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ORIGINAL RESEARCH

RETRACTED ARTICLE: Oncolytic Vaccinia Virus-Mediated Antitumor Effect and Cell Proliferation Were Promoted in PTC by Regulating circRNA_103598/miR-23a-3p/IL-6 Axis

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Background: Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancy, and cases have been rising steadily worldwide in the past few decades. Despite great progress having been made in surgery and chemotherapy for PTC, the survival rate of PTC patients has not increased significantly. Therefore, there is an urgent need to explore novel treatment strategies.

Materials and Methods: The levels of circRNA_103598, miR-23a-3p and IL-6 mRNA in PTC tissues and cells were examined by qRT-PCR assay. Cell proliferation and IC_{50} values of oncolytic vaccinia virus (OVV) were detected by CCK-8 assay. A dual-luciferase reporter assay was performed to detect the relationships among circRNA_103598, miR-23a-3p and IL-6. ELISA was carried out to detect the expression of IL-6.

Results: We found that circRNA_103598 was increased in PTC tissues and cell lines and acted as a sponge for miR-23a-3p. Moreover, knockdown of miR-23a-3p suppressed the OVV-mediated antitumor effect and cell proliferation in PTC. In addition, we revealed that circRNA_103598 bound to miR-23a-3p as a sponge to promote IL-6 expression.

Conclusion: Our study first revealed the high expression and oncogenic function of circRNA_103598 in PTC cells. Then, circRNA_103598 sponged miR-23a-3p to upregulate IL-6 expression, with the resulted that cell proliferation was promoted and the OVV-mediated antitumor effect was enhanced by strengthening the viral replication, providing new insights into future therapy for PTC.

Keywords: OVV, cell proliferation, circRNA_103598, miR-23a-3p, IL-6, PTC

Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancy, and cases have been rising steadily worldwide in the past few decades.[1] Despite great progress having been made in surgery and chemotherapy for PTC, the survival rate of PTC patients has not increased significantly.[2,3] Therefore, there is an urgent need to explore novel treatment strategies.

Many reports have revealed the regulatory mechanisms of non-coding RNAs (ncRNAs) involved in the progression of cancer.[4–7] Circular RNAs (circRNAs) have been identified in various human cells, especially in tumor cells.[8,9] For example, circRNA circ_0067934 promotes tumor growth and metastasis in hepatocellular carcinoma through regulation of the miR-1324/FZD5/Wnt/β-catenin

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axis,[10] circRNA fibroblast growth factor receptor 3 promotes tumor progression in non-small cell lung cancer by regulating Galectin-1-AKT/ERK1/2 signaling,[11] while circRNA cRAPGEF5 inhibits the growth and metastasis of renal cell carcinoma via the miR-27a-3p/TXNIP pathway.[12] In addition, it has been found that circRNAs are associated with multidrug resistance in tumors. For example, circRNA PVT1 modulates cell metastasis via the miR-181a-5p/NEK7 axis and cisplatin chemoresistance through miR-181a-5p-mediated autophagy in non-small cell lung cancer,[13] and circRNA EIF6 sponges miR-144-3p to promote the cisplatin resistance of human thyroid carcinoma cells by autophagy regulation.[14] However, circRNAs have rarely been studied in oncolytic viruses. It has been found that oncolytic viruses exhibit superior antitumor effects in cancer treatment.[15,16] Therefore, it is of great significance to explore the relationship between circRNAs and oncolytic viruses.

In this work, we identified a novel circRNA (circRNA_103598) by analyzing the GEO database, and found the circRNA_103598 was upregulated in PTC tissues compared to non-tumor tissues. We also found that cell proliferation and oncolytic vaccinia virus (OVV)-mediated antitumor effects were promoted in PTC [illegible] regulating the circRNA_103598/miR-23a-3p/IL-6 axis. Thus, this study will provide new and important [illegible]ecular targets for the diagnosis and treatment of PTC.

Materials and Methods

Clinical Samples and Cells

Tumor tissues and aired normal tumor (with [illegible]5 cm around tumors) tissues were collected from 100 PTC patients who received surgery at Shanxi Provincial People's Hospital from April 2015 to June 2019. All patients provided written informed consent. The Institutional Ethical Committee of Shanxi Provincial People's Hospital approved all aspects of the study.

PTC cell lines (BHP5-16, TPC-1, BHP2-7 and BCPAP) and normal human thyroid follicular epithelial cells (Nthy-ori-3-1) were purchased from the Cell Bank of Type Culture Collection (Shanghai City, China). All cells were cultured in DMEM (Gibco, USA) with 10% fetal bovine serum (FBS; Gibco, USA) and 1% penicillin (Sigma-Aldrich, St Louis, MO, USA)/streptomycin (Enpromise, Hangzhou, China). All cells were maintained at 37°C in a humidified chamber supplemented with 5% CO_2.

Cell Transfection

The shRNA against circRNA_103598 (sh-circRNA_103598: 5′-CACCGCACCCACGTTTCTCCTTGGACG AATCCAAGGAGAAACGTGGGTGC-3′) was synthesized by GenePharma (Shanghai, China). BHP5-16 or TPC-1 cells in six-well plates were transfected with sh-circRNA_103598 or pcDNA3.1-IL-6 using Lipofectamine 2000 reagent (Invitrogen) according to the manufacturer's instructions.

RNA Isolation and Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) Assay

Total RNA was isolated from PTC tumor tissues and cells based on the established protocol of TRIzol reagent (Thermo Fisher Scientific). The PrimeScript RT reagent kit (Takara Bio, Japan) was used to synthesize the cDNA, which was subjected to qRT-PCR in the presence of iQ™ SYBR® Green Supermix (Bio-Rad Laboratories, Philadelphia, PA, USA). The results were calculated with the $2^{-\Delta\Delta Ct}$ method with normalization to GAPDH. The qRT-PCR primers used were as follows: circRNA_103598 forward: 5′-GAGA TTTATTCTCCCAGGGAATC-3′, reverse: 5′-ACCATCCA GATACCCATGAAGG-3′; IL-6 forward: 5′-GAAAACA CCAGGGTCAGCAT-3′, reverse: 5′-CAGCCACTGGTTT TTCTGCT-3′; GAPDH forward: 5′-ACAACTTTGGTAT CGTGGAAGG-3′, reverse: 5′-GCCATCACGCCACAGTT TC-3′.

Cell Proliferation Assay

Cell proliferation was detected using the Cell Counting Kit-8 (CCK-8, ab228554; Abcam) assay according to the manufacturer's instructions. PTC cells were seeded into 96-well plates (5000 cells per well). After being cultivated in the incubator for 24, 48 and 72 h, cells were incubated with 10 μL CCK-8 reagent for 4 h. Finally, OD values were measured at 450 nm.

Nude Mouse Xenograft Assay

Ten female BALB/c nude mice (18–20 g, 4–5 weeks old) were obtained from the Shanghai Lab Animal Research Center (Shanghai, China). TPC-1 cells were injected subcutaneously into the posterior flank of BALB/c nude mice according to the Guide for the Care and Use of Laboratory Animals of the US National Institutes of Health. Animal protocols were approved by the Institutional Animal Care and Use Committee of Tongde Hospital of Zhejiang

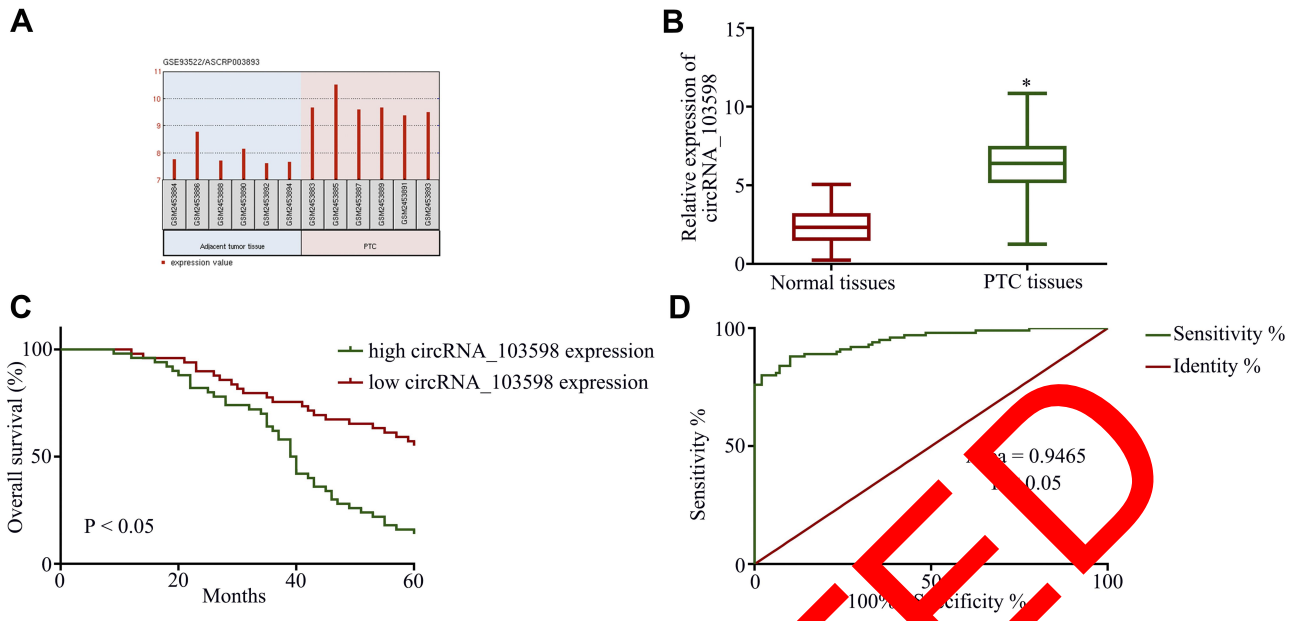

Figure 1 Clinical significance of circRNA_103598 in indicating PTC progression. (**A**) circRNA_103598 was highly expressed in PTC tissues. (**B**) qRT-PCR assay of circRNA_103598 expression in PTC tissues and normal tissues. (**C**) Kaplan–Meier overall survival curves for 100 patients with PTC classified according to relative circRNA_103598 expression level. (**D**) Expression level of circRNA_103598 had potential clinical significance as a tumor biomarker by the receiver operating characteristics (ROC) curve. *p<0.05.

Province. Tumor volumes were measured according to the formula: Volume (mm^3) = 1/2 × $width^2$ × length.

IC_{50} Assay

Cell viability was detected using the CCK-8 (ab228554, Abcam) assay according to the manufacturer's instructions. PTC cells were seeded into 96-well plates (5000 cells per well) and treated with vaccinia virus. After being cultivated in the incubator for 48 h, cells were incubated with 10 μL CCK-8 reagent for 4 h. Finally, OD values were measured at 450 nm.

Dual-Luciferase Reporter Assay

BHP5-16 or TPC-1 cells were plated in a six-well plate. Then, BHP5-16 or TPC-1 cells were co-transfected with reporter vectors and the indicated transfection plasmids for 48 h, and finally examined by the dual-luciferase reporter assay system (Promega) according to the manufacturer's instructions.

ELISA

IL-6 expression was detected using IL-6 ELISA kits (R&D Systems, Minnesota, USA) according to the manufacturer's instructions.

OVV Replication

BHP5-16 or TPC-1 cells were plated in 24-well plate, then treated with OVV at 1 MOI. After 6, 12, 24 and 48 h, cells and medium were collected and virus yield was examined by the TCID50 assay in HEK293 cells according to the manufacturer's instructions.

Statistical Analysis

All data were collected from at least three independent biological replicates and were expressed as mean ± SD (standard deviation). Difference analysis was performed by the Student's t-test (comparison for two groups) using GraphPad Prism 7 software (GraphPad, La Jolla, CA, USA). Values of p<0.05 were statistically significant.

Results

Clinical Significance of circRNA_103598 in Indicating PTC Progression

To begin with, the GEO data set (GSE93522) for circRNAs was analyzed from PTC tissues using the bioinformatics tool GEO2R, and circRNA_103598 was found to be highly expressed in PTC tissues (Figure 1A). In addition, circRNA_103598 was noticeably increased in PTC tissues (n=100) compared with the adjacent normal tissues (Figure 1B). As summarized in Table 1, high

Table 1 Correlation Between Clinicopathological Features and circRNA_103598 Expression in 100 Cases of PTC Tissues

Characteristics	circRNA_103598		*p*
	Low	High	
Age (years)			0.649
≤57	29	23	
>57	21	27	
Gender			0.523
Male	26	22	
Female	24	28	
Tumor size			<0.05
<5 cm	36	15	
≥5 cm	14	35	
TNM stage			<0.05
I–II	39	13	
III–IV	11	37	
Metastasis status			<0.05
No	37	12	
Yes	13	38	

expression of circRNA_103598 was associated with metastasis status, TNM stage and tumor size, while there was no significant relationship with gender and ag Moreover, Kaplan–Meier survival analysis revealed tha the patients with high expression of circRN 03598 had lower overall survival rates than th e wit low expression of circRNA_103598 (Fig 1C circRNA_103598 expression level h pote l clinical significance as a tumor biomarke the receiv perating characteristics (ROC) curve (Figur D). These results revealed that circRNA_10 98 may play role in the development of PTC.

CircRNA_103598 Knockdown Inhibited Cell Proliferation and OVV-Mediated Antitumor Effect in PTC

Owing to the hi r expression of circRNA_103598 in BHP5-16 or TPC-1 cells, they were chosen for further functional analysis (Figure 2A). Applying the back-splice junction-specific shRNAs (sh-circRNA_103598), we successfully knocked down circRNA_103598 expression in BHP5-16 or TPC-1 cells (Figure 2B). As analyzed in cell proliferation and nude mouse xenograft assays, knockdown of circRNA_103598 remarkably suppressed the proliferation of PTC cells in vitro (Figure 2C) and in vivo (Figure 2D). In addition, the mice with knockdown of circRNA_103598 had higher overall survival rates (Figure 2E). Furthermore, we found that knockdown of circRNA_103598 significantly decreased the IC_{50} value of OVV in PTC (Figure 2F), suggesting that OVV exhibited a better antitumor effect in PTC cells with high circRNA_103598 expression. Thus, circRNA_103598 knockdown inhibited cell proliferation and the OVV-mediated antitumor effect in PTC.

CircRNA_103598 Promoted Cell Proliferation and OVV-Mediated Antitumor Effect in PTC via Sponging miR-23a-3p

Considering that circRNAs may sponge miRNAs, we investigated the candidate miRNAs of circRNA_103598. The online software miRBase and Circinteractome were used to predict the potential target of circRNA_103598. The putative binding sites between circRNA_103598 and miR-23a-3p and the mutant sequence of circRNA_103598 are described in Figure Thus, t confirm this prediction, the circRNA_103598 sequence with a miR-23a-3p binding site was inserted downstream of a luciferase gene to construct the pluc- circRNA_103598 vector for the dual-luciferase reporter assay. The ts showed that luciferase activity of BHP5-16 or C-1 cells in the circRNA_103598-WT group was markably reduced by the introduction of miR-23a-3p, but ot significant in the circRNA_103598-MUT group (Figure 3B). In addition, miR-23a-3p expression was significantly promoted by knockdown of circRNA_103598 in BHP5-16 or TPC-1 cells (Figure 3C). Furthermore, miR-23a-3p expression was noticeably decreased in PTC tissues and was negatively correlated with circRNA_103598 expression (Figure 3D and E). Functionally, the suppression of PTC cell proliferation and decreased IC_{50} value of OVV caused by silencing circRNA_103598 could be reversed by transfecting miR-23a-3p inhibitor (Figure 3F and G), suggesting that circRNA_103598 promoted cell proliferation and OVV-mediated antitumor effect in PTC via sponging miR-23a-3p.

OVV-Mediated Antitumor Effect and Cell Proliferation Were Promoted in PTC by Regulating circRNA_103598/miR-23a-3p/IL-6 Axis

To elucidate the underlying network of miR-23a-3p in PTC, bioinformatics analysis was conducted to predict the potential target. The putative binding sites between IL-6 and miR-23a-3p are shown in Figure 4A. Subsequently, the

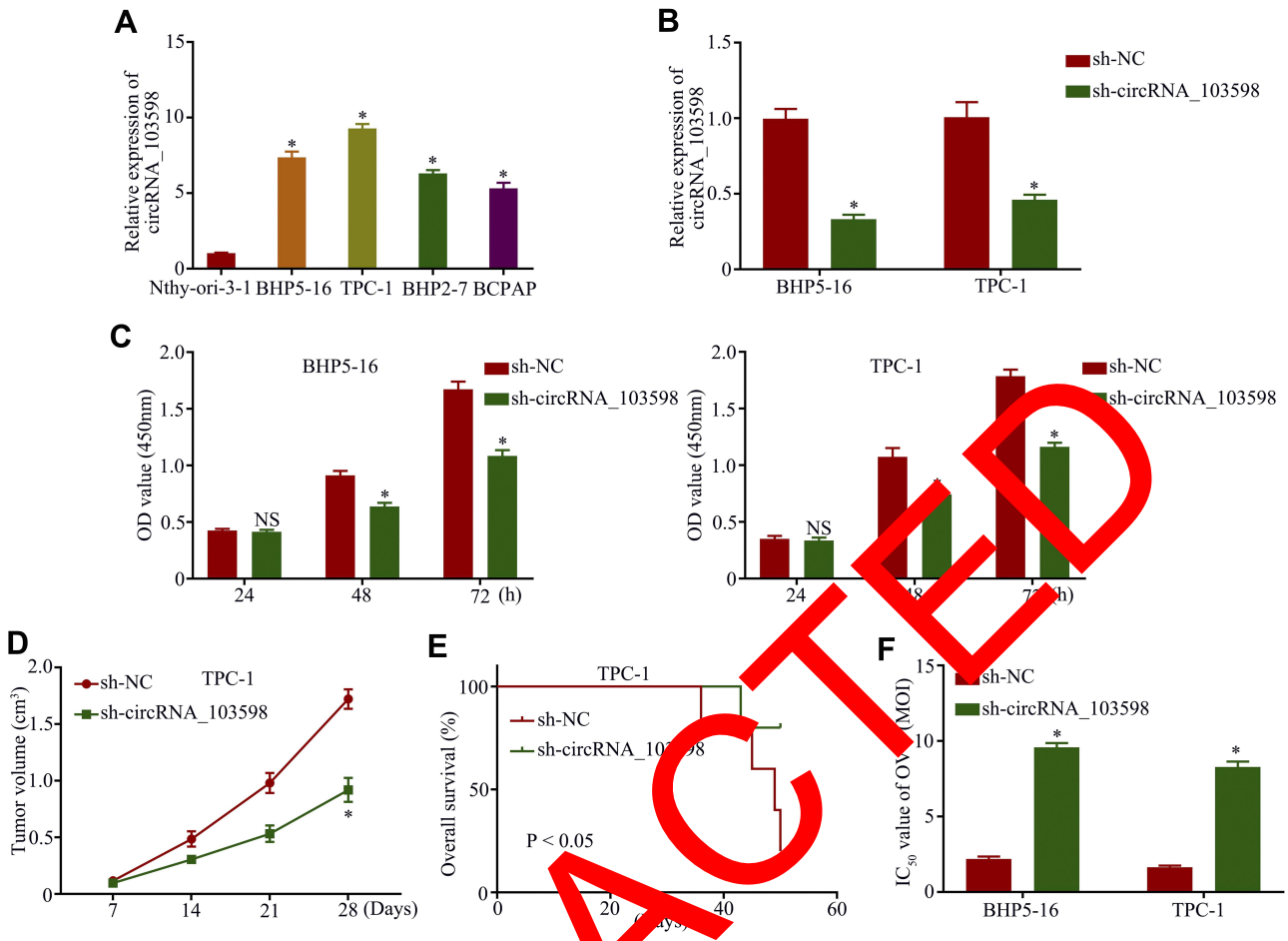

Figure 2 Knockdown of circRNA_103598 inhibited cell proliferation and OVV-mediated antitumor effect in PTC. (**A**) qRT-PCR analysis of circRNA_103598 expression in PTC cells. (**B**) The relative expression of circRNA_103598 in BHP5-16 and TPC-1 cells was detected by qRT-PCR assay after transfection with circRNA_103598. (**C**) Cell proliferation in BHP5-16 and TPC-1 cells was examined by CCK-8 assay. (**D**) circRNA_103598 knockdown decreased tumor volume in nude mice. (**E**) Mice with knockdown of circRNA_103598 had higher overall survival rate. (**F**) Knockdown of circRNA_103598 significantly decreased IC_{50} values of OVV in PTC. *p<0.05.

dual-luciferase reporter assay indicated that luciferase activity of BHP5-16 or TPC-1 cells in the IL-6-WT group was remarkably reduced by the introduction of miR-23a-3p, but not significantly the IL-6-MUT group (Figure 4B). In addition, the qRT-PCR assay (Figure 4C) and ELISA (Figure 4F) revealed that IL-6 expression was remarkably decreased by transfecting miR-23a-3p mimic and was significantly increased by transfecting IL-6 in BHP5-16 or TPC-1 cells, and IL-6 expression was noticeably increased in PTC tissues (Figure 4E). IL-6 expression was negatively correlated with miR-23a-3p expression (Figure 4F) and showed a positive trend with circRNA_103598 expression (Figure 4G). Functionally, PTC cell proliferation (Figure 4H) and the IC_{50} value of OVV (Figure 4I) in HP5-16 or TPC-1 cells could be suppressed by transfecting miR-23a-3p mimic, which was abrogated by transfecting IL-6. Moreover, the viral replication of OVV in HP5-16 or TPC-1 cells could be inhibited by transfecting miR-23a-3p mimic, which was reversed by transfecting IL-6, suggesingd that the OVV-mediated antitumor effect was promoted by regulating circRNA_103598/miR-23a-3p/IL-6 axis-mediated viral replication (Figure 4J).

Discussion

In the study of the molecular mechanisms of PTC, a lot of attention has been focused on miRNA, lncRNAs and protein-coding genes, whereas circRNAs, which act as cancer drivers, are not well illustrated in terms of their expression or potential molecular mechanism. PTC-involved circRNAs such as circRNA_102171,[17] circBACH2[18] and circZFR[19] were indicated to enhance the invasion, migration and proliferation capacities of PTC cells. In this study, we first found that circRNA_103598 expression was remarkably increased in PTC tissues and cells. Knockdown of circRNA_103598 significantly suppressed PTC cell proliferation in vitro and in vivo. Moreover, high expression of circRNA_103598 was

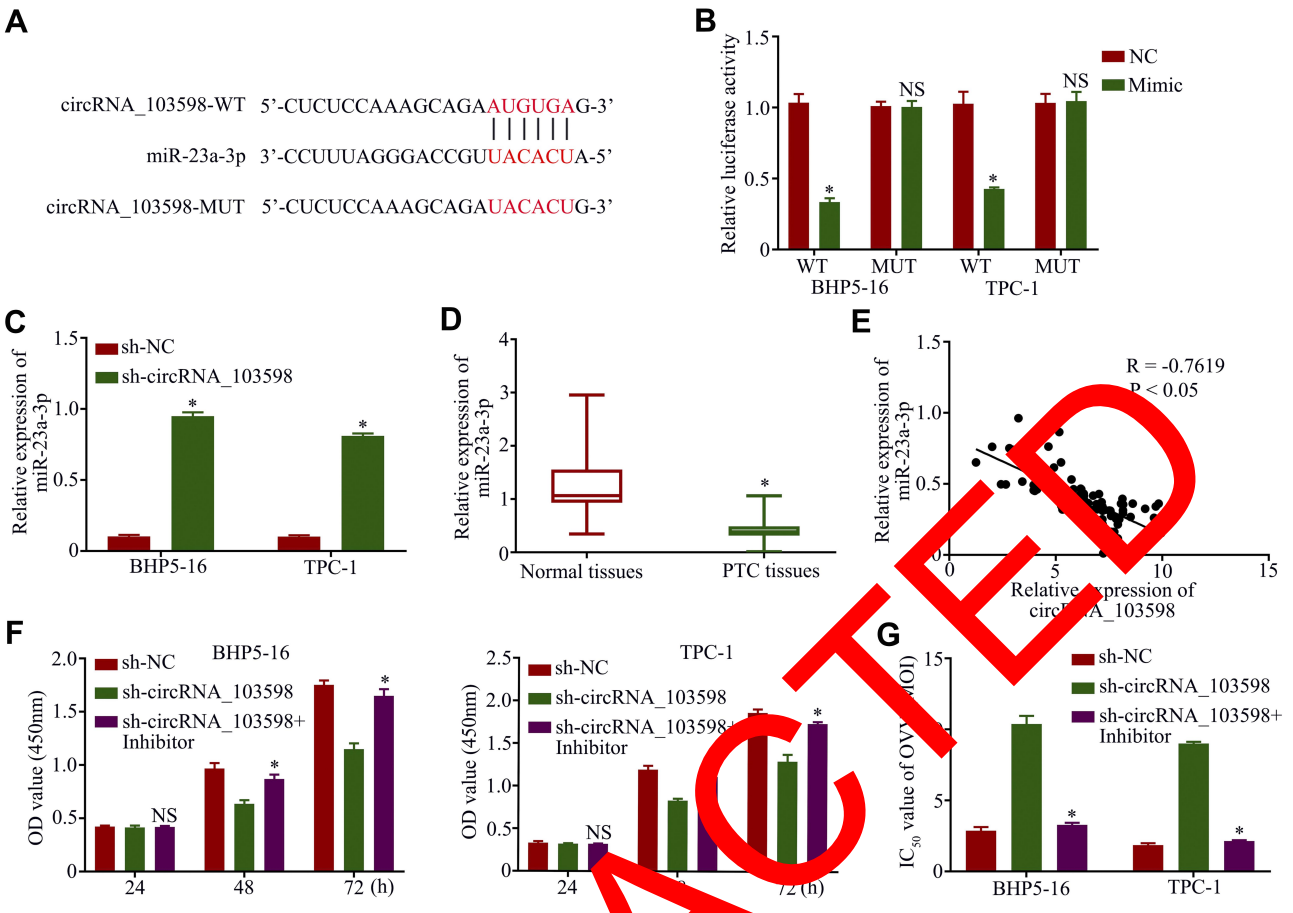

Figure 3 Circular RNA_103598 promoted cell proliferation and OVV-mediated antitumor effect in PTC via sponging miR-23a-3p. (**A**) Potential targeting sites of circRNA_103598 and miR-23a-3p. (**B**) Relative luciferase activity of luciferase reporter assay. (**C**) Expression of miR-23a-3p was increased by silencing circRNA_103598 in BHP5-16 and TPC-1 cells. (**D**) qRT-PCR assay of miR-23a-3p expression in PTC tissues and normal tissues. (**E**) Expression of miR-23a-33p was negatively correlated with circRNA_103598 expression. Suppression of PTC cell proliferation (**F**) and decreased IC_{50} values of OVV (**G**) caused by silencing circRNA_103598 could be reversed by transfecting miR-23a-3p inhibitor. *p<0.05.

associated with metastasis status, TNM stage, tumor size and survival rates, implying that circRNA_103598 may act as a tumor biomarker in PTC.

A previous study revealed that circRNAs can act as ceRNAs (competing endogenous RNAs) of miRNAs to suppress the function of miRNAs on target genes. For example, circRNA_100269 is downregulated in gastric cancer and suppresses tumor cell growth by targeting miR-630.[9] Comprehensive circRNA profiling revealed the regulatory role of the circRNA-000911/miR-449a pathway in breast carcinogenesis.[20] circC3P1 suppresses hepatocellular carcinoma growth and metastasis through the miR-4641/PCK1 pathway.[21] In this study, the bioinformatics prediction combined with the dual-luciferase reporter assay revealed that circRNA_103598 acts as an endogenous sponge by binding miR-23a-3p. Moreover, we first found that IL-6 is a direct target for miR-23a-3p. Some studies have indicated that low expression of miR-23a-3p and overexpression of IL-6 can contribute to tumor growth.[22,23] Thus, cell proliferation was promoted in PTC by regulating the circRNA_103598/miR-23a-3p/IL-6 axis.

Earlier studies showed that overexpression of IL-6 enhances multidrug resistance in tumor treatment. For example, inhibition of IL-6 enhances chemosensitization in multidrug-resistant human breast cancer cells.[24] Tumor-derived mesenchymal-stem-cell-secreted IL-6 enhances resistance to cisplatin via the STAT3 pathway in breast cancer.[25] Another study showed inhibition of the IL-6–Stat3 pathway and reversal of Taxol and cisplatin resistance in drug-resistant ovarian cancer cell lines by a synthetic triterpenoid CDDO-Me.[26] Thus, exploration of a novel therapy strategy in PTC is urgently needed, and we found that the OVV-mediated antitumor effect was enhanced in PTC by regulating the circRNA_103598/miR-23a-3p/IL-6 axis. Therefore, this study may help to establish a therapeutic strategy for PTC according to circRNA_103598 expression.

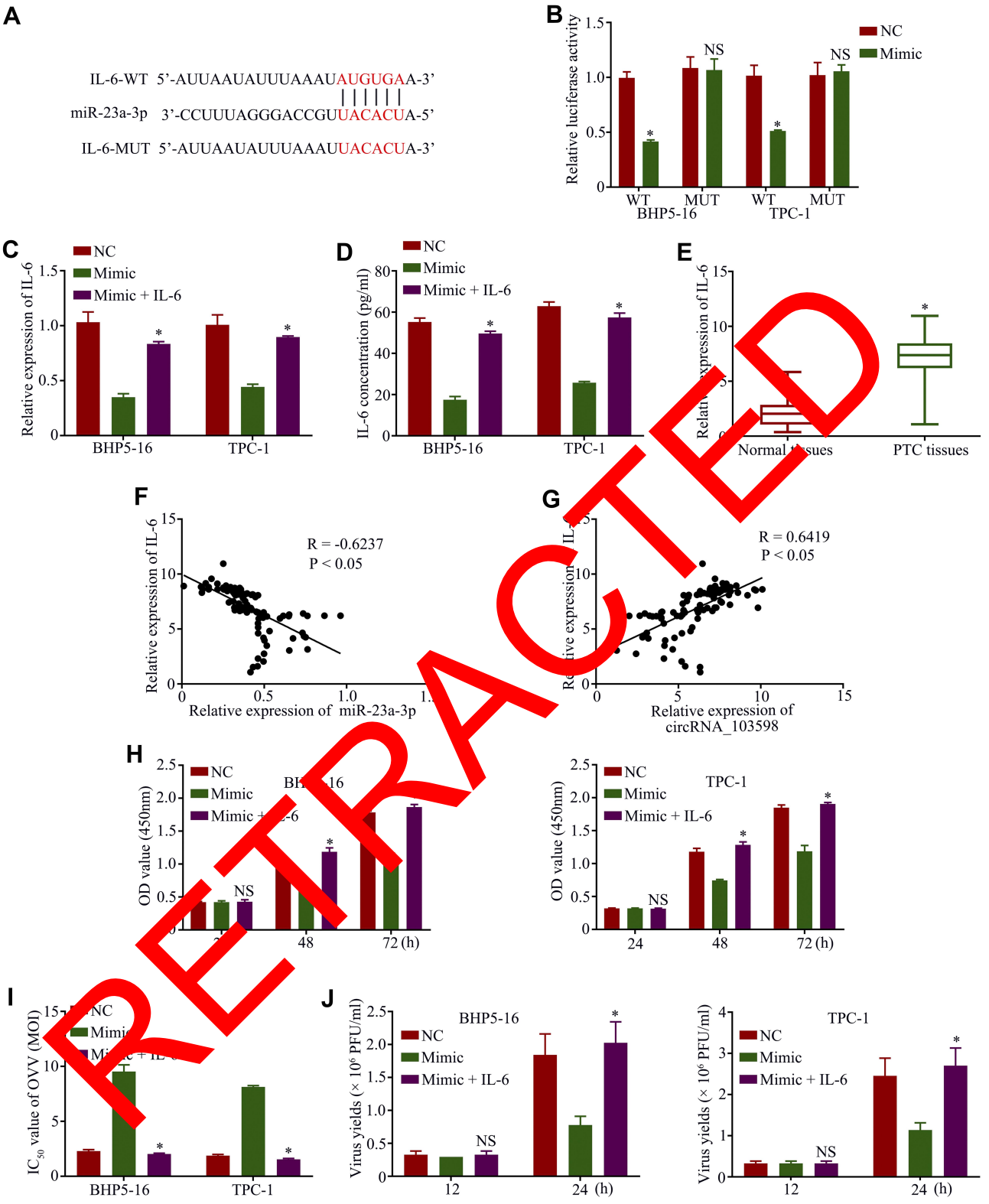

Figure 4 OVV-mediated antitumor effect and cell proliferation were promoted in PTC by regulating the circRNA_103598/miR-23a-3p/IL-6 axis. (**A**) Potential targeting sites of IL-6 and miR-23a-3p. (**B**) Relative luciferase activity–dual luciferase report assay. IL-6 expression was detected by qRT-PCR assay (**C**) and ELISA (**D**). (**E**) qRT-PCR assay of IL-6 expression in PTC tissues and normal tissues. (**F**) The expression of miR-23a-33p was negatively correlated with IL-6 expression. (**G**) Expression of circRNA_103598 showed a positive trend with circRNA_103598 expression. (**H**) Cell proliferation in BHP5-16 and TPC-1 cells was examined by CCK-8 assay. (**I**) IC_{50} values of OVV in BHP5-16 and TPC-1 cells were detected by CCK-8 assay. (**J**) The viral replication of OVV in HP5-16 or TPC-1 cells was examined by TCID50 assay. *p<0.05.

Conclusions

Our study first revealed the high expression and oncogenic function of circRNA_103598 in PTC cells. Then, circRNA_103598 sponged miR-23a-3p to upregulate IL-6 expression, with the result that cell proliferation was promoted and the OVV-mediated antitumor effect was enhanced by strengthening the viral replication, providing new insights into future therapy for PTC.

Disclosure

The authors report no conflicts of interest in this work.

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