

Evaluation of IL-4, IL-17, and IFN- γ Levels in Patients With Breast Cancer

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Introduction

Breast cancer is one of the most prevalent types of females' malignancies, and its metastasis is considered to be the cause of most deaths in these patients.¹ Solid tumor consists of a heterogeneous population of cells comprising both malignant cell population and adjacent stromal cells such as macrophages, lymphocytes, neutrophils, natural killer cells, endothelial cells, and fibroblasts. A complex interaction is present between different cell

types within the tumor niche through a complex network of extracellular cues including many cytokines and their receptors.¹ Cytokines and inflammatory factors can alter immune activity, tumor growth, tissue remodeling and angiogenesis process.² Interactions between the neoplastic cells and the surrounding microenvironment have an important role in the proliferation and invasive processes of malignant cells.³ Therefore, the growth and development of breast tumor not only depend on

Abstract

Introduction: Tumor growth depends on intrinsic properties of malignant tumor and tumor microenvironment. Cytokines are secreted substances of the tumor microenvironment which are widely produced by tumor and immune cells. The aim of this research was to evaluate concentrations of interleukin 4 (IL-4), interleukin 7 (IL-17) and interferon gamma (IFN- γ) in the breast cancer microenvironment.

Methods: One hundred sixteen women between 18-73 years of age (61.15 ± 24.39) were enrolled in this study. Based on pathologic diagnostic assessment, patients were divided into 2 categories: those affected with benign breast tumor, and the subjects suffering from malignant breast tumors. Biopsy specimens were collected. Following homogenization, IFN- γ , IL-17, and IL-4 concentrations were determined in tumor tissues, adjacent tissues of the tumor, and blood serum samples of these 2 groups of patients by enzyme-linked immunosorbent assay (ELISA) method.

Results: Concentrations of IFN- γ , IL-17, and IL-4 were measured in tumor tissue samples, adjacent tissues of the tumor, and blood serum samples in both groups. Malignant breast tumor samples had significantly higher concentrations of IL-4 and IL-17 compared with benign breast tumor samples. And also the concentration of IFN- γ in adjacent tissues of the tumor and in blood serums in patients with malignant breast tumors was significantly higher than that in the benign breast tumor samples. However, there was no significant difference between the concentration of IFN- γ in neoplastic breast tumor tissues and that in the benign breast tumor tissues ($P > 0.05$).

Conclusion: Our data indicated that IL-17 and IL-4 cytokines but not IFN- γ had higher concentrations in the subjects with malignant tumor compared with those with benign tumor. The present findings indicated that the concentrations of IL-4 and IL-17 in tumor tissues may be associated with the severity of breast malignancy.

Keywords: Tumor microenvironment, Cytokines, Benign tumor, Malignant tumor.

its malignant cells, but also on all interactions and all secreted substances that are produced by different cell types such as malignant, stromal, endothelial and immune cells within the local tumor microenvironment.⁴ A great deal of studies suggest that some types of inflammatory cells that are in the tumor microenvironment have an important effect on the tumor development and progression.⁵ IL-17 (interleukin 17) is a proinflammatory cytokine generated by Th17 cells, and has a dual and contradictory role in the cancer process. IL-17 can activate a cell-mediated cytotoxicity against tumor cells, that can in turn inhibit tumor progression, while it has a critical role in facilitating the angiogenesis.⁶⁻⁸ Interferon gamma (IFN- γ) has antitumor function and its decrement has been associated with poor prognosis in breast cancer patients.⁹⁻¹¹ Th2 produced inflammatory cytokines including IL-4, IL-13, and IL-10 are very effective in attracting the innate immune cells. Moreover, IL-4, IL-13, and IL-10 inactivate cytotoxic T lymphocyte (CTL) cytotoxicity, and decrease antigen presenting capacity by antigen presenting cells.¹²⁻¹⁵ We speculated that the determination of such cytokines in normal and cancerous breast tissues may have implications in predicting cancer relapse, evaluating antitumor immunity and hence the disease outcome. We aimed to investigate and compare the concentrations of IL-4, IL-17, and IFN- γ cytokines in normal, and cancerous breast tissues, and serums.

Methods

The present study was conducted during a period of 13 months from May 2012 to June 2013 at a public hospital of Iran (Imam Ali hospital, Shahrekord). The patients with breast cancer lesion detected by biopsy at the time of referral to the diagnostic centers entered the study. Patients' characteristics such as age and sex were documented. Informed written consent was obtained from each patient prior to the specimen collection.

Biopsy specimens were obtained from patients who were suspected of breast tumor according to the internal review and the Ethics Boards of the Iranian public hospitals. Collected tissues from operating room were placed in the normal saline containers followed by several washes with normal saline within 1-2 hours to remove serum proteins and red blood cells. The tissue weights were then measured. In addition to tissue samples, 3 mL of blood samples (on the same day of surgery and in the possible shortest time) was collected from the patients. Therefore 3 different samples including tumor tissue, normal tissue surrounding the tumor, and blood serum samples were obtained from each patient.

One hundred sixteen patients with breast tumors were enrolled in the present study. The age range and the mean age of patients were 18-73 and 61.15 ± 24.39 years respectively. Based on pathologic diagnostic assessment, patients were divided into 2 groups: patients with benign breast tumor and patients with malignant breast tumor. Fifty-six patients with the mean age of 48.8 ± 13.6 years had malignant tumors (invasive ductal carcinoma grade

II and III) and 60 with the mean age of 30.3 ± 11.8 years had benign tumors (Fibroadenoma).

All samples were stored at -80°C . To obtain a homogenous tissue solution, tissue samples were homogenized by a Homogenizer (Topsonic, Iran) for 15 minutes. The resultant homogeneous solutions were then centrifuged for 15 minutes at 2500 rpm. After centrifugation, the tissue pellets were discarded and supernatants were harvested and assayed by enzyme-linked immunosorbent assay (ELISA) for the presence of IL-4, IL-17 and IFN- γ . Concentrations of 3 given cytokines were measured using commercially available ELISA kits (IL-4, IL-17 and IFN- γ ELISA kit, Bender MedSystems, USA). The absorbance was read at a wavelength of 450 nm on an ELISA plate reader (MTP, Germany).

ELISA Technique

Concentrations of IFN- γ , IL-4 and IL-17 were measured in the tumor tissues and adjacent tissues of tumor as well as serum samples of patients using ELISA technique.

Statistical Analyses

All statistical analyses were carried out by SPSS15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11. Data were expressed as means \pm standard deviation (SD). A 2-sided *P* value of 0.05 was considered as statistically significant. Independent samples *t* test and bivariate correlations were applied for between-group analysis, and performed using Spearman rank correlation. Microsoft Word was applied to generate graphs and tables.

Results

The concentration of IL-4 in malignant tumor tissue and benign tumor tissue samples was determined. Comparison of 2 given groups indicated a significant increase of IL-4 in malignant tumor tissue ($P < 0.001$). Moreover, the concentration of IL-4 in samples obtained from adjacent tissues of the malignant tumor and adjacent tissues of the benign tumor was determined and compared in 2 given groups ($P = 0.037$). The comparison represented a significant increase of IL-4 in tissues surrounding malignant tumor. Then, the concentration of IL-4 in serum samples of patients with malignant tumors and in serum samples of patients with benign tumors was measured. Comparison of 2 given groups revealed a significant increase of IL-4 in the serum samples of patients with malignant tumors ($P = 0.02$; Table 1).

In this study, IL-17 concentration in the malignant and benign tumor tissues was measured. The comparison of 2 given groups represented a significant increase of IL-17 in malignant tumor tissue ($P < 0.001$). IL-17 concentration in samples obtained from the adjacent tissues of malignant and benign tumors was also determined. Comparison of 2 mentioned groups indicated a significant increase of IL-17 in the surrounding tissues of malignant tumor ($P = 0.023$). IL-17 concentration in the serum samples of patients with malignant and benign tumors was determined. Comparison of 2 given groups revealed a significant

Table 1. Comparison of IL-4 Concentration in Malignant and Benign Tumors, Adjacent Tissues of Malignant and Benign Tumors, and Serum Samples

Groups	Number	Mean pg/mL	SD pg/mL	P Value
Benign tumor tissue	60	65.6	14.0	0.01
Malignant tumor tissue	56	112.3	15.3	0.01
Adjacent tissue of benign tumor	60	65.8	14.1	0.03
Adjacent tissue of malignant tumor	56	85.01	28.8	0.03
Serum samples of patients with benign tumor	56	21.0	2.7	0.02
Serum samples of patients with malignant tumor	56	24.2	3.9	0.02

increase of IL-17 in the serum samples of patients with malignant tumors ($P=0.017$; Table 2).

In this study, IFN- γ concentration in malignant and benign tumor tissues was calculated. Comparison of 2 given groups demonstrated no significant relationship between IFN- γ concentration and malignant tumor tissue or benign tumor tissue ($P=0.494$). Then, the concentration of IFN- γ in adjacent tissues of the malignant tumor and adjacent tissues of the benign tumor was determined. Comparison of 2 given groups showed a significant increase of IFN- γ in the tissues surrounding malignant tumor ($P=0.004$). Next, the concentration of IFN- γ in the serum samples of patients with malignant and benign tumors was measured. Their comparison showed a significant increase of IFN- γ in the serum samples of patients with malignant tumors ($P=0.045$; Table 3).

The serum samples from benign and malignant tumor patients revealed a positive statistical correlation between IL-4 and IL-17 in tumor tissue ($P=0.001$, $r=0.930$). There was a positive statistical correlation between IL-4 in breast tumor tissue (benign and malignant) and IL-17 in the serum of these patients ($P=0.001$, $r=0.480$). A positive statistical correlation between IL-4 in the adjacent tissues in patients with breast tumors (benign and malignant) and IFN- γ in the adjacent tissue of tumor ($P=0.008$, $r=0.483$) was observed. A positive statistical correlation between IL-17 in the adjacent tissues of tumor in all patients, and IFN- γ cytokine in the adjacent tissues of the tumor ($P=0.009$, $r=0.479$) was demonstrated. Moreover, there was a positive statistical correlation between IL-17 and IL-4 in the tumor adjacent tissues of all patients ($P=0.001$, $r=0.987$).

Discussion

The production of cytokines by neoplastic cells and the

surrounding cells present in tumor niche represents a critical role in appropriate immunity against tumor cells. The cytokines produced by Th1 cells lead to the activation of CTLs. The activated CTLs act as immune effectors and induce apoptotic death in target cells. Conversely, Th2-type cytokines induce immunosuppression at the tumor site.¹⁶ The aim of this study was to detect the concentrations of IFN- γ , IL-17, IL-4 in breast tumor microenvironment. Our study revealed a significant increase in IL-4 concentration in malignant tumor tissue in comparison to benign tumor tissue. This was consistent with the study of Camp et al who assessed in situ cytokine production by lymphocytes in breast carcinoma and benign breast lesion using immunohistochemistry. They showed that IL-4 was produced and secreted by 36% of tumor-infiltrating lymphocytes (TILs) in malignant tumor tissue.¹⁷⁻¹⁹ However, the study of Asporid et al showed no increased secretion of IL-4 from breast tumor tissue (33 ± 11 pg/mL).²⁰ Contrary to Asporid et al results, our study exhibited a significant increase in the level of IL-4 secreted from breast tumor tissue and surrounding tissue.

Analyzing the data raised the possibility that the amount of IL-4 has been increased significantly in malignant tumor adjacent tissue than in benign tumor adjacent tissue. It seems that the elevated level of IL-4 in adjacent tissue of malignant tumor may be due to the release of cytokines from the malignant tumor tissue to the surrounding tissue. A study by Shurin et al reported the elevation of IL-4 and IL-10 cytokines in the serum of patients with breast cancer.¹⁹ In our study, serum level of IL-4 was elevated in tumor and adjacent tissue. In another study, estimated serum levels of IL-4 in patients with malignant breast cancer and normal woman were observed as 6.55 ± 1.68 pg/mL and 3.86 ± 0.15 pg/mL respectively. Herein, we

Table 2. Comparison of IL-17 Concentration in Malignant and Benign Tumors, Adjacent Tissues, and Serum Samples

Groups	Number	Mean pg/mL	SD pg/mL	P Value
Benign tumor tissue	60	9.2	2.4	0.01
Malignant tumor tissue	56	16.9	2.3	0.01
Adjacent tissue of benign tumor	60	9.9	2.4	0.02
Adjacent tissue of malignant tumor	56	13.0	4.4	0.02
Serum samples of patients with benign tumor	56	3.1	0.4	0.01
Serum samples of patients with malignant tumor	56	3.6	0.5	0.01

Table 3. Comparison of IFN- γ in Malignant and Benign Tumors, Adjacent Tissues, and Serum Samples

Groups	Number	Mean pg/mL	SD pg/mL	P Value
Benign tumor tissue	60	13.8	2.3	0.49
Malignant tumor tissue	56	14.6	3.8	0.49
Adjacent tissue of benign tumor	60	11.9	2.3	0.01
Adjacent tissue of malignant tumor	56	15.3	3.4	0.01
Serum samples of patients with benign tumor	56	3.8	0.5	0.04
Serum samples of patients with malignant tumor	56	4.3	0.8	0.04

reported a higher level of IL-4 in the serum of patients with malignant breast cancer (24.197 ± 3.932 pg/mL) and in the serum of patients with benign breast cancer (21.02 ± 2.722 pg/mL), though the numerical difference showed a similar increase of this cytokine in the serum of patients with malignant tumors.²¹ In this study, the cytokine IL-17 was significantly increased in malignant breast tissue compared to the amount of this cytokine in benign tumor tissue. Maniati et al showed an elevated level of IL-17 among several types of cancers including ovarian cancer, prostate cancer, breast and stomach cancer.²² An earlier study demonstrated an elevated level of IL-17 in tumor tissue.²³ We found significant increased level of IL-17 in adjacent tissue of malignant tumor compared to the surrounding tissue of benign tumor. Our results were consistent with those of Zhu et al.²⁴

The results of current study elucidated no significant difference between IFN- γ level in malignant tumor tissue and benign tumor tissue. These results were in agreement with the findings of Rosen et al, which demonstrated that, contrary to IL-4, there was no significant difference between the secretion level of Th1 cytokines such as IFN- γ in concanavalin A- (Con A) and P43 antigen-treated T cells of malignant breast cancer patients and benign tumor patients as well as serum level of IFN- γ between breast cancer patients and women with suspected breast cancer who had negative pathological features of breast cancer.¹⁸

In this effort, we measured the level of cytokine IFN- γ in the serum samples of patients with malignant breast cancer and benign breast tumor as 4.14 ± 0.835 pg/mL and 3.75 ± 0.53 pg/mL respectively. Our results were very similar to those obtained by Alimhojaeva who measured the level of IFN- γ in serums of patients with malignant breast cancer and normal woman as 6.3 ± 0.82 pg/mL and (4.55 ± 0.84) pg/mL respectively.²¹ Many studies assessed the in-situ production of cytokines within breast carcinoma and benign breast lesions using immunohistochemistry. In this regard, it was exhibited that IFN- γ was only produced and secreted by three percent of TILs in malignant tumor tissues and there was not any significant increase in the level of IFN- γ in breast cancer.¹⁸ Similarly, we did not observe a significant increase of IFN- γ in breast cancer.

IL-17 may exert its effects on tumor cells via 2 pathways: direct effect and indirect effect. IL-17 was shown to directly inhibit the death of multiple cancer cell lines in vitro. This cytokine also indirectly mediates its immune inductive activities through the induction of

epithelial cells, fibroblast and endothelial cells to secrete cytokines such as MMP, IL-4, IL-6, IL-8, IL-10.²⁵ Certain investigators such as Nam et al suggested the direct effects of the cytokine rather than the indirect effects,²⁶ though, Kozlowski et al reported that the serum concentrations of the cytokines such as IL-6, IL-8, and IL-10 are strongly associated with the breast cancer and with the clinical stage of the disease.²⁵ Muranski and Restifo showed that CD8+ T cell-derived IL-17 can directly act on a breast cancer cell line and exert pro-survival and anti-apoptotic effects.²⁷

According to our study, a relationship between the cytokine IL-4 and breast cancer was observed ($P < 0.001$) as it seems this cytokine is correlated with breast cancer. Toi et al reported that IL-4 suppressed the proliferation of cancer cells in vitro.²⁸ IL-4 is a cytokine with wide range of activities and is produced by mast cells and T lymphocytes. It also promotes the proliferation and immunoglobulin class switching to IgE in B cell. Gooch et al described IL-4 as an inhibitor of the growth and an inducer of apoptosis in some cancer cells in vitro. Gooch et al also showed that the IL-4 receptors are present on the cell surface membrane of tumor cells. These characteristics has potentiated this cytokine to be considered as a molecular option for targeted therapy in breast malignancies.²⁹ On the contrary, Conticello et al suggested that IL-4 may confer resistance to tumor cells upon apoptosis induction in some human malignancies. This may be promoted by Th2 responses programmed cell death in tumor cell.¹⁶

Conclusion

Collectively, cytokines IFN- γ , IL-4 and IL-17 are key players in antitumor/protumor immunity; thus, the present findings indicate that the concentration of IL-4 and IL-17 in tumor tissue may be associated with the severity of breast cancer. In order to confirm this observation, further research is needed to provide more definitive evidence.

Ethical Approval

Ethical approval was obtained from Ethics Boards of the Iranian public hospitals.

Conflicting Interests

No potential conflict of interests exists.

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