

Original Article

Expression and clinical significance of Th1/Th2 cells in different HPV types of cervical cancer

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Abstract: Cervical cancer (CC) is a common gynecological malignant tumor with the second incidence rate and increasing trend. Human papillomavirus (HPV) is a risk factor for cervical cancer. Th1/Th2 cells are in dynamic balance in normal physiological state. The expression and clinical significance of Th1/Th2 cells in different HPV-type cervical cancers have not been fully elucidated. A total of 42 CC patients with HPV infection and 28 patients with cervical intraepithelial neoplasia (CIN) were enrolled. Another 30 healthy women who underwent physical examination were selected as control group. Flow cytometry was used to analyze the expression of Th1 cells and Th2 cells to calculate the ratio change. The serum levels of Th1 cytokine γ -interferon (IFN- γ), tumor necrosis factor- α (TNF- α), and Th2 cytokine interleukin-4 (IL-4) and IL-10 were detected by enzyme-linked immunosorbent assay (ELISA). Th1 cells were reduced, Th2 cells were elevated, Th1/Th2 ratio was decreased, IFN- γ and TNF- α expressions were down-regulated, and IL-4 and IL-10 expressions were enhanced in CC and CIN patients compared with the control group ($P < 0.05$). Their changes in CC patients were more significant compared with the CIN group ($P < 0.05$). CC and CIN patients were divided into HPV high-risk group (51 cases) and HPV low-risk group (19 cases) according to HPV state. The ratio of Th1/Th2 was decreased and the expressions of IFN- γ and TNF- α were declined, whereas IL-4 and IL-10 expressions were enhanced in HPV high-risk group compared with HPV low-risk group ($P < 0.05$). Prognostic factors analysis showed that there were significant differences in age, FIGO score, and histological type between high-risk group and low-risk group ($P < 0.001$). The expressions of Th1 and Th2 cytokines in peripheral blood of CC patients were abnormal. High-risk HPV infection promoted the migration of Th1 cells to Th2 cells, leading to immune escape and tumor development.

Keywords: Cervical cancer, human papillomavirus, Th1, Th2, cytokine

Introduction

As one of the most common gynecological tumors in women, cervical cancer ranks second in the incidence of female cancer [1, 2]. Cervical cancer is more common in developing countries and underdeveloped areas with high morbidity and mortality. It is mainly caused by insufficient screening, prevention, and early intervention [3, 4]. In spite of fast development of economy in China, large population makes the promotion of vaccine prevention low. Therefore, the incidence of cervical cancer is only after breast cancer, lung cancer, and colorectal cancer. The incidence and mortality of cervical cancer in China are much higher than in developed countries [5, 6]. Recent epidemiological investigation found that the age of

onset of cervical cancer becomes younger [7]. Cervical cancer has become a serious threat to the health around the world, especially in developing countries. It brought serious economic burden to patients and the global economy, and thus received the attention of gynaecologists [7, 8].

Human papillomavirus (HPV) is an epithelial virus with double-stranded DNA structure that infects the body through skin or mucous membrane. It is distributed in the human reproductive tract and has a high transmission rate of sexual behavior or contact under the reproductive mucosa environment [9]. HPV infection is closely related to the occurrence of cervical cancer, and can be divided into high-risk type and low-risk type [10]. HPV 16/18 is a common

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carcinogenic HPV type, while HPV6 and HPV11 belong to low-risk HPV. 70% HPV 16/18 infected patients can develop cervical cancer [11, 12]. In the case of poor immune status or immunosuppression, high-risk HPV viruses proliferate quickly, continue to infect and invade the cervical epithelium, and induce cervical cancer [13]. The imbalance of cytokine secretion by Th1 and Th2 cells is a key factor leading to the occurrence and progression of various diseases, such as tumors and autoimmune diseases [14]. The cytokines secreted by Th1 mainly include IFN- γ and TNF- α , which can promote the phagocytic-mediated anti-infective immunity and cause autoimmune diseases [15]. The cytokines secreted by Th2 mainly include IL-4 and IL-10, which assist the proliferation and differentiation of B lymphocytes, produce antibodies, and participate in humoral immune response [16]. However, the expression and clinical significance of Th1/Th2 cells in different HPV-type cervical cancer patients have yet to be further elucidated.

Materials and methods

General information

Cervical cancer and CIN patients diagnosed by pathological examination in Affiliated Hospital of North Sichuan Medical College (Nanchong, Sichuan, China) from January 2017 to December 2017 were selected. All enrolled patients were treated by surgery with mean age of 58.2 ± 5.6 (24-74) years old, including 42 cervical cancer patients with mean age of 59.1 ± 6.7 (25-73) years old and 28 CIN patients with mean age of 57.5 ± 4.9 (24-74) years old. Inclusion criteria included confirmed HPV infection, first time found, and no other treatments such as surgery, chemotherapy, or radiotherapy [17]. Exclusion criteria included recurrent cervical cancer; previous treatment; combined with other diseases at admission, such as infectious disease, malignant tumor, severe liver and kidney disease, cardiac insufficiency, hypertension and diabetes, secondary renal disease, hypertension, systemic immune disease, pregnancy or lactation; patients who were unwilling or unable to cooperate with this study and follow-up [17]. Thirty healthy women who underwent physical examination in our hospital were selected as the control group with an average age of 58.9 ± 5.1 (22-75) years old. There were

no statistical differences in the general data among the three groups. The study was approved by the Medical Ethics Committee of Affiliated Hospital of North Sichuan Medical College (Nanchong, Sichuan, China), and all selected subjects had signed informed consent.

Main reagents and instruments

Th1 cytokines IFN- γ , TNF- α , and Th2 cytokines IL-4, and IL-10 ELISA assay kits were purchased from R&D. Th1 detection antibody IFN- γ -APC and Th2 detection antibody IL-4-PE-cy5 were purchased from eBSCIENCE. The blood collection needle and the vacuum condensation tube were purchased from the BRAHMS diagnostic company. HPV nucleic acid amplification typing test kit was purchased from Guangzhou Kaipu Biochemical Co., Ltd. Lab system Version 1.3.1 microplate reader was purchased from Bio-rad Corporation. BC-30 automated blood cell analyzer was purchased from Mindray. C6 flow cytometer was purchased from BD Corporation. Proflex PCR instrument was purchased from Thermo Fisher.

Methods

Blood sample collection: A total of 4 ml blood was extracted from the upper extremity vein of patients and healthy volunteers and centrifuged at 2000 rpm for 10 minutes. The serum was stored at -70°C . 2 ml was used for flow analysis, and the left 2 ml was used for ELISA to detect IFN- γ , TNF- α , IL-4, and IL-10 expressions.

ELISA: IFN- γ , TNF- α , IL-4, and IL-10 expressions in the supernatant of each group were detected by ELISA. The 96-well plate was added with 50 μl sequentially diluted standard to the corresponding reaction wells. 50 μl samples were added to the reaction well. After added with the corresponding reagent at 37°C for 10 min, the plate was treated with 50 μl stop solution. The OD value of each well was measured by a microplate reader, and a standard curve was prepared according to the OD value. The corresponding sample concentration was calculated.

Flow cytometry: 2 ml peripheral venous blood was extracted and anticoagulated with EDTA.

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Table 1. General information comparison

Index	CC	CIN	P
Cases (n)	42	28	
Age (years old)	59.1 ± 6.7	57.5 ± 4.9	0.078
Weight (kg)	51.9 ± 5.3	50.2 ± 6.2	0.062
High-risk HPV (%)	41 (97.8)	10 (35.7)	0.0024
Low-risk HPV (%)	1 (2.2)	18 (64.3)	0.00054

The blood was diluted by RPMI1640 at 1:1 and added with 10 µl of CD4⁺ antibody. After incubated at room temperature for 15 min, the sample was centrifuged at 2000 r/min and added with relevant detection antibodies at room temperature avoid of light for 20 min. After washed with PBS, the sample was analyzed by flow cytometry.

HPV type detection: HPV was detected by a special cervical brush to collect the exfoliated cells inside and outside the cervix. The sample was stored in a special preservation solution and centrifuged at 2000 r/min for 3 min. DNA was extracted using the genomic extraction reagent and amplified by PCR. The sample was hybridized and identified.

Statistical analysis

The measurement data were presented as mean ± standard deviation ($\bar{x} \pm SD$) and compared by t test or ANOVA. All data analyses were performed using SPSS 11.5 software. The enumeration data were compared by χ^2 test. Correlation analysis was performed by Pearson. $P < 0.05$ was considered as statistical difference.

Results

General information and HPV typing analysis in CC and CIN patients

42 CC patients and 28 CIN patients infected by HPV were enrolled. According to HPV detection, there were 51 patients (72.9%, 51/70) with high-risk HPV and 19 patients with low-risk HPV (27.1%, 19/70). There was no statistical difference in age and weight between the groups (Table 1).

Th1 and Th2 cell changes in CC and CIN patients

Flow cytometry was used to analyze Th1 and Th2 cell changes in CC and CIN patients. Th1

cells were reduced, Th2 cells were elevated, and Th1/Th2 ratio was decreased, in CC and CIN patients compared with the control group ($P < 0.05$). Their changes in CC patients were more significant compared with the CIN group ($P < 0.05$) (Figure 1).

Th1 cytokines analysis in CC and CIN patients

Th1 cytokines IFN- γ and TNF- α expressions were downregulated in CC and CIN patients compared with the control group ($P < 0.05$). Their changes in CC patients were more significant compared with the CIN group ($P < 0.05$) (Figure 2).

Th2 cytokines analysis in CC and CIN patients

Th2 cytokines IFN- γ and TNF- α expressions were downregulated in CC and CIN patients compared with the control group ($P < 0.05$). Their changes in CC patients were more significant compared with the CIN group ($P < 0.05$) (Figure 3).

Th1 and Th2 cell ratio changes in CC patients with different types of HPV infection

CC patients were divided into HPV high-risk group and HPV low-risk group according to HPV state. The ratio of Th1/Th2 was decreased in HPV high-risk group compared with HPV low-risk group ($P < 0.05$) (Figure 4).

Th1 cytokines changes in CC patients with different types of HPV infection

CC patients were divided into HPV high-risk group and HPV low-risk group according to HPV state. The expressions of IFN- γ and TNF- α were declined in HPV high-risk group compared with HPV low-risk group ($P < 0.05$) (Figure 5).

Th2 cytokines changes in CC patients with different types of HPV infection

CC patients were divided into HPV high-risk group and HPV low-risk group according to HPV state. IL-4 and IL-10 expressions were enhanced in HPV high-risk group compared with HPV low-risk group ($P < 0.05$) (Figure 6).

Analysis of prognosis of patients with different HPV risks

Different cytokine expressions in patients with different HPV types lead to a corresponding

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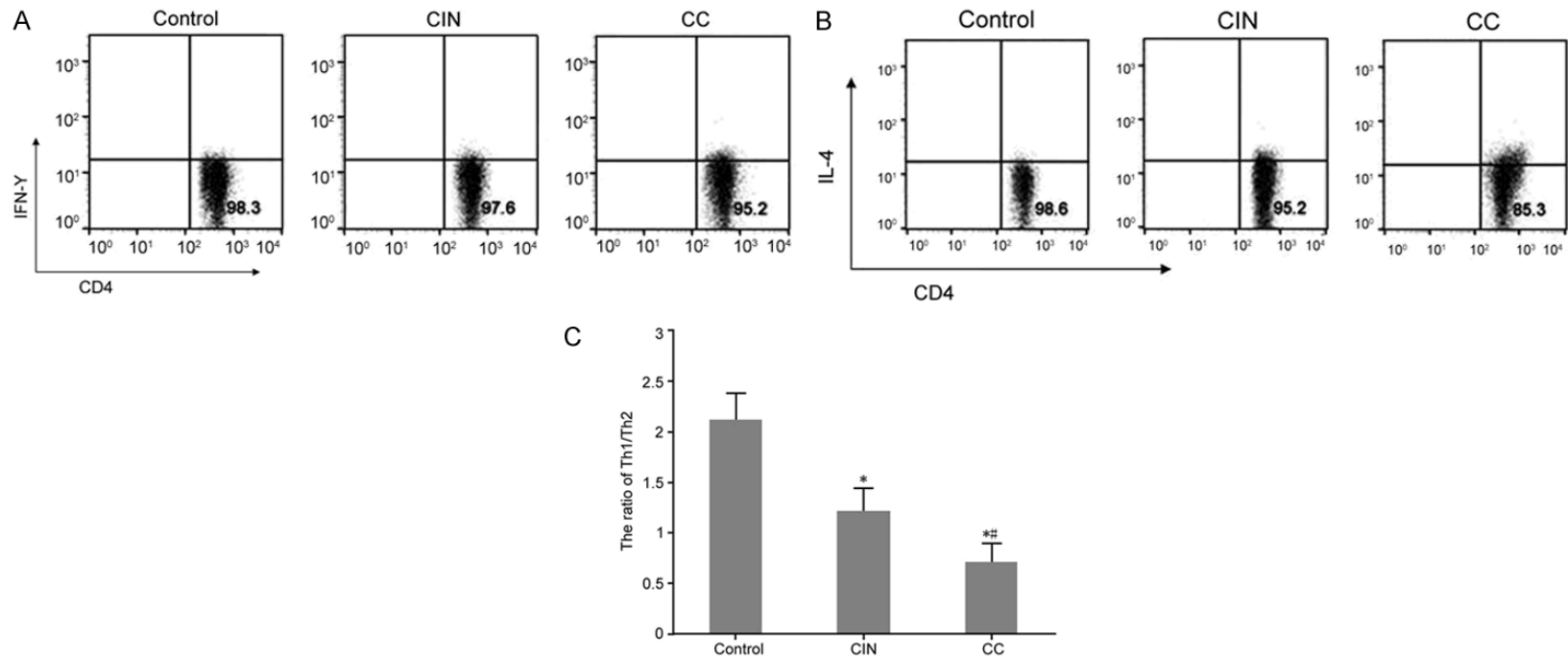


Figure 1. Th1 and Th2 cell changes in CC and CIN patients. A. Th1 cell distribution; B. Th2 cell distribution; C. Th1/Th2 ratio. *P < 0.05, compared with control. #P < 0.05, compared with CIN group.

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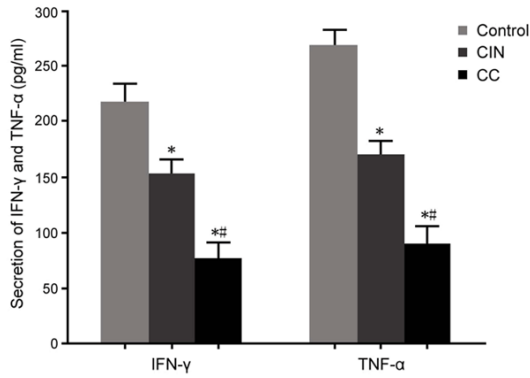


Figure 2. Th1 cytokines analysis in CC and CIN patients. *P < 0.05, compared with control. ##P < 0.05, compared with CIN group.

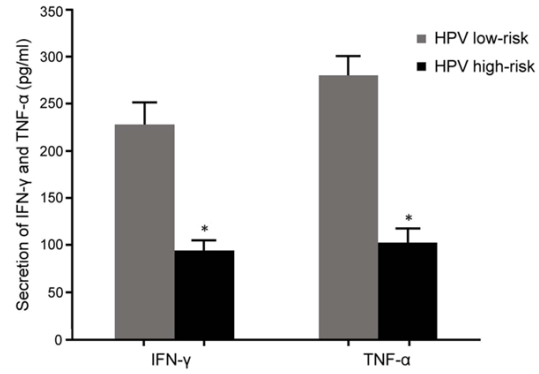


Figure 5. Th1 cytokines changes in CC patients with different types of HPV infection. *P < 0.05, compared with HPV low-risk.

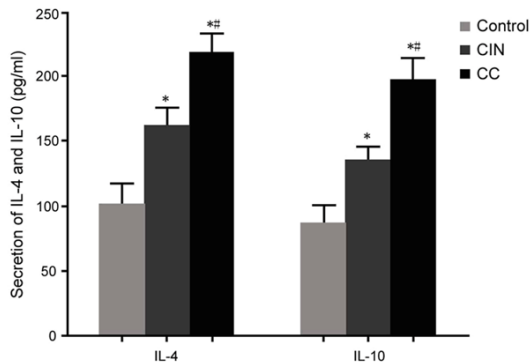


Figure 3. Th2 cytokines analysis in CC and CIN patients. *P < 0.05, compared with control. ##P < 0.05, compared with CIN group.

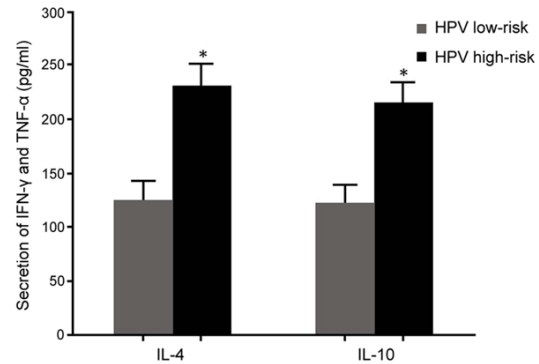


Figure 6. Th2 cytokines changes in CC patients with different types of HPV infection. *P < 0.05, compared with HPV low-risk.

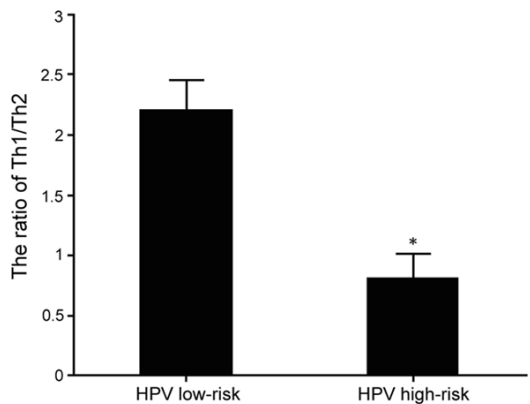


Figure 4. Th1 and Th2 cell ratio changes in CC patients with different types of HPV infection. *P < 0.05, compared with HPV low-risk.

prognostic relevance that requires further study. Prognostic analysis showed that age was a prognostic analysis in both high-risk and low-

risk groups (P < 0.001). There were also statistically significant differences between the high-risk group and the low-risk group in the different FIGO reference international scores (P < 0.001). There were also statistical differences between the high-risk group and the low-risk group in the histological type. Therefore, there were statistical differences in the high and low risk groups in different prognostic analyses (Table 2).

Discussion

The incidence of cervical cancer is increasing with younger trend. Recent epidemiological survey showed that the onset age becomes further younger [18]. Its morbidity and mortality in China account for 25% of the world. Moreover, due to insufficient prevention and early diagnosis, most cervical cancer patients are often in the advanced stage [19]. HPV infection is an important and necessary factor for cervical

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Table 2. Analysis of prognosis of patients with different HPV risks

Factors	High-risk (%)	Low-risk (%)	Total (%)	<i>P</i>
Age				< 0.001
< 30	12 (23.5)	2 (10.5)	14 (14.2)	
30-50	25 (49.0)	11 (57.8)	36 (51.4)	
> 50	14 (27.4)	6 (31.5)	20 (28.5)	
FIGO status				< 0.001
IA	9 (17.6)	2 (10.5)	11 (15.7)	
IB	21 (41.1)	6 (31.5)	27 (38.5)	
II	10 (19.6)	4 (20.0)	14 (20.0)	
III+	9 (17.6)	6 (31.5)	15 (21.4)	
Histological types				< 0.001
Squamous cell carcinoma	38 (74.5)	13 (68.4)	(74.1)	
Adenocarcinoma	9 (17.6)	4 (21.0)	(18.5)	
Adenosquamous carcinoma	3 (5.8)	1 (5.2)	(4.2)	
Othres	1 (2.6)	1 (5.2)	(3.2)	

cancer. HPV enters basal cells through skin wounds or infected epithelial tissues. Its DNA virus continues to integrate into host epithelial cells, causing malignant proliferation, leading to rapid progress of precancerous lesions and even tumors. According to the HPV type and the risk of cervical cancer, it is divided into high-risk and low-risk types. High-risk HPV can be detected in most CC patients [20, 21]. In this study, according to HPV detection, there were 51 patients (72.9%, 51/70) with high-risk HPV and 19 patients with low-risk HPV (27.1%, 19/70). Among them, HPV high-risk type of cervical cancer patients reached 97.8%, suggesting that high-risk HPV participates in the occurrence and development of cervical cancer.

Th1/Th2 cells maintain a dynamic balance under normal physiological condition and form a stable inter-influenced and mutually constrained cytokine network by secreting corresponding cytokines. Th1 cytokines IFN- γ and TNF- α mainly mediate cellular immune response, while Th2 cytokines IL-4 and IL-10 are mainly involved in humoral immune response. Cytokines released by Th1 and Th2 cells can antagonize each other and inhibit Th reaction and release of related factors. Th1 cytokine IFN- γ can antagonize the release of Th2 cytokines IL-4 and IL-10, thereby inhibiting Th2 response [22, 23]. Cellular immunity is the main immune response to tumor immunity. Therefore, the body is in a good anti-tumor state if Th1 cells and secreted cytokines are the main dominant cells. If they deviate to Th2

cells and related cytokines, it will interfere with anti-tumor immunity [24, 25]. This study confirmed that Th1 cells were reduced, Th2 cells were elevated, Th1/Th2 ratio was decreased, IFN- γ and TNF- α expressions were downregulated, and IL-4 and IL-10 expressions were enhanced in CC and CIN patients compared with the control group. Their changes in CC patients were more significant compared with the CIN group. The ratio of Th1/Th2 was decreased

and the expressions of IFN- γ and TNF- α were declined, whereas IL-4 and IL-10 expressions were enhanced in HPV high-risk group compared with HPV low-risk group. The results showed that the Th1/Th2 balance of high-risk HPV-infected CC patients drifted to the Th2 direction, indicating that Th1 cells were decreased in patients with high-risk HPV-infected cervical cancer. Since the secretion of related cytokines was decreased, it leads to inhibited cell functional activity and attenuated anti-tumor activity, which is beneficial to escape immune surveillance and promote tumor progression. In further studies, we will investigate the HPV genotypes of cervical cancer and the expressions of Th1 and Th2 cells in different TNM stages, and analyze their correlation with clinicopathology to explore the possible mechanisms.

Conclusion

The expressions of Th1 and Th2 cytokines in peripheral blood of CC patients were abnormal. High-risk HPV infection promoted the migration of Th1 cells to Th2 cells, leading to immune escape and tumor development.

Disclosure of conflict of interest

None.

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