Scientific Research Publishing

Advances in Reproductive Sciences, 2022, 10, 106-114
https://www.scirp.org/journal/arsci
ISSN Online: 2330-0752
ISSN Print: 2330-0744

# The Role of IL-2, IL-4, IL-10 and IFN-γ Cytokines Expression in the Microenvironment of Cervical Intraepithelial Neoplasia

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**How to cite this paper:** Cai, Y., Zhai, J.J., Wu, Y.M., Chen, R. and Tian, X.Y. (2022) The Role of IL-2, IL-4, IL-10 and IFN-γ Cytokines Expression in the Microenvironment of Cervical Intraepithelial Neoplasia. *Advances in Reproductive Sciences*, **10**, 106-114.
https://doi.org/10.4236/arsci.2022.104010

**Received:** August 21, 2022
**Accepted:** October 25, 2022
**Published:** October 28, 2022

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## Abstract

**Objective:** To investigate the role of IL-2, IL-4, IL-10 and IFN-γ cytokines in the microenvironment of cervical intraepithelial neoplasia. **Methods:** 180 patients participating were enrolled in this trial, where 50 cases are in control group, 50 cases are in low-grade squamous intraepithelial lesion (LSIL) group, 50 cases are in high-grade squamous intraepithelial lesion (HSIL) group, and 30 cases have cervical carcinoma. ELISA methods are used to detect the expression of IL-2, IL-4, IL-10 and IFN-γ in the lavage fluid, and all data is analyzed using one-way analysis of variance. **Results:** The expression of IL-2 and IFN-γ in cervical lavage fluid gradually decreases with the aggravation of the lesion. The expression of IL-4 and IL-10 increases by the aggravation of pathological changes. There were statistically significant differences in IL-2 level among the four groups. IFN-γ levels are significantly different between the cervical cancer group and the other groups, also between HSIL and LSIL group, and between HSIL and the control group, but no statistically significant difference was observed in IFN-γ e between LSIL and the control group. The expressions of IL-4 and IL-10 between the cervical cancer group and the other groups were significantly different, and also between HSIL and the control group. But there was no statistically significant difference between LSIL and the control group, HSIL and LSIL. **Conclusion:** The cytokines of IL-2, IL-4, IL-10 and IFN-γ in the microenvironment of the cervix play an important role in the occurrence and development of cervical intraepithelial neoplasia. This study may provide the evidence for diagnosis and treatment of cervical intraepithelial neoplasia.

## Keywords

Cervical Intraepithelial Neoplasia, IL-2, Il-4, IL-10, IFN-γ, Vaginal Lavage

Fluid

## 1. Introduction

Cervical cancer is the most common malignant tumor in the department of gynecology, and many studies have demonstrated that cervical cancer and cervical intraepithelial neoplasia (CIN) (including CINI, CINII, CINIII), namely Low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL), are infected by HPV. With the rapid advance of science and technology and the improvement of human papillomavirus (HPV) detection technology, the incidence of cervical intraepithelial neoplasia is increasing year by year and presents a younger trend. Most of the pathology is cervical CIN [1] [2] [3]. In the past, the treatment of cervical CIN mainly focused on cervical electrotomy and physical lesion treatment. After the operation, wound debridement, bleeding, infection and cervical incompetence will affect fertility in the future, and the cost is high. After treatment, the infection of HPV and CIN may be persistent or reoccur. Therefore these treatment methods cannot be used repeatedly [1] [2]. Studies in recent years have found that both CINI and young CINII patients can be treated with conservative vaginal administration [3], which suggests an improvement in the microenvironment of the cervix is effective in preventing and treating cervical intraepithelial neoplasia [4] [5] [6]. As important immune effector cells, helper t cells (Th) mediate and regulate the immune response by secreting specific cytokines that transmit molecular signals between cells, they play an important role in the process of inflammation and carcinogenesis. Stimulated by different antigens, Th can be differentiated into two subpopulations namely Thl and Th2. Thl cytokines, such as IL-2, IFN-$\gamma$, etc., must have immune stimulating function and can restrict tumor growth. Th2 type cells, such as IL-4 and Il-10, mainly play the role of immunosuppressive function and can promote tumor growth. Two kinds of cytokines interact with each other to maintain the immune steady-state of the body. The dominant expression of Th1 or Th2 is not a simple causal relationship with anti-inflammatory/proinflammatory and anti-tumor/promoting tumors. Under different conditions such as cytokine concentration, immune response time, effector cells, and the environment, its effects could have multiple directions, presenting different immunological characteristics in the course of the disease [7] [8] [9]. In this study, the expression of four cytokines, IL-2, IL-4, IL-10, and IFN-$\gamma$ secreted by helper T cells (Th) Th1 and Th2 in vaginal lavage fluid was used to understand the local microenvironment of the cervix in patients with cervical intraepithelial neoplasia. The immune status of the local microenvironment is to explore its relationship with the occurrence and development of cervical cancer, which would provide a theoretical basis for further diagnosis and treatment of cervical intraepithelial neoplasia.

## 2. Materials and Methods

### 2.1. Materials

180 patients, who were eligible for the study and agreed to participate from the cervical lesion center of Beijing Tongren Hospital from January 2018 to December 2020, were assigned to four groups according to the pathological results of cervical biopsy. Criteria for inclusion: 1) Patients in the cervicitis group had to be selected at the same time, with a history of sexual activity, no vaginal bleeding during non-pregnancy, no acute genital inflammation, and negative for Thinprep cytologic test (TCT) and HPV; 2) The pathological findings of colposcopy biopsy of HPV infected patients were confirmed to be LSIL, HSIL, c and cervical carcinoma by two experienced pathologists; 3) No history of systemic antibiotic use in 2 weeks; 4) No history of sex hormone use or radiotherapy or chemotherapy in 3 months; 5) No history of vaginal use, sex life, pelvic bath, vaginal lavage and operation in 3 days prior to consultation; 6) The vaginal smear was negative before taking the material; 7) The informed consent of the individual was obtained before the specimens were obtained. This study was approved by the Medical Research Ethics Committee of Beijing Tongren Hospital Affiliated to Capital Medical University. Exclusion criteria: 1) Women during pregnancy or lactation; 2) Patients with systemic acute inflammation and serious diseases of heart, lung, liver, kidney and hemopoietic system; 3) Patients with a low immune function who are susceptible to malignant tumors, various immune disorders, or are on immunosuppressive drugs and so on. According to clinical case observation and control study, there were 50 cases of cervical biopsy with inflammation in the control group, aged from 25 to 60 years old, with an average age of 38.01 ± 14.17 years; 50 cases in the LSIL group, aged from 22 to 58 years old, with an average age of 38.24 ± 15.40 years old; 50 cases of HSIL, aged from 23 to 60 years old, with an average age of 39.24 ± 14.40 years old; 30 cases in the cervical squamous group, aged 36 to 60 years old, with an average age of 45.70 ± 13.06 years old. The age variances among the four groups were uniform, and the age difference among the groups was not statistically significant ($P > 0.05$).

### 2.2. Experimental Methods

All research subjects are instructed to come to the hospital on the 3rd day after the end of menstruation, and menopausal women who meet the selection criteria can come to the hospital for specimen collection at any time. Preparation of vaginal lavage fluid is explained as the following steps. Take the lithotomy position of the bladder, stretch the vagina with a speculum, exposed the cervix, and flush the cervical surface and the upper 1/3 segment of the vagina with 5 mL normal saline. 3 - 4 mL of lavage fluid was aspirated from the posterior fornix (removing the sample mixed with blood to avoid the interference of cytokines in the blood), and then mixed into 1.5 mL EP tube, centrifuged at 4˚C for 5 minutes under 2000 R/min. The supernatant was then put into a sterile EP tube, kept in a refrigerator at −80˚C, and kept in reserve (specimens must not freeze

or thaw repeatedly).

The main reagents: IL-2, IL-4, IL-10 and IFN-$\gamma$ ELISA kits were purchased from Nanjing Boersai Biotechnology Co., Ltd., China.

Methods: IL-2, IL-4, IL-10 and IFN-$\gamma$ were detected by enzyme-linked immunosorbent assay (ELISA). 100 L supernatant samples were collected and operated according to the instruction, and the OD 450 value of each hole was read on the enzyme marker, and the result was as follows: the OD value of each standard sample and specimen should be subtracted from the OD value of the blank hole. The concentration of IL-2, IL-4, IL-10 and IFN-in the corresponding position samples was calculated by drawing the standard curve with the software.

Statistical methods: SPSS20.0 was used for statistical analysis, and measurement data were expressed as ($\overline{x}$ ± s). The comparison of multiple group means was performed by one-way analysis of variance, and the Dunnett-t test was used to analyze different types of data. $P < 0.05$ indicates that the difference is statistically significant.

## 3. Results

### 3.1. One-Way Analysis of Variance of Various Cytokines among Groups

In the control group, LSIL, HSIL and cervical cancer group, the expressions of IL-2 in cervical irrigation fluid were 44.89 ± 5.59 pg/mL, 36.12 ± 3.60 pg/mL, 24.18 ± 6.83 pg/mL, 7.90 ± 6.41 pg/mL, respectively. There was significant difference among the groups ($F = 334.422$, $P < 0.05$). In four groups, the expression of IFN-$\gamma$ in cervical irrigation fluid were 30.65 ± 4.63 pg/mL, 25.81 ± 4.89 pg/mL, 17.35 ± 3.54 pg/mL, 7.39 ± 4.47 pg/mL, respectively. There was significant difference among the groups ($F = 192.063$, $P < 0.05$). This indicates that the expression of IL-2 and IFN-$\gamma$ in cervical irrigation fluid gradually decreased with the aggravation of the lesion in the four groups of cases. In the control group, LSIL, HSIL and cervical cancer group, the expression of IL-4 in cervical irrigation fluid were 4.76 ± 2.54 pg/mL, 8.23 ± 2.65 pg/mL, 15.51 ± 3.19 pg/mL, 29.67 ± 4.51 pg/mL, respectively. In four groups, the expression of IL-10 in cervical irrigation fluid were 15.17 ± 5.54 pg/mL, 19.50 ± 5.58 pg/mL, 24.48 ± 6.60 pg/mL, 46.48 ± 7.71 pg/mL, respectively. The expression of IL-4 and IL-10 in these groups increased in sequence with the aggravation of pathological changes, and there was significant difference among the groups ($F = 343.193$, $P < 0.05$; $F = 308.914$, $P < 0.05$). See Table 1.

### 3.2. Pairwise Comparison of Various Cytokines in Each Group

Each monitoring indicator is compared in pairs in four groups. For example, there were statistically significant differences in IL-2 among the four groups ($P < 0.05$). IFN-$\gamma$ expression is statistically significantly different between the cervical cancer group and the remaining groups, *i.e.* the control group, LSIL group, HSIL group ($P < 0.05$). The difference is also statistically significant between the HSIL

**Table 1.** Univariate analysis and comparison multiple indexes of patients in different groups.

| group | N | IL-2 (pg/mL) | IFN-$\gamma$ (pg/mL) | IL-4 (pg/mL) | IL-10 (pg/mL) |
|---|---|---|---|---|---|
| control | 50 | $44.89 \pm 5.59^{\Delta\#}$ | $30.65 \pm 4.63^{\Delta}$ | $4.76 \pm 2.54^{\Delta}$ | $15.17 \pm 5.54^{\Delta}$ |
| LSIL | 50 | $36.12 \pm 3.60^{*\Delta}$ | $25.81 \pm 4.89^{\Delta}$ | $8.23 \pm 2.65^{\Delta}$ | $19.50 \pm 5.58^{\Delta}$ |
| HSIL | 50 | $24.18 \pm 6.83^{*\Delta\#}$ | $17.35 \pm 3.54^{*\Delta\#}$ | $15.51 \pm 3.19^{*\Delta}$ | $24.48 \pm 6.60^{*\Delta}$ |
| Cervical cancer | 30 | $7.90 \pm 6.14^{*\#}$ | $7.39 \pm 4.47^{*\#}$ | $29.67 \pm 4.52^{*\#}$ | $46.48 \pm 7.71^{*\#}$ |
| F | | 334.422 | 192.063 | 343.193 | 308.914 |
| P | | <0.001 | <0.001 | <0.001 | <0.001 |

Note: $^{*}P < 0.05$, when compared with the control group; $^{\Delta}P < 0.05$, when compared with cervical cancer group; $^{\#}P < 0.05$, when comparison with LSIL group.

and LSIL group and between the HSIL and the control group ($P < 0.05$). The difference between LSIL and the control group is not statistically significant ($P > 0.05$).

The differences in IL-4 and IL-10 measurement are statistically significant between the cervical cancer group and the other groups, *i.e.*the control group, LSIL group, and HSIL group ($P < 0.05$). The difference between HSIL and the control group was also statistically significant ($P < 0.05$). But no statistically significant difference could be observed between LSIL and the control group, also no difference between HSIL and LSIL ($P > 0.05$). See Table 1.

## 4. Discussion

Most cervical cancers are related to HPV and gradually develop from precancerous lesions, but HPV is not the sole element to promote the occurrence of cervical cancer and the development of tumors. Low Immune response is often observed in cancer patients. Moreover, each stage of a tumor's evolution interacts with its surrounding environment, a "microenvironment" for tumor growth, which is different from the normal internal environment of the human body. The transformation of tumor cells is determined by inherent genetic changes, and its progress is also regulated by the interaction of tumor local microenvironment, inflammation, and immune response [10]. Cytokines are the signal transmission molecules between tumor cells and the microenvironment, and are the key factors in mediating the inflammatory-to-cancerous transformation [11].

Th cells play an important role in human immunity, secreting different cytokines and exerting different immune effects. Thl cells mainly secrete IL-2, IL-12, IFN-$\gamma$ and TNF to enhance the cytotoxicity of killer cells, induce delayed type hypersensitivity (dth), and participate in cellular immunity and transplantation rejection. Th2 cells mainly secrete IL-4, IL-5, IL-6 and IL-10, which are involved in humoral immunity and allergic reactions. This study focused on exploring the expression of four cytokines, specifically IL-2, IL-4, IL-10, and IFN-$\gamma$, in the cervical microenvironment, in order to understand their role in the occurrence and development of cervical intraepithelial neoplasia. IL-2 acts on a variety of target

cells and plays a fundamental role in promoting proliferation and activating the cytotoxicity of NK cells and T cells. Studies have shown that IL-2 is a key regulator of immune function, which can not only fight HR-HPV infection, but also play an anti-tumor role [12]. IL-2 sends signals through IL-2R Complex, which is essential for normal lymphocyte proliferation and anti-tumor activity. Therefore, IL-2 level can directly affect anti-tumor immune function and local immune state. IL-2 can induce the differentiation of NK cells and cytotoxic lymphocyte cells (CTL), etc. Without IL-2, CTL activity and immunity are decreased, thus promoting the occurrence and development of tumors. IL-2 can also induce the activation of immune cells to produce IFN-$\gamma$. IL-2 and IFN-$\gamma$ can inhibit the proliferation of tumor cells, induce apoptosis, and enhance the recognition and cleavage of specific cytotoxic T cells to tumor cells. It is beneficial for the removal of cervical cancer cells [12] [13] [14].

In this study, the expression of IL-2 and IFN-in vaginal lavage fluid decreased with the aggravation of lesions, and the expression of IL-2 and IFN-$\gamma$ in vaginal lavage fluid of cervical cancer patients was the lowest, and there was significant difference between groups ($P < 0.05$). This may be due to the mobilization of the immune system by IL-2 in the early stage of the disease in order to eliminate viral infection and reverse the LSIL lesion to normal. It may also be related to the low number of cases in this study, which requires further study. It also indicates that IL-2 and IFN-$\gamma$ have protective effects on organisms. IL-4 and IL-10 that are produced by Th2 cells promote the differentiation of Th2 cells, produce antibodies, and inhibit the function of Thl cells. IL-4 and other factors have been reported to contribute to the development of bowel and breast cancer, and IL-10 is associated with the risk of gastric cancer after helicobacter pylori infection [15] [16]. The results showed that the expression of IL-4 and IL-10 in vaginal lavage fluid in LSIL group, HSIL group and cervical carcinoma group increased with the degree of lesion, and the difference was statistically significant ($P < 0.05$). At the same time, IL-4 and IL-10 play the role of immunosuppression. It also shows that with the increasing severity of cervical disease, the expression of IL-2 and IFN-$\gamma$ in vaginal lavage fluid drops gradually. On the contrary, the expression of IL-4 and IL-10 increases sequentially. This indicates that the local microenvironmental immune function of the cervix is unbalanced, and the body cannot effectively carry out cellular and humoral immune responses, leading to continuous HPV infection, which may promote the occurrence and development of cervical cancer.

This study showed that the differences of IL-2 in vaginal lavage fluid between each group of cervical intraepithelial neoplasia and the control group were statistically significant ($P < 0.05$). This indicates the significant role of IL-2 in the evaluation of cervical intraepithelial neoplasia at all levels, which is consistent with the previous reports [17] [18]. IL-2 is a key regulator of normal immune function and plays a vital role in the activation and expansion of immune response after antigen stimulation, and canceration. Studies have also shown that increasing the human body's IL-2 content can play a role in the treatment of

cervical intraepithelial neoplasia, which can be used to explain the obvious effect of the previous treatment of cervical CINII with recombinant interleukin-2 combined with Baofukang [3]. Our study shows that IFN-$\gamma$ is particularly of importance in the evaluation of high-grade lesions and cervical cancer, and can be used to detect whether the lesions are cancerous, which is consistent with the previous studies [19] [20]. This study also shows that the expression of IL-4 and IL-10 are significantly elevated in cervical cancer, which is of great significance in evaluating cervical cancer. It also shows that the local cervix immune function is unbalanced. With decreasing IL-2 and IFN-$\gamma$, and increasing IL-4 and IL-10, the body would become unable to effectively carry out cellular and humoral immune responses, leading to imbalance of immune function in the local microenvironment of the cervix and persistent HPV infection, which may promote the occurrence and development of cervical cancer [21]. These are aligned with some studies that IL-4 and IL-10 destroy the body's immune system and promote tumor invasion and metastasis [15] [16] [22]. This study found that patients with cervical cancer have reduced Th1 cytokines and increased Th2 cytokines in vaginal lavage fluid, which is the phenomenon of Th1/Th2 drift, which is consistent with the results of most studies [21] [23] [24].

Although this study is only an observational study with a small sample size, it has its limitations. The expression of IL-2 and IFN-$\gamma$ in vaginal lavage fluid was negatively correlated with the severity of cervical cancer-$\gamma$, while the level of IL-4 and IL-10 in vaginal lavage fluid is positively correlated with the aggravation of cervical cancer, which suggests that cellular immunity and local immunity of cervix interact and restrict each other. If the disturbance of the local microenvironment of the cervix could be detected, it may be a significant contribution to the prevention, diagnosis, and the treatment of cervical cancer. It is also conducive to further research.

## Acknowledgements

Professor Yu-Mei Wu in the Department of Gynecology and Oncology, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, provided the clinical guidance.

Rui Chen, teacher in the department of laboratory medicine, Beijing Tongren Hospital affiliated to Capital Medical University, provided technical support.

## Conflicts of Interest

The authors have declared that no competing interests exist.

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