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Original Article

Expression and clinical significance of TTK in cervical cancer

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Abstract: Background: The purpose of this study was to investigate the expression levels of monopolar spindle 1 (TTK, also termed MPS1) protein kinase in patients with cervical cancer and to explore whether TTK could be used for a prognosis factor for cervical cancer. Materials and methods: We analyzed the expression level of TTK in cervical cancer and normal tissue by using GEO dataset of NCBI, and then we investigate expression level of TTK in the carcinogenesis process of cervical. Meanwhile, we analyzed the relationship between the expression of TTK and T staging, N staging, tumor hypoxia score (THS), 3p loss, and the remission after radiotherapy and chemotherapy in patients with cervical carcinoma. Then, we investigated the TTK expression in a tissue microarray (TMA) by using immunohistochemistry (IHC) to verify the results. Results: Data from GEO database showed that the expression level of TTK in tumor was higher than normal tissue, but not related to T, N staging, tumor hypoxia score (THS) and 3p loss. IHC results verified that TTK expression in tumor was higher than normal tissue, but not significantly related to Tstaging, clinical staging, N staging or differentiation. Interestingly, we found that TTK expression in cervical cancer was correlated with the remission of patients with cervical cancer that after radiotherapy and chemotherapy. Conclusion: TTK expression in cervical cancer was high than that in normal tissue, and it was correlated with the remission of patients with cervical cancer that after radiotherapy and chemotherapy.

Keywords: Cervical cancer, TTK, tissue microarray, GEO dataset, remission

Introduction

Human cervical cancer, which is forth most frequent malignant tumors in females in the world according the global cancer statistics 2012, increased 528,000 new cases and caused 266,000 deaths in 2012 [1]. The incidence rates are high in development country, such as China, India and African, low in American and Europe [2]. In China, cervical cancer is one of nine leading cause of cancer death in women, with an estimated 98,900 new cases and 30,500 deaths in 2015 [3]. Treatment of cervical cancer is depended on the patient's clinical stage, and ranged from surgery alone to combination of radiation, chemotherapy and surgery in special situations [4]. Despite the surgery technique, radiation and chemotherapy developed, little improvement has been achieved on the survival rate [5-9]. In the other hand, the molecular mechanism of cervical cancer still remains exclusive. Thus, it is meaningful to seek for novel molecular target of cervical cancer.

Protein kinases play a key role in catalytic activity and signaling functional transducing of critical cellular processes [10]. The expression of protein kinases in tumors contributed to carcinogenesis and is associated with tumor progression and patient's clinical outcome [11-13]. TTK, a dual-specificity protein kinase that was thought to be a mitosis kinases involved in mitotic spindle assembly checkpoint could control the cell cycle program [14]. Targeting this kinase may effectively blockades the chromosome segregation during mitosis, and may be a great invention for cervical cancer therapy.

The protein kinase TTK is highly expressed in many types of tumors, such as breast cancer, lung cancer and thyroid cancer [15]. Liu and Winey reviewed that the TTK gene is rarely

Table 1. Details of the characteristics of Tissue microarray (TMA)

Variable N=110	Age (years)		Stage		
	Range	Mean	I	II	III
Squamous cell carcinoma N=95	29~80	48.9	53	35	7
Adenocarcinoma N=3	46~49	48	2	1	0
Endometrioid adenocarcinoma N=2	47~51	49	1	1	0
Adjacent cervical canals tissue N=2	58~63	60.5	0	0	0
Adjacent chronic cervicitis N=4	70~70	70	0	0	0
Adjacent cervix tissue N=4	40~72	58	0	0	0

mutated during carcinogenesis [16]. Over expression of TTK correlates with increased grade and aggressiveness of breast cancers patients, which may due to the function of promoting proliferation or survival of cancer cells [17, 18]. Liu, X et al confirmed that overexpression of TTK could promote the proliferation of hepatocellular carcinoma cells via activating the AKT signaling pathway [19]. Based on the previous research about TTK in cancer, TTK may be a new target gene for cancer treatments. So, analyze the correlation between TTK and different types cancers is significant and expectant for tumor targeted therapy.

Herein, our team analyzed data obtained from microarray database GEO established by US National Center for Biotechnology Information (NCBI), we found that TTK expression in cervical cancer was high than that in normal tissue, and it was correlated with the remission of patients with cervical cancer that after radiotherapy and chemotherapy. Further, we collected cervical cancer tissues for the further testify.

Materials and methods

Cervical cancer associated database obtained from GEO microarray database

The Gene Expression Omnibus (GEO) repository of National Center for Biotechnology Information (NCBI) is a public functional genomics data repository. In this study, seven cervical cancer associated database, GSE63514, GSE52904, GSE7410, GSE14404, GSE52904, GSE27469, GSE56363 were retrieved from GEO database, respectively. In detail, GSE52904 and GSE7410: Affymetrix expression data from cervical cancer patient tissues; GSE63514: Gene expression analysis of cervical cancer progression; GSE14404: Gene expression studies in normal, dysplastic and malignant cervical tissues; GSE52904: Impact of Gene Dosage on Gene Expression, Biological Processes and Survival in Cervical Cancer: a Genome-Wide Follow-Up Study; GSE27469: Drivers of gene expression in cervical cancer; GSE56363: Gene expression profiling reveals activation of the FA/BRCA pathway in advanced squamous cervical cancer with intrinsic resistance and therapy failure.

Tissue microassay

Commercial cervical cancer tissue microarray (TMA) (Product No.CR1101) bought from Alina Biotechnology co., LTD, Xi'an, China, including 48 normal cervical tissues, 58 cervical cancer tissues, all of which were derived from patients at an average age of 54.5 years. The detailed information of the tissue sources contained in TMA was presented in **Table 1**.

Immunohistochemical staining (IHC)

The expression of TTK of TMA was detected by IHC. The TMA was deparaffined with standard pure xylene for 15 minutes three times at room temperature and hydrated in graded alcohols, phosphate buffer saline (PBS) was used to wash the TMA. Antigen retrieval was performed in boiling citrate buffer (PH 6.0) for 15 minutes. Then TMA was cooled down to room temperature in the buffers. After washing TMA in PBS for 5 minutes three times, 0.3% hydrogen peroxide phosphate-citrate buffer was used to block endogenous peroxidase activity for 10 minutes. Rinsed with PBS for 5 minutes, TMA was incubated with primary antibody TTK (Sigma-Aldrich; dilution 1:100) for 12 hours at 4°C. The TMA was incubated with Poly-HRP Goat anti-rabbit (Maixin. Bio, FuZhou, China) for 30 minutes. Slides were dyed with diaminobenzidine for 5 minutes. Haematoxylin was used to counterstain the nucleus, followed by dehydration and mounted. Images of TMA were taken using an Olympus BX40 microscope and CC-12 Soft-Imaging System (Olympus, Tokyo, Japan).

Evaluation of immunohistochemical staining

TTK was located in the cell. TTK expression was analyzed and scored for intensity (0-3) and frequency (0-100%). The intensity was scored as grade (0), negative; grade (1), weak intensity;

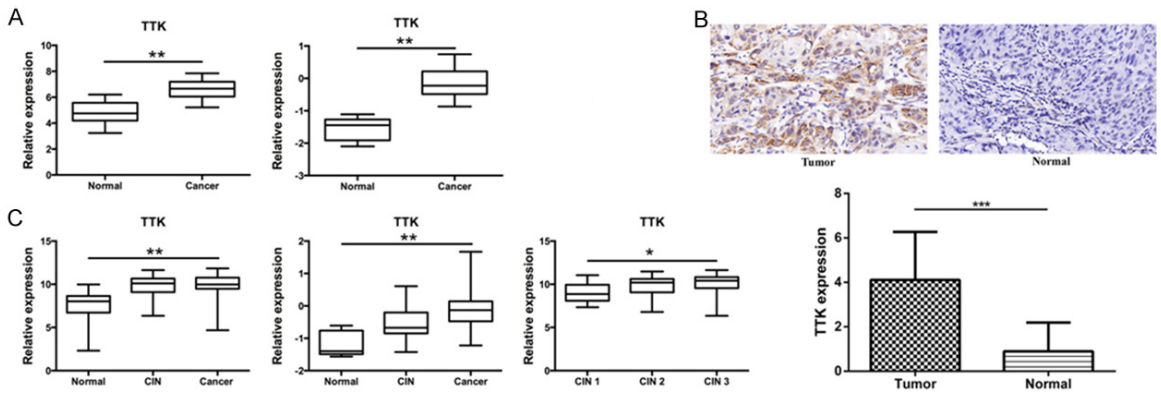

Figure 1. The expression of TTK is significantly higher in cervical cancer and CIN than normal tissues. A. The differences of TTK expressions in paired normal tissues and cancer tissues from the cervical cancer patient tissues were analyzed by using GEO database, GSE52904 and GSE7410, **P<0.001; B. Representative of TKK in the cervical cancer tissues or paired normal colon tissues were detected by using immunohistochemistry (up) and the statistical analysis was shown in (down), ***: P<0.0001. C. The expression of TTK inpaired normal tissues, cancer tissues and CIN from the patient tissues were analyzed by using GEO database, GSE63514 and GSE14404, *P<0.05, **P<0.001.

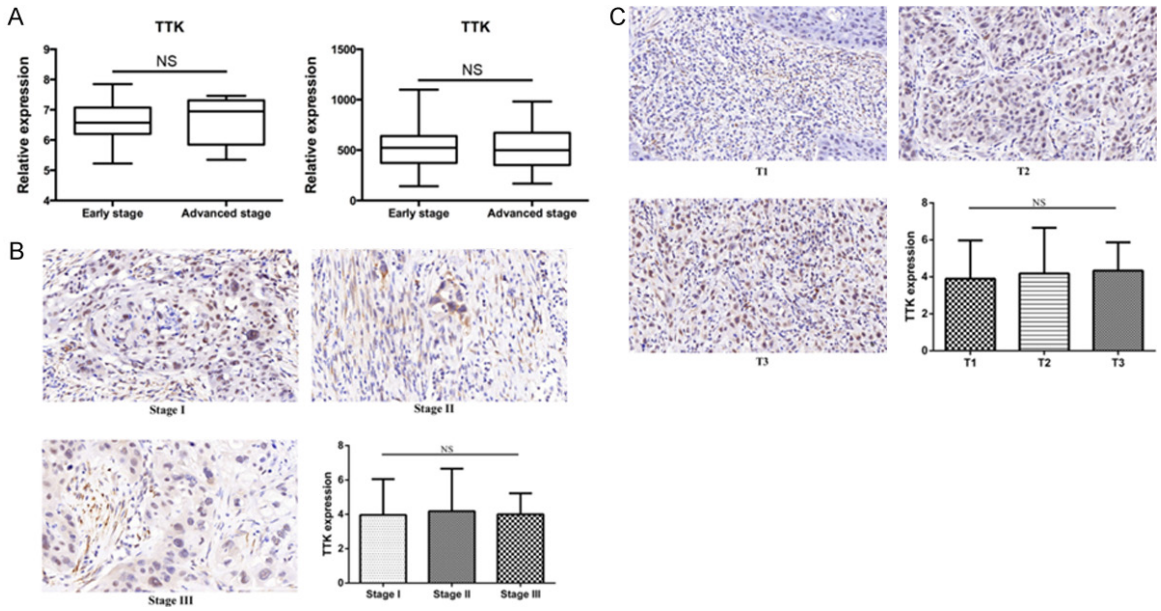

Figure 2. TTK expression is not significantly related to the progressive stages in cervical cancer. A. The differences of TTK expressions in different AJCC-stages from the cervical cancer patient tissues were analyzed by using GEO database, GSE52904 and GSE27469, NS means no significant. B. Representative immunohistochemical stains of TTK was analyzed in different AJCC-stages from the cervical cancer patient tissuesby using immunohistochemistry, NS means no significant. C. Representative immunohistochemical stains of TTK was analyzed in different T-stage from the cervical cancer patient tissuesby using immunohistochemistry, NS means no significant.

grade (2), moderate intensity; grade (3), strong intensity. The frequency scores were respectively assigned when 0-25, 26-50, 51-75 and 76-100% of the tumor cell were positive. To use statistical analysis, TTK protein intensity and frequency were transformed into a Composit Expression Score (CES) utilizing the formula CES = Intensity × Frequency. The range of CES was from 0 to 12. The CES was scored as negative (0), weak positive (1~4), positive (5~8), strong positive (9~12).

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 software. Gene expression profiling data downloaded from GEO database

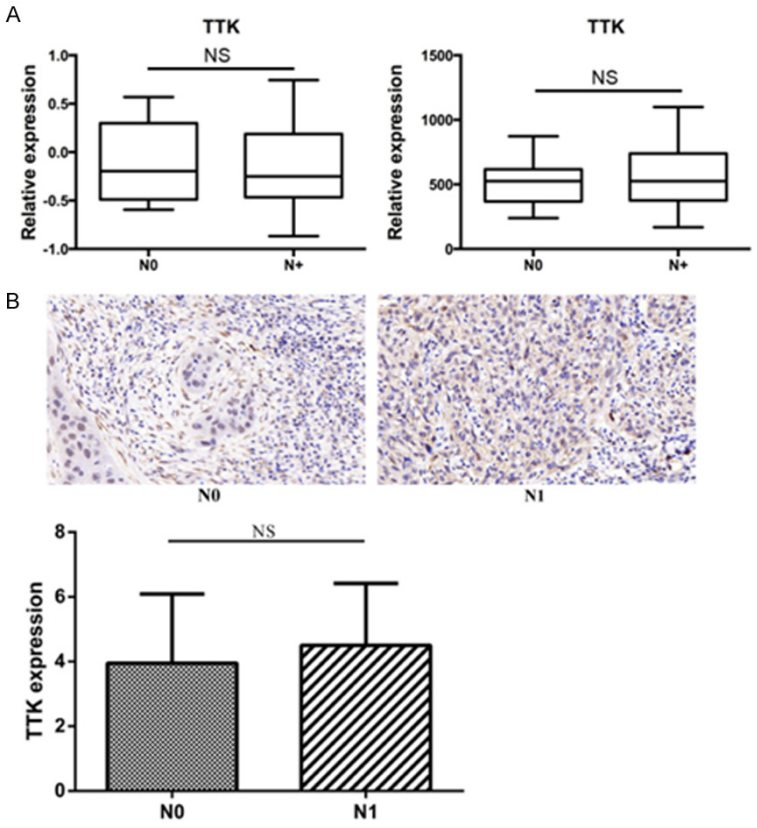

Figure 3. The expression of TTK has no significantlyrelevance among N stages of cervical cancer. A. The differences of TTK expressions in different N-stage from the cervical cancer patient tissues were analyzed by using GEO database, GSE7410 and GSE27469, NS means no significant. B. Representative immunohistochemical stains of TTK was analyzed in different N-stage from the cervical cancer patient tissuesby using immunohistochemistry, NS means no significant.

was extracted into Microsoft Excel for further statistical analysis. The differences expression of TTK was analyzed with Chi-squared test, fisher exact test and independent samples t-test. TTK expression in TMA was analyzed by one-way of ANOVA and Bonferroni's multiple comparison tests among groups. For all analyses, *P* values <0.05 were considered statistically significant.

Results

The expression of TTK is significantly higher in cervical cancer than normal tissues

The data of GSE52904 and GSE7410 were originated from GEO database, shows that the expression of *TTK* gene is significantly higher in cervical cancer tissues than normal tissues (**Figure 1A**). Furthermore, we found that the protein of TTK in cervical cancer tissues was higher than normal tissues which validated by using immunohistochemistry (**Figure 1B**). These results suggested that the expression of TTK may play an important role in cervical cancer. Then, we analyzed the TTK expression in carcinogenesis process of cervical epithelial cell with the GEO database.

The expression of TTK was significantly increased in carcinogenesis process of cervical epithelial cell

The data of GSE63514 and GSE14404 downloaded from the GEO database were analyzed. We found that the expression of TTK in carcinogenesis process of cervical epithelial cell was gradually increased (**Figure 1C**). The expression of TTK is higher in cervical cancer tissues than cervical intraepithelial neoplasia (CIN) tissues, while CIN tissue is higher than normal tissue (**Figure 1C**). Intrestingly, the same trend was observed in CIN, the expression of TTK in CIN3>CIN2>CIN.

TTK expression is not significantly related to the progressive stages in cervical cancer

The data GSE52904 and GSE27469 were extracted from the GEO database and were analyzed the relation of TTK expression and progressive stages of cervical cancer. The results show that TTK expression has no significant difference between early stage and advanced stage (**Figure 2A**). Meanwhile, the results showed in TMA by immunohistochemistry further confirmed that the expression of TTK has no significant difference among stage I, stage II and stage III (**Figure 2B**). Also, we found that TTK expression has no significant difference among T1, T2 and T3 stage (**Figure 2C**).

By using GSE7410 and GSE27469 we analyzed the relationships between TTK expression and tumor N stage. The results show that the expression of TTK has no significantly differ-

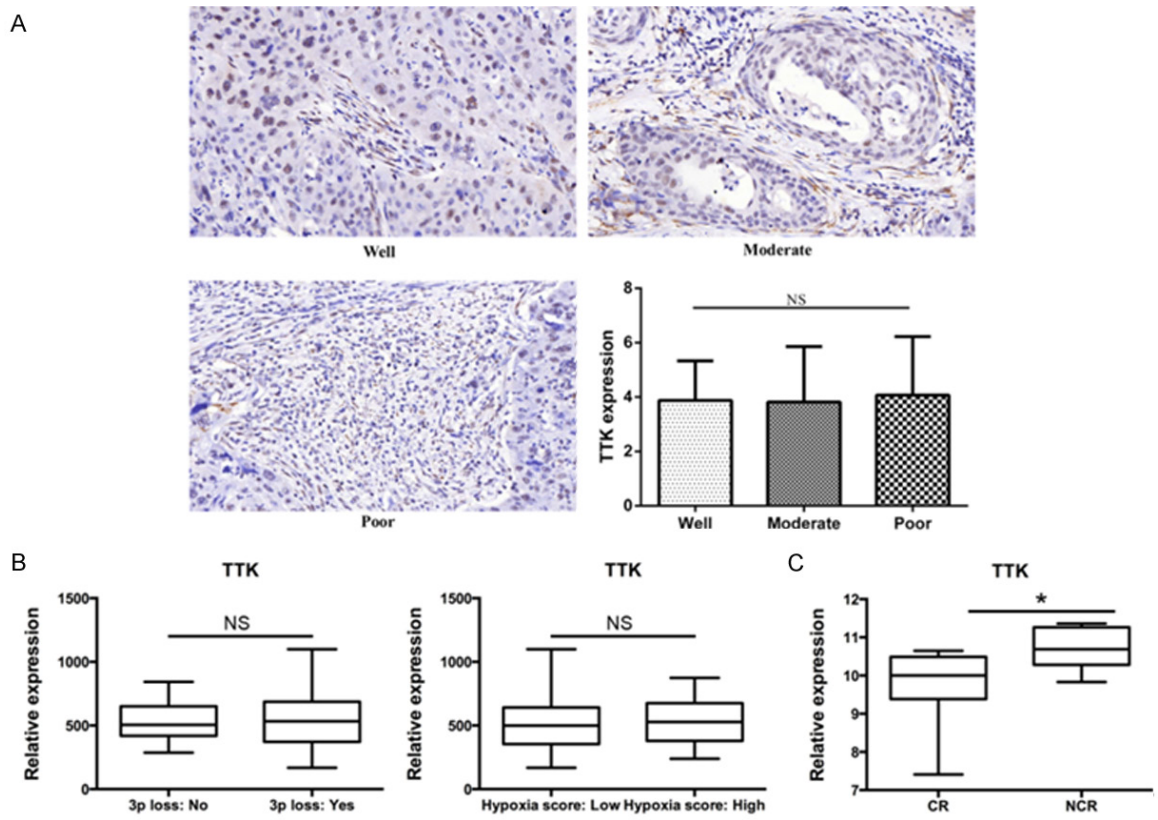

Figure 4. The expression of TTK is not significantly relevant to the differentiation of cervical cancer,but correlated with the remission of patients with cervical cancer that after radiotherapy and chemotherapy. A. Representative immunohistochemical stains of TTK was analyzed in different differentiation of cervical cancer from the cervical cancer patient tissuesby using immunohistochemistry, NS means no significant. B. The differences of TTK expressions in paired 3p loss and normal cancer tissues, high hypoxia score and low hypoxia score cancer tissues were analyzed by using GEO database, GSE27469, NS means no significant. C. The differences of TTK expressions in paired complete remission (CR) and non-complete remission (NCR) of patients with cervical cancer that after radiotherapy and chemotherapy were analyzed by using GEO database, GSE56363, *P<0.05.

ence between N0 stage and N+stage in patients with cervical cancer (**Figure 3A**), and the immunohistochemistry result in TMA further confirmed these results (**Figure 3B**).

TTK expression is not significantly related to the differentiation of cervical cancer, but correlated with the remission of patients with cervical cancer that after radiotherapy and chemotherapy

Differentiation play an important role in prognosis of patients with cervical cancer [20]. To investigate whether the expression of TTK in cervical cancer tissues is correlated with the differentiation of cervical cancer, we detected the TTK protein in tissues in different differentiation type cervical cancer. The results suggested that the expression of TTK has no significantly difference among well differentiation, moderate differentiation and poor differentiation (**Figure 4A**). Loss of 3p is a frequent event in epithelial cancer and a candidate prognostic biomarker in cervical cancer [21], and tumor hypoxia is a primary driver of malignancy through its negative impact on the efficacy of radiation, immune surveillance, apoptosis, genomic stability, and accelerated angiogenesis [22]. Nevertheless, the data GSE27469 showed that the expression of *TTK* gene in cervical cancer is incorrelated with 3p loss and tumor hypoxia score (**Figure 4B**). Interestingly, the data of GSE56363 that download from GEO database showed that the expression of TTK is correlated with the remission of patients with cervical cancer that after radiotherapy and chemotherapy, the expression level of TTK in complete remission (CR) patients that after radiotherapy and chemotherapy is significantly lower

than non-complete remission (NCR) patients (**Figure 4C**).

Discussion

Protein kinase monopolar spindle 1 (hMps1/TTK), a dual serine/threonine kinase involved in the mitotic spindle assembly checkpoint (SAC) [23, 24], are highly increased in many types of cancers, plays critical roles in cell division [25]. Although, there were many studies reported that high expression of TTK correlated with unfavorable prognosis in many types of tumor patients [14, 26-28], the mechanisms underlying the effect of TTK on tumor progression remain to be elucidated. Moreover, there were rare reports about relationship between cervical cancer and TTK. Our data in this study clearly demonstrate that TTK is highly expressed in cervical cancer tissues. Nevertheless, the bioinformatic analyses according GEO database show that TTK was not related to the stages or differentiation of cervical cancer. Interestingly, we found that the expression of TTK in cervical cancer is correlate with the remission of patients that after radiotherapy and chemotherapy.

There is a certain consistency between the risk factors of cervical cancer and precancerous lesion of cervical [29]. Dysplasia that is seen on a biopsy of the cervix is called cervical intraepithelial neoplasia (CIN) [30]. There are strong evidences to suggest that CIN is a risk factor of cervical cancer [31]. Treating high-grade (HG)-CIN reduces the incidence and mortality caused by invasive cervical cancer in women with these lesions [32]. In our study, we found that the high expression of TTK is correlated with the carcinogenesis process of cervical epithelial cell. The expression of TTK is higher in high-grade (HG)-CIN than normal tissue, but lower than cervical cancer tissues. This result suggested that the TTK may be involved in the malignant transformation of cervical epithelial cell.

The researches rarely indicated the mutation of TTK in cancer [16]. The molecular regulation mechanism of TTK expression in cervical cancer is still exclusive. We speculate that the expression of TTK may mainly regulate through epigenetically mechanism. A study indicated that miR-132 could directly suppresses the expression of TTK in glioma cells, while overexpression of TTK reverse the proliferation inhibition function of miR-132 in glioma cells [33]. Whether miR-132 could suppresses the expression of TTK and how miR-132 regulate the TTK in cervical cancer cells still unknown and need for more exploration.

Many investigations have showed that there were many types of TTK inhibitors have been described for the preclinical research of cancer treatment [34], such as AZ3146, Mps-IN-1, Mps-IN-2, Reversine, 3MB-PP1, 23-dMB-PP1 and 1-NM-PP1. These inhibitors could inhibit the mitosis of cells by target the expression of TTK [35]. In addition, previously research has demonstrated that silencing the expression of TTK *in vivo* could inhibit the intrahepatic spreads of hepatocellular cells in tumor-bearing liver by decreased the tumor cell aggressiveness, and increased the tumor cell senescence and autophagy in hepatocellular carcinoma model [36]. Interestingly, this result was also confirmed in other cancer models, such as pancreatic cancer, ovarian cancer and gastric cancer [26, 37, 38]. All of these studies provide a novel potential target for treatment of different cancers, it maybe include cervical cancer.

In summary, the present study revealed that the expression of TTK was significantly up-regulated in cervical cancer, and the protein of TTK may play an important role in malignant transformation of cervical epithelial cell. This finding may offer additional help for the early diagnosis. Moreover, the expression of TTK can be used as a prognostic indicator in patients with cervical cancer after radiotherapy and chemotherapy. However, more evidences and researches between TTK and cervical cancer should be further performed.

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Informed consent was obtained from all individual participants included in the study.

Disclosure of conflict of interest

None.

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