Interleukin-17 activates JAK2/STAT3, PI3K/Akt and nuclear factor-κB signaling pathway to promote the tumorigenesis of cervical cancer

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Abstract. Interleukin (IL)-17 has been regarded as a significant factor in inflammation. In addition, IL-17 is known to be involved in the progression of cancers; however, the function of IL-17 in cervical cancer remains unclear. In the present study, cell viability was detected by Cell Counting Kit-8 assay. Quantitative PCR and western blotting were performed to detect gene and protein expression levels, respectively, in cancer cells or tissues. Ki-67 staining was used to evaluate cell proliferation. Wound-healing assay was used to detect cell migration. Moreover, Transwell assay was performed to investigate the invasion of cervical cancer cells. The results revealed that IL-17 significantly promoted the proliferation of cervical cancer cells. Additionally, IL-17 notably enhanced the migration and invasion of cervical cancer cells in vitro. IL-17 promoted the progression of cervical cancer via the activation of JAK2/STAT3 and PI3K/Akt/NF-κB signaling. In conclusion, IL-17 was a key regulator during the progression of cervical cancer through the JAK2/STAT3 and PI3K/Akt/nuclear factor-κB signaling pathway, which may serve as a novel target for the treatment of cervical cancer.

Introduction

Cervical cancer ranks third in terms of incidence of malignant tumors worldwide, and is the most frequent type of gynecological cancer in developing countries (1-3). The increasing trend in cervical cancer in developing countries is attributed to the early beginning of sexual activities, certain sexual behaviors such as high number of partners, early age at first intercourse, infrequent use of condoms, multiple pregnancies with Chlamydia association, and immunosuppression with human immunodeficiency virus, which is associated with higher risk of infection by human papillomavirus (HPV) (4,5). In USA, the HPV16 and 18 types are detected in 70% of high-grade squamous intraepithelial lesions, as well as in invasive cervical cancer cases (6,7). To date, chemotherapy and surgery are the two major strategies for treating cervical cancer (8). However, the prognosis of cervical cancer remains poor. Thus, it is urgent to identify novel methods for the treatment of cervical cancer.

Recent studies have shown that interleukin (IL)-17 plays an important role in cervical cancer (9,10). IL-17A is a member of the IL-17 family, which has been regarded as a pro-inflammatory cytokine (11). In addition, IL-17 is secreted by various cells, including T helper cells, CD8+ T cells, γδ T cells and natural killer cells in the tumor microenvironment (12). IL-17 and its receptor are expressed in a variety of cell types, including fibroblasts and tumor cells, leading to the secretion of pro-inflammatory cytokines, such as IL-6, various chemokines and metalloproteinases (13). Previous studies have shown that an inflammatory environment may lead to tumor growth by generating tumor-promoting cytokines, decreasing cytotoxic T cells and developing myelogenous inhibitory cells, and further production can promote tumor growth (14-16). Besides, previous findings have revealed that the risk of cervical cancer is associated with IL-17 polymorphism in both Chinese and Western populations (17,18). However, the mechanism by which IL-17 modulates the development of cervical cancer remains unclear.

Thus, the present study aimed to explore the potential molecular mechanism of IL-17 in cervical cancer. The results may provide experimental basis for the possibility of using IL-17 as a key marker to predict prognosis of cervical cancer.

Materials and methods

Sample collection. In total, 30 pairs of cervical cancer samples and adjacent normal tissues were collected from Gansu Provincial Cancer Hospital between June 2018 and June 2019.

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Key words: interleukin-17, cervical cancer, JAK2/STAT3, PI3K/Akt, nuclear factor-κB

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The clinical and pathological data of these patients (n=30) were collected with their written informed consent. The patient exclusion criteria were as follows: i) Patients (women) who suffered from other diseases and were currently under treatment; ii) pregnant and lactating women; iii) patients allergic to probiotics or have used/are using antibiotics recently; and iv) alcoholics (people who drink ≥5 bottles of beer at a time, or the alcohol content in the blood reaches ≥0.08). The patient inclusion criteria were as follows: Women ≥18 years old who have been diagnosed with cervical cancer and have undergone surgery. Each tissue sample was stored at -80℃ until RNA extraction. In addition, the serum samples were collected from the patients. The present study was approved by the Ethics Committee of Gansu Provincial Cancer Hospital. The distribution of age and sex (30 females; mean age, 52 years; age range, 32-68 years) among the patients with cervical cancer was presented in Table I.

Meanwhile, serum was also collected from healthy donors (n=50; age, 21-58 years; sex, 28 males and 22 females). The informed consent was also obtained from healthy individuals for blood donation in the present study. The inclusion criteria of individuals without cervical cancer as control blood donors were as follows: i) Aged from 20-60 years old; and ii) no history of cancer.

**Cell culture.** The HeLa cell line was obtained from the Shanghai Cell Bank of Chinese Academy of Sciences. Cells were cultured in DMEM (Thermo Fisher Scientific, Inc.) with 10% fetal bovine serum (FBS; Thermo Fisher Scientific, Inc.), 1% penicillin (Thermo Fisher Scientific, Inc.) and streptomycin (Thermo Fisher Scientific, Inc.) at 37℃ in the presence of 5% CO2.

**Cell transfection.** HeLa cells were seeded at a density of 3x10^5 cells/well in a 6-well plate and cultured until 70% confluence. Then, the cells were transfected with small interfering RNA (si)STAT3 (10 nM), siJAK2 (10 nM) or negative control (empty vector, siNC, 10 nM) using Lipofectamine® 2000 reagent (Thermo Fisher Scientific, Inc.). For siRNA knockdown, the sequence of siRNA targeting JAK2 (siJAK2) or STAT3 (siSTAT3) was designed and synthesized from Shanghai GenePharma Co., Ltd. The efficiency of transfection was detected by reverse transcription-quantitative PCR (RT-qPCR). The sequences of siRNAs were as follows: i) NC, 5'-ACGUAGCGUUCCGAGAUU-3'; ii) siJAK2, 5'-ATCGAGUGAGAGCUAUA-3'; iii) siSTAT3, 5'-CUUUAGAGCUACCGCAUCU-3'. After 24 h of transfection, transfected cells were used in subsequent experiments.

**RT-qPCR.** Total RNAs were extracted from tissues or cell lines with TRIzol reagent (Invitrogen; Thermo Fisher Scientific, Inc.). RT-qPCR was conducted with PrimeScript RT Reagent kit (Takara Bio, Inc.) and SYBR Premix Ex Taq II kit (Takara Bio, Inc.). The temperature and duration of RT were as follows: 37℃ for 60 min and 85℃ for 5 min. The thermocycling conditions were as follows: Initial denaturation for 10 min at 95℃; 40 cycles of 95℃ for 15 sec and 60℃ for 30 sec; and final extension for 1 min at 60℃. The primers were purchased from Nanjing Jinsirui Biotechnology Co., Ltd. β-actin was used as the internal control. The primers were as follows: STAT3, 5'-CATCCTGAAGCTGACCCAGG-3'; STAT3 reverse, 5'-TCCCTCACATGGGGAGGTAG-3'; JAK2 forward, 5'-GAGACAATCTGAGCCGCTT-3'; JAK2 reverse, 5'-GTCAGCTCCACTACATC-3'; IL-17 forward, 5'-CCTTGGGAATCTCCACCCGCA-3'; IL-17 reverse, 5'-GAGCTCTTATGGCACTATGT-3'; IL-17A forward, 5'-CTAACACCAGGACACCTCACC-3'; IL-17A reverse, 5'-AGCCCCAGGACACGATTATC-3'; IL-17F forward, 5'-GTGTCGAGGAGGTAGTATGA-3'; IL-17F reverse, 5'-TGATGTCACGCCCAATGTCTTA-3'; and β-actin reverse, 5'-GTCGTCACCCTCCAGGTT-3'. The 2-ΔΔCq method (19) was used to measure relative expression.

**Wound-healing assay.** HeLa cells (5x10^4 per well) were plated into a 24-well Cell Culture Cluster. Once cells reached 80-90% confluence, the layer of cells was scratched perpendicularly with a small pipette head. After washing with PBS for 3 times, serum-free medium was used for further culture, and the scratch widths at 0 and 24 h were recorded under an optical light microscope (magnification, x200). The experiment was repeated 3 times.

**Enzyme-linked immunosorbent assay (ELISA).** The levels of IL-17 in tissues of patients were detected using an ELISA kit (Hangzhou Multisciences Biotech Co., Ltd., cat. no. 70-EK117/2-96), according to the manufacturer's instructions.

**Transwell assay.** For cell invasion analysis, Transwell assay was performed. The upper chamber was pre-treated with 100 µl Matrigel. HeLa cells were seeded into the upper chamber in medium with 1% FBS, and the density was adjusted to ~1.0x10^5 cells per chamber. RPMI-1640 medium with 10% FBS was added to the lower chamber. After 24 h of incubation at 37℃, the Transwell chamber was rinsed twice with PBS (5 min each time), fixed with 5% glutaraldehyde at 4℃, stained with 0.1% crystal violet at room temperature for 30 min, washed twice with PBS and observed under an optical light microscope (magnification, x200). The number of cells invading the Matrigel was regarded to represent the invasion ability.

**Cell Counting Kit-8 (CCK-8) assay.** HeLa cells were seeded in 96-well plates (5x10^4 per well) overnight. Then, cells were treated with 0, 5, 10, 50 or 50 ng/ml IL-17 for 72 h. Next, 10 µl CCK-8 reagent was added to each well and further incubated for 2 h at 37℃. Finally, the absorbance was measured at 450 nm using a microplate reader (Thermo Fisher Scientific, Inc.).

**Western blotting.** Total protein was isolated from tissue or cell lysates using RIPA buffer (Shanghai GenePharma Co., Ltd.), and quantified using a BCA protein assay kit (Beyotime Institute of Biotechnology). Proteins (30 µg/lane) were resolved on 10% SDS-PAGE gel, and then transferred to PVDF membranes (Bio-Rad Laboratories, Inc.). After blocking with 5% skimmed milk for 1 h at room temperature, the membranes were incubated with primary antibodies at 4℃ overnight, and then incubated with an HRP-conjugated secondary anti-rabbit antibody (1:5,000; cat. no. ab7090; Abcam) at
room temperature for 1 h. Membranes were scanned using an Odyssey Imaging System and analyzed with Odyssey v2.0 software (LI-COR Biosciences). The visualization was performed using an ECL chemiluminescent kit (Beyotime Institute of Biotechnology) according to the manufacturer's instructions. The primary antibodies used in the present study were as follows: Anti-JAK2 (1:1,000; cat. no. ab108596; Abcam), anti-IL-17A (1:1,000; cat. no. ab79056; Abcam), anti-IL-17F (1:1,000; cat. no. ab168194; Abcam), anti-STAT3 (1:1,000; cat. no. ab68153; Abcam), anti-vascular endothelial growth factor (VEGF; 1:1,000; cat. no. ab32152; Abcam), anti-Akt (1:1,000; cat. no. ab8805; Abcam), anti-p65 (1:1,000; cat. no. ab32536; Abcam), anti-p-STAT3 (1:1,000; cat. no. ab267373; Abcam), p-p65 (1:1,000; cat. no. ab76302; Abcam), anti-p-JAK2 (1:1,000; cat. no. ab32101; Abcam), anti-p-Akt (1:1,000; cat. no. ab76302; Abcam) and anti-GAPDH (1:1,000; cat. no. ab8245; Abcam). GAPDH was used as an internal control.

**Immunofluorescence.** Cervical cancer cells (1x10^4 per well) were seeded in 24-well plates overnight and treated as following: Control, IL-17, IL-17 plus siRNA-NC, IL-17 plus siRNA-STAT3 or IL-17 plus siRNA-JAK2 for 72 h. After that, the cells were prefixed in 4% paraformaldehyde at 4°C for 10 min, and fixed in pre-cold methanol at 4°C for another 10 min. Next, cells were incubated with primary antibodies overnight at 4°C: Anti-Ki67 (Abcam; cat. no. ab15580; 1:1,000). The nuclei were stained with DAPI (Beyotime Institute of Biotechnology). Goat anti-rabbit IgG antibody (Abcam; cat. no. ab150077; 1:5,000) was used as the secondary antibody. The samples were visualized by fluorescence microscope (magnification, x200; Olympus CX23; Olympus Corporation) immediately.

**Statistical analysis.** In total, 3 independent experiments were performed, and all data are expressed as the mean ± standard deviation. GraphPad Prism 7 (GraphPad Software, Inc.) was used for all statistical analyses. The comparison between two groups was analyzed using paired Student's t-test (Figs. 1A and 2) or unpaired Student's t-test (Fig. 1B). One-way ANOVA followed by Tukey's test was used for comparisons between multiple groups. P<0.05 was considered to indicate a statistically significant difference.

**Results**

**IL-17 mRNA expression level is upregulated in cervical tumor tissues compared with that in normal tissues.** In order to investigate the role of IL-17 in the progression of cervical cancer, RT-qPCR was employed. As indicated in Fig. 1A, the expression level of IL-17 was significantly upregulated in tumor tissues compared with that in normal tissues; to verify this result, ELISA was performed. The results demonstrated that the level of IL-17 in serum of patients with cervical cancer was significantly increased (Fig. 1B). Taken together, the results showed that IL-17 was upregulated during the tumorigenesis of cervical cancer.

**JAK2/STAT3, NF-κB, VEGF and PI3K signaling are involved in the tumorigenesis of cervical cancer.** For the purpose of exploring the role of JAK2/STAT3, NF-κB, VEGF and PI3K signaling in development of cervical cancer, western blotting was used. As shown in Fig. 2A-C, the expression levels of JAK2 and STAT3 in tumor tissues was notably increased compared with that in normal tissues; to verify this result, ELISA was performed. The results demonstrated that the level of IL-17 in serum of patients with cervical cancer was significantly increased (Fig. 1B). Taken together, the results showed that IL-17 was upregulated during the tumorigenesis of cervical cancer.

**IL-17 promotes the growth of HeLa cells.** To verify the function of IL-17 in the progression of cervical cancer, CCK-8 assay was performed. As shown in Fig. 3A, IL-17 notably increased the proliferation of HeLa cells. Moreover, a concentration of 50 ng/ml exhibited the most proliferative effect. Therefore, 50 ng/ml was used in the following experiments. Next, RT-qPCR and western blotting were used to detect the
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The data demonstrated that the expression of JAK2 in HeLa cells was significantly decreased by knockdown of JAK2 (Fig. 3B–D). Similarly, the expression of STAT3 in cervical cancer cells was notably inhibited after STAT3 silencing (Fig. 3B–D). These results suggested that JAK2 and STAT3 siRNA were stably transfected into HeLa cells. Then, the results of Ki‑67 staining demonstrated that IL‑17 significantly promoted the proliferation of cervical cancer cells. However, knockdown of JAK2 or STAT3 partially rescued the proliferative effect of IL‑17 (Fig. 3E). Overall,
these data suggested that IL-17 could promote the growth of cervical cancer cells via activation of JAK2/STAT3 signaling.

**IL-17 significantly promotes the migration and invasion of cervical cancer cells.** To further investigate the effect of IL-17 on the migration and invasion of cervical cancer cells, wound-healing and Transwell assays were performed. As shown in Fig. 4A and B, the migration and invasion of cervical cancer cells were notably inhibited in the presence of IL-17, which were partially reversed by downregulation of JAK2 or STAT3. These data confirmed that IL-17 could promote the migration and invasion of cervical cancer cells via the JAK2/STAT3 signaling pathway.

**IL-17 promotes the tumorigenesis of cervical cancer via upregulation of IL-17A and IL-17F.** IL-17A and IL-17F are two major isoforms of IL-17 that can regulate the cancer tumorigenesis (20,21). Thus, these two isoforms were selected for investigations. As indicated in Figs. 5A and B and S1A-D, the levels of IL-17A and IL-17F in cervical cancer cells were significantly upregulated by IL-17, while JAK2 or STAT3 knockdown reversed this phenomenon. Taken together, IL-17 promotes the tumorigenesis of cervical cancer via the upregulation of IL-17A and IL-17F.

**IL-17 promotes the progression of cervical cancer through JAK2/STAT3, PI3K/Akt and NF-κB signaling.** To further verify the mechanism by which IL-17 modulates the progression of cervical cancer, western blotting was used. The results indicated that the expression levels of VEGF, phosphorylated (p)-JAK2, p-STAT3, p-Akt and p-p65 were significantly upregulated by IL-17, which was notably rescued by silencing of JAK2 or STAT3 (Figs. 6A and B, 7A and B). Taken together, the results confirmed that IL-17 promoted the progression of cervical cancer through the upregulation of JAK2/STAT3 signaling.

**Discussion**

The IL-17 family was identified in 1993 by gene screening of mouse T cells. It was originally named CTLA-8, and was regarded as a cytokine called IL-17 in 1995 (22). The IL-17 family includes at least 17 members, which are classified into two families: the IL-17A family and the IL-17F family. The IL-17A family includes IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F, while the IL-17F family includes IL-17F and IL-17G. The IL-17 family plays a crucial role in a variety of biological processes, including inflammation, immune response, and tumorigenesis. In this study, we investigated the role of IL-17 in cervical cancer. Our results showed that IL-17 could promote the growth, migration, invasion, and tumorigenesis of cervical cancer cells via activation of JAK2/STAT3 signaling. These findings provide new insights into the molecular mechanisms of cervical cancer and may have potential implications for the development of therapeutic strategies.
family contains 6 members (23). IL-17 is an important inflammatory regulator that may activate tissue responses and guide immune defense (24). Previous studies have reported that IL-17 could be involved in tumorigenesis due to the fact that inflammatory factors in the tumor microenvironment can promote tumors to produce cytokines and decrease cytotoxic T cells, thereby promoting tumor growth (12,25). However, the mechanism by which IL-17 regulates the development of cervical cancer remains unclear. The present study is the first to identify that IL-17 could promote the progression of cervical cancer via the activation of JAK2/STAT3. Moreover, Zhang et al (26) found that IL-17 could be closely associated with the progression of thyroid cancer. Besides, a previous study indicated that IL-17 significantly promoted the occurrence of biliary tract cancer via self-producing cytokines (27). The present data further supplemented these previous results, indicating that IL-17 could act as a JAK2/STAT3 promoter during the occurrence of multiple diseases. According to Song et al (20), IL-17 could act as an oncogene in laryngeal cancer via the activation of PI3K/AKT/FAS/FASL signaling. Consistently, the present finding suggested that PI3K/Akt signaling could be activated by IL-17 in cervical cancer. It has been reported that IL-17 could activate PI3K/AKT in malignant tumors (28,29). Thereby, the function of IL-17 might

Figure 4. IL-17 significantly promotes the migration and invasion of cervical cancer cells. (A) Migration of HeLa cells was detected by wound-healing assay. Scale bar, 100 µm. (B) Invasion of HeLa cells was tested by Transwell assay. Scale bar, 100 µm. **P<0.01. IL, interleukin; siRNA, small interfering RNA; NC, negative control.
contribute to the consistence. On the other hand, IL-12, IL-23 and IL-17 are known to be pro-inflammatory cytokines in immunology (30), and TGF-β is an immunosuppressive cytokine (31). A previous report indicated that IL-12, IL-23 and IL-17 could be upregulated in acute lymphoblastic leukemia, while TGF-β was downregulated (32). Consistently, the present data indicated that IL-17 was upregulated in cervical cancer. Meanwhile, IL-12, IL-23 and TGF-β will be investigated in the future.

According to the literature, the JAK2/STAT3 signaling pathway is commonly associated with the metastasis of malignant tumors (33-35). Moreover, the JAK2/STAT3 signaling pathway has been also found to regulate the process of cancer metastasis (36,37). Therefore, it was hypothesized that the knockdown of IL-17 could mediate the JAK2/STAT3 signaling pathway and suppress the growth of cervical cancer cells. As expected, IL-17 could activate JAK2/STAT3 signaling. The present findings are consistent with those from previous studies (38,39), indicating that JAK2/STAT3 signaling could play a key role during tumorigenesis.

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The present study also revealed that IL-17 could activate NF-κB and PI3K/Akt signaling. Various evidence suggest that numerous signaling pathways are involved in the regulation of tumorigenesis, and the JAK2/STAT3, PI3K/Akt and NF-κB signaling axes have been shown to play important roles in this process (40,41). It has been previously confirmed that the STAT3 transcription factor could be constitutively activated through phosphorylation by upstream JAK kinases in various cancer types, including gastric cancer, glioma and esophageal cancer, in response to various stimuli such as cytokines and growth factors (42,43). STAT3 was activated to translocate to the nucleus, where it promotes cell proliferation and cell cycle progression, and inhibits apoptosis by activating the transcription of downstream oncogenes, such as Bax and Bcl-2 (44,45). The PI3K/Akt signaling pathway is also involved in the regulation of multiple cellular functions. Once activated, AKT phosphorylates a variety of substrates, resulting in cell cycle progression and inhibition of apoptosis (46,47). NF-κB is a major transcription factor that is involved in the inflammatory regulation of cells by responding to pro-inflammatory stimuli (48). In the present study, IL-17 increased the expression of p-Akt and p-p65. However, the knockdown of JAK2 or STAT3 significantly reversed the effect of IL-17 on these two signaling pathways. Increasing reports have indicated that the STAT3, NF-κB and PI3K/Akt signaling pathways could exert their function interactively or independently in different cellular contexts (49-51). These data were similar to the results of the present study, which indicated that IL-17 was the upstream factor of the aforementioned three signaling pathways in the tumorigenesis of cervical cancer. The present findings also indicated that knockdown of JAK2 or STAT3 could reverse the effect of IL-17 on the expression levels of PI3K- and NF-κB-associated proteins. Therefore, it is urgent to determine whether there is an association between STAT3, Akt and NF-κB signaling pathways in IL-17-treated cervical cancer cells.

Figure 5. IL-17 promotes the tumorigenesis of cervical cancer via upregulation of IL-17A and IL-17F. (A and B) HeLa cells were transfected with JAK2 siRNA or STAT3 siRNA. The expression levels of IL-17A and IL-17F were detected in HeLa cells by western blotting. The relative expression levels were quantified by normalization to GAPDH. **P<0.01. IL, interleukin; siRNA, small interfering RNA; NC, negative control.
Epigenetic modifications often play important roles in cancer tumorigenesis (52). In the present study, STAT3 was demonstrated to play a key role in IL‑17‑mediated cervical cancer progression. According to Zhang et al (53), STAT3 could induce the transcription of the DNA methyltransferase 1 gene (DNMT1) in malignant T lymphocytes. Based
on the aforementioned study (53), STAT3 activation might promote the transcription of DNMT1 in cervical cancer.

The present study is the first to explore the function of IL-17 in cervical cancer, and the first to identify that IL-17 could promote the progression of cervical cancer via the activation of JAK2/STAT3. In addition, IL-17 was demonstrated to activate JAK2/STAT3, PI3K/Akt and NF-κB in cervical cancer. However, the present study has the following limitations: i) More IL-17 isoforms need to be detected; ii) some rescue experiments are needed to further verify the association between IL-17 and NF-κB signaling. Thereby, more investigations are required in the future.
In conclusion, IL-17 significantly promoted the progression of cervical cancer, which may serve as a potential novel target for the treatment of cervical cancer.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Study design, literature research, experimental study was performed by YB, HL and RL. Data acquisition, data analysis and statistical analysis were performed by YB. RL and YB confirmed the authenticity of all the raw data. All authors were responsible for guarantor of integrity of entire study, manuscript preparation and manuscript editing, and all authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was carried out in accordance with the World Medical Association Declaration of Helsinki approved by Gansu Provincial Cancer Hospital (approval no. GPCH20190220). The clinical and pathological data of patients were collected with their written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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