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Review article

Roles of inflammatory cytokines in the progression of gastric cancer: friends or foes?

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Abstract

Increasing evidence is being reported regarding the hypothesis that several proinflammatory and anti-inflammatory cytokines may promote tumor progression and affect the host antitumor response. However, the manner in which a local cytokine network operates in tumor development remains unclear. We reviewed the literature to examine the consequences of novel insights into inflammatory cytokines associated with gastric cancer progression. The Medline and EMBASE databases were searched for publications regarding the role of inflammatory cytokines in the development of gastric cancer. A number of studies have suggested that several proinflammatory and anti-inflammatory cytokines promote tumor progression through the direct activation of nuclear factor-κB (NF-κB) and the upregulation of angiogenesis and adhesion molecules. Furthermore, these processes suppress host antitumor immunity, leading to tumor progression and metastasis. In patients with advanced gastric cancer, most cytokines that enhance or suppress host antitumor immunity appear to have elevated serum and local expression levels. The net cytokine environment fluctuates at various stages of tumor development. In conclusion, a more detailed understanding of the differential roles of malignant cell-derived and host-derived cytokines at different stages of the malignant process could, consequently, open new avenues for the manipulation of cytokine expression and function in cancer immunotherapy for gastric cancer.

Key words Tumor immunity · Cytokine · Tumor progression

Introduction

Gastric cancer is the fourth most common cancer and the second most frequent cause of cancer-related deaths, accounting for 10.4% of cancer deaths worldwide [1]. Although the etiology of gastric cancer has been completely obscure for many decades, several considerable advances in the knowledge of the carcinogenesis and development of gastric cancer have been made in the present era. First, it is well known that *Helicobacter pylori* infection is associated with the carcinogenesis and development of gastric cancer, suggesting that chronic inflammation may be implicated in the development of intestinal metaplasia and mutations in oncogenes that precede the development of gastric cancer; indeed, the International Agency for Research on Cancer classified *H. pylori* as a class I human carcinogen in 1994 [2]. Second, the long-suspected influence of genetic susceptibility has been elucidated and several polymorphisms of inflammatory cytokine genes have been implicated as risk factors for gastric cancer [3–7].

Although immune cells constitute an additional and prominent component of the host response to cancer, their participation in tumor pathogenesis remains unclear. Increasing evidence is being reported regarding the hypothesis that several proinflammatory and anti-inflammatory cytokines may promote tumor progression and affect the host antitumor response. Efforts to understand cytokine function during tumor development are complicated by the pleiotropy and redundancy of cytokine action and the manner in which the overall cytokine environment shapes the effects of individual cytokines [8]. At present, most current data support the notion that acute inflammation triggered by tumor-infiltrating lymphocytes (TILs) does not induce the normal immunoprotective mechanisms that lead to the eradication of an evolving cancer. Instead, excessively and chronically produced proinflammatory mediators are thought to promote tumor progression [9–12]. In the tumor microenvironment, there is a delicate balance between antitumor immunity and tumor-originated proinflammatory activity, which weakens antitumor immunity [12–14]. Many researchers have reported that perioperative blood transfusion [15, 16], postoperative

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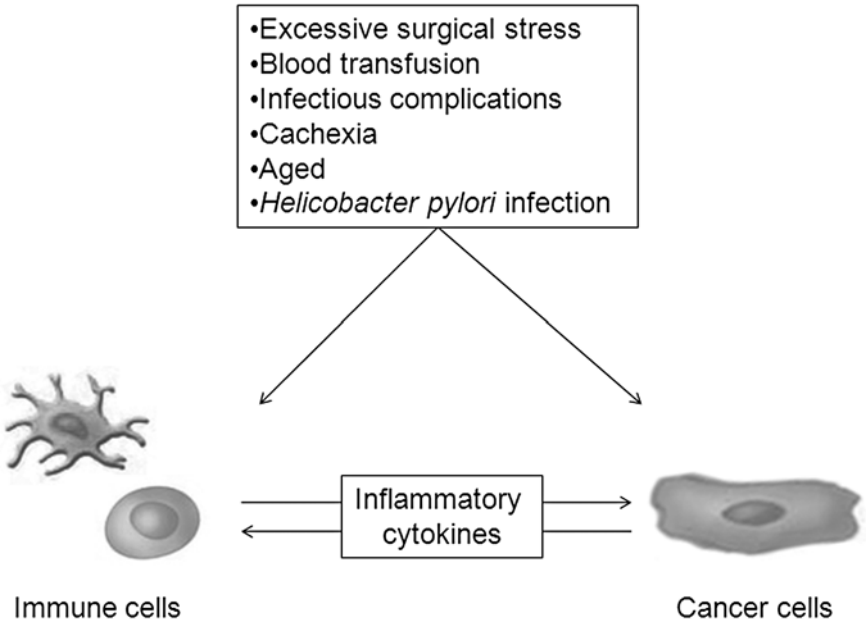

Fig. 1. Relationship between cancer progression and various factors associated with the production of proinflammatory and anti-inflammatory cytokines. In the tumor microenvironment, there is a delicate balance between immunocompetent cells and cancer cells through the production of proinflammatory and anti-inflammatory cytokines, which are induced by various factors such as excessive surgical stress, perioperative blood transfusion, postoperative infectious complications, cachexia, aging, and infection of *Helicobacter pylori*

infectious complications [17], and excessive surgical stress [18, 19], factors which result in the production of proinflammatory and anti-inflammatory cytokines, may contribute to a high rate of recurrence and unfavorable long-term survival in various malignancies (Fig. 1). However, the precise mechanisms remain unclear.

In this review, we focus on the role of humoral mediators produced by cancer cells and/or host immunocompetent cells; in particular, proinflammatory and anti-inflammatory cytokines, in terms of gastric cancer progression and influence on host antitumor immunity. Although there is increasing evidence that several polymorphisms of inflammatory cytokine genes have been implicated as risk factors for gastric cancer, this topic is beyond the scope of this article, but readers are referred to several excellent reviews [4, 5].

Search strategy

The search strategy in this study was based on previous guidelines for systematic review [20]. Literature databases such as PubMed Medline (National Library of Medicine) and EMBASE were searched from 1980 to 2009. The following medical subject headings were searched: "gastric cancer (or carcinoma)" and "inflammation", "gastric cancer (or carcinoma)" and "cytokine", "gastric cancer (or carcinoma)" and "mediator", and "gastric cancer (or carcinoma)" and "tumor immunity". In addition, references in the cited articles were reviewed. Using this search, we found 4342 manuscripts, and we selected 812 manuscripts for this review; 804 and 2726 manuscripts were excluded because they were not written in English and manuscript content was not applicable for this review, respectively.

Mechanisms of relationships between cytokines and cancer progression

Increasing evidence is being reported for the hypothesis that several polymorphisms of inflammatory cytokine genes, such as those for tumor necrosis factor (TNF) and interleukin-1 (IL-1), may increase the risk of gastric cancer [3, 21, 22]. This evidence suggests that several cytokines may contribute to carcinogenesis and cancer progression in gastric cancer. Remarkable advances in molecular medicine have revolutionized the study of carcinogenesis, inflammatory cytokines, and human immunology. Several possible direct and indirect mechanisms of cytokines contributing to tumor progression may include cytokines directly stimulating carcinogenesis and cancer proliferation, and cytokines locally and/or systemically suppressing host antitumor immunity, thus indirectly leading to cancer progression (Table 1, Fig. 2).

TNFα

The critical role of TNFα in inflammatory diseases, including rheumatoid arthritis, Crohn's disease, and psoriasis, is well established, and its tumor-promoting effects have also been demonstrated in animal models [23, 24]. TNFα, produced by malignant cells, leukocytes, and other cells in tumor microenvironments, acts

Table 1. List of proinflammatory and anti-inflammatory cytokines associated with gastric cancer progression and influence on host antitumor immunity

Cytokines	Main cellular sources	Mechanisms
Direct activation causing tumor progression		
TNFα	Macrophages, dendritic cells, B cells, NK cells, keratinocytes	Promoting DNA damage, inhibiting DNA repair, and induction of angiogenic factors
IL-1	Macrophages, dendritic cells, B cells, NK cells, keratinocytes	Enhancing COX-2, iNOS, PGE2, ICAM-1, VCAM-1, and angiogenesis
IL-6	Macrophages, T cells, B cells, fibroblasts, endothelial cells	Activating JAK/ STAT3 pathway
IL-18	Macrophages	Binding receptor for IL-18 expressed on tumor cells
TGFβ	Macrophages, regulatory T cells	Activating JNK and ERK pathway
Chemokines	Macrophages, T cells, eosinophils, fibroblasts, endothelial cells, platelets	Promoting angiogenesis, and binding chemokine receptors expressed on tumor cells
Suppression of antitumor immunity		
TGFβ	Macrophages, regulatory T cells	Suppression of host antitumor immunity
IL-10	Macrophages, T cells, B cells, mast cells	Suppression of host antitumor immunity
Activation of antitumor immunity		
IFNγ	NK cells, NKT cells, T cells	Direct antiproliferative and proapoptotic effects on tumor cells, induction of cell cycle arrest, and activation of NK and NKT cells and macrophages
IL-12	Macrophages, dendritic cells, B-cells	Activating NK, NKT cells to produce IFNγ
IL-18	Macrophages	Activating NK, NKT cells to produce IFNγ

TNF, tumor necrosis factor; IL, interleukin; TGF, transforming growth factor; IFN, interferon; COX-2, cyclooxygenase-2; iNOS, inducible isoform of nitric oxide synthase; PGE2, prostaglandin E2; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; NK, natural killer (cell); NKT, natural killer T

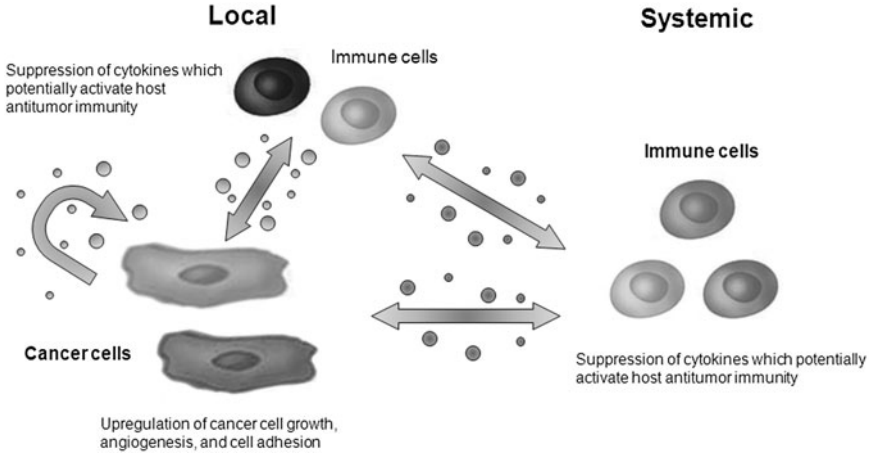

Fig. 2. Possible direct and indirect mechanisms of cytokines contributing to tumor progression. Several cytokines, which are produced by immunocompetent cells associated with tumors and the tumor cells themselves, can directly stimulate carcinogenesis, cancer proliferation, angiogenesis, and cell adhesion, and several cytokines can locally and/or systemically suppress host antitumor immunity, thus indirectly leading to cancer progression

primarily through TNF receptor 1 in an autocrine and a paracrine manner [23]. TNFα promotes DNA damage and inhibits DNA repair by upregulating nitric oxide (NO)-dependent pathways [25]. TNFα can induce the collapse of tumor vasculature and can also promote angiogenesis [26]. Thus, it may contribute to the development of the tissue architecture necessary for tumor growth and metastasis and may induce other cytokines, angiogenic factors, and matrix metalloproteinases (MMPs) to contribute to DNA damage and increase the growth and survival of tumor cells through nuclear factor-κB (NF-κB) pathways [23]. Using a green fluorescence protein (GFP)-tagged human gastric cancer cell line, Mochizuki et al. [27] demonstrated that the administration of TNFα to mice promoted the progression of peritoneal metastasis.

In the clinical setting, several researchers have reported the clinical significance of serum TNFα levels in patients with gastric cancer. Kabir and Daar [28] reported that the serum level of TNFα was greatly reduced (by

approximately one-third) in patients with gastric cancer compared to the level in age-matched controls. Wu et al. [29] did not demonstrate a prognostic value of serum TNFα levels in patients with gastric cancer. However, Forones et al. [30] have demonstrated that patients with stage III or IV gastric cancer had significantly elevated levels of TNFα compared to levels in those with less advanced disease. Thus, the clinical significance of serum TNFα levels in patients with gastric cancer is still controversial. These conflicting findings may be due to the short half-life of TNFα and/or the low sensitivity of commercially available kits for the detection of TNFα.

IL-1

IL-1 is an important cytokine because it possesses several biological properties resulting in the increased expression of proinflammatory genes. Several researchers have demonstrated that IL-1α enhances angiogenesis and vascular endothelial cell proliferation in gastric cancer cell lines [31, 32]. Uefuji et al. [33] reported that exogenous IL-1α stimulated cancer cell growth in gastric cancer cell lines, while such growth stimulation was suppressed by an anti-IL-1α antibody or IL-1 receptor antagonist. In the clinical setting, the incidence of IL-1α mRNA expression was significantly higher in patients with pT2-pT4 tumors than in those with pT1 tumors [33]. Tomimatsu et al. [34] demonstrated that the immunohistochemical expression of IL-1α in primary gastric cancer tissue showed a significant correlation with liver metastasis. Furuya et al. [35] also demonstrated that a significantly higher concentration of IL-1α, measured in homogenized tumor samples by enzyme-linked immunosorbent assay, was observed in tumors from patients with liver metastasis than in those from patients without liver metastasis. Hence, IL-1α was suggested to be a potent inducer of tumor cell proliferation and angiogenesis, resulting in tumor progression and hepatic metastasis [35].

Similar to findings for IL-1α, Beales [36] demonstrated that IL-1β stimulated the proliferation of gastric cancer cell lines, via the receptor-mediated activation of a tyrosine kinase pathway, in a dose-dependent manner. Furthermore, this author [36] revealed that the proliferation activity of IL-1β was significantly reduced by the neutralization of granulocyte macrophage colony-stimulating factor (GM-CSF), suggesting that the growth stimulatory action of IL-1β was due to an autocrine intermediary action of GM-CSF. In the clinical setting, the presence of IL-1β genotype polymorphism associated with enhanced IL-1β production significantly increases the risk of gastric cancer and precancerous lesions [37, 38]. Deans et al. [39] reported that tumor IL-1β expression was associated with serum C-reactive protein levels in patients with gastric cancer, an association which resulted in reduced survival.

IL-6

IL-6 is a pleiotropic cytokine produced by a wide variety of cells and it plays important roles both in stimulating B-cell differentiation to antibody-forming plasma cells and in regulating the innate immune response. Ito et al. [40] demonstrated that several gastric cancer cell lines expressed IL-6 mRNA, and it was observed that IL-6 could stimulate gastric cancer cell growth, while anti-IL-6 antibody inhibited this growth. IL-6 secreted from cancer cells combines with IL-6 receptors expressed on the surface of cancer cells. IL-6 and IL-6 receptors act on cancer cells directly via the Janus kinase (JNK)/signal transducer and activator of transcription 3 pathways [41]. Furthermore, IL-6 may act on cancer cells through hepatocyte growth factor (HGF) by promoting and accelerating invasion as well as lymph node and/or hepatic metastasis [42]. Several authors have demonstrated significant relationships between elevated serum IL-6 levels and tumor stage, depth of tumor, lymphatic invasion, venous invasion, lymph node metastasis, hepatic metastasis, and unfavorable outcome in gastric cancer patients [28, 42, 43].

IL-10

When first discovered, IL-10 was termed "cytokine synthesis inhibitory factor". IL-10 inhibits the gene expression and synthesis of T-cell and macrophage pro-inflammatory cytokines and suppresses the function of antigen-presenting cells. Very few studies have evaluated the direct role of IL-10 in carcinogenesis. Sugai et al. [44] demonstrated that the intracellular IL-10 level in the monocytes of patients with advanced gastric cancer was significantly increased compared to the levels in patients with early disease or the levels in healthy individuals. Morisaki et al. [45] and Sakamoto et al. [46] reported that gastric cancer tissue expressed IL-10, and its expression was correlated with poor outcomes. There is increasing evidence that higher expression of IL-10 in serum and the peritoneal cavity is associated with the progression of the tumor and prognosis in patients with gastric cancer [47–51]. These findings suggest that the immunosuppressive properties of IL-10 may contribute to tumor progression through the suppression of host antitumor immunity. Although IL-10 has been recently reported to be a potent angiogenic factor in non-small cell lung carcinoma, it is uncertain whether it exhibits a similar property in gastric cancer [52].

IL-12

IL-12 is an immunoregulatory cytokine that acts on T cells and natural killer cells. It is also the major cytokine responsible for T-helper type 1 (Th1)-cell differentiation,

allowing potent production of interferon gamma (IFNγ). Furthermore, IFNγ has a powerful enhancing effect on the ability of phagocytes and dendritic cells to produce IL-12, thereby creating a potent positive feedback mechanism that promotes strong cell-mediated antitumor immunity [53].

In the clinical setting, Shibata et al. [54] and Murakami et al. [55] have reported that the production of IL-12 by peripheral blood mononuclear cells (PBMCs), and its serum levels, decrease significantly with advancing stages of cancer, especially in patients with distant metastases. These findings support the hypothesis that the suppression of IL-12 may promote tumor progression through the disruption of host antitumor immunity, although the precise mechanism responsible for the impaired production of IL-12 in the advanced stage of gastric cancer remains unresolved. Nonetheless, cell-mediated antitumor immunity seems to be disrupted through the effects of IL-12 and IFNγ in the advanced stage of gastric cancer.

IL-18

IL-18 was first described in 1989 as an IFNγ-inducing factor [56] which was believed to induce the Th1 immune response [57]. Majima et al. [58] had previously indicated that gastric cancers but not colon cancers expressed the IL-18 receptor. In that study, the authors also showed that IL-18 dose-dependently enhanced the proliferation of gastric cancer, which was accompanied by NK-κB activation. Similar results were not observed for colon cancer. Furthermore, when IL-18-pretreated gastric cancer cells were cultured with cytokine-activated peripheral blood killer lymphocytes, the antitumor machineries (perforin and IFNγ production of killer lymphocytes) decreased, resulting in the decreased susceptibility of cancer cells to killer lymphocytes [58].

In the clinical setting, Kawabata et al. [59] reported that gastric cancer patients with higher IL-18 serum levels experienced a significantly lower survival rate than those who had lower IL-18 serum levels, after undergoing potentially curative resection. IL-18 synergizes with IL-12 for the production of IFNγ and the proliferation of T cells, which may lead to enhanced antitumor immunity [60]. Thus, IL-18 may have paradoxical properties that enhance the proliferation of cancer cells and IL-18-treated cancer cells result in decreased antitumor immunity in gastric cancer.

Transforming growth factor β (TGFβ)

TGFβ, like IL-10, is not only a powerful immunosuppressive and anti-inflammatory cytokine but is also a central regulator of regulatory T-cell (Treg) proliferation and function [61, 62]. Saito et al. [63] demonstrated that TGFβ1 expression was detected in 22.8% of patients with gastric cancer, in whom the expression was mainly localized in the cytoplasm of carcinoma cells. In addition to its immunosuppressive activity, TGFβ appears to possess pleiotropic functions in terms of gastric cancer progression. Yanagihara and Tsumuraya [64] showed that exogenous TGFβ1-induced cell death occurred by an apoptotic process in human scirrhous-type gastric cancer, but not in nonscirrhous type. Recently, Fu et al. [65] demonstrated that TGFβ promoted the invasion and metastasis of gastric cancer cells via the JNK and extracellular signal-regulated kinase pathway. Inoue et al. [66] reported that TGFβ and HGF produced by gastric fibroblasts stimulated the invasiveness of scirrhous-type gastric cancer cells. In contrast, Komuro et al. [67] demonstrated that the disruption of TGFβ signaling in diffuse-type gastric cancer cells accelerated tumor growth through increased angiogenesis. These discrepant results may be due to the differences in the cancer cell types employed in the studies, i.e., diffuse- or intestinal-type tumors, or the differences in investigated TGFβ signaling subtypes.

Many clinical studies have shown positive correlations of TGFβ1 expression with lymph node metastasis and poor prognosis in gastric cancer [68, 69]. Saito et al. [70] emphasized that there was a strong correlation between TGFβ1 expression and vascular endothelial growth factor (VEGF) expression in gastric cancer tissue, suggesting that tumor progression was promoted indirectly by the stimulation of angiogenesis through the upregulation of VEGF expression in gastric carcinoma.

Another important role of TGFβ is the induction and activation of Tregs, which can inhibit immune responses mediated by CD4 (+) and CD8 (+) T-cells [61, 62]. There is accumulating evidence that increased populations of Tregs are present in patients with gastric cancer [71, 72]. Ichihara et al. [73] demonstrated that populations of Tregs in peripheral blood and TILs were significantly higher in patients with gastric and esophageal cancers than in healthy donors or normal mucosa. Furthermore, Sasada et al. [74] demonstrated that gastric cancer patients with higher percentages of Tregs in PBMCs had significantly poorer prognoses than those with lower percentages of Tregs. In summary, the complex role of TGFβ in direct tumor suppression and progression may be dependent on the stage and cancer cell type, as well as depending on the systemically induced immunosuppressive and anti-inflammatory properties of this molecule.

Chemokine families

There is accumulating evidence that chemokines play a pivotal role in promoting tumor growth and metastasis

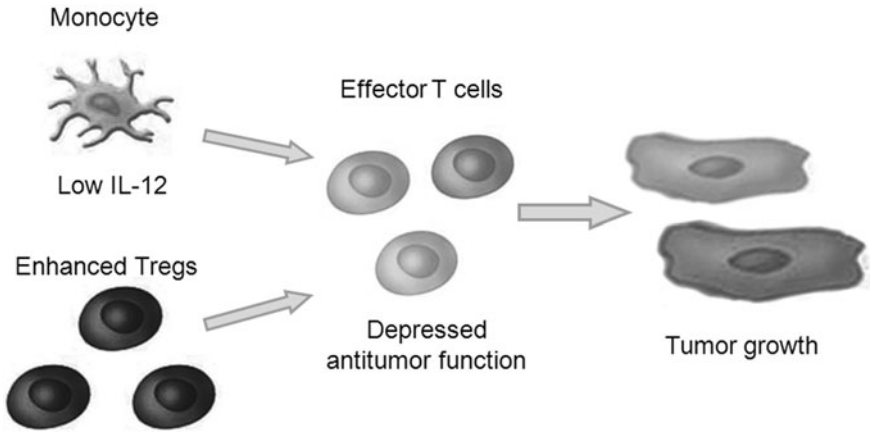

Fig. 3. Proposed mechanisms of depressed T-cell function in the development of gastric cancer. In the advanced stage of gastric cancer, suppressed interleukin-12 (*IL-12*) production by peripheral blood mononuclear cells (PBMCs) and an increased number of regulatory T cells (*Tregs*) have been reported; both of these factors strongly suppress the antitumor immunity of effector T cells, leading to tumor progression and metastasis

in several malignancies [75, 76]. IL-8 has been reported to have mitogenic activity, enhance cell adhesion, and upregulate VEGF and MMP-9 in gastric cancer [77, 78]. In addition, gastric cancer cells in surgical specimens overexpress IL-8 compared to corresponding normal gastric mucosa, and the IL-8 mRNA level is directly correlated with the vascularity of the tumors [79]. Furthermore, the transfection of gastric cancer cells with the *IL-8* gene in the gastric wall of nude mice enhanced their tumorigenic and angiogenic potential [80]. Sugasawa et al. [81] have demonstrated that human recombinant CC chemokine ligand 5 (CCL5), also known as RANTES (regulated on activation, normal T cell expressed and secreted) can augment the proliferative capacity of gastric cancer cells in a dose-dependent manner. In that study, it was revealed that the main producer of CCL5 was TILs and not cancer cells. Furthermore, receptors for CCL5 were expressed by cancer cells and not TILs [81, 82]. These findings strongly support the hypothesis that chemokines and chemokine receptors may directly contribute to tumor growth in an autocrine and/or a paracrine fashion, and may also promote tumor metastasis via enhanced angiogenesis and cell adhesion [83].

Defective T-cell function and IL-12 production by PBMCs in the development of gastric cancer

It is well known that T cells and cytokines produced by innate immune cells play pivotal roles in the host's antitumor immunity. There is increasing evidence that the cytokine production and proliferative capacity of peripheral blood T cells were clearly depressed in the advanced stage of gastric cancer [84]. Jang [85] has demonstrated that the number of Tregs, which regulate the cytokine production and the proliferation of effector T cells, is increased in *H. pylori*-associated gastritis and gastric cancer tissues. In addition, Shibata et al. [54] demonstrated that the production of IL-12 by PBMCs decreased significantly with advanced stages of gastric cancer, especially in patients with distant metastases. These findings suggest that the depressed antitumor function of effector T cells, which is caused by enhanced Tregs and depressed IL-12 production by PBMCs, may lead to the development of gastric cancer (Fig. 3).

A paradox of inflammation and cancer; local inflammation and systemic anti-inflammation in the development of gastric cancer

In terms of inflammatory reactions, neoplastic disorders constitute a paradox. Immunocompetent cells associated with tumors, and the tumor cells themselves, produce inflammatory cytokines and chemokines, resulting in tumors being infiltrated by leukocytes. However, neoplastic disorders are associated with a defective capacity to mount inflammatory reactions at sites other than the tumor, and circulating monocytes from cancer patients are defective in their capacity to respond to chemoattractants [86]. Cancer cells can grow by escaping the attack of immune cells by disrupting the host immune system, which is progressively suppressed as a result of tumor progression and metastasis [87].

Various locally produced factors originating in the tumor microenvironment may contribute to the systemic anti-inflammation associated with cancer (Fig. 2). Inflammatory cytokines and chemokines leaking into the systemic circulation are likely to desensitize circulating leukocytes. The serum and local expressions of proinflammatory and anti-inflammatory cytokines in relation to the development of gastric cancer are summarized in Table 2. In patients with advanced gastric cancer, most cytokines, except for IFNγ and IL-12, both of which enhance or suppress host antitumor immunity, appear to have increased serum and local expression levels. The manner in which the local cytokine network

Table 2. Serum and local expressions of proinflammatory and anti-inflammatory cytokines in relation to the development of gastric cancer

Cytokines	Source	Cytokine level	Authors	Reference nos.
TNFα	Serum	Reduced	Kabir and Daar	28
	Serum	Elevated	Forones et al.	30
IFNγ	Peritoneal cavity	Reduced	Majima et al.	48
IL-1α	Serum	Elevated	Kabir and Daar	28
	Cancer tissue	Elevated	Uefuji et al.	33
	Cancer tissue	Elevated	Tomimatsu et al.	34
IL-1β	Serum	Elevated	Kabir and Daar	28
IL-6	Serum	Elevated	Kabir and Daar	28
	Serum	Elevated	Ashizawa et al.	42
	Serum	Elevated	Ikeguchi et al.	43
IL-10	Cancer tissue	Elevated	Sakamoto et al.	46
	Serum	Elevated	De Vita et al.	47
	Peritoneal cavity	Elevated	Majima et al.	48
	Serum	Elevated	Szaflarska et al.	49
	Serum	Elevated	Fortis et al.	51
IL-12	Serum	Reduced	Shibata et al.	54
	Serum	Reduced	Murakami et al.	55
IL-18	Serum	Elevated	Kawabata et al.	59
TGFβ	Serum	Elevated	Maehara et al.	68
Chemokines	Serum (IL-8)	Elevated	Konno et al.	78
	Cancer tissue (IL-8)	Elevated	Kitadai et al.	80
	Serum (RANTES)	Elevated	Sugasawa et al.	81

RANTES, regulated on activation, normal T cell expressed and secreted

operates in tumors is determined by the array of expressed cytokines, cytokine receptor expression patterns, and the relative concentrations of the cytokines, i.e., the Th1/Th2 balance. The net cytokine environment likely fluctuates at various stages of tumor development.

Concluding remarks and suggestions for future work

When host-mediated antitumor activity is weaker than tumor-mediated immunity, tumor cells undergo immune escape and grow rapidly. However, when the host-mediated antitumor immunity is stronger than the tumor-mediated immunosuppressive activity, tumor cells are eliminated. The net outcome of a persistent inflammatory microenvironment is enhanced tumor promotion, accelerated tumor progression, invasion of the surrounding tissues, angiogenesis, and often metastasis [88].

However, for all the local inflammation in tumors, in many cases the overall innate immunity of the host is reduced. The challenge for the future is to normalize the inflammatory network to regain a normal host response overall, by decreasing the high levels of tumor-promoting molecules, such as proinflammatory cytokines, in infiltrating cells and increasing their levels of tumor-suppressing molecules, such as anti-inflammatory cytokines. In this manner, we can harness activities that are antitumor and suppress those that are protumor.

Despite continuous progress in the development of conventional therapies such as surgery, chemotherapy, and radiotherapy, as well as novel target-protein-based cancer therapy, gastric cancer is still the most lethal cancer in Asia. Emerging modalities provide promise to combat this malignancy [89]. Besides these treatment strategies, clinical trials of cytokine-based therapy have been performed in several malignancies [11]. However, proinflammatory or anti-inflammatory treatments for gastric cancer have been considered a double-edged sword. Several inflammatory cytokines; for example, IL-18, are known to be responsible for Th1-cell differentiation, which enhances antitumor immunity; however, they cause enhanced proliferation of gastric cancer cells [58]. A more detailed understanding of the differential roles of malignant cell-derived and host-derived cytokines at different stages of the malignant process could, consequently, open new avenues for the manipulation of cytokine expression and function in immunotherapy for gastric cancer.

Conflict of Interest

The authors have no conflict of interest regarding this manuscript.

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