieto-Nieto et al. 2019; Gomez et al. 2018). Additionally, ΔNp73 can interact with wild-type p53 or TAp73 to efficiently counteract wild-type p53 and TAp73 mediated apoptosis and growth suppression (Zaika et al. 2002). However, TAp73 contains the NH2-terminal domain and plays a similar role to p53 as a tumor suppressor (Rodriguez et al. 2018; Tomasini et al. 2008). TAp73 is relevant to DNA damage response and exerts its apoptotic action on mitochondrial apoptosis.
signaling pathways through upregulating proapoptotic Bcl-2 family members (Muller et al. 2005). Recently, studies elucidated that the ratio of TAp73 and ∆Np73 might contribute to tumorigenesis, therapy resistance and cell fate decision (Lucena-Araujo et al. 2015). Our results showed that overexpressed PCBP1 is involved in p73 splicing through upregulating the ratio of TAp73/∆Np73 and cause apoptosis of HeLa cells (Fig. 4), which will have a certain inspiration for cancer treatment. Taken together, our data indicated that PCBP1 is an important tumor suppressor and means great significance to splicing targeted therapy of cervical cancer.

To further study the mechanism of PCBP1 induced apoptosis, we examined the expression of proteins related to intrinsic apoptosis pathways after transfection of PCBP1. Indeed, our data revealed that overexpression of PCBP1 significantly decreased the expression of Bcl-2 and increased the Bax/Bcl-2 ratio (Fig. 5). It has been confirmed that Bax/Bcl-2 ratio regulated cytochrome c release from mitochondria (Raisova et al. 2001; Kwak 2006). Therefore, we further detected the expression level of cytochrome c, which can activate the caspase-3 and the downstream cell death pathway. We discovered that cytochrome c levels were elevated, while procaspase-3 expression levels were significantly reduced. In light of our previous work, TAp73/∆Np73 ratio also plays an important role in regulating apoptosis via mitochondrial pathway (Di et al. 2015; Zhang et al. 2019). We suspect that PCBP1 may initiate a mitochondria-mediated apoptotic pathway by inducing TAp73 alternative splicing. Based on the above findings, we concluded that PCBP1 might play a pivotal role in cell cycle arrest, apoptosis regulation, as well as p73 splicing regulation of human cervical carcinoma cells. The induced splicing switch of p73 may be another downstream signaling pathway independent of p53 (Fig. 6). In conclusion, our results suggested that PCBP1 could be used as a potential candidate for cervical cancer therapy and it has broad prospects as a molecular therapeutic target for cervical cancer. However, this also requires the use of tumor-bearing animal models and clinical trials to further study the effects of PCBP1.

Materials and methods

Cell culture and transfection

The human cervical carcinoma HeLa cells were obtained from the First Hospital of Lanzhou University and cultured...
in Dulbecco’s modified Eagle’s medium (DMEM, Minghai Biochem, Lanzhou, China) supplemented with 10% fetal bovine serum (Minghai Biochem, Lanzhou, China) at a culture temperature of 37 °C, 5% CO₂ in incubator (Thermo, USA). DNA transfection was carried out using Exfect2000 transfection reagent (Vazyme, Nanjing, China) as a mediator according to the manufacturer’s instruction. The pEGFP-N1-PCBP1 and non-targeting negative control pEGFP-N1 was purchased from Invitrogen (Invitrogen Life Technologies, CA, USA). To transfect HeLa cells with plasmid vector, cells were plated into either 60 mm dish or a 100 mm dish and allowed to adhere for 24 h. Exfect2000 transfection reagent was utilized for the transfection. After pEGFP-N1 or pEGFP-N1-PCBP1 transfection, cells were

Fig. 5 Overexpression of PCBP1 induced apoptosis through mitochondrial pathway in human cervical carcinoma HeLa cells. A Analysis of correlation between indicated genes and PCBP1 expression by using TIMER database in different cancers. B Analysis of correlation between indicated genes and PCBP1 expression by using GEPIA database in CESC. C Western blot results. D Quantitative analysis of Bax/Bcl-2 ratio in HeLa cells. E Quantitative analysis of cytochrome c expression in HeLa cells. F Quantitative analysis of Cleaved caspase-3 expression in HeLa cells. All experiments were repeated at least three times. The data are expressed as the mean ± SD. ***P < 0.001 (vs. mock group). **P < 0.01 (vs. mock group)

Fig. 6 Schematic representation of PCBP1 mechanism in human cervical carcinoma HeLa cells. Overexpression of PCBP1 upregulated TAp73 and downregulated ΔNp73, and induced a significant increase in G2/M phase arrest and the ratio of Bax/Bcl-2, to further increased the release of cytochrome c and the expression of caspase-3
Cultured for 5 h and then the medium was replaced with fresh medium supplemented with 10% fetal bovine serum. Cells were harvested 24–48 h after transfection. To generate HeLa cells knocking-down PCBP1, cells were transfected with siRNAs for 24 or 48 h when grew to 50% confluence.

**Cell survival detection**

Cell viability was investigated using the methyl tetrazolium salt (MTS) assay. Cells were plated into 96-well plates (Promega, Beijing, China) and incubated 24 h. Then used transfection reagent to transfect pEGFP-N1 or pEGFP-N1-PCBP1 and cultured 24 h and 48 h to detect viability. 20 μl/well of MTS solution was added to each 100 μl of DMEM medium, and incubated for 60 min at a 37 °C constant temperature incubator. Then the absorbance was detected with multifunction microplate reader (Tecan Infinite M200, Swiss) at 490 nm. The survival rate of cells in each well was shown as a percentage of control.

**Quantitative RT-PCR analysis and agarose gel electrophoresis**

Total RNA was extracted from cells with TRizol reagent (Takara Biotech Co., Ltd.) and the complementary DNA (cDNA) was synthesized by using Transcriptor First Strand cDNA Synthesis System kit, real-time PCR analysis of PCBP1 and the reference gene β-Actin was treated by using a SYBR Green reaction kit (TIANGEN, China) in real-time PCR instrument (Thermo, USA), according to instruction. All experiments were carried out in triplicate and analyzed using the comparative threshold cycle ($2^{-ΔΔCT}$) method. Products were run in 1% agarose gel and the band intensity was scanned. The results were normalized by β-Actin levels.

**Colony formation assay**

The cells were harvested for 24 h after transfection, and seeded into 60 mm dishes. After incubated at 37 °C for 10–14 days, the culture was terminated when macroscopic clones appeared in the dishes. The clone was fixed with paraformaldehyde and stained with crystal violet. Count clones containing more than 50 cells, calculated clone formation rate and collected images. Each experiment was performed in triplicate.

**Cell cycle assay**

After pEGFP-N1 or pEGFP-N1-PCBP1 transfection and cultured for 24 h, cells were collected. Whole proteins were lysed from the cells using RIPA lysis buffer (Solarbio, China) added PMSF. Western blot analysis was performed according to standard procedures. Proteins were fractionated by 10% SDS-PAGE and transferred to a methanol activated PVDF membrane (GE Healthcare, Beijing, China). Antibodies against TAp73, ΔNp73 (Imgenex, San Diego, USA), β-Actin (Bioss, Beijing, China) and Bax, Bcl-2, Cytochrome c, procaspase-3, cleaved caspase-3 (Santa Cruz, CA, USA) were used according to the instruction. HRP-linked anti-mouse or anti-rabbit IgG antibodies (Bioss, Beijing, China) were used as secondary antibodies. The results were normalized by β-Actin levels.

**Immunofluorescence**

Cells were transfected with pEGFP-N1 or pEGFP-N1-PCBP1 and harvested at 48 h. First, cells were washed in 0.01 M PBS (pH 7.4), fixed with paraformaldehyde, propidium iodide (PI, Sigma, USA) was added after washing three times with PBS, and the cells were incubated for 30 min in the dark. The samples were collected with a minimum of 20,000 cells and analyzed with a flow cytometer FlowSight (Amnis, Seattle, WA, USA). The results were analyzed with FlowJo 7.6 software and each experiment was repeated at least three times.
permeabilized with 0.5% Triton X-100/PBS for 15 min on ice, and blocked with 5% BSA for 60 min at RT. Incubated with antibodies against PCBP1 (Santa Cruz, CA, USA) at 4 °C overnight, then added fluorescent secondary antibody and incubated at RT for 1 h in the dark. Finally, 0.01 M PBS was used to wash three times for 5 min each wash and DAPI was added. After added glycerol, the samples were detected with a confocal laser microscope (LSM, Carl Zeiss AG, Germany).

Statistical analysis

Data are presented as means ± SD. Statistical analysis were showed on the means of the data obtained from at least three independent experiments. Student’s t-tests program in Microsoft Excel was used to compare the differences between the mock group, vector group and the PCBP1 group. P < 0.05 was considered significant.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00432-022-04170-3.

Author contributions

YH Chen, ZH Dou, CX Di and HZ Hong and Q Li conceived the literature and wrote the initial draft of the manuscript. DP Zhao, TJ Che, W Su, T Qu, TT Zhang, CP Xu and HW Lei participated in writing the manuscript. All authors reviewed the manuscript.

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Data availability

The data presented in this study are available in the article.

Declarations

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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