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.

Özet

Genel bilgiler: Son yıllarda mide kanseri üzerindeki çalışmalar, kanser ilişkili immün sistem aktivasyonu ve immün sistem markırları seviyelerindeki değişiklikleri içermektedir. TNF-α (tümör nekroz faktör-alfa) ve IL-6 (interlökin-6)'nın enflamasyon ilişkili karsinogenezde rol oynadıkları 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 adenokarsinomu olan hastalar ile dispeptik katılımcılar, toplam 55 hasta dahil edildi. Serum sIL-1RII, TNF-α ve IL-6 konsantrasyonları ölçüldü.
Bulgular: Hastaların sIL-1RII medyan değerleri, kontrol grubun medyan değerlerine göre istatistiksel olarak anlamlı düşük idi (3111 ng/mL; 3601 ng/mL, sırasıyla) ($p=0.003$). Fakat TNF-α ve IL-6 medyan değerleri (58.17 ng/mL; 10.22 ng/mL, sırasıyla) sayısal olarak kontrol grubun medyan değerlerine göre daha yüksek idi (16.62 ng/mL; 5.74 ng/mL, sırasıyla). Aynı zamanda, hastaların medyan TNF-α değerleri istatistiksel olarak anlamlı yüksek olarak bulundu ($p=0.034$).
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 regülasyonunun, yeni bir anti-kanser strateji olabileceğini önermekteyiz.

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Genel önemi: Çalışmamız, mide kanseri patofizyolojisi ile ilgili yapılacak ileri çalışmalar için hedef yolaklar sağlamaktadır.

Anahtar Kelimeler: Mide adenokarsinomu; Erkek hastalar; Solubl IL-1 tuzak reseptör; Tümör nekroz faktör-alfa; Interlökin-6

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 bonafide 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

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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 use 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.

Table 1: Comparison of baseline characteristics/findings between patients and the control group.

Baseline characteristics/ findings	Gastric adenocarcinoma	Control	p-Value
n	30	25	
Sex (M)	30	25	
Age	64.26 ± 9.84	58.32 ± 13.89	NS
BMI			NS
< 24.9	19	8	
25–29.9	10	14	
30–34.9	1	3	
35–39.9	–	–	
> 40	–	–	
Histological type[a]			
MA	4	–	
PA	19	–	
SRC	4	–	
UC	3	–	
Stage			
II	4		
III	15	–	
IV	3	–	
Distant metastasis			
M0	27	–	
M1	3	–	
sIL-1RII (ng/mL)	3111[b] (2631; 3351)	3601[b] (3016; 3816)	0.003
TNF-α (ng/mL)	58.17[b] (17.48; 98.60)	16.62[b] (7.82; 30.58)	0.034
IL-6 (ng/mL)	10.22[b] (2.31; 11)	5.74[b] (1.41; 13.88)	> 0.05

[a]Histological type: MA, moderately differentiated adenocarcinoma; PA, poorly differentiated adenocarcinoma; SRC, signet ring cell carcinoma; UC, undifferentiated. [b]Mann-Whitney test. Data are median and interquartile range (25%; 75%). NS, non-significant.

Table 2: Patients' serum IL-6, TNF-α and sIL-1RII levels (mean ± SD) for each histological types of gastric cancer.

Histological type[a]	n	IL-6	TNF-α	sIL-1RII
MA	4	19.79 ± 4.31	30.57 ± 22.56	3051 ± 1509.53
PA	19	10.87 ± 7.0	55.31 ± 48.86	3174.59 ± 519.04
SRC	4	8.17 ± 1.28	64.16 ± 54.26	2806 ± 473.15
UC	3	15.32 ± 0.14	52.76 ± 33.80	2791 ± 423.63

[a]MA, moderately differentiated adenocarcinoma; PA, poorly differentiated adenocarcinoma; SRC, signet ring cell carcinoma; UC, undifferentiated.

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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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 NFκB (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.

References

1. Atrkar-Roushan Z, Kazemnejad A, Mansour-Ghanaei F, Zayeri F. Trend analysis of gastrointestinal cancer incidences in guilan province: comparing rates over 15 years. Asian Pac J Cancer Prev 2013;14:7587–93.
2. Kunz PL, Gubens M, Fisher GA, Ford JM, Lichtensztajn DY, Clarke CA. Long-term survivors of gastric cancer: a California population-based study. J Clin Oncol 2012;30:3507–15.
3. Hartgrink HH, Jansen EP, vanGrieken NC, Vande Velde J. Gastric cancer. Lancet 2009;374:477–90.
4. Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest 2007;117:1175–83.
5. Germano G, Allavena P, Mantovani A. Cytokines as a key component of cancer –related inflammation. Cytokine 2008;43:374–79.
6. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–67.
7. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883–99.
8. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436–44.
9. Grivennikov SI, Karin M. Inflammation and oncogenesis: a vicious connection. Curr Opin Genet Dev 2010;20:65–71.
10. Multhoff G, Molls M, Radons J. Chronic inflammation in cancer development. Front Immunol 2011;2:98.
11. Łukaszewicz M, Mroczko B, Szmitkowski M. Clinical significance of interleukin-6 (IL-6) as a prognostic factor of cancer disease. Pol Arch Med Wewn 2007;117:247–51.
12. Jablonska E, Piotrowski L, Kiluk M, Jablonski J, Grabowska Z, Markiewicz W. Effect of IL- 15 on the secretion of IL-1beta, IL-1Ra and sIL-1RII by PMN from cancer patients. Cytokine 2001;16:173–77.
13. Pruitt JH, Welborn MB, Edwards PD, Harward TR, Seeger JW, Martin TD, et al. Increased soluble interleukin-1Type 1 receptor concentrations in postoperative patients and in patients with sepsis syndrome. Blood 1996;87:3282–88.
14. Garlanda C, Riva F, Bonavita E, Gentile S, Mantovani A. Decoys and regulatory "receptors" of the IL-1/Toll-like receptor superfamily. Front Immunol 2013;4:180–93.
15. Mantovani A, Locati M, Vecchi A, Sozzani S, Allavena P. Decoy receptors: a strategy toregulate inflammatory cytokines and chemokines. Trends Immunol 2001;22:328–36.
16. van Dielen FM, Veer C, Schols AM, Soeters PB, Buurman WA, Greve JW. Increased leptin concentrations correlate with

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increased concentrations of inflammatory markers in morbidly obese individuals. Int J Obes 2001;25:1759–66.
17. Colotta F, Re F, Muzio M, Bertini R, Polentarutti N, Sironi M, et al. Interleukin-1 type II receptor: a decoy target for IL-1 that is regulated by IL-4. Science 1993;261:472–75.
18. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Ann Oncol 2005;16:481–88.
19. Pellicano R, Mladenova I, Martinotti R, Fagoonee S, Rizzetto M. Gastric cancer and Helicobacter pylori: an interdisciplinary point of view. Minerva Med 2006;97:31–38.
20. Greten FR, Karin M. NF-kB: linking inflammation and immunity to cancer development and progression. Nat Rev Immunol 2005;5:749–59.
21. Wu CW, Wang SR, Chao MF, Wu TC, Lui WY, P'eng FK, et al. Serum interleukin-6 levels reflect disease status of gastric cancer. Am J Gastroenterol 1996;91:1417–22.
22. Ashizawa T, Okada R, Suzuki Y, Takagi M, Yamazaki T, Sumi T, et al. Clinical significance of interleukin-6 (IL-6) in the spread of gastric cancer: role of IL-6 as a prognostic factor. Gastric Cancer 2005;8:124–31.
23. Lin MT, Lin BR, Chang CC, Chu CY, Su HJ, Chen ST, et al. IL-6 induces AGS gastric cancer cell invasion via activation of the c-Src/RhoA/ROCK signaling pathway. Int J Cancer 2007;120:2600–08.
24. Gorouhi F, Islami F, Bahrami H, Kamangar F. Tumour-necrosis factor-A polymorphisms and gastric cancer risk: a meta-analysis. Br J Cancer 2008;98:1443–51.
25. Huang FY, Chan AO, Rashid A, Wong DK, Seto WK, Cho CH, et al. Interleukin-1β increases the risk of gastric cancer through induction of aberrant DNA methylation in a mouse model.Oncol Lett 2016;11:2919–24.
26. Matveeva LV, Mosina LM. The role of interleukin-1 and associated cytokines in gastric carcinogenesis. Vestn Ross Akad Med Nauk 2012;11:59–65.
27. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta 2011;1813:878–88.

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