

WJG 20th Anniversary Special Issues (8): Gastric cancer**Role of the tumor microenvironment in the pathogenesis of gastric carcinoma**

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Core tip: The intensive interplay that exists between tumor cells and the tumor microenvironment can play an important role in tumor initiation, growth and metastasis. A better understanding of the molecular pathogenesis of the tumor microenvironment of Gastric carcinoma would be crucial for the design of novel molecular targets. In this review, we have provided an overview of the currently available knowledge of the role of the TME in gastric cancer and have highlighted the potential prognostic and therapeutic implications.

Abstract

Gastric carcinoma (GC) is the 4th most prevalent cancer and has the 2nd highest cancer-related mortality rate worldwide. Despite the incidence of GC has decreased over the past few decades, it is still a serious health problem. Chronic inflammatory status of the stomach, caused by the infection of *Helicobacter pylori* (*H. pylori*) and through the production of inflammatory mediators within the parenchyma is suspected to play an important role in the initiation and progression of GC. In this review, the correlation between chronic inflammation and *H. pylori* infection as an important factor for the development of GC will be discussed. Major components, including tumor-associated macrophages, lymphocytes, cancer-associated fibroblasts, angiogenic factors, cytokines, and chemokines of GC microenvironment and their mechanism of action on signaling pathways will also be discussed. Increasing our understanding of how the components of the tumor microenvironment interact with GC cells and the signaling pathways involved could help identify new therapeutic and chemopreventive targets.

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INTRODUCTION

Gastric carcinoma (GC) is the 4th most prevalent cancer and has the 2nd highest cancer-related mortality rate worldwide. The risk of developing GC is 1 in 115, with a 5-year survival rate of only 20%-30%^[1]. Despite that the incidence of GC has decreased over the past few decades, it is still a serious health problem^[2]. The prognosis of advanced GC (AGC) with extensive node invasion and metastasis remains poor, while early GC is associated with excellent long-term survival^[3].

Ever since Rudolf Virchow, the founder of modern pathology, observed the connection between tumor cells and their surrounding tumor microenvironment (TME),

TME has long been suspected to play an important role in the initiation and progression of tumors^[4,5]. TME is thought to determine the behavior of cancers not only through genetic or epigenetic makeups of the tumor cells, but also through the surrounding milieu that the tumor cells interact with for survival, growth, proliferation and metastasis. The TME is composed of many different kinds of cells such as endothelial cells, fibroblasts, lymphocytes and macrophages. It also consists of numerous soluble molecules such as growth factors, cytokines, chemokines, antibodies, proteases, various types of enzymes, and metabolites as well as an extracellular matrix. As the tumor progresses, states of hypoxia and acidosis develop in the TME^[6-8], and the intensive relationship that exists between tumor cells and the TME plays a major role in tumor initiation, growth and metastasis.

Among the numerous factors in the TME, inflammatory mediators have received attention recently, and an estimated 15%-20% of cancer deaths are associated with chronic infection and inflammation. Population-based studies have shown that individuals who are prone to chronic inflammatory disorders have an increased risk of cancer development^[9]. Accordingly, treatment with non-steroidal anti-inflammatory agents decreases the incidence and mortality of several tumor types^[10,11]. In the case of GC, the chronic inflammatory state of the stomach, caused by *Helicobacter pylori* (*H. pylori*) infection, as well as the production of inflammatory mediators, such as cytokines and chemokines within gastric tissues, is suspected to play an important role in the initiation and progression of GC.

Better understanding of the special interplay between GC cells and the surrounding microenvironment may be useful for recognizing the mechanism underlying tumor development and progression as well as the discovery of novel molecular therapeutic targets^[12,13]. In this review, we have provided an overview of the currently available knowledge of the role of the TME in GC and have highlighted the potential prognostic and therapeutic implications.

CHRONIC INFLAMMATION AND

H. PYLORI IN GC

H. pylori, a microaerophilic, spiral gram-negative bacterium, colonizes the human stomach and, is a major cause of chronic gastritis, peptic ulcers, and gastric malignancies, including gastric non-cardia adenocarcinoma and mucosal-associated lymphoid tissue lymphoma^[14]. *H. pylori* infects over 50% of the world's population, with 1% of those infected going on to develop GC. An estimated 75% of all GC cases are associated with *H. pylori* infection^[15].

The carcinogenic potential of *H. pylori* is driven by the interplay between bacterial virulence factors and the host's immune responses resulting in chronic inflammation, which in turn leads to tumorigenesis^[16]. Four major virulence factors have been identified from *H. pylori*, that is cytotoxin-associated antigen A (CagA), cag-pathogenicity island (cagPAI), vacuolating cytotoxin, and outer mem-

brane proteins. *H. pylori* cagPAI encodes approximately, 30 genes, including type four secretion system genes, which are essential for pathogenesis and are responsible for the delivery of CagA protein and peptidoglycan into host cells^[17,18]. It has recently reported that CagA binds an Src homology 2-containing tyrosine phosphatase (SHP-2) in a tyrosine phosphorylation-dependent manner and activates the phosphatase activity of SHP-2^[19]. Deregulation of SHP-2 by CagA is an important mechanism by which CagA-positive *H. pylori* promotes gastric carcinogenesis. *H. pylori* is a potent activator of nuclear factor- κ B (NF- κ B) in gastric epithelial cells^[20,21] causing the production of tumor necrosis factor- α , TNF-inducing protein (Tip), which in turn activates NF- κ B in gastric epithelial cells using an independent pathway involving virulence factors such as CagA^[18].

Activation of NF- κ B by *H. pylori* infection induces the expression of a variety of genes, including those encoding the cytokines interleukin (IL)-1, IL-6, IL-8, TNF- α , vascular endothelial growth factor (VEGF), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), cell-cycle regulators, the matrix metalloproteinases (MMP)-2, MMP-7, MMP-9 and adhesion molecules^[22,23]. High level of COX2 mRNA and protein expression and enzymatic activity are detected in GC cells^[24], and COX-2 activity is induced by a variety of mediators including inflammatory cytokines such as TNF- α , interferon (IFN)- γ and IL-1^[25]. COX-2 facilitates tumor growth by inhibiting apoptosis, promoting cell proliferation and stimulating angiogenesis within cancer cells^[26]. *H. pylori* infection produces reactive oxygen and nitrogen species that cause DNA damage, followed by chronic gastritis and intestinal metaplasia. Nitric oxide generated by iNOS is converted to reactive nitrogen species that bring about direct DNA mutation such as those in p53, causing protein damage, inhibition of apoptosis, and promotion of angiogenesis^[27,28]. CagA also activates the nuclear factor of activated T-cells signaling pathway, and interacts with E-cadherin to deregulate β -catenin signaling, which induces the expression of genes downstream of β -catenin, such as Caudal type homeobox gene-1 and promotes the transdifferentiation of intestinal cells^[29].

SIGNALING PATHWAY OF GC-RELATED INFLAMMATION

Multiple steps and multiple factors are involved in the development of GC. More than 90% of GCs are adenocarcinomas, which are divided into two histological types, intestinal and diffuse, based on the Lauren's classification^[30]. *H. pylori* infection and chronic inflammation are important factors, particularly in the intestinal type of GC. The Correa's hypothesis postulates that there is a progression from chronic gastritis to gastric atrophy, intestinal metaplasia, dysplasia, and finally to cancer ("gastritis-dysplasia-carcinoma" sequence)^[31]. In each step of GC progression, many cytokines and intracellular sig-

naling pathways are involved.

GC-related inflammation activate transcription factors, mainly NF- κ B, hypoxia-inducible factor (HIF)-1 α , and signal transducer and activator of transcription (STAT)-3, which are the key inducers of inflammatory mediators such as cytokines, chemokines, prostaglandins, nitric oxide^[32].

The transcription factor NF- κ B is a key orchestrator of innate immunity and inflammation and recent evidence suggests that it play an important role in development and maintenance of cancer-related inflammation^[53]. In cancer and epithelial cells exposed to carcinogens, NF- κ B promotes cell survival and proliferation through the activation of genes encoding proteins that are important for cell cycle progression such as cyclin D1, and c-Myc and the anti-apoptotic pathway (cIAPs, A1/BFL1, BCL-2, c-FLIP)^[34,35]. In GC, NF- κ B potentiates inflammation in response to *H. pylori* infection. Some studies reported that *H. pylori* induces expression of the pro-inflammatory cytokine IL-8 through activation of NF- κ B^[20,36]. Moreover, NF- κ B amplifies the inflammatory signals of other cytokines, such as tumor necrosis factor and interferon^[37]. A previous study reported that the positive rate of NF- κ B/RelA is 42.6% in South Korea and NF- κ B/RelA expression in tumor tissues was also related to serum levels of IL-6 ($P = 0.044$) and C-reactive protein ($P = 0.010$)^[38]. Interestingly, several microRNAs (miRNA) which target NF- κ B have been shown to be involved in development and progression of GC. miR-146a expression is up-regulated in a majority of gastric cancers where it targets Caspase recruitment domain-containing protein 10 and COP9 signalosome complex subunit, inhibiting G protein coupled receptor-mediated activation of NF- κ B, thus reducing expression of NF- κ B-regulated tumor-promoting cytokines and growth factors^[39].

HIF-1 α is centrally involved in multiple aspects of tumorigenesis including tumor angiogenesis, proliferation, metabolism, metastasis, differentiation, as well as responses to radiation and chemotherapy^[40]. HIF-1 α is up-regulated in inflammatory conditions and there is accumulating evidence indicating the presence of interconnections and compensatory pathways between the NF- κ B and HIF-1 α systems^[41]. The expression of HIF-1 α commonly increases in a variety of human solid tumors and elevated HIF-1 α expression is associated with poor patient outcome in pancreatic cancer, glioblastoma, GC and other cancers^[40,42]. Furthermore, the contribution of HIF-1 α to chemoresistance has been observed in several solid tumors, including GC^[43,44]. Interestingly, inhibition of HIF-1 α *via* RNA interference or pharmacological compounds has improved their anti-tumor efficacy in murine cancer models^[45] through modulation of the p53 and NF- κ B signaling pathway. In this regards, a recent study has demonstrated that HIF-1 α expression correlates with the metastatic phenotype of human GC^[46].

STAT-3 is constitutively activated in several human cancer cells and tumor associated leukocytes and it represents a point of convergence for several oncogenic sig-

naling pathways^[47]. In approximately 50% of human GC, STAT3 is overactivated^[48,49], and its high activation and/or expression status has been shown to correlate with a lower survival rate for GC patients^[50]. This transcription factor supports oncogenesis through different mechanisms, ranging from the activation of genes crucial for proliferation and survival to the enhancement of angiogenesis and metastasis. In GC, IL-11 produced from tumor cells and TME activate the common signal-transducing gp130 β -receptor subunit to activate the JAK/STAT-3, Ras/Mitogen-activated protein kinase and phosphoinositide-3-kinase (PI3K)/Akt signaling pathways^[51-53]. Activated STAT-3 signaling pathway directly induces the transcription of the *Tlr2* gene in the gastric epithelium, which upon overexpression promotes proliferation and inhibits apoptosis of gastric epithelial cells^[48]. The activation of STAT-3 in tumor cells also has been shown to increase the capacity of tumors to evade the immune system by inhibiting the maturation of dendritic cells (DCs)^[54], thereby suppressing the immune response^[55]. A recent study showed that STAT-3 plays a divergent role in the modulation of IL-23 and IL-12, two related cytokines, which play opposite roles in tumour development. In particular, STAT-3 inhibits anti-tumor IL-12p35 expression in DCs while promoting the expression of the pro-carcinogenic IL-23 cytokine in TAMs^[56].

Epidemiological studies have highlighted that treatment with non-steroidal anti-inflammatory agents, such as COX-2 inhibitors, decrease the risk of developing certain cancers, such as colon cancer, breast cancer, and GC^[10,11,57,58]. The frequency of COX-2 expression did not differ between gastric adenomas and early intestinal carcinomas, indicating that COX-2 expression might act as one of the factors related to early tumorigenesis in the stomach. Interestingly, the frequency of COX-2 expression was significantly higher in advanced carcinomas than in early carcinomas and was higher in intestinal-type carcinomas than in diffuse-type carcinomas. COX-2 expression may be more important for the progression of intestinal-type carcinomas than that of diffuse-type carcinoma^[59].

Transforming growth factor (TGF)- β 1 mRNA and protein are highly expressed in GC cells^[60-62]. TGF- β 1 is closely related to invasion and metastasis and the TME; it alters the biologic behavior of malignant gastric lesion^[63]. TGF- β 1 produced by carcinoma cells stimulates collagen synthesis in both fibroblasts and cancer cells, which leads to diffuse fibrosis in the case scirrhous GC^[63].

The receptor tyrosine-protein kinase (HER) family consists of four members: HER-1 [epidermal growth factor receptor (EGFR)], HER-2, HER-3 and HER-4. Activation of these receptors leads to homo- or hetero-dimerization that in turn initiates phosphorylation cascades and subsequent activation of the PI3K-Akt-mammalian target of rapamycin (mTOR) and Ras-Raf-mitogen-activated mitogen-activated protein kinase/extracellular signal-related kinase (ERK) kinase (MEK)-ERK pathways, which are important in cancer cell proliferation and survival^[64,65].

EGFR overexpression, observed in 27%-44% of gas-

tric cancer cases, is generally reported to be a poor prognostic factor, despite contradictory evidence^[66]. HER-2 overexpression is observed in 10%-38% of gastric cancer tumor samples^[67,68], with a higher prevalence in intestinal-type and gastroesophageal junction tumors than that in diffuse-type and gastric tumors^[68,69]. The prognostic value of HER-2 overexpression in gastric cancer remains controversial; it is generally associated with a poorer outcome^[70,71], although contradictory evidence exists^[72,73]. In fact, *PIK3CA* activating mutation was reported in 4%-36% of gastric cancer cases^[74,75] and phosphatase and tensin homolog loss was reported in 20%-36% of cases^[74,76]. For gastric cancer, the *KRAS* mutation was observed in 2%-20% of cases^[77,78], and the *BRAF* mutation was observed in 0%-2.7% of cases^[77,79].

The overexpression/activation of c-Met, a receptor for hepatocyte growth factor, leads to proliferation and antiapoptotic signals^[80]. It was found to be activated both in vitro in human gastric cancer cell lines and in vivo in human gastric cancer tissue^[81], and this may result from the infection of gastric cells by *H. pylori*^[82].

The Hedgehogs (Hh) protein family includes Sonic (Shh), Indian (Ihh) and Desert (Dhh). In gastric cancer, the aberrant activation of Shh, through binding Patched 1 receptor and subsequent disinhibition of Smoothened in turn activates the transcription factor Gli-1^[83].

COMPONENT OF MICROENVIRONMENT OF GC TAM

Macrophages recruited to the tumor stroma are called TAMs. The role of TAMs in tumor progression is complicated and wide ranging. Although activated macrophages may have anti-tumor activity, tumor cells have been reported to evade the anti-tumor activity of TAMs^[84,85]. Indeed, removal of macrophages by genetic mutation reduces tumor progression and metastasis^[86]. TAMs are recruited from circulating monocytes into tissues in response to chemoattractants, and interact with tumor cells to make up the cancer stroma. Macrophage infiltration into tumor tissue correlates significantly with tumor vascularity in human esophageal cancer and GC^[87,88]. There is a direct association between the degree of TAM infiltration and depth of tumor invasion, nodal status, and clinical stage of GC^[88]. Macrophage recruitment is mediated by a variety of chemoattractants, including the following; monocyte chemoattractant protein-1 (MCP-1/CCL2), macrophage inflammatory protein-1 α (MIP-1 α /CCL3); and regulated upon activation, normal T cell expressed and secreted (RANTES/CCL5)^[87,88].

Lymphocytes

Regulatory T cells (Tregs) are functionally immune-suppressive subsets of T cells that are reported to play important roles in immunological self-tolerance^[89-92]. Tregs are defined more strictly as CD4⁺CD25⁺Foxp3⁺ cells. The frequency of Tregs among tumor infiltrating lymphocytes (TILs), lymphocytes derived from tumor-

draining regional lymph nodes, and peripheral blood lymphocytes is higher in GC and esophageal cancer patients than their normal counterparts^[93,94]. In addition, patients with a higher proportion of Tregs showed poorer survival rates than those with a lower proportion. Interestingly, after patients underwent curative resection for GC, the proportion of Tregs decreased and was restored to levels comparable to those for normal healthy donors^[95]. These results strongly suggest that tumor-related factors induce the expansion and the accumulation of Tregs in GC. Furthermore, the frequencies of CCL17⁺ cells and of CCL22⁺ cells, both of which induce in vitro migration of Tregs, within tumors were significantly higher than those in normal gastric mucosa. Increased levels of TGF-1 in GC patients have been correlated with the frequency of Tregs, and, conversely, numerous studies have reported a correlation between an increased frequency of circulating Treg and increased levels of TGF-1 during GC progression^[96-98]. On the other hand, some reports have indicated that activated effector T cells are converted into Treg cells, capable of suppressing autologous effector T cells^[99-101]. Thus, it is likely that naturally occurring Foxp3⁺ Tregs in peripheral sites faintly perceive tumor-related signals such as CCL17 or CCL22, migrate to the tumor site, and create a favorable environment for tumor growth.

Recently, a subset of IL-17 producing T cells that are distinct from Th1 and Th2 cells have been described as key players in inflammation and autoimmune diseases as well as cancer development. Interestingly, IL-17 also has been reported to be up-regulated in *H. pylori* infected gastric mucosa. IL-17 positively regulates the synthesis of IL-8 by gastric mononuclear cells and epithelial cells, which thus emphasizes the role of IL-17 in *H. pylori*-driven inflammation^[102]. When the ratio of Th17/Treg cells of TILs was evaluated in GC patients, it was found to be markedly higher in early disease than in advanced disease. The accumulation of Th17 cells as well as of Tregs in the TME of GC occurs in early disease following which the infiltration of Th17 cells gradually decrease as the disease progresses, in contrast to the increased accumulation of Tregs.

Cancer associated fibroblasts

Cancer associated fibroblasts (CAFs) are a central elements of TME. They are the most prominent cell type within the tumor stroma of many cancers and play a critical role in tumor-stromal interactions^[103,104]. CAFs demonstrate differential gene expression profiles compared to normal fibroblasts^[105], and they acquire a modified phenotype, similar to fibroblasts associated with wound healing. Although the mechanisms that regulate activation of fibroblasts and their accumulation in tumors are not fully understood, platelet-derived growth factor, TGF- β 1, and fibroblast growth factor-2 (FGF-2) are known to be partly involved in this process^[106]. There are some candidates for the origins of CAFs, such as following; fibroblasts residing in local tissues^[105], periaxillary cells including

pericytes and vascular smooth muscle cells^[107], endothelial cells^[108], and bone marrow-derived cells including various stem cells^[109]. Worthley *et al.*^[110] recently reported that bone marrow-derived cells can differentiate into CAFs in human GC that developed in female recipients of male allogeneic stem cell transplantation. A previous study showed that direct interaction between scirrhous-type GC cells and gastric fibroblasts could promote fibrosis of the gastric wall and increasing the malignant behavior of cancer cells through vascular cell adhesion molecule-1 and induced Snail expression, and through the resultant E-cadherin suppression and vimentin induction in HSC-39 cells^[111].

Angiogenic factors

Angiogenesis which is necessary for tumor progression, is also influenced by the tumor microenvironment. Stromal reaction (desmoplasia) is observed in GC, but not in non-invasive neoplasms^[112]. The generation of tumor stroma is triggered by tumor cells and induces the ingrowth of new blood vessels and mesenchymal cells from the adjacent normal tissue^[113]. However, recent studies have shown that bone marrow-derived stem cells are integrated into the tumor stroma and differentiate into myofibroblasts and vascular endothelial cells^[109,114]. A recent study reported that the density of blood vessels directly correlates with the incidence of metastasis in GC^[114-117]. Angiogenesis of tumor is mediated by various molecules released by tumor cells and TME^[118,119] and GC cells produce various angiogenic factors, including VEGF^[120], IL-8^[121], FGF-2^[122], and platelet-derived endothelial cell growth factor (PD-ECGF)^[123]. VEGF-A promotes the angiogenesis and progression of human GC, especially those of the intestinal type. A significant correlation between lymph node metastasis and VEGF-C expression has been reported in human GC^[124,125]. However, no association was found between VEGF-D immunoreactivity and clinicopathologic features in submucosally invasive GC^[126]. These results suggest that VEGF-C is a dominant regulator of lymphangiogenesis in early-stage human GC.

Stem cells

The stem cell niche or microenvironment is composed of different populations of cells, including not only stem cells, but also differentiated cells, soluble factors, and extracellular matrix, all of which are critical for stem cell fate and differentiation^[127]. Important signaling pathways such as the Wnt, Notch, Hedgehog, PI3K, NF- κ B, endothelial growth factor (EGF), TGF- β and STAT-3 pathways have been shown to regulate stem cell renewal and maintenance, and their effects overlap in both normal and cancer stem cells^[128]. The Interactions of stem cells with their surroundings are currently under intensive investigation. The inflammatory mediators and oncogenic pathways also regulate stem cell differentiation either directly or indirectly and are frequently deregulated in tumors^[129-131]. Given the fact that gastric stem cells are such a rare population of cells and can be affected by so many

intrinsic and extrinsic factors, it is very complicated to identify the specific role of a signaling factor in regulating their differentiation and migration. It has been noted that NF- κ B, IL-6, VEGF, HIF-1 α , angiogenesis, reactive oxygen species and tissue factors are all involved in the maintenance of stem cell and cancer stem cells^[127] and that *H. pylori* infection can alter most of their expression. This suggests that *H. pylori* might impact the local microenvironment and affect stem/progenitor cell differentiation, and also cause genetic or epigenetic damages in these cells, leading to carcinogenesis. However, further studies addressing these pathways and mediators of gastric stem cells and progenitors during infection are awaited.

CYTOKINES/CHEMOKINES

Infection by *H. pylori* also disrupts gastric homeostasis and induces the production of multiple inflammatory cytokine within the local mucosa. Expression of IL-1 β , TNF- α , and IL-10 is associated with an increased risk for developing GC^[132,133].

IL-1 β is a proinflammatory cytokine involved in inflammation and immunity. IL-1 β polymorphisms are associated with enhanced IL-1 β production and increased risk of GC^[133], IL-1 β also inhibits gastric acid secretion. In transgenic mice, stomach specific overexpression of IL-1 β induces stepwise spontaneous gastric inflammation, metaplasia, dysplasia, and carcinoma.

Overexpression of IL-1 β also mobilizes myeloid-derived suppressor cells and induces NF- κ B activation as well as the expression of downstream genes such as IL-6 and TNF- α in these cells. In addition, IL-1 β alone is sufficient to induce gastric preneoplasia. However, the mechanisms by which IL-1 β overexpression itself finally results in oncogenic transformation is unclear. Interestingly, other inflammatory mediators can exert opposite effects. One example is IFN- γ , which is produced primarily by activated T cells, and natural killer cells and is a key mediator of innate and adaptive immunity. IFN- γ mediates responses to bacterial infection and autoimmune disease, and acts as a tumor suppressor^[134]. In mice, stomach specific overexpression of IFN- γ alone has minimal effects on the gastric mucosa, but inhibits IL-1 β - and *Helicobacter felis*-induced gastritis and neoplasia. The mechanism has been attributed to IFN- γ induced inhibition of gastric epithelial cell proliferation, acceleration of apoptosis of gastric T lymphocytes and decrease in the production of pro-inflammatory Th1 and Th17 cytokines. These effects may balance epithelial cell proliferation, restrain inflammation, and ultimately inhibit tumor formation^[134]. Therefore, disruption of host cell inflammatory cytokine production is involved in gastric oncogenesis.

Chemokines are involved in the chemoattraction of leukocytes to inflammatory sites and can be produced by many kinds of cells in the TME including leukocytes, endothelial cells, fibroblasts and epithelial cells^[135,136]. Recent reports described that chemokines not only play a role in

the immune system, but also promote tumorigenesis and metastasis of cancer. CXC chemokines and their receptors (CXCR) modulate tumor behavior by three important mechanisms: regulation of angiogenesis, activation of a tumor-specific immune response and stimulation of tumor cell proliferation in an autocrine or paracrine fashion^[137].

CXC chemokines containing the ELR (Glu-Leu-Arg)-motif such as IL-8/CXCL8 have been described to promote tumor growth by stimulation of angiogenesis and chemoattraction of neutrophilic granulocytes^[138-140]. Previous studies have shown that IL-1, TNF- α and infection with *H. pylori* induce or enhance the secretion of IL-8 by several gastric adenocarcinoma cell lines *in vitro*^[141,142]. In addition, CXCR1 and CXCR2 expression increased in gastric carcinoma cells after infection by *H. pylori*^[143,144]. In GC, expression of IL-8 in gastric adenocarcinoma is associated with increased tumor vascularization, aggressiveness, invasion, and metastasis. In addition, IL-8 may act as a diagnostic marker as it was demonstrated to be significantly elevated in serum samples of patients with gastric cancer^[145,146]. IL-8 also enhances the expression of the EGFR, MMP-9, VEGF and IL-8 itself^[122,147,148]. Furthermore, the polymorphism of *IL-8* promoter gene is associated with higher IL-8 protein expression, more severe neutrophil infiltration, enhanced angiogenesis, especially with secretion of MMP-9 and angiopoietin-1, and increased risk of poorly differentiated gastric cancer, lymph node, and liver metastasis^[149-151].

In contrast, CXC chemokines lacking the ELR-motif such as interferon- γ , inducible protein-10 (IP-10)/CXCL10, possess angiostatic activities and chemoattract anti-tumoral lymphocytes through binding to CXCR3^[139,140]. It has been described that Mig, IP-10 and I-TAC were constitutively expressed in GC cell lines, and the production can be enhanced by IFN- γ in synergy with TNF- α . In contrast, *in vitro* infection with *H. pylori* inhibited the IFN- γ /TNF- α induced Mig and IP-10 production by GC cells. Increased expression of CXCR3 ligands by endothelial cells and mononuclear cells, especially antigen-presenting cells within GC, results in the chemoattraction and activation of cytotoxic T lymphocytes that favor tumor regression.

Stromal cell-derived factor-1 (SDF-1)/CXCL12 is an exception on this rule as this chemokine lacks the ELR-motif, has angiogenic properties and mediates the dissemination of CXCR4-positive tumor cells to distant organs^[140]. SDF-1 modulates the angiogenic process directly by binding to its receptors CXCR4 and/or CXCR7 expressed on endothelial cells or indirectly by the induced secretion of matrix-metalloproteinases or angiogenic factors such as IL-8, VEGF, respectively^[152,153]. Many studies have demonstrated that both CXCL12 and CXCR4 are differentially expressed in GC^[154,155], and overexpression of CXCR4 in gastric cancer cells is associated with aggressive tumor behavior, such as tumor invasion, lymph node metastasis, liver metastasis, and poor differentiation as well as peritoneal carcinomatosis^[156]. In addition, peritoneal mesothelial cells contained high concentrations of SDF-1 indicating that SDF-1 induces the migration

of CXCR4-positive tumor cells to the peritoneum^[157]. *H. pylori* increased CXCR4 expression in gastric cancer through increased secretion of TNF- α . CXCR4 has also been found in leukocytes and microvascular blood vessels, confirming that SDF-1 binds to endothelial cells^[158]. In addition to cancer cells, stromal cells such as endothelial cells, tumor-infiltrating lymphocytes and cancer-associated fibroblasts have been demonstrated to produce elevated levels of SDF-1^[158,159].

Matrix metalloproteinases

MMPs lead to tissue remodeling, inflammation, tumor cell growth, migration, invasion and metastasis in many cancers. They are major modulators of the tumor microenvironment, playing key roles in tumorigenesis^[160]. Different stromal and cancer cells produce various types of MMPs whose main subtypes are collagenases (MMP-1, MMP-8, MMP-13), gelatinases (MMP-2, MMP-9), matrylisins (MMP-7, MMP-26), membrane type MMPs (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24, MMP-25) and stromelysins (MMP-3, MMP-10, MMP-11).

Previous studies reported that MMP-1^[161], MMP-7^[162-164] and MMP-9^[165,166] are important in development of gastritis during infection by *H. pylori* and these molecules are utilized as molecular markers. It has been suggested that overexpression of MMP-1^[167] and MMP-7^[162,168] is dependent upon the pathogenicity island of *H. pylori* and, interestingly, it is known that MMP-7 participates in the epithelial mesenchymal transition^[169] and is also overexpressed in GC^[170]. Moreover, the activity of MMP-9 is increased in macrophages resident in the gastric mucosa of subjects infected with *H. pylori*^[171] and its activity is known to be reduced by the eradication of *H. pylori*^[172].

MMPs are noncovalently inhibited by the tissue inhibitors known as TIMP, a family comprising four members (TIMP-1, TIMP-2, TIMP-3, TIMP-4). TIMP-3 is the only inhibitor associated with the extra cellular matrix (ECM) and the rest of the TIMP are soluble proteins^[173].

The disintegrins and metalloproteinase (ADAM) family are proteases related to the MMP and comprise more than 20 proteins that are anchored to the cell membrane and present various functions which are cell adhesion, cell fusion, activation of signaling pathways and release of substrates such as cytokines and growth factors from the cell membrane or the ECM^[174]. In patients with gastritis and *H. pylori* infection, levels of ADAM-10 and ADAM-17 are elevated^[175], and these play key roles in cell signaling^[174]. E-cadherin is a substrate of ADAM-10 and the Notch signaling pathway, in which ADAM-17 participates, and these pathways are also involved in the development of GC. ADAM-17 has been associated with the generation of transient hypochlorhydria in patients infected with *H. pylori*^[176] and interestingly, high levels of hypochlorhydria are founded in GC patients.

NEW THERAPEUTIC APPROACHES

According to our understanding of the molecular basis

of TME of GC, targeted agents have led to a modest improvement in the outcome of advanced gastric cancer (AGC) patients.

Previous studies showed that EGFR, HER-2, tyrosine kinase inhibitors (TKIs) as well as VEGF were most attractive target for molecular therapy. The ToGA trial targeted HER-2 and AVAGAST trial targeted VEGF have marked the beginning of a new era in AGC treatment. A number of other phase III clinical trials that target different target molecules are ongoing.

Notably, the ToGA trial, which is a large, phase III, randomized controlled multicenter trial^[177], showed that trastuzumab in combination with chemotherapy led to a significantly higher overall response rate (ORR 47% *vs* 35%, $P = 0.0017$), significantly longer progression free survival interval (PFS; 6.7 mo *vs* 5.5 mo, $P = 0.0002$), and significantly longer overall survival duration (OS; 13.8 mo *vs* 11.1 mo, $P = 0.0046$) than that of the controls. Moreover, the trastuzumab-containing regimen was generally well tolerated and did not affect quality of life. To date, trastuzumab is the first and only targeted agent for gastric cancer approved by both the United States^[178] and European^[179] authorities.

Although the phase III Avastin[®] in Gastric Cancer (AVAGAST) trial did not meet its primary endpoint of OS and was thus a negative trial for this endpoint, the ORR was significantly better in the bevacizumab arm (46% *vs* 37%, $P = 0.0315$) and the PFS interval was significantly longer (6.7 mo *vs* 5.3 mo, HR = 0.8; $P = 0.0037$) than that of the controls^[180].

In first-line phase II trials, cetuximab, a recombinant human-mouse chimeric monoclonal antibody targeting EGFR, showed that the ORR was in the range of 40%-60%, the time to progression (T_{0P}) was 5.5-8.0 mo, and the OS time was 9.5-16.0 mo^[181,182]. Other study reported that cetuximab showed no clinically significant benefit in combination with docetaxel plus oxaliplatin^[183]. Other EGFR targeted therapy including Erbitux[®], panitumumab, matuzumab, and nimotuzumab are under evaluation in phase II / III trials in combination with chemotherapy. The EGFR TKIs such as gefitinib and erlotinib were evaluated in phase II trials but produced disappointing results as monotherapy for AGC.

Lapatinib (Tykerb), a dual TKI inhibiting both HER-2 and EGFR are under investigation in two phase III trials. One is the LoGIC trial that is the lapatinib Optimization Study in ErbB2 (HER-2)⁺ GC patient^[184], and the other is TYTAN trial that is investigating the lapatinib with paclitaxel (Taxol) in Asian ErbB2⁺ (HER2⁺) GC patients^[185].

A few signaling pathways have attracted a lot of enthusiasm. The ubiquitin-proteasome pathway that is involved in cell cycle control is one good target.

Bortezomib, a proteasome inhibitor, was shown to induce apoptosis and suppress tumor growth in GC cell lines^[186]. The overexpression/activation of c-Met, a receptor for hepatocyte growth factor, leads to proliferation and antiapoptotic signals^[80]. A phase II study of GSK1363089 (GSK089, formerly XL880), a c-Met TKI,

showed minimal activity in a cohort of metastatic GS patients unselected for c-Met^[187]. The Hedgehog (Hh) pathway further complicates the complex signaling in gastric cancer cells^[83]. Clinical use of Hh inhibitors is currently only in the early phases of development^[183].

Inhibition of other biological pathways in AGC is in preclinical or early clinical evaluation. Insulin like growth factor-1 receptor antibody, figitumumab, in combination with docetaxel was well tolerated in a phase I trial of patients with advanced solid tumors^[188]. FGFR inhibitors, HSP90 inhibitors, histone deacetylase and IL-6 antibody also may play a role in AGC treatment^[189-193].

CONCLUSION

Although recent phase III clinical trials with conventional chemotherapeutic agents have shown encouraging results in advanced GC, overall survival rates continue to be suboptimal. This highlights the need for new therapeutic strategy using targeted therapy to improve the result of GC treatment.

The association between chronic gastritis and tumors is well documented in the step-wise histopathologic (Correa) model of GC. A better understanding of the molecular pathogenesis of GC would help for improving the knowledge on this relationship and would be crucial for the design of novel molecular targets.

Previous studies reported that a synergistic interplay among the components of TME of GC, including *H. pylori* infection, immune cells and mediators, and several proteins along with matrix metalloproteinases, is essential for the initiation, progression and metastasis of GC. The understanding of how these mechanisms regulate the relationship among those components of TME of GC would contribute strongly to identifying key signaling pathways that serve as both novel biomarkers for early detection and molecular targets for new therapeutic strategies.

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