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Original Article

LncRNA PTCSC3 suppressed cervical carcinoma cell invasion and proliferation via regulating miR-574-5p

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Abstract: LncRNAs have been shown to invovled in the development of various cancers. However, the function and potential mechanism of PTCSC3 in cervical carcinoma progression remains unknown. In this reference, we showed that PTCSC3 expression was downregulated in 4 cervical carcinoma cell lines (Caski, Siha, Hela and C4-1) compared to control cell line (GH329). Expression of PTCSC3 was downregulated in cervical carcinoma samples compared to non-cancerous samples. Ectopic expression of PTCSC3 inhibited miR-574-5p expression and enhanced the expression of SCAI both in Hela cell and Siha cell. We proved that the miR-574-5p expression was overexpressed in 4 cervical carcinoma cell lines (Caski, Siha, Hela and C4-1) compared to control cell line (GH329). Expression of miR-574-5p was overexpressed in cervical carcinoma samples compared to non-cancerous samples. Furthermore, we indicated that expression of miR-574-5p was negatively correlated with expression of PTCSC3 in cervical carcinoma. Ectopic expression of PTCSC3 decreased cell proliferation and invasion. Finally, we indicated that PTCSC3 overexpression suppressed cervical carcinoma progression via regulating miR-574-5p expression. These data suggested that PTCSC3 played as an oncogene in progression of cervical carcinoma.

Keywords: Cervical carcinoma, PTCSC3, miR-574-5p, lncRNA

Introduction

Cervical carcinoma ranks as the 3rd most common female malignancy worldwide, with recently raising incidence [1-5]. Human papillomavirus (HPV) was reported to be the most crucial etiological factor in cervical carcinoma [6-8]. However, studies indicated that the infection of HPV is insufficient to lead to tumorigenesis and genetic variations were also critical for the development of cervical carcinoma [9-12]. Despite the treatment such as radiotherapy, surgery and chemotherapy has been developmed, the five-year survival of advanced cervical carcinoma patients were not improved [11, 13, 14]. Thus, novel and effective cure methods are important to decrease mortality and impove survival of cervical carcinoma patients.

Long non-coding RNAs (lncRNAs, long ncRNAs) are longer than two hundred nucleotides and are have no or limitied protein coding capability with the ability to modulate gene expression at the expression level of chromatin transcription, modification and post-transcriptional [15-19]. Growing studies suggested that lncRNAs have authentic biological cell roles such as cell development, migration, pluripotency, cycle, apoptosis and invasion [20-24]. LncRNAs are found to be deregulated in several tumors including gastric tumor, endometrial carcinoma, lung cancer, esophageal squamous cell carcinoma and osteosarcoma [16, 25-28]. Recently, a novel lncRNA PTCSC3 was found to be involved in the development of various cancers [29-31]. For instance, Fan et al. found that PTCSC3 overexpression decreased thyroid cancer cell proliferation, cycle and promoted cell apoptosis [29]. Wang et al. also revealed that PTCSC3 expression was decreased in thyroid carcinoma cell and samples and PTCSC3 overexpression suppressed cell migration and proliferation via modulating Wnt/β-catenin expression [32]. In addition, Wang and their workmates showed that expression of PTCSC3 was decreased in breast cancer specimens and plasma and elevated expression of PTCSC3 inhibited breast cancer cell growth via suppressing H19 expres-

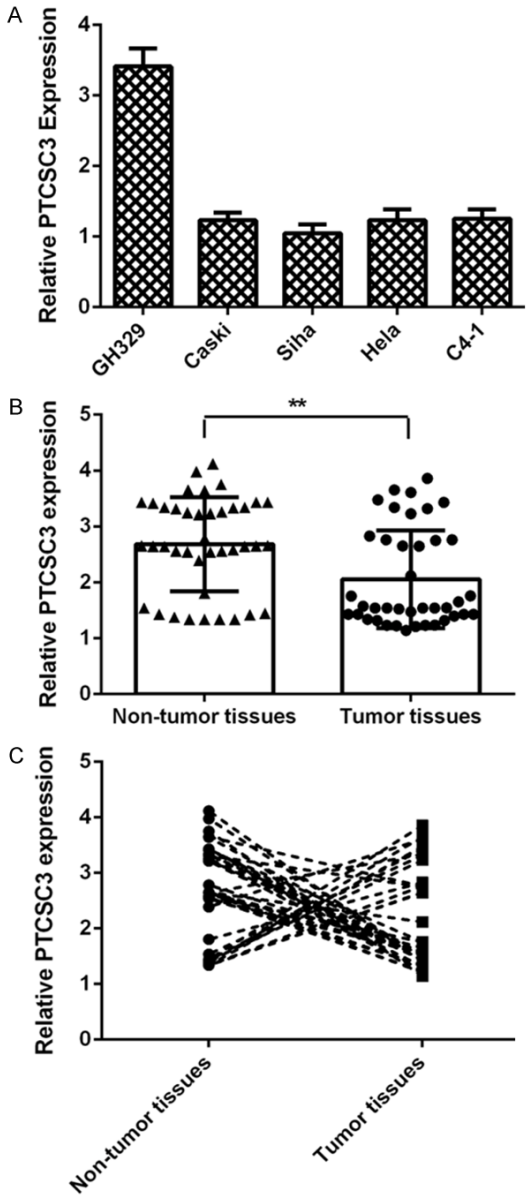

Figure 1. PTCSC3 expression was downregulated in cervical carcinoma. A. The expression of PTCSC3 in 4 cervical carcinoma cell lines (Caski, Siha, Hela and C4-1) and control cell line (GH329) was determined by qRT-PCR analysis. B. The PTCSC3 expression was determined in 40 cervical carcinoma samples and their adjacent non-cancerous samples via qRT-PCR. C. Of forty tissues, PTCSC3 was decreased in 28 patients (28/40, 70%) compared to non-cancerous samples. ***P<0.001.

sion [33]. However, the function and potential mechanism of PTCSC3 in cervical carcinoma progression remains unknown.

In this reference, we tried to study the function and potential mechanism of PTCSC3 in cervical carcinoma progression. We firstly showed that PTCSC3 expression was downregulated in cervical carcinoma cell lines and samples. Ectopic expression of PTCSC3 decreased cell proliferation and invasion.

Materials and methods

Cervical carcinoma tissue specimens and cell lines

A total of 40 pairs of cervical carcinoma samples and their adjacent no-tumor cervical tissues were obtained from Cangzhou central hospital (Cangzhou, Hebei, China). These samples specimens were rapidly frozen in the liquid nitrogen and stored until protein or RNA extraction. Informed consent was collected from all patients and ethics were approved by clinical Ethical Committee of Cangzhou central hospital. Cervical tumor cell lines (Caski, Siha, Hela and C4-1) and control cell line (GH329) were obtained from ATCC Company (Manassas, VA, USA). Cells were keplt in the RPMI-1640 medium (Gibco, USA) and 1% penicillin/streptomycin and fetal bovine serum were added into the medium. pcDNA3.1-PTCSC3 plasmid and pCDNA3.1-control vector; miR-574-5p and miR-NC were synthetized by Invitrogen (USA) and were transfected into cells by using Lipofectamine 3000 kit (Invitrogen, Carlsbad, USA).

Reverse transcription reactions and quantitative real-time PCR

Total RNA for lncRNA or miRNA assay was extracted from cells or tissues using TRIzol kit (Invitrogen, CA, USA) according to manufacturer's explanation. Complementary DNA (cDNA) was synthesized from 2 μg RNA. To quantify miRNA and lncRNA expression, qRT-PCR analysis was used using the ABI PRISM 7500 Sequence examination System (Applied Biosystems, Foster City, USA) with SYBR kit (TaKaRa, Dalian, China) following to the manufacturer's explanation. GAPDH or U6 was used as an endogenous control for the normalization. The relative expression level was determined by $2^{-\Delta\Delta Ct}$ method. The primers were used in this study shown as following: miR-574-5p, 5'-TCTGA GTGTG TGTGT GTG-3' and 5'-GACTG TTCCT CTCTT CCTC-3'. PTCSC3, 5'-GGCTT GAACA ATCTT CCCAC CTT-3' and 5'-TTTGG CAACA CCCTC ACAGA CAC-3'. GAPDH, 5'-GCGAA

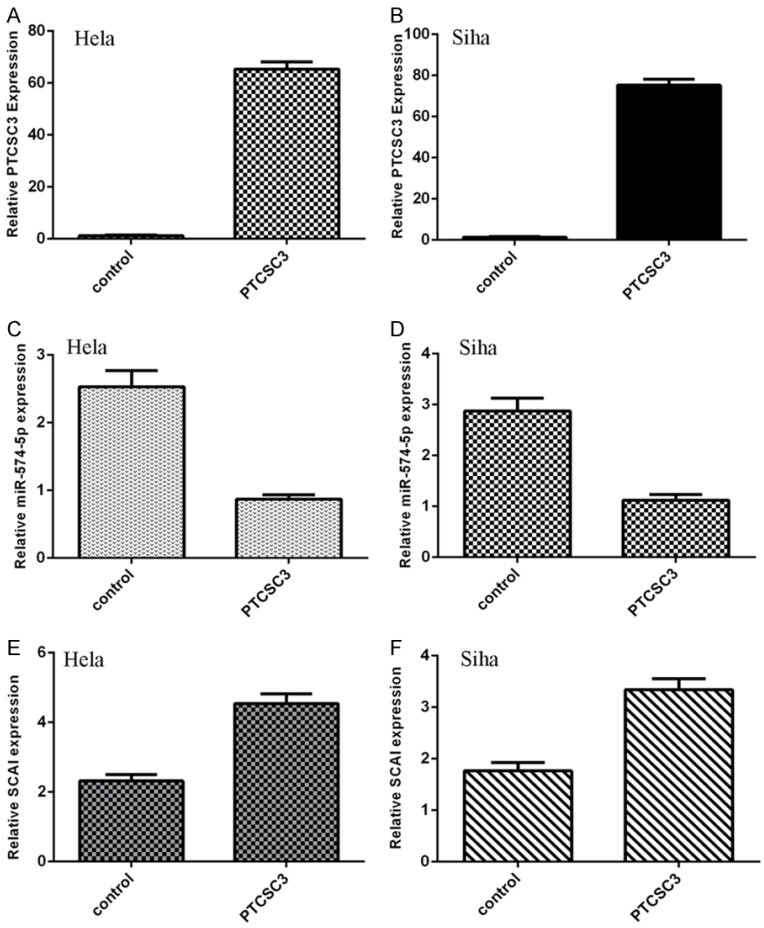

Figure 2. PTCSC3 overexpression suppressed miR-574-5p expression. A. The expression of PTCSC3 was measured in the Hela cell by qRT-PCR assay. B. The expression of PTCSC3 was measured in the Siha cell by qRT-PCR assay. C. Ectopic expression of PTCSC3 inhibited miR-574-5p expression in Hela cell. D. The expression of PTCSC3 was measured by qRT-PCR assay. E. The expression of SCAI was measured by qRT-PCR assay. F. The expression of SCAI was measured by qRT-PCR assay.

TTCCG TGTCC CCACT GCCAA CGTGTC-3'; and 5'-GCTAC TCGAG TTACT CCTTG GAGGC CATGT GG-3'.

Cell proliferation and invasion transwell assay

Cell proliferation analysis was performed by utilizing Cell Counting kit-8 (CCK-8, Dojindo, Janpan) following to explanations. Cells were cultured in the 96-well plate and were incubated with CCK-8 solution at the 37°C for 3 hours. The absorbance at the 450 nm was determined by using spectrophotometer (Thermo Fisher Scientific). For cell invasion, transwell chamber was applied. Cells were plated in upper chamber transwell with coating Matrigel and 10% FBS was added into bottom chamber. Invaded cell was fixed by methanol and stained and then counted.

Statistical analysis

Results were expressed as means ± SD (standard deviation) and $P<0.05$ was considered to be statistically significant. The significant difference between two groups was assessed with Student's t test. All statistical analysis was performed using SPSS 18.0 software system.

Results

PTCSC3 expression was downregulated in cervical carcinoma

Firstly, we proved that the PTCSC3 expression was downregulated in 4 cervical carcinoma cell lines (Caski, Siha, Hela and C4-1) compared to control cell line (GH329) (**Figure 1A**). As indicated in **Figure 1B**, the PTCSC3 expression was determined in 40 cervical carcinoma samples and their adjacent non-cancerous samples via qRT-PCR. Expression of PTCSC3 was downregulated in cervical carcinoma samples compared to non-cancerous samples. Of forty tissues, PTCSC3 was decreased in 28 patients (28/40, 70%) compared to non-cancerous samples (**Figure 1C**).

PTCSC3 overexpression suppressed miR-574-5p expression

The transfection efficiency of pcDNA-PTCSC3 vector was detected by qRT-PCR assay. It has shown that PTCSC3 expression was overexpressed in the Hela cell (**Figure 2A**) and Siha cell (**Figure 2B**) after transfection with pcDNA-PTCSC3 vector. Ectopic expression of PTCSC3 inhibited miR-574-5p expression both in Hela cell (**Figure 2C**) and Siha cell (**Figure 2D**). Moreover, overexpression of PTCSC3 enhanced

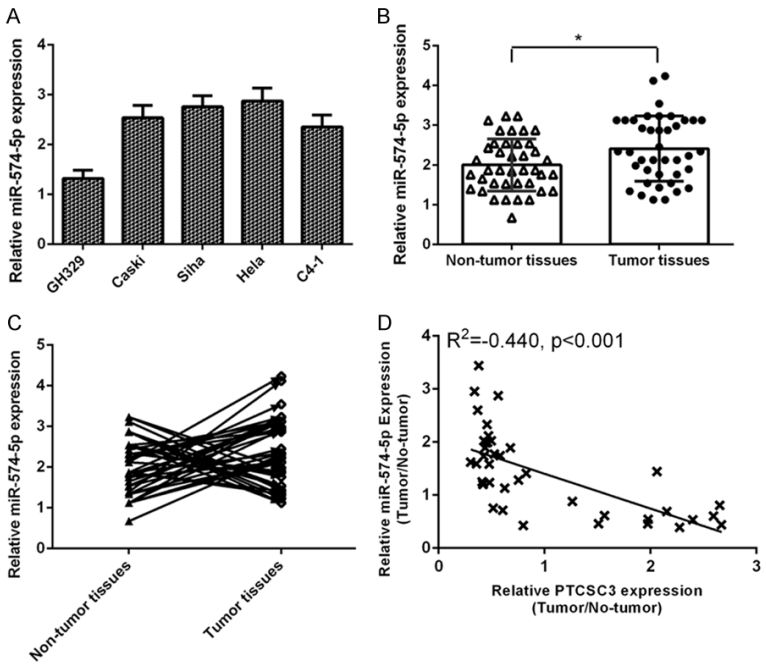

Figure 3. The expression of miR-574-5p was overexpressed in cervical carcinoma. A. The miR-574-5p expression in 4 cervical carcinoma cell lines (Caski, Siha, Hela and C4-1) and control cell line (GH329) was determined by qRT-PCR analysis. B. The miR-574-5p expression was determined in 40 cervical carcinoma samples and their adjacent non-cancerous samples via qRT-PCR. C. Of forty tissues, miR-574-5p was increased in 26 patients (26/40, 65%) compared to non-cancerous samples. D. Expression of miR-574-5p was negatively correlated with expression of PTCSC3 in cervical carcinoma. *P<0.05.

the expression of SCAI both in Hela cell (**Figure 2E**) and Siha cell (**Figure 2F**).

The expression of miR-574-5p was overexpressed in cervical carcinoma

Then, we proved that the miR-574-5p expression was overexpressed in 4 cervical carcinoma cell lines (Caski, Siha, Hela and C4-1) compared to control cell line (GH329) (**Figure 3A**). As indicated in **Figure 3B**, the miR-574-5p expression was determined in 40 cervical carcinoma samples and their adjacent non-cancerous samples via qRT-PCR. Expression of miR-574-5p was overexpressed in cervical carcinoma samples compared to non-cancerous samples. Of forty tissues, miR-574-5p was increased in 26 patients (26/40, 65%) compared to non-cancerous samples (**Figure 3C**). Furthermore, we indicated that expression of miR-574-5p was negatively correlated with expression of PTCSC3 in cervical carcinoma (**Figure 3D**).

The influences of PTCSC3 overexpression on cell proliferation and cell invasion

CCK-8 and transwell invasion assay were performed to measure cell proliferatin and invasion ability. As indicated in **Figure 4A** and **4B**, ectopic expression of PTCSC3 decreased cell proliferation both in Hela cell and Siha cell. Overexpression of PTCSC3 inhibited the cyclin D1 expression in Hela cell (**Figure 4C**) and Siha cell (**Figure 4D**). In addition, PTCSC3 overexpression decreased the Hela cell invasion (**Figure 4E**). Ectopic expression of PTCSC3 suppressed the Siha cell invasion (**Figure 4F**).

PTCSC3 overexpression suppressed cervical carcinoma progression via regulating miR-574-5p

Thus, we carried out rescue experiments to study whether PTCSC3 overexpression suppressed cervical carcinoma progression via regulating miR-574-5p. As indicated in the **Figure 5A**, miR-574-5p expression was overexpressed in the Hela cell after transfection with pcDNA-PTCSC3 vector. According to result of CCK-8, we showed that overexpression of miR-574-5p enhanced cell growth in the PTCSC3-overexpressing Hela cell (**Figure 5B**). In addition, ectopic expression of miR-574-5p promoted the cyclin D1 expression in the PTCSC3-overexpressing Hela cell (**Figure 5C**). Elevated expression of miR-574-5p induced cell invasion in the PTCSC3-overexpressing Hela cell (**Figure 5D** and **5E**).

Discussion

In this reference, we tried to study the function and potential mechanism of PTCSC3 in cervical carcinoma progression. We firstly showed that PTCSC3 expression was downregulated in 4 cervical carcinoma cell lines (Caski, Siha, Hela and C4-1) compared to control cell line

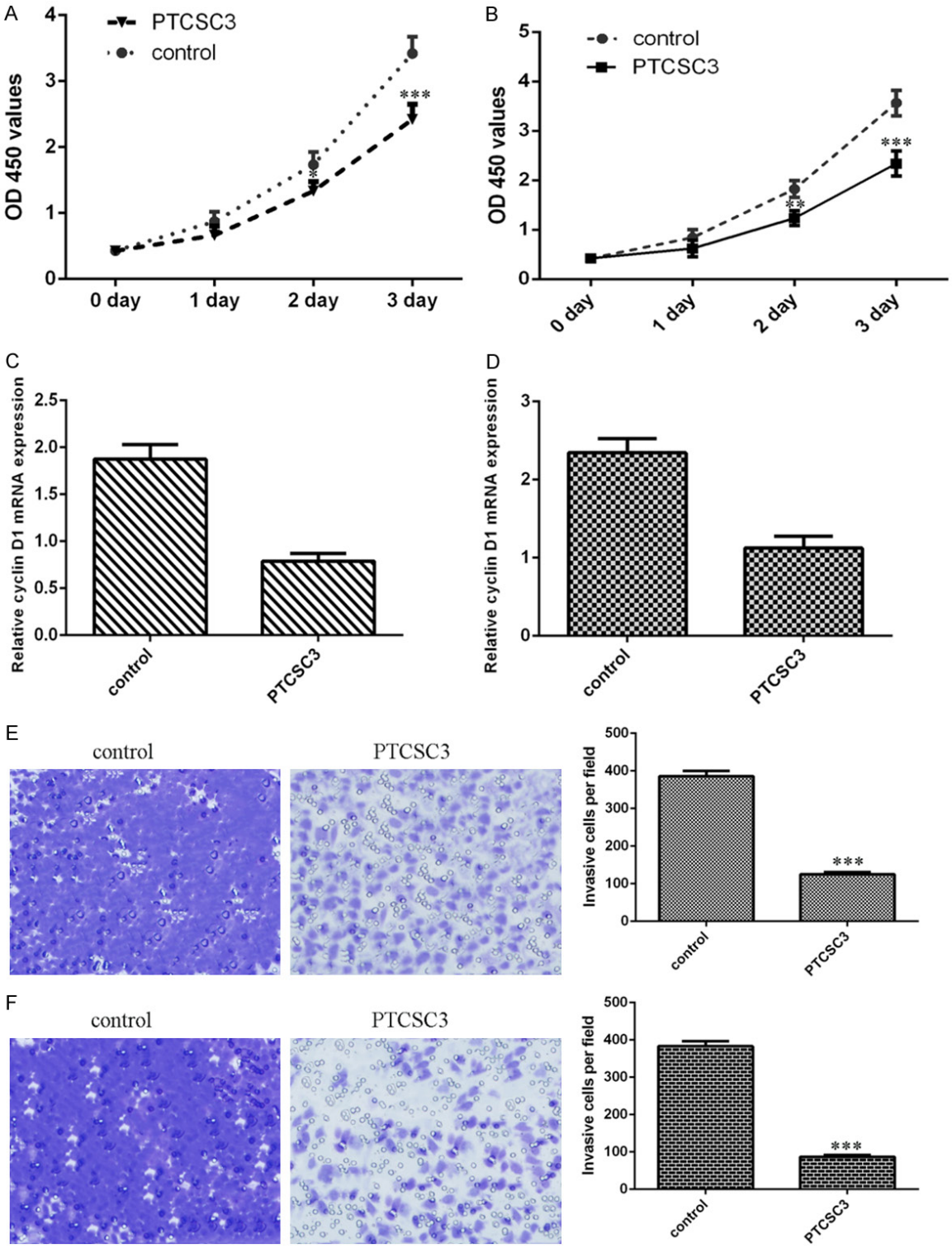

Figure 4. The influences of PTCSC3 overexpression on cell proliferation and cell invasion. A. Ectopic expression of PTCSC3 decreased cell proliferation in Hela cell. B. Elevated expression of PTCSC3 decreased cell proliferation in Siha cell. C. Overexpression of PTCSC3 inhibited the cyclin D1 expression in Hela cell. D. The expression of cyclin D1 was measured by qRT-PCR analysis. E. PTCSC3 overexpression decreased the Hela cell invasion. F. Ectopic expression of PTCSC3 suppressed the Siha cell invasion. *P<0.05, **P<0.01 and ***P<0.001.

(GH329). Expression of PTCSC3 was downregulated in cervical carcinoma samples compared to non-cancerous samples. Ectopic expression of PTCSC3 inhibited miR-574-5p ex-

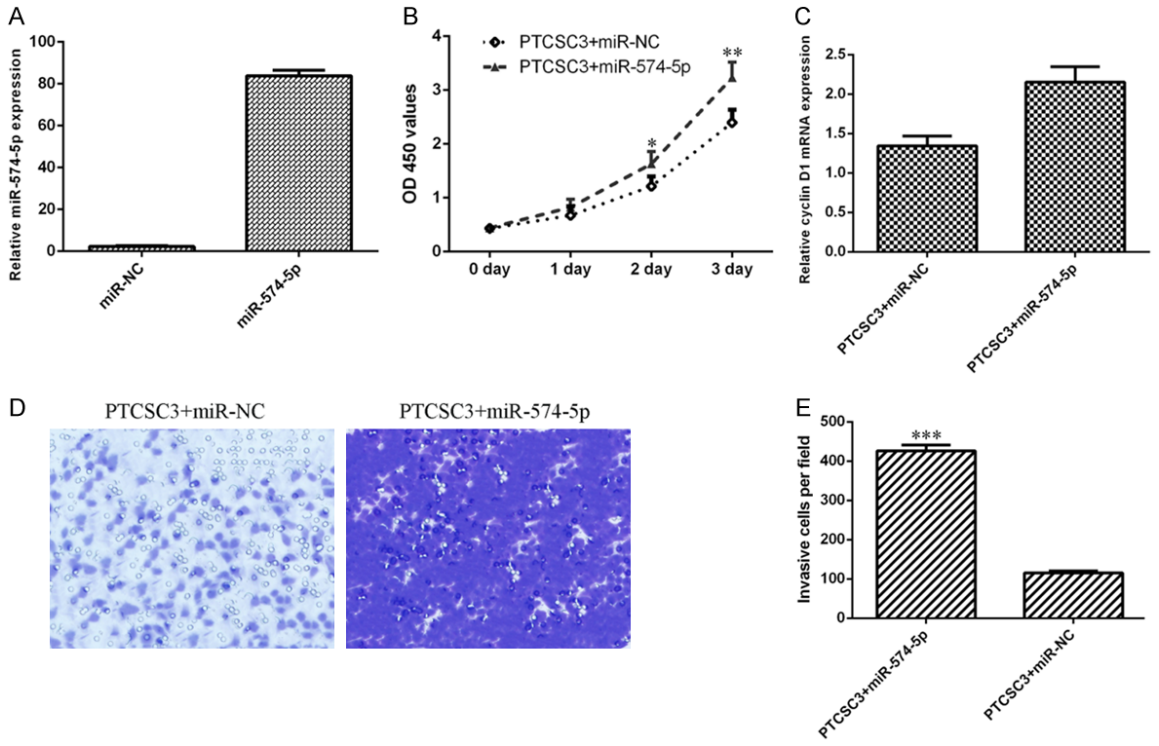

Figure 5. PTCSC3 overexpression suppressed cervical carcinoma progression via regulating miR-574-5p. A. The expression of miR-574-5p was detected by qRT-PCR analysis. B. The cell proliferation was determined by CCK-8 assay. C. Ectopic expression of miR-574-5p promoted the cyclin D1 expression in the PTCSC3-overexpressing Hela cell. D. Elevated expression of miR-574-5p induced cell invasion in the PTCSC3-overexpressing Hela cell. E. The relative invasive cells were shown. *P<0.05, **P<0.01 and ***P<0.001.

pression and enhanced the expression of SCAI both in Hela cell and Siha cell. We proved that the miR-574-5p expression was overexpressed in 4 cervical carcinoma cell lines (Caski, Siha, Hela and C4-1) compared to control cell line (GH329). Expression of miR-574-5p was overexpressed in cervical carcinoma samples compared to non-cancerous samples. Furthermore, we indicated that expression of miR-574-5p was negatively correlated with expression of PTCSC3 in cervical carcinoma. Ectopic expression of PTCSC3 decreased cell proliferation and invasion. Finally, we indicated that PTCSC3 overexpression suppressed cervical carcinoma progression via regulating miR-574-5p expression. These data suggested that PTCSC3 played as an oncogene in progression of cervical carcinoma.

Nowadays, increasing studies indicated that upregulation or downregulation of lncRNAs acted critical functions in development and progression of several tumors [22, 34, 35]. Recently, a new lncRNA PTCSC3 was found to be involved in the development of various tumors [29-32, 36]. For instance, Fan et al. found that PTCSC3 overexpression suppressed thyroid cancer cell proliferation, cycle and induced cell apoptosis [29]. Wang et al. [32]. also revealed that PTCSC3 expression was downregulated in thyroid carcinoma cell and samples and PTCSC3 overexpression inhibited cell migration and proliferation via modulating Wnt/β-catenin expression. In addition, Wang and their workmates showed that expression of PTCSC3 was decreased in breast cancer specimens and plasma and ectopic expression of PTCSC3 inhibited breast cancer cell growth via suppressing H19 expression [33]. However, the function and potential mechanism of PTCSC3 in cervical carcinoma progression remains unknown. In this reference, we firstly showed that PTCSC3 expression was downregulated in 4 cervical carcinoma cell lines (Caski, Siha, Hela and C4-1) compared to control cell line (GH329). Then, the PTCSC3 expression was determined in 40 cervical carcinoma samples and their adjacent non-cancerous samples via qRT-PCR. Expression of PTCSC3 was downregulated in cervical carcinoma samples com-

pared to non-cancerous samples. Of forty tissues, PTCSC3 was decreased in 28 patients (28/40, 70%) compared to non-cancerous samples. Ectopic expression of PTCSC3 decreased cell proliferation and invasion.

Accumulating references suggested that lncRNAs played as ceRNAs via binding with these miRNAs [37-39]. For examples, lncRNA XIST has been found to induce cervical carcinoma progression through inducing Fus expression via binding with the miR-200a [40]. Xu et al. [41]. found that lncRNA RP11-552M11.4 induced cervical carcinoma development and tumorigenesis through regulating miR-3941 expression. Dai et al. showed that lncRNA WT1-AS supressed cervical cancer cell aggressiveness through modulating miR-203a-5p expression [42]. Wang et al. found that PTCSC3 decreased papillary thyroid carcinoma cell migration and growth via regulating miR-574-5p expression [32]. In line with this, we proved that ectopic expression of PTCSC3 inhibited miR-574-5p expression and enhanced the expression of SCAI both in Hela cell and Siha cell. Previous research demonstrated that expression of miR-574-5p was upregulated in cervical cancer samples and ultraviolet irradiation supressed miR-574-5p expression in the HeLa cell [43]. In our research, we revealed that miR-574-5p expression was overexpressed in 4 cervical carcinoma cell lines (Caski, Siha, Hela and C4-1) compared to control cell line (GH329). Expression of miR-574-5p was overexpressed in cervical carcinoma samples compared to non-cancerous samples. Furthermore, we indicated that expression of miR-574-5p was negatively correlated with exprression of PTCSC3 in cervical carcinoma. PTCSC3 overexpression suppressed cervical carcinoma progression via regulating miR-574-5p expression.

In summary, we indicated that expression of PTCSC3 was downregulated in cervical carcinoma cell and samples and PTCSC3 overexpression suppressed cervical carcinoma progression via regulating miR-574-5p expression. These data suggested that PTCSC3 played as an oncogene in progression of cervical carcinoma.

Disclosure of conflict of interest

None.

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