ORIGINAL ARTICLE

AG-2018-77
dx.doi.org/10.1590/S0004-2803.201800000-83

Serum cytokine of IL-2, IL-10 and IL-12 levels in patients with stomach adenocarcinoma

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Received 12/6/2018
Accepted 13/9/2018

ABSTRACT – **Background** – Gastric adenocarcinoma is the fourth most common cause of cancer-associated death worldwide. **Objective** – We evaluated the immunological status of patients with gastric cancer before surgery and circulating cytokines as potential diagnostic biomarkers for gastric cancer. **Methods** – We included 90 healthy controls and 95 patients with distal Gastric adenocarcinoma in Mazandaran, Sari, Iran. We measured serum IL-2, IL-10 and IL-12 Levels by a sandwich enzyme-linked immunosorbent assay using the IBL international GMBH kit. **Results** – The serum IL-10 levels in the patients with Gastric adenocarcinoma were significantly higher than those of the healthy controls (P=0.02). There were no significant differences in serum IL-2 and IL-12 levels between patients with gastric cancer and healthy controls. **Conclusion** – Increased levels of IL-10 might be useful as diagnostic biomarkers for Gastric adenocarcinoma; however, this needs to be confirmed with larger number of patients and with control groups other than blood donors, properly age paired. These results suggest that positive expression of IL-10 may be useful as a molecular marker to distinguish stage of gastric cancers which can be more readily controlled.

HEADINGS – Stomach neoplasms. Adenocarcinoma. Cytokines.

INTRODUCTION

Gastric cancer (GC) is the third type of cancer to its malignity and the second most common cause of death by cancer worldwide; approximately it is two thirds of new cases per year occur in the developing countries[1,2]. Mortality rates are higher in Asian and Latin American countries, where cases are usually diagnosed at later stages, leading to very low survival rates. It arises more in men, than women (2:1), 95% of cases are adenocarcinomas which is the most common malignant tumor regardless of age, race or inclining factors presented by a patient[3,4].

It has been found that the immune microenvironment in tumor tissues is highly organized in a molecular and cellular level[5]. It is complex of many diverse kinds of cells: such as endothelial cells, fibroblasts, lymphocytes and macrophages. It also contains numerous soluble molecules: such as growth factors, cytokines, chemokines which may have protumoral or anti-tumoral possessions that depend on the situation of the immune response[6-8]. It has been shown that through cytokine production, may promote tumor angiogenesis, metastasis and induce to T cell differentiation and activation. In different tumors, a propensity is detected on the expression of anti-inflammatory cytokines and a decreased expression of proinflammatory cytokines; this change in expression could ease tumor progression by subversion of the mechanisms of cell immunosurveillance[9-11].

Interleukin 2 (IL-2) is generated in an immune response Th1 cytokine, and interleukin 4 and 10 (IL4, IL10) are an immune response Th2 cytokines. These cytokines are crucial mediators of the Th1/ Th2 stability and they are involved in the process of inflammation-mediated carcinogenesis in human organs, including the gastrointestinal tract[3,12].

Interleukin-10 (IL-10) is a pleiotropic cytokine produced by macrophages, T-helper 2 (Th2) cells, and B lymphocytes and both can stimulate and suppress the immune response[13]. IL-10 production and secretion may be rationally presumed to be up-regulated in cancer patients. Actually, increased serum levels of IL-10 have been established in patients with diverse histotypes of solid and hematopoietic tumors and these levels have been shown to associate with level of disease[14,15]. In addition, it has been proposed that IL-10 may be released not only by immune cells but directly by tumor cells because serum levels of this cytokine often associate with tumor load, while surgical excision of neoplasia may be followed by a reduction in IL-10 serum levels[14,16,17].

Interleukin-12 (IL-12) was initially recognized as a natural killer (NK) cell stimulatory factor, being a disulfide-linked heterodimeric cytokine composed of 35 and 40 KDa subunits. Secreted mainly by antigen presenting cells (APC), such as macrophages, some B cells, and dendritic cells, IL-12 activates NK cells and T cells to produce interferon-γ (INF-γ), and expands their cytotoxic activity and proliferation[18]. Interleukin-12 was newly found to induce antitumor effects against a different types of tumors in vivo. Besides, it is an immunoregulatory cytokine, which may provide a vital connec-

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
The authors declare that there is no conflict of interest regarding the publication of this article.
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tion between nonspecific immune mechanisms and the expansion of a specific T cell-mediated immune response[19-21]. A primary in vitro study proposed that the administration of IL-12 produced immunomodulatory activity and generated noticeable antitumor activity. Although some detectives have inspected the effects of intravenous IL-12 on patients with metastatic renal cell cancer or malignant melanoma, there are very few reports on serum IL-12 levels in cancer-bearing patients[20,22].

The inflammatory mediators produced nearby in the gastric mucosa may spread on the blood circulation and be found in plasma samples. In this study, we tested the hypothesis that circulating levels of inflammatory cytokines could work as indirect indicators of tissue damage, and that their measurement might be a useful biomarker for the early detection of GC, resulting in a better long-term prognosis. Therefore, we measured the serum IL-2, IL-10 and IL-12 levels of patients with gastric cancer before surgery, to evaluate the preoperative immunological status of these patients.

METHODS

Study population and blood samples

We examined 95 patients aged from 22 to 90 years, admitted to hospital for surgical treatment. As a control for normal serum, IL-2, IL-10 and IL-12 concentrations, 90 healthy clinical personnel volunteered. Written informed consent was obtained from all patients. Blood samples were collected before surgery and specimens were stored at -80°C until later analysis.

Cytokine assays

The concentration of IL-2, IL-10 and IL-12 in plasma samples was measured by ELISA using commercially available kits, (IBL international IBL GMBH, Germany) via captur-sandwich assay according to the manufacturer's instructions. The concentration of cytokines was calculated based on standard curves provided with the kits, and results were expressed in ng/ml. For ELISA all samples were tested in duplicate and the average values were used in the analysis[4].

Statistical analysis

A statistical descriptive analysis was performed using Prism statistical software Results are expressed as mean ±SD. One-way analysis of variance (ANOVA) followed by Tukey's multiple comparison post hoc tests was used to compare the results of all assays. Value of $P<0.05$ was considered to be significant[8].

RESULTS

TABLE 1 shows the demographics of the 60 male and 35 female enrolled patients and healthy controls.

TABLE 2 shows the Serum IL-2, IL-10 and IL-12 levels in healthy subjects and patients with gastric adenocarcinoma.

FIGURE 1 shows the serum levels of Serum IL-2, IL-10 and IL-12 levels in patients and healthy controls. We found significantly increased IL-10 serum levels in GC patients, in comparison to healthy controls ($P=0.02$). Circulating levels of all IL-2 and IL-12

TABLE1. Characteristics of patients and healthy controls.

Sample	Number	Age (mean)	Gender		Tumor type		Tumor stage		
			Male	Female	Adenocarcinoma	SCC	I	II	III
Patient	95	62	60	35	69	26	40	30	25
Normal	90	51	50	40	–	–		–	

TABLE 2. The Serum IL-2, IL-10 and IL-12 levels in healthy subjects and patients with gastric adenocarcinoma.

IL	Mean ± SEM of cancer	Mean ± SEM of control	Difference between means	95% confidence interval	R squared	*P* value
IL2	0.152 ± 0.045	0.152 ± 0.045	0.152 ± 0.045	0.152 ± 0.045	0.152 ± 0.045	0.152 ± 0.045
IL10	0.02752 ± 0.002	0.02752 ± 0.002	0.02752 ± 0.002	0.02752 ± 0.002	0.02752 ± 0.002	0.02752 ± 0.002
IL12	0.3483 ± 0.028	0.3483 ± 0.028	0.3483 ± 0.028	0.3483 ± 0.028	0.3483 ± 0.028	0.3483 ± 0.028

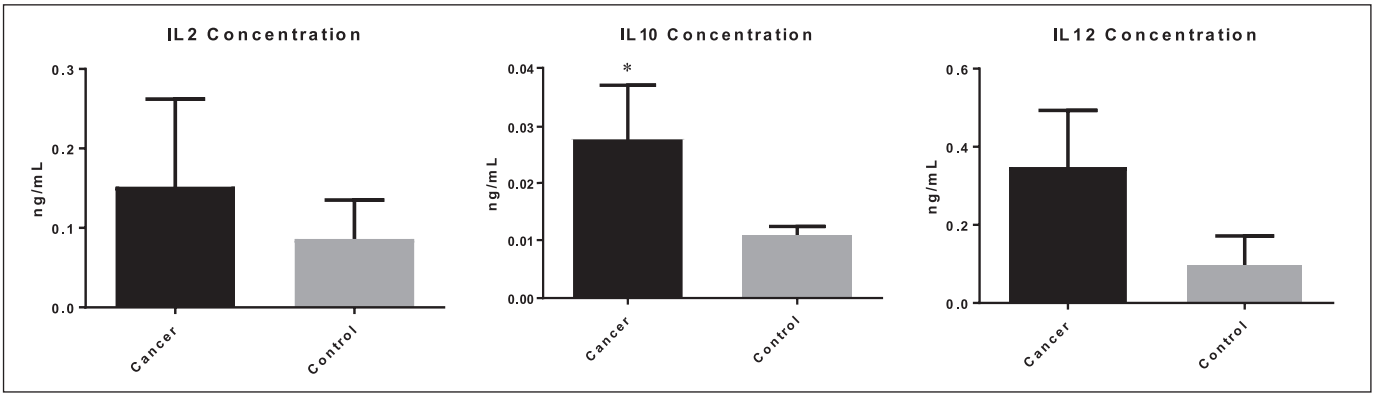

FIGURE 1. The serum levels of Serum IL-2, IL-10 and IL-12 levels in patients and healthy controls. The sign (*) show significantly ($P<0.05$) increased compared to the control group.

were higher in GC patients than in the healthy control group but there were no significant differences among them.

DISCUSSION

Over the last few years, a number of findings, ranging from the molecular characterization of tumor antigens to the recognition of costimulatory molecules, have provided critcal visions into our knowledge of tumor immunology[23,24]. The immune system is capable to respond to cancer, because activated mononuclear cells can be established both peripherally and at the tumor site; however, failure by lymphocytic infiltrates to contain tumor growth proposes an insuffisient immune response to neoplasms[25]. Indications proofs the idea that the type of T-helper (Th) response may be relevant to the expansion of an effective immune response because of the communally conflicting effects of the cytokines produced. In fact, although Th1-type cytokines (i.e., IL-2 and interferon-γ) have been shown to increase the antitumor activity of cytotoxic T-cells in vitro, Th2-type cytokines, and IL-10 in particular, have been confirmed to apply reverse effects[26-28]. IL-10 inhibits the Th1-type pathway activation, averts APC from procurement access to tumor antigens, and down-regulates surface expression of costimulatory molecules CD80 or CD86 on tumor cell. As it is known that IL-10 is Th2- cytokine, which increases antibody synthesis, indorses the humoral immune response and suppresses the antitumor immunity, established by Stanilov et al.[29,30]. who showed that Functional antagonist of IL-12p70 is the IL-10 which was of high level in the serum of a 48 colorectal cancer patients.IL-10 appears to be more of a pro-tumor than anti-tumor properties. The pro-tumor properties of IL-10 can be clarified by the inhibitory effect on the Th1-cytokine production, in particular IL-12p70, its inhibitory effect by involving apoptosis and stimulation of cell proliferation[31,32]. Also, there is confirmation that the tumor infiltrated lymphocytes inside the tumor mass are not effective because some tumor cells secrete IL-10. IL-10 secretion is one of the mechanisms with which the tumor cells "prevent" the immunological surveillance which at the end will also associate to increase the IL-10 serum level which can elucidate the important increased level of serum IL-10 in our study[33,34]. The essential roles of different cytokines in regulating antimicrobial immunity and inflammation make them attractive candidates for being genetic host markers in assessing individual susceptibility to Gastric Cancer progress[35].

In this investigation we have studied the levels of inflammation-associated cytokines such as IL-2, IL 10 and IL-12 in the sera of gastric cancer patients. Since the levels of IL-2, IL-10 and IL-12 may be produced by normal cells, it was important to establish the levels of these cytokines in benign conditions. As expected based on its in vitro properties, in the current study a positive correlation between the presence of gastrointestinal tumors and high IL-10 concentrations was found. Elevated serum levels of IL-10 in fact were observed in patients with advanced gastrointestinal malignancies when compared with healthy controls; moreover, IL-10 serum levels were demonstrated to be higher in patients with metastatic disease compared with patients with disseminated disease. In our study the significant increase of the IL10 serum level may be because the association of IL-10 genotypes (single nucleotide polymorphism) with Gastric Cancers appears to be biologically and clinically important. IL-10 is a key immunosuppressive cytokine that gears the immune response towards a Th2 cell response. Such IL-10 haplotypes are related to susceptibility and severity of Gastric Cancers. The finding that there was an increased risk of Gastric Cancers in high IL-10 producer haplotype was in agreement with the concept that Th2 cytokines including IL-10 are highly expressed in patients with Gastric Cancers as was shown in our study results and This idea could partially be clarified by reported findings that increased expression of mRNA and raised serum levels of IL-10 are correlated with the progression of Gastric Cancers[15,36-37]. Similar results recently have been reported in patients with different histotypes of solid and hematopoietic tumors suggesting that IL-10 overproduction may be a communal survival strategy of several types of human malignancies[38]. Also keeping in mind that inflammatory cells may be less frequent within metastases than in primary lesions, it is likely that the main source of IL-10 may be the tumor itself rather than the inflammatory infiltrates[39].

Certainly, a number of studies have uttered on IL-10 gene activation and IL-10 protein production in some tumor specimens and cell lines[40-43]. In addition, IL-10 serum levels showed an advance significant increase in nonresponder patients, whereas these levels were shown to be unmodified in responder patients at the end of the follow-up period. These results suggest that positive discovery of IL-10 expression may be used as a molecular marker for characterizing of gastric. Xiong-Fei in his paper said that since IL-10 can both reduce and enhance anti-cancer possessions, it may be significant to discover the role of IL10 polymorphisms in the development of Gastric Cancer in different clinical stages, or Gastric Cancer of different subsites[44]. Results of another study demonstrated that the intraperitoneal with IL-10 treatment was able suppressed peritoneal dissemination of gastric cancer cells and reduce peritoneal metastasis and increase survival rate, in the inoculated mice[3]. Relative to IL-10, Jing Liang, found increased expression of IL 10 in patients with stages III and IV with low level differentiations possessed significantly higher positive detection ratios than patients with moderate or high-level differentiation in the Chinese population[3,45,46]. Whence is necessary and very important, to study a larger population of patients with cancer, to understand the role of the IL-2, IL-10 and IL-12 cytokines in the immune response suppression induced by tumor cell in gastric cancer, to be used as molecular markers to distinguish different stages of cancer, offering the patient a better quality of life and a longer survival rate.

In conclusion, the increased IL10 serum level in gastric cancer may be due to the Functional antagonism of IL-10 toward IL-12p70 which will cause more IL10 secretion and may be the secretion of this cytokine by the tumor cell itself to modulate the Immune system towards Th2 rather than Th1. While in gastric cancers the association of IL-10 genotypes with Gastric Cancers specifically the single nucleotide polymorphism of the IL10 promoter region may be the cause of such serum elevation. If this hypothesis is true, the inhibition of IL-10 production or the administration of anti-IL-10 agents could become a new therapeutic tools for treating patients with GC. The results of the current study show that measurement of basal levels of serum IL-10 is of independent prognostic utility in patients with advanced gastrointestinal carcinoma and may be useful for the detection of disease progression.

Shokrzadeh M, Mohammadpour A, Hoseini V, Abediankenari S, Ghassemi-Barghi N, Tabari YS. Níveis séricos de citocinas IL-2, IL-10 e IL-12 em pacientes com adenocarcinoma do estômago. Arq Gastroenterol. 2018;55(4):385-9.

RESUMO – **Contexto** – O adenocarcinoma gástrico é a quarta causa mais comum de morte relacionada ao câncer em todo o mundo. **Objetivo** – Avaliar o status imunológico dos pacientes com câncer gástrico antes da cirurgia e as citocinas circulantes como potenciais biomarcadores diagnósticos para câncer gástrico. **Métodos** – Incluímos 90 indivíduos controles saudáveis e 95 pacientes com adenocarcinoma gástrico distal em Mazandaran, Sari, Iran. Os níveis de soro Il-2, IL-10 e Il-12 foram medidos por um ensaio de imunoabsorção enzimática pela técnica de sanduíche usando o kit IBL International GmbH. **Resultados** – Os níveis séricos IL-10 nos pacientes com adenocarcinoma gástrico foram significativamente superiores aos dos controles saudáveis (P=0,2). Não houve diferenças significativas nos níveis de soro IL-2 e IL-12 entre pacientes com câncer gástrico e controles saudáveis. **Conclusão** – Níveis aumentados de IL-10 podem ser úteis como biomarcadores diagnósticos para adenocarcinoma gástrico; no entanto, isso precisa ser confirmado com maior número de pacientes e com grupos de controle que não sejam doadores de sangue, adequadamente emparelhado por idade. Estes resultados sugerem que a expressão positiva do IL-10 pode ser útil como um marcador molecular para distinguir a fase de câncer gástrico que pode ser mais facilmente controlada.

DESCRITORES – Neoplasias gástricas Adenocarcinoma. Citocinas.

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