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Original Article

STAT4 expression is correlated with clinicopathological characteristics of cervical lesions

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Abstract: Background: STAT4 has been proved to play a crucial role in several malignancies, but its clinical significance in cervical diseases has not been clearly defined. Aims: The purpose of the present study was to evaluate the expression of STAT4 and its correlation with clinicopathological features in patients with cervical lesions, particularly cervical cancer. Materials and methods: The expression of STAT4 was assessed in 494 cases of diagnosed cervical lesions by immunohistochemistry, including chronic cervicitis (n=54), condyloma acuminate (CA, n=42), carcinoma in situ (CIS, n=38), adenocarcinoma (n=63), adenosquamous carcinoma (n=34) and squamous cell carcinoma (SCC, n=263). The relationship between STAT4 expression and clinical data was conducted by SPSS. Results: The positive expression rates of chronic cervicitis, CA, CIS, adenocarcinoma, adenosquamous carcinoma and SCC were 25.93%, 28.57%, 39.47%, 55.56%, 64.71% and 66.54%, respectively. The expression of STAT4 in cancer tissues was statistically higher compared with non-cancerous tissues (P<0.001). Spearman correlations analysis showed that STAT4 expression in cervical cancers was positively correlated with the status of lymph node metastasis (r=0.395), histological type (r=0.276), TNM stage (r=0.418), FIGO stage (r=0.434), and pathological grade (r=0.293) (all P<0.001), but no significant correlation of STAT4 expression with age (r=0.076, P=0.093) was observed. Conclusions: STAT4 might be associated with the tumorigenesis and progress of cervical carcinoma, and the expression of STAT4 could be an important biological marker for evaluating of cancer progression of cervical cancer.

Keywords: Signal transducer and activator of transcription 4, cervical carcinoma, chronic cervicitis, condyloma acuminate, immunohistochemistry

Introduction

Cervical cancer is one of the crucial public health care problems in the world. In 2012, there were 266,000 deaths from cervical cancer all over the world and about 87% deaths arose in developing countries [1]. In United States, there were approximately 12900 new cervical cancer cases and 4100 deaths arose in 2014 [2]. As cervical cancer threatens the health and even life of females seriously, and traditional surgery, radiotherapy and chemotherapy all have certain limitations [3, 4], thus it is urgent to explore new methods of cervical cancer diagnosis and treatment.

Signal transducers and activators of transcription (STAT) family is a type of proteins which plays essential roles in the transcription of nuclear genes. The aberrant activation of STAT proteins was found to affect immunity, cellular differentiation, proliferation and oncogenesis [5-7]. STAT4 is a member of STAT family, which has been proved to be of extreme importance in the development of T cells and the immunity of the body. Therefore, most of the studies on STAT4 were focused on immune diseases [8]. In recent years, researchers found that STAT4 was involved in the development of several malignancies, such as hepatocellular carcinoma (HCC) [9], colon and rectal cancer [10] and gas-

Table 1. Characteristics of patients and tumor

Characteristic	No. of patients (n=494)	%
Age (y)		
Median	44	-
Mean	43.6	-
Range (min-max)	19 - 82	-
Histological type (n=494)		
Chronic cervicitis	54	10.9
CA	42	8.5
CIS	38	7.7
SCC	263	53.2
Adenocarcinoma	63	12.8
Adenosquamous carcinoma	34	6.9
Pathological grade (n=398, CIS-carcinoma)		
Grade I: Well differentiated	28	7.0
Grade II: Moderately differentiated	157	39.4
Grade III: Poorly differentiated	141	35.4
Undetermined	72	18.1
FIGO stages (n=360, Carcinoma)		
I	248	68.9
II	16	4.4
IIIB	93	25.8
IVA	3	0.8
TNM stages (n=398, CIS-carcinoma)		
0	38	9.5
I	248	62.3
II	16	4
III	93	23.4
IV	3	0.8
Lymph nodes metastasis (n=360, Carcinoma)		
Negative	264	73.3
Positive	96	26.7

CA: condyloma acuminate, CIS: carcinoma in situ, SCC: squamous cell carcinoma; FIGO: International Federation of Gynecology and Obstetrics (2009); TNM: According to American Joint Committee on Cancer (AJCC) Cervix Uteri Cancer Staging 7th edition.

tric cancer [11]. These findings indicated that STAT4 might be a latent significant biomarker for diagnosis, prognosis assessment and molecularly targeted therapy in malignancies.

However, no study has focused on STAT4 expression in cervical cancer tissues. Therefore, the aim of our study was to detect the expression level of STAT4 in different cervical tissues and attempt to illuminate the relationship between STAT4 expression and clinicopathological characteristics, also to provide a new direction for the clinical diagnosis and treatment of cervical cancer.

Materials and methods

Patients and tissue samples

A total of 494 cases of cervical tissues from patients diagnosed as different cervical diseases were obtained from the Pathology Department of the First Affiliated Hospital of Guangxi Medical University during a period from January 2011 to December 2014, including chronic cervicitis (n=54), condyloma acuminate (CA, n=42), carcinoma in situ (CIS, n=38), adenocarcinoma (n=63), adenosquamous carcinoma (n=34), squamous cell carcinoma (SCC, n=263). The clinical staging of all patients classified as cervical carcinoma were assessed according to the International Federation of Gynecology and Obstetrics (FIGO) criteria 2009. Pathological differentiation of tumor was graded based on the criteria of World Health Organization (WHO) and TNM stage of tumor was based upon the American Joint Committee on Cancer (AJCC) Cervix Uteri Cancer Staging 7th edition. All the patients in this study were treated without chemotherapy or radiotherapy before surgery. The clinicopathological characteristics, such as age, histological type, pathological grade, FIGO stage, TNM stage and lymph nodes metastasis, were collected and shown in **Table 1**. Patients and clinicians agreed to the use of the experimental materials for research purposes and institutional review board-approved written documents were obtained. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University.

Immunohistochemistry

All selected cervical tissues were fixed in 100 g/L of par formaldehyde, embedded in paraffin, serially sectioned into 4 μm thick sections and transferred onto slides for immunohistochemistry to detect the expression of STAT4. The sections were stained with hematoxylin eosin. Slices were coped with high pressure hot fix, immunohistochemical PV and DAB chromogenic, hematoxylin retying, hydrochloric acid-alcohol differentiation, anhydrous ethanol dehydration, neutral gum sealing piece. Immunostaining for STAT4 was performed by using STAT4 mouse

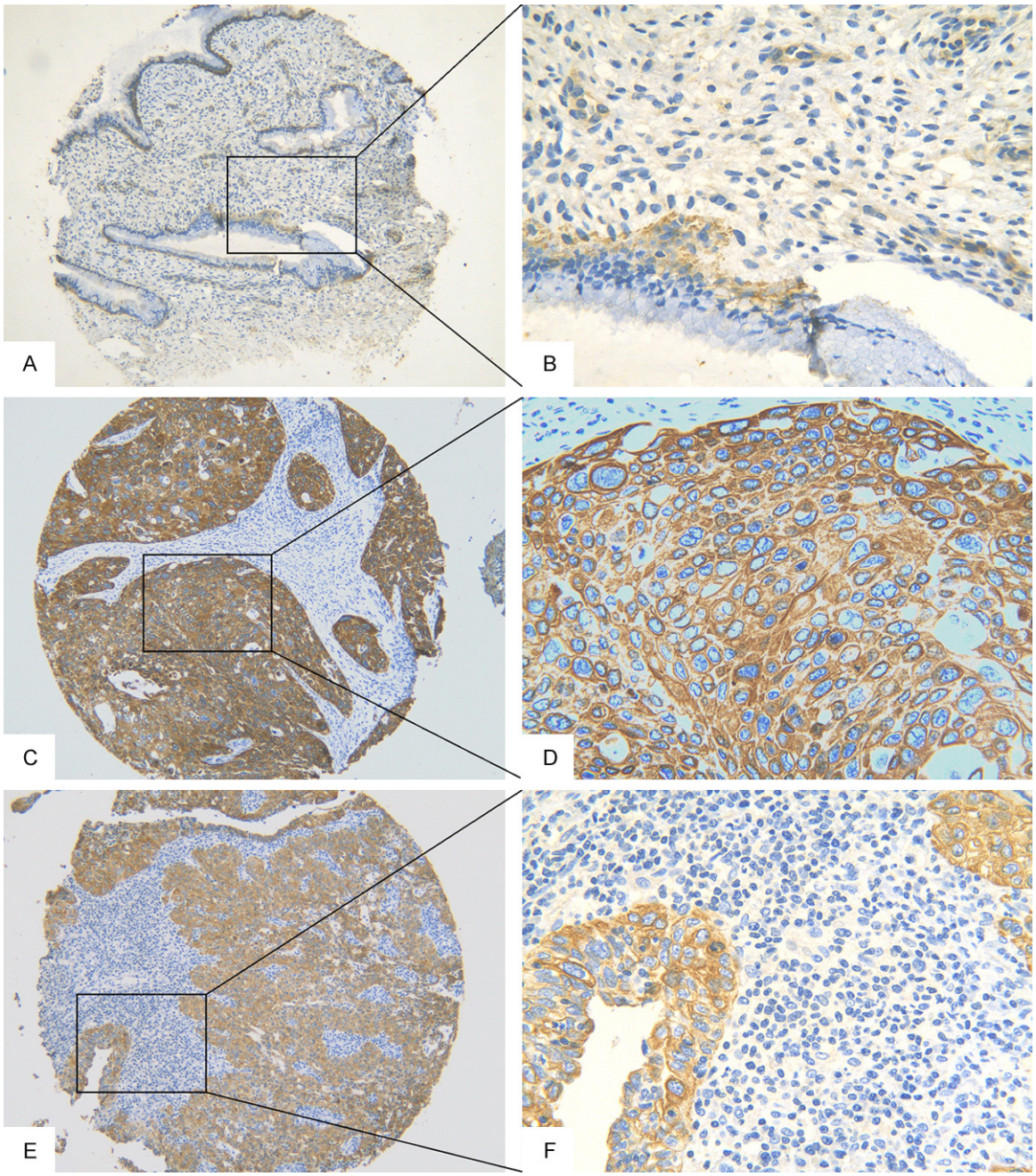

Figure 1. Immunohistochemical staining for STAT4 in cervical lesions. A and B showed immunohistochemical staining for STAT4 in chronic cervicitis. C and D showed immunohistochemical staining for STAT4 in squamous carcinoma. E and F showed immunohistochemical staining for STAT4 in adenosquamous carcinoma. (Original magnification of A, C, E was ×100; original magnification of B, D, F was ×400).

monoclonal antihuman STAT4 antibody (PL-68, CA, USA, 1:300 dilution) and immunohistochemical kit were purchased from Beijing Jinqiao Biological co. LTD. All steps were strictly performed according to the manufacturer. PBS of 0.01 mol/L (pH 7.4) was served as a negative control.

Immunohistochemical evaluation

The immunohistochemical staining was evaluated by two authors (Yiwu Dang and Kanglai Wei) and an agreement regarding controversial case was reached at a multithreaded microscope after discussion with the third author

Table 2. Difference of STAT4 expression associated with various clinicopathological features in cervical lesions

Features	All cervical lesions		*P**-value	SCC		*P**-value	Adenocarcinoma		*P**-value	Adenosquamous carcinoma		*P**-value
	No. of patients	Positive (%)		No. of patients	Positive (%)		No. of patients	Positive (%)		No. of patients	Positive (%)	
Age												
Young (≤44)	263	137 (52.09%)	0.131	138	89 (64.49%)	0.461	27	10 (37.04%)	0.011	19	13 (68.42%)	0.615
Old (>44)	231	136 (58.87%)		125	86 (68.80%)		36	25 (69.44%)		15	9 (60.00%)	
Lymph node status												
Negative	264	140 (53.03%)	<0.001	193	107 (55.44%)	<0.001	45	19 (42.22%)	0.001	26	14 (53.85%)	0.019
Positive	96	92 (95.83%)		70	68 (97.14%)		18	16 (88.89%)		8	8 (100%)	
Histological type												
Chronic cervicitis	54	14 (25.93%)	<0.001		--	--		--	--		--	--
CA	42	12 (28.57%)										
CIS	38	15 (39.47%)										
Adenocarcinoma	63	35 (55.56%)										
Adenosquamous Carcinoma	34	22 (64.71%)										
SCC	263	175 (66.54%)										
TNM stage												
0-II	302	155 (51.32%)	<0.001	193	107 (55.44%)	<0.001	45	19 (42.22%)	0.001	26	14 (53.85%)	0.019
III-IV	96	92 (95.83%)		70	68 (97.14%)		18	16 (88.89%)		8	8 (100%)	
FIGO stage												
I-II	264	140 (53.03%)	<0.001	193	107 (55.44%)	<0.001	45	19 (42.22%)	0.001	26	14 (53.85%)	0.019
IIIB-IVA	96	92 (95.83%)		70	68 (97.14%)		18	16 (88.89%)		8	8 (100%)	
Pathological grade												
Grade I	28	12 (42.86%)	<0.001	18	8 (44.44%)	<0.001	10	4 (40%)	0.021		no data	
Grade II	157	85 (54.14%)		119	67 (56.3%)		38	18 (47.37%)				
Grade III	141	113 (80.14%)		126	100 (79.36%)		15	13 (86.67%)				
Histological type												
Non-cancer tissues	96	26 (27.10%)	<0.001		--	--		--	--		--	--
Cancer tissues	398	247 (62.10%)										

*P**-Value was from non parametric test (Mann-Whitney U test and Kruskal-Wallis H test).

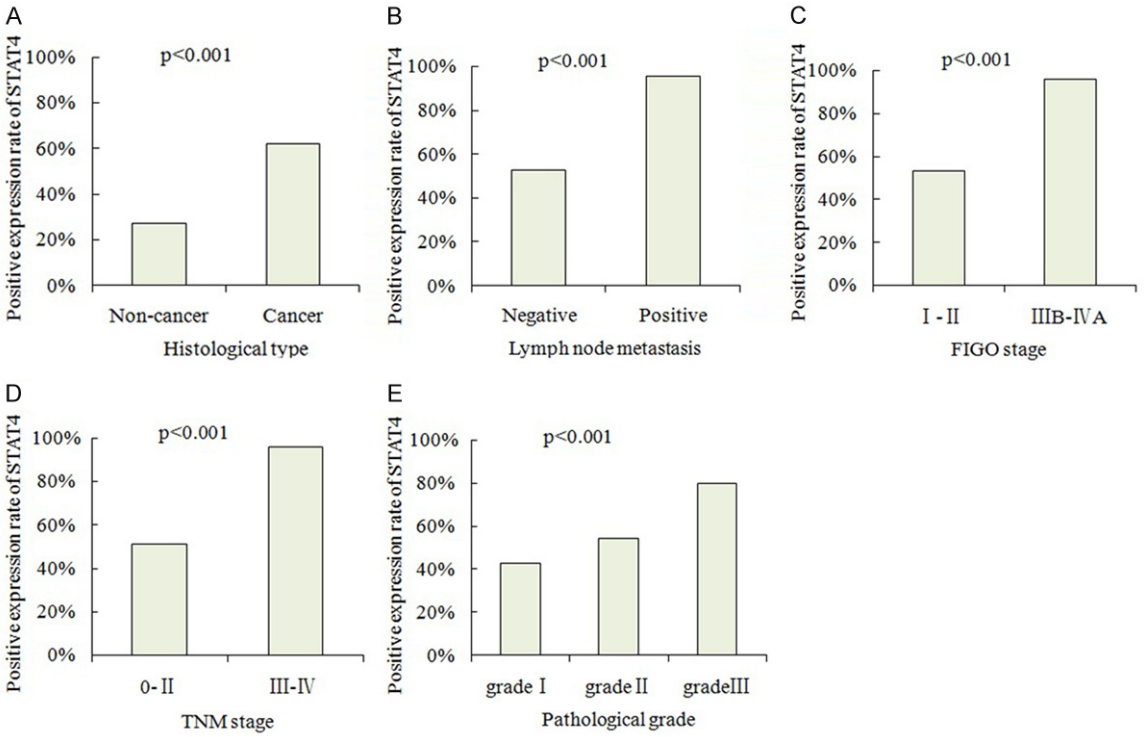

Figure 2. The expression of STAT4 in cervical lesions associated with clinicopathological features. A: The relationship between STAT4 expression and histological pattern. B: The relationship between STAT4 expression and lymph node metastasis. C: The relationship between STAT4 expression and FIGO stage. D: The relationship between STAT4 expression and TNM stage. E: The relationship between STAT4 expression and pathological grade.

(Gang Chen). STAT4 expression was scored semi quantitatively according to the following criterions: 0 (no staining); 1 (weak staining presenting as focal or fine granular pattern), 2 (moderate staining presenting as linear or cluster pattern), and 3 (strong staining presenting diffuse or intense pattern). Staining intensity was graded according to the amounts of positive cell: 1 (<25% positive cells), 2 (26-50% positive cells), 3 (51-75% positive cells) and 4 (>76% positive cells). The samples were divided into negative group and positive group of the expression of STAT4 according to the multiplicationof the scores as follows: 0-2: negative (-); 3-12: positive (+).

Statistical analysis

The software SPSS edition 20.0 was used for statistical analysis. The comparison of STAT4 expression associated with clinicopathological parameters between two groups was examined by Mann-Whitney U test and Kruskal-Wallis H test was used for the comparison among three or more groups. Correlation of STAT4 expression levels with clinicopathological characteristics was estimated by Spearman's correlation test. A two-tailed of *P* value less than 0.05 was considered as statistically significant.

Results

STAT4 expression in cervical lesions

To define the role of STAT4 in cervical lesions, we measured the expression level of STAT4 in 494 cases of different cervical diseases. The immunohistochemical results showed that the positive expression rates were 25.93% in chronic cervicitis, 28.57% in CA, 39.47% in CIS, 55.56% in adenocarcinoma, 64.71% in adenosquamous carcinoma and 66.54% in SCC, respectively. The expression modes of STAT4 in cervical lesions estimated by immunohistochemical analysis were illustrated in **Figure 1**. The relationship between STAT4 expression and various clinicopathological features in cervical lesions was revealed in **Table 2**. We found that the expression of STAT4 in total cancer tissues (62.10%, including adenocarcinoma, ade-

Table 3. Spearman correlations between STAT4 and clinicopathological features in cervical lesions

Features	Total cervical cancers	SCC	Adenocarcinoma	Adenosquamous carcinoma
	R (*P**-value)	R (*P**-value)	R (*P**-value)	R (*P**-value)
Age	0.076 (P=0.093)	0.007 (P=0.907)	0.298 (P<0.001)	-0.151 (P=0.395)
Lymph node status	0.395 (P<0.001)	0.391 (P<0.001)	0.408 (P<0.001)	0.410 (P=0.016)
Histological type	0.276 (P<0.001)	--	--	--
TNM stage	0.418 (P<0.001)	0.437 (P<0.001)	0.415 (P<0.001)	0.472 (P=0.005)
FIGO stage	0.434 (P<0.001)	0.437 (P<0.001)	0.415 (P<0.001)	0.472 (P=0.005)
Pathological grade	0.293 (P<0.001)	0.268 (P<0.001)	0.373 (P<0.001)	no data

*P**-Value was from Spearman's correlation test.

nosquamous carcinoma and SCC) was statistically higher in comparison with that in non-cancerous tissues (27.10%, P<0.001, including chronic cervicitis and CA, **Figure 2A**). STAT4 expression in each cancer type was also significantly higher than that in chronic cervicitis and CA separately (P<0.001, data not shown). Furthermore, STAT4 expression in cancer tissues with lymph node metastasis (95.83%) was also observed higher than negative group (53.03%, P<0.001, **Figure 2B**). Besides, STAT4 positive expression in advanced FIGO stage (95.83%) was higher compared to the early stage (53.03%, P<0.001, **Figure 2C**) and the similar result was also discovered in the comparison of STAT4 expression between advanced TNM stage (95.83%) and early stage (51.32%, P<0.001, **Figure 2D**). Additionally, the difference of STAT4 expression among various pathological grades was also significantly noticed, which showed the positive rates of 42.86%, 54.14%, 80.14% in grade I, II and III, respectively (P<0.001, **Figure 2E**). However, no significant difference of STAT4 expression between young (52.09%) and old (58.87%) age was found (P=0.131).

Correlation of STAT4 expression levels with clinicopathological data in cervical lesions

Spearman correlations of STAT4 expression with various clinicopathological features were presented in **Table 3**. We found that STAT4 expression was positively correlated with metastasis of lymph node (r=0.395), histological type (r=0.276), TNM stage (r=0.418), FIGO stage (r=0.434), and pathological grade (r=0.293) (all P<0.001), but no significant correlation of STAT4 expression with age (r=0.076, P=0.093) was observed. In order to achieve deeper understanding of STAT4 in different histological types of cervical cancers, we performed a subgroup spearman correlations analysis in different types of cervical cancers. The result showed that STAT4 expression in SCC was positively correlated with lymph node metastasis (r=0.391), TNM stage (r=0.437), FIGO stage (r=0.437), and pathological grade (r=0.268) (all P<0.001), but no significant correlation of STAT4 expression with age (P=0.907) was discovered. In adenocarcinomas, STAT4 expression was positively correlated with age (r=0.298), lymph node metastasis (r=0.408), TNM stage (r=0.415), FIGO stage (r=0.415), and pathological grade (r=0.373) (all P<0.001). In adenosquamous carcinoma, STAT4 expression was positively correlated with lymph node metastasis (r=0.410), TNM stage (r=0.472), FIGO stage (r=0.472) (all P<0.05), but no significant correlation of STAT4 expression with age (P=0.395) was noticed.

Discussion

Cervical cancer is the fourth most malignant cancer behind breast, colorectal and lung cancer in women according to GLOBOCAN 2012. STAT4 is a member of STAT family which mediates the intracellular effects of IL-12, leading to the production of IFN-γ and natural killer cells cytotoxicity [9, 12]. Currently, STAT4 has been reported to act as an important regulator in several cancers, especially in HCC [13, 14]. However, to date, no studies have been reported on the clinical significance of STAT4 expression in patients with cervical cancer. This study was the first one to explore the relationship between STAT4 and the progression of cervical cancer.

In the current study, we investigated the STAT4 expression in different cervical lesions and analyze the role in the tumorigenesis and deterioration of cervical cancer. The positive expres-

sion rate of STAT4 rose markedly in cancer tissues in comparison with non-cancerous tissues. Besides, the over-expression of STAT4 in cervical lesions was closely related to histological type, lymph node metastasis, TNM stage, FIGO stage and pathological grade, which indicated that the up-regulation of STAT4 might play a vital role in the occurrence and development of cervical cancer. Hence, STAT4 could become a useful biomarker to identify the risk and predict the progression of cervical cancers. However, one study of HCC found that down-regulation of STAT4 had significant correlations with TNM stage and tumor differentiation, also patients who had higher STAT4 expression had better recurrence-free survival in HCC [9], contrary to the trend of STAT4 in the current study in cervical cancer. These contradictory results implied that STAT4 might be tumor specific and have different influence on variant malignancies via undiscovered mechanisms.

Nowadays, great efforts have been made to explore the molecular mechanisms and pathogenesis of cancer, but the exact mechanisms still remain confusion or unknown. It is has been proved that the deregulation of STAT signal was related to the pathogenesis for several human tumors [7]. However, there is little known on the mechanism behind the deregulation of STAT4 in cancers. The recent studies have demonstrated that STAT4 could be a key transcription factor in the production of IFN-γ by JAK/STAT pathway [15]. IFN-γ has an effect on tumor phenotype, growth and metastasis [16], preventing primary tumor development and shaping tumor immunogenicity [17]. Further, recent advances showed that STAT4 was indirectly regulated by microRNAs and mediated important biological mechanisms. For example, the upregulation of STAT5 could increase the expression of oncogenic microRNA-155 by subsequently targeting STAT4 and the activation of STAT5 also resulted in the downregulation of STAT4 indirectly [18, 19]. MicroRNA-155 has been known to be of crucial importance in the development of cancer from inflammation [20], and the correlation between STAT4 and this microRNA in cervical cancer remains interesting to be investigated. Besides, a study has been shown that IL-12 could contribute to up-regulate and maintain the STAT4 expression [21]. The regulation of STAT4 was induced by IL-12 through phosphatidylinositol3-kinase (PI3K) and Ras-independent signal transduction pathways and related to mitogen-activated protein kinases (MAPK) Erk1 and Erk2 [22], which could also be a potential mechanism of STAT4 in cervical diseases.

Although this was the first study to investigate the STAT4 expression in cervical lesions, there were still some limitations. Our results showed that STAT4 might play a role in the occurrence and development of cervical cancer; however, the molecular mechanisms remain to be explored in the future. In conclusion, the current study demonstrates that high expression of STAT4 is closely correlated with clinical progression of cervical cancer. STAT4 may become a promising biomarker for prevention, diagnosis and treatment of cervical cancer. Also, a longitudinal analysis with larger scale and deeper in vitro, in vivo experiment are necessary to evaluate the function and molecular mechanism of STAT4 in cervical carcinoma.

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Disclosure of conflict of interest

None.

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