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CYTOKINES AND GASTRIC CANCER: CLINICAL ASPECTS

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Abstract:

Gastric cancer (GC) is one of the leading causes of cancer-related deaths worldwide. Interest in early diagnosis and effective therapy of this disease is steadily growing. The progression of malignant tumors, as well as the effectiveness of treatment and prognosis of disease development, are closely related to changes in the immune system. Cytokines are protein signaling molecules that play a key role in the interaction between cells of the immune system and other body systems. Recent studies have revealed the influence of cytokines on the development of malignant tumors of the stomach. Cytokines are involved in the process of carcinogenesis, exhibiting both pro-oncogenic and anti-oncogenic properties. Helicobacter pylori infection causes chronic inflammation in the stomach wall, which is the first step in the path of gastric carcinogenesis. The influence of cytokines on the development of GC in H. pylori infection has been noted. One of the most important aspects of the clinical characteristics of cytokines in GC is the prognosis of treatment effectiveness. In addition, studies of the role of cytokines in gastric cancer are important for diagnostics and open up new approaches to therapy.

Keywords: stomach cancer, cytokines, carcinogenesis, diagnostics, prognosis, treatment, Helicobacter pylori.

Introduction

Introduction

Gastric cancer (GC) is a global health problem, as it is the fifth most common malignant disease in the world and the fourth most common cause of mortality [1]. Cytokines in GC are associated with angiogenesis, metastasis, and chemoresistance, which are key factors that can affect tumor progression, quality of life, and patient survival [2]. During the development of a malignant tumor, cytokines have a multidirectional effect on the tumor, stimulating or inhibiting it. The study of the role of cytokines in GC expands the range of diagnostic and therapeutic possibilities.

Cytokines in diagnostics and prognosis of gastric cancer

Interleukin (IL) receptor type 1 2 (IL-1R2), also known as CD121b, is a member of the IL-1 receptor family. IL-1R2 acts as a negative regulator of the IL-1 system by modulating the availability of IL-1 for the signaling receptor. IL-1R2 is highly expressed in GC tissues, and overall survival in patients with advanced GC and high IL-1R2 expression is significantly lower than in advanced GC and low IL-1R2 expression [3].

IL-4 and IL-13 are known to regulate inflammatory and immune responses. These ILs can mediate survival and metastasis in GC [4].

One of the important cytokines in the tumor microenvironment is IL-6, which is involved in the differentiation of T cells, natural killers and macrophages. Patients with GC have been found to have higher expression of IL-6, so this cytokine may be a useful diagnostic marker of GC [5]. High levels of IL-6 correlate with poor survival in patients with GC [6].

A correlation was found between the levels of serum amyloid A, IL-6, advanced stage and distant metastases in GC [7]. The clinical significance of circulating tumor cells and cytokines in peripheral blood in preoperative prediction of peritoneal metastases in advanced GC was investigated. The levels of circulating tumor cells and IL-6 in patients with GC with peritoneal metastases were higher than in patients without peritoneal metastases [8].

The ratio of IL-6/IL-10 mRNA expression is considered an independent prognostic marker of overall survival in gastric adenocarcinoma [9].

A member of the chemokine family, IL-8, promotes tumor angiogenesis and the immunosuppressive nature of its microenvironment through neutrophil and myeloid-derived suppressor cell chemotaxis. Analysis of clinical data on adenocarcinoma of the esophagogastric junction showed a significant correlation between the depth of tumor invasion, lymph node metastases, TNM stage, and serum IL-8 levels. Serum IL-8 is a potential diagnostic biomarker for the detection of early stage adenocarcinoma of the esophagogastric junction [10]. Positive IL-8 expression levels correlated with lymph node metastases and TNM stage of gastric cancer. Three-year survival of IL-8-positive patients with gastric cancer was 20% [11]. Interleukin-10 is a pleiotropic cytokine secreted by type 2 helper T cells (Th2) that promotes oncogenic activation or inactivation of tumor suppressor genes. It was studied whether hypomethylation of IL10 CpG islands is associated with the risk of developing gastric cancer and the prognosis of these patients. Hypomethylation of IL10 CpG islands was significantly associated with the risk of developing gastric cancer in patients who were non-smokers or had no family history of cancer. The results of the Kaplan-Meier survival analysis showed that hypomethylation of IL10 CpG islands correlated with significantly shorter overall survival in patients with gastric cancer [12].

Interleukin-16 is a proinflammatory cytokine. Sarcopenia accompanied by high expression of IL-16 indicates a poor prognosis in gastric cancer [13].

IL-17A has been established to be the main member of the IL-17 cytokine family and is produced mainly by T-helper type 17 (Th17). Increased IL-17A levels correlate with the development of autoimmune diseases and malignant tumors [14]. M. Karabulut et al. [15] reported that the average IL-17 levels in the blood serum of 76 patients with GC were higher than in 30 control group individuals. Later, B.G.M.C. Carneiro et al. [16] presented completely different results: IL-17 levels in 20 patients with GC were lower than in 20 control group individuals. IL-27 has been shown to play a dual role in the immune response by stimulating or inhibiting Th17 cells. The concentration of IL-27 in GC and duodenal ulcer (DU) was assessed. IL-27 was not detected in patients with GC, but its concentration was very high in patients with duodenal ulcer [17]. It is known that IL-32, a proinflammatory factor, can induce immunosuppression, and its expression in GC can promote

metastasis. IL-32 expression is significantly increased in GC and correlates with high invasiveness and poor prognosis [18].

Accumulated data indicate that IL-33, a member of the IL-1 family, plays a critical role in tissue homeostasis and repair, type II immunity, inflammation, and viral infection. IL-33 is considered as one of the factors contributing to oncogenesis, angiogenesis, and cancer progression [19]. IL-33 expression is high in serum and tissues in GC, and its level does not depend on other tumor markers. Thus, this cytokine should be considered as a potential biomarker for detecting GC and predicting disease development [1].

Metodology Interleukin-35 is an anti-inflammatory cytokine that is involved in tumor development and progression. High serum IL-35 levels correlate with poor prognosis in GC and may become a new and promising prognostic biomarker for this disease [20]. Increased IL-35 expression in GC is associated with increased microvessel density, distant metastases, and poor prognosis [21].

Interleukin-36 is a category of inflammatory cytokines. Different types of IL-36 play different roles in cancer development. For example, high expression of IL-36α was found in GC patients with high overall survival. The relationship between cancer prognosis and IL-36β or IL-36γ expression requires further research [22].

Result

Transforming growth factor β (TGF-β) is a pleiotropic cytokine involved in the regulation of cellular processes such as cancer cell proliferation, apoptosis, and metastasis [23]. TGF-β signaling plays a key role in tumor formation and progression, inhibition of the antitumor activity of immune cells. High expression of TGF-β2 and high levels of TGF-β2 hypomethylation are negative factors in the prognosis of GC [24]. CXC class chemokines and chemokine receptors cause inflammation, initiation and progression of GC, promoting angiogenesis, tumor transformation, invasion, metastatic spread and intercellular interactions [25]. CC chemokine receptors can be used as an effective biomarker for prognostication of GC [26]. The presence of CCL19 and CCR7 correlates with poor prognosis in GC [27]. CXCL1 is closely associated with oncogenesis in GC, since its expression positively correlates with the TNM stage, lymph node metastasis, and tumor size. Increased CXCL1 expression in GC tumors correlated with both worse overall survival and a favorable prognosis [28].

Cytokines in Helicobacter pylori infection in patients with gastric cancer

Inflammation caused by Helicobacter pylori is considered the first step in gastric carcinogenesis. IL-6 levels are elevated in H. pylori infection cohorts from East Asia, the Middle East, and Southeast Asia, but not from North America, Europe, Russia, and Africa. IL-6 levels correlate with the risk of developing GC [29]. H. pylori infection causes chronic inflammation in the gastric wall and leads to an increase in the level of proinflammatory cytokines, such as CCL5, CCL3, CXCL9, CCL20, CXCL2, CXCL1 [28]. In addition, tumor necrosis factor α (TNF-α) expression is significantly increased in patients with GC during this infection [30]. Serum TNF-α concentrations were measured in H. pylori-positive patients with dyspepsia, normal gastric mucosa, chronic gastritis, and GC. In the group with normal gastric mucosa, average levels of TNF-α (19.9±19.5 pg/ml) were detected; this indicator was almost twice as high in patients with chronic gastritis (35.7±28.0 pg/ml) and sharply decreased in patients with gastric cancer (1.8±5.9 pg/ml) [31].

H. pylori infection induces gastric inflammation in patients with gastrointestinal metaplasia and dysplasia. It has been shown that the level of IL-17A in the blood serum is significantly increased in H. pylori-infected patients with gastrointestinal metaplasia and dysplasia [32].

H. pylori suppresses gastric acid secretion by inhibiting the activity of H+,K+-adenosine triphosphatase and stimulating the expression of IL-1β. A decrease in the level of IL-1β mRNA in

patients with GC/dysplasia after eradication of H. pylori contributes to the prevention of metachronous GC [33]. At the same time, the level of CXCL1 expression correlates with the amount of H. pylori and decreases after antibacterial therapy [28].

Descussion

Cytokines for predicting the effectiveness of gastric cancer treatment

Chemoresistance remains the main obstacle to achieving an optimal prognosis in gastric cancer. It has been established that high levels of IL-8 in the serum before treatment in patients with gastric cancer correlate with a poor response to platinum-based therapy, gradually increase during neoadjuvant chemotherapy and decrease after radical surgery. According to the results of an immunohistochemical study, high expression of IL-8 was found in tissues with chemoresistant forms of gastric cancer [34].

The level of IL-6 in the serum before treatment is considered a promising prognostic biomarker for patients with adenocarcinoma of the stomach and gastroesophageal junction. Comparison of IL-6 levels before and after neoadjuvant therapy allows predicting the response to neoadjuvant therapy. No changes or a decrease in IL-6 levels predicted complete or almost complete tumor regression with a sensitivity and specificity of 80% [35]. The level of IL-6 was studied during treatment with monoclonal antibodies against programmed cell death protein 1 (PD-1) (pabolizumab, nabulizumab, sindilimab, carrelizumab, treprizumab) in combination with chemotherapy (oxaliplatin, teggio, paclitaxel, capecitabine) in advanced GC. A decrease in IL-6 levels predicted longer progression-free survival. High levels of IL-6 in patients after two cycles of immunochemotherapy indicated the development of resistance. Thus, IL-6 should be considered a promising prognostic biomarker in the treatment of patients [36]. A study of cytokine levels was also conducted in patients with metastatic GC who received monoclonal antibodies against PD-1. With effective treatment, IL-5 and interferon γ (IFN-γ) levels significantly decreased compared to baseline and, conversely, significantly increased as the tumor progressed [37].

Interleukin-9 is a T-cell cytokine that is associated with inflammation and allergy. Patients with GC and high IL-9 expression were characterized by better overall survival and a better response to adjuvant chemotherapy based on 5-fluorouracil. High IL-9 expression correlated with an increase in the number and function of intratumoral CD8+ T cells [38].

Interleukin-2 is a cytokine important for T-cell proliferation and stimulation of immune responses, as well as for increasing the activity of natural killer cells. IL-2 can be considered as a predictor of a favorable response to treatment. In patients with GC treated with PD-1 inhibitors (cintilimab, camrelizumab, tislelizumab) and chemotherapy (oxaliplatin, teggio, paclitaxel, capecitabine), higher baseline IL-2 levels correlated with a significant increase in overall survival and progression-free survival [39].

Elevated IL-4 levels predict a good response to treatment of GC with monoclonal antibodies against PD-1 (pabolizumab, nabulizumab, sindilimab, carrelizumab, treprizumab) in combination with chemotherapy (oxaliplatin, teggio, paclitaxel, capecitabine) [36].

High baseline IFN-γ levels in CD8+ T cells predict a better response to combination therapy for GC: monoclonal antibodies against PD-1 (camrelizumab) plus chemotherapy (mFOLFOX6) [40]. In addition, high baseline IFN-γ levels correlate with a better prognosis when treated with anti-PD-1 monoclonal antibodies (pabolizumab, nabulizumab, sindilimab, carrelizumab, treprizumab) in combination with chemotherapy (oxaliplatin, teggio, paclitaxel, capecitabine) in advanced GC [36].

Conclusion

Cytokines are a wide range of intercellular signaling proteins that play a key role in almost all links of human immunity. Of particular interest is the key role of cytokines in modulating the immune response to tumor cells. The study of the role of cytokines in the development of malignant tumors of the stomach is relevant. The ambiguous effect of cytokines on carcinogenesis processes has been shown. Cytokines can exhibit both pro-oncogenic and anti-oncogenic properties. In the future, the data presented in the work can become the basis for the development of individual approaches to the treatment of patients with gastric cancer, taking into account changes in the level of cytokines.

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