Research Article

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Soluble IL-1 decoy receptor is associated with gastric adenocarcinoma
Solubl IL-1 tuzak reseptör mide adenokarsinomu ile ilişkilidir

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Abstract

**Background:** In recent years, studies on gastric cancer include changes in cancer associated immune system activation and the levels of immune system markers. It has been demonstrated that TNF-α (tumor necrosis factor-alpha) and IL-6 (interleukin-6) play a role in inflammatory associated carcinogenesis.

**Objective:** Our aim was to investigate serum soluble IL-1 decoy receptor (sIL-1RII), TNF-α and IL-6 levels in gastric adenocarcinoma patients.

**Materials and methods:** Male gastric adenocarcinoma patients and dyspeptic participants, in total 55 cases were included. Serum sIL-1RII, TNF-α and IL-6 concentrations were measured.

**Results:** The median sIL-1RII levels of the patients were statistically significantly lower than the median of the control group (3111 ng/mL; 3601 ng/mL, respectively) (p = 0.003). But the median TNF-α and IL-6 levels (58.17 ng/mL; 10.22 ng/mL, respectively) were both numerically higher than those of control group levels (16.62 ng/mL; 5.74 ng/mL, respectively). Also, patients’ median TNF-α levels were found statistically significantly higher (p = 0.034).

**Conclusion:** This study showed the increase of TNF-α, IL-6 levels and for the first time the decrease of sIL-1RII in gastric cancer patients. We propose that negative regulation of gastric cancer using sIL-1RII could be a new anti-cancer strategy.

**General significance:** Our study provides target pathways for further studies in the pathophysiology of gastric cancer.

**Keywords:** Gastric adenocarcinoma; Male patients; Soluble IL-1 decoy receptor; Tumor necrosis factor-alpha; Interleukin-6.

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Özet

**Genel bilgiler:** Son yıllarda mide kanseri üzerindeki çalışmaları, kanserili immun sistem aktivasyonu ve immun sistem markırları seviyelerindeki değişiklikleri içermektedir. TNF-α (tümör nekroz faktör-alfa) ve IL-6 (interlökin-6)’nın enfamasyon ilişkili karsinogenezde rol oynamalarını kanıtlanmıştır.

**Amaç:** Amacımız, mide adenokarsinomlu hastalarda serum solubl IL-1 tuzak reseptör (sIL-1RII), TNF-α ve IL-6 seviyelerini araştırmak idi.

**Materyal ve Metodlar:** Erkek mide adenokarsinoma hastaları ve dispeptik katılımcılar, toplam 55 hasta dahil edildi. Serum sIL-1RII, TNF-α ve IL-6 seviyelerini araştırmak idi.

**Bulgular:** Hastaların sIL-1RII seviyeleri, kontrol grubunun medyan seviyelerinden (3111 ng/mL; 3601 ng/mL, sırasıyla) (p = 0.003) anlamlı düşüktü. Fakat, hastaların TNF-α ve IL-6 seviyeleri (58.17 ng/mL; 10.22 ng/mL, sırasıyla) kontrol grubunun seviyelerinden (16.62 ng/mL; 5.74 ng/mL, sırasıyla) anlamlı yüksekti (p = 0.034).

**Sonuç:** Bu çalışma mide kanserli hastalarda TNF-α, IL-6 düzeylerinde artış ve ilk kez sIL-1RII düzeylerinde azalma olduğunu gösterdi. sIL-1RII kullanarak mide kanserinin negatif regüasyonunun, yeni bir anti-kanser strateji olabileceğini önermektedir.
Introduction

Gastric cancer is the fourth most commonly diagnosed malignancy and the second leading cause of cancer death, worldwide [1]. Recurrence and metastasis are the main causes of death in gastric cancer patients and the only potentially curative treatment is surgery. The prognosis of gastric cancer has improved in the recent few decades, but the overall 5-year survival rate is still poor [2, 3].

Epidemiological studies have reported the relationship between inflammatory markers in circulatory system and the risk of chronic diseases. Initially, cytokines were discovered as the secretory proteins controlling several immune functions. Today it is clear that they can interfere cancer biology [4]. Causal relationship between inflammation and cancer has been proven [5–7]. Several types of inflammation potentially can increase cancer risk and can promote cancer development and progression [8].

Tumor associated inflammation requires presence and activation of inflammatory cells, such as macrophages and granulocytes, around the tumor microenvironment, formation of inflammatory mediators by tumor cells and stromal cells, tumor remodeling and angiogenesis. The reciprocal relationship between the anti-tumor (immunesurveillance) and pro-tumor (cancer promoting inflammation) arms of the immune system should be kept in mind because it is important to evaluate the therapeutic efficacy of agents that interfere with activation of protumorigenic pathways in combination with agents or treatment that enhance anti-tumor immunity [9].

TNF-α, showing the effects through type 1 and type 2 receptor, is a 26 kDa transmembrane protein. IL-6 is a glycoprotein cytokine, consists of 184 amino acids and approximately 26 kD molecular weight. They show their effects on tumors with different biological mechanisms such as causing DNA damage, stimulation of the proliferation and metastasis of tumor cells and inhibition of apoptosis by activation of NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) [10, 11]. Members of the IL-1 (interleukin-1) family play a key role in innate and adaptive immunity and in the pathogenesis of various diseases such as cancer, arthritis, heart disease, pancreatitis, multiple myeloma and stroke [12, 13]. IL-1 system comprises two agonists (IL-1alfa and IL-1beta), converting enzymes, antagonists, two receptors: Interleukin 1 receptor type I and type II (IL-1RI and IL-1RII) and an IL-1 receptor accessory protein. IL-1RII, is not a signal generating molecule. Several lines of evidence are consistent with the view that the IL-1RII is a bona fide IL-1 decoy. IL-1RII is the first defined pure decoy receptor. In membrane-bound or soluble form of IL-1RII acts as a decoy, capturing with high affinity to IL-1, and preventing it from interacting with IL-1RI and reducing IL-1 bioavailability [14]. Decoy receptors regulate the primary pro-inflammatory cytokines’ and chemokines’ efficacy. Decoy receptors are candidate targets for therapeutic interventions. To evaluate the regulation and the potential of decoy receptors are important approaches [15]. So, it is clinically important to evaluate circulatory soluble receptor levels. In the assessment of systemic inflammation processes, changings in sIL-1RII levels as an anti-inflammatory marker were observed in various studies [16, 17]. To the best of our knowledge, this is the first report describing the relation between sIL-1RII and gastric adenocarcinoma.

Materials and methods

Patients

Patients group included 30 male patients who were referred for upper gastrointestinal endoscopy, and whose endoscopic biopsy samples were diagnosed as gastric adenocarcinoma in histopathological examination. Twenty five male dyspeptic subjects, in terms of body mass index similar to patients’ group, were included to the study as a control group. None of the participants had undergone gastrointestinal surgery before our study. Secondary malignancy, hypertension, diabetes mellitus and other metabolic diseases were the exclusion criterions. All samples were obtained with written informed consent of the patients prior to their inclusion and the study was approved by Kayseri Erciyes University Faculty of Medicine Human Ethics Committee.

Evaluation of sIL-1RII, TNF-α and IL-6 concentrations

After 12 h fasting, on the day of endoscopy, venous blood samples were taken between 08.00 and 09.00 a.m. They
were centrifuged for 10 min at 2000 rpm and serum was separated and stored at –80°C until the assay was determined. Serum sIL-1RII, TNF-α and IL-6 concentrations were measured by commercial enzyme linked immunosorbent assay kits (Adipo Bioscience; California, United States and Boster; United States ELISA kits), based on the protocol provided by the manufacturer.

Statistical analyses

Statistical analysis was done by using the SPSS version 17 (Statistical Package for Social Science; Chicago, IL, USA). The results of groups with normal distribution are presented as mean±SD, and the median was used to present results that showed abnormal distribution. To determine significant differences between the groups, t-test for data with normal distribution and Mann-Whitney U test for data with non-normal distribution were used. The p values ≤0.05 of the obtained results was accepted as statistically significant.

Results

Baseline characteristics and clinical findings of patients with gastric adenocarcinoma and control subjects are listed in Table 1. The 30 male patients with a mean age of 64.26±9.84 years were enrolled in our study. The control group included 25 dyspeptic male subjects with a mean age of 58.32±13.89 years. The median sIL-1RII levels of the patients were found to be statistically significantly lower compare to the median of the control group (3111 ng/mL and 3601 ng/mL, respectively) (p=0.003). But the median TNF-α and IL-6 levels (58.17 ng/mL and 10.22 ng/mL, respectively) were both numerically higher than those of control group levels (16.62 ng/mL and 5.74 ng/mL, respectively). Median TNF-α levels of the patients were also found statistically significantly higher (p=0.034) (Table 1). For each histological types of gastric cancer, patients’ serum IL-6, TNF-α and sIL-1RII levels were shown as mean±SD in Table 2.

Discussion

Gastric cancer are often diagnosed incidentally and with further complications. The prognosis is poor and in many industrial countries 5-year survival from the diagnosis is only 10% [18]. Eating habits, infections, genetic predisposition, a variety of environmental risk factors are responsible for the development of gastric cancer [19]. At least 20% of all cancer arises in the relationship between infection and chronic inflammation. High levels of cytokine

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<th>Table 1: Comparison of baseline characteristics/findings between patients and the control group.</th>
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<sup>a</sup>Histological type: MA, moderately differentiated adenocarcinoma; PA, poorly differentiated adenocarcinoma; SRC, signet ring cell carcinoma; UC, undifferentiated. <sup>b</sup>Mann-Whitney test. Data are median and interquartile range (25%; 75%). NS, non-significant.

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<th>Table 2: Patients’ serum IL-6, TNF-α and sIL-1RII levels (mean±SD) for each histological types of gastric cancer.</th>
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<td><strong>Histological type&lt;sup&gt;a&lt;/sup&gt;</strong></td>
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<sup>a</sup>MA, moderately differentiated adenocarcinoma; PA, poorly differentiated adenocarcinoma; SRC, signet ring cell carcinoma; UC, undifferentiated.
expressions with dense inflammatory infiltrates can be seen in the tumor microenvironment. Many cytokines, play a role as a growth and survival factor in premalignant cells, stimulate angiogenesis, tumor progression and metastasis, and even continues to tumor developing inflammation [9, 20]. TNF-α and IL-6 show their effects on tumors with different biological mechanisms such as causing DNA damage, stimulation of the proliferation and metastasis of tumor cells and inhibition of apoptosis by activation of NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells) [10, 11]. The role of these agents in gastric cancer has been mentioned in past studies. There are several reports demonstrating that elevated serum TNF-α and IL-6 levels correlate with disease status and could be used as prognostic factors [21–24]. In our study, in accordance with the literature, we found patients’ TNF-α and IL-6 levels higher than controls’.

Pro-inflammatory cytokine IL-1 is thought to play a role in many diseases such as cancer, arthritis, heart diseases, pancreatitis, multiple myeloma and stroke. Recent studies showed that gastric metaplastic changes were dependent on IL-1 signaling and also cytokines associated with interleukin-1 involved into gastric carcinogenesis [25, 26]. But to the best of our knowledge, there is no study about its decoy receptor: sIL-1RII.

Thousands or millions of defense mechanisms are available in the human organism. IL-1 decoy receptor is a subtype of IL-1 receptors and is identified as one of these defense mechanisms. IL-1RII binds to a ligand and inhibits its activity, in other words, fulfills the role of decoy receptor. Basically, the primary purpose of the measurement of soluble IL-1RII is to clarify the relationship between chronic inflammation and gastric cancer. The limitation of our study is its number of participants. There is a need for further studies evaluating sIL-1RII levels with a larger number of patients with gastric adenocarcinoma and new researches should focus on whether we need new treatment strategies for these patients using sIL-1RII.

In conclusion, IL-1, IL-6 and TNF-α are elevated in, if not all, but in most inflammatory diseases and have been noticed as targets of therapeutic interventions. IL-6 is secreted as a pro-inflammatory agent and anti-inflammatory effect of IL-6 is known to be mediated by TNF-α [27]. This study showed an increase of these two parameters (IL-6 and TNF-α) in gastric cancer patients. In this study, performed for the first time in gastric cancer patients, sIL-1RII levels were found to be statistically significantly lower, compare to the levels of the control group. Our findings suggest that TNF-α and IL-6 should be taken into account the role in the growth and pathogenesis of malignancies such as gastric cancer. In addition, decreased levels of sIL-1RII in patients showed us the serious damage in the defense mechanism (sIL-1RII) in gastric adenocarcinoma.

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Conflict of interest: No conflict of interest was declared by the authors.

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