Inflammatory microenvironment contributes to epithelial-mesenchymal transition in gastric cancer

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Abstract

Gastric cancer (GC) is the fifth most common malignancy in the world. The major cause of GC is chronic infection with *Helicobacter pylori* (*H. pylori*). Infection with *H. pylori* leads to an active inflammatory microenvironment that is maintained by immune cells such as T cells, macrophages, natural killer cells, among other cells. Immune cell dysfunction allows the initiation and accumulation of mutations in GC cells, inducing aberrant proliferation and protection from apoptosis. Meanwhile, immune cells can secrete certain signals, including cytokines, and chemokines, to alter intracellular signaling pathways in GC cells. Thus, GC cells obtain the ability to metastasize to lymph nodes by undergoing the epithelial-mesenchymal transition (EMT), whereby epithelial cells lose their epithelial attributes and acquire a mesenchymal cell phenotype. Metastasis is a leading cause of death for GC patients, and the involved mechanisms are still under investigation. In this review, we summarize the current research on how the inflammatory environment affects GC initiation and metastasis via EMT.

Key words: Gastric cancer; Inflammation; Epithelial-mesenchymal transition; Microenvironment; Immune cells

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Core tip: The major cause of gastric cancer (GC) is *Helicobacter pylori* infection, resulting in an inflammatory microenvironment in GC. Meanwhile, the leading cause of death for GC patients is metastasis. The major pathway for metastasis is the epithelial-mesenchymal transition (EMT). Therefore, a thorough understanding of how the inflammatory microenvironment contributes to the promotion of the EMT is indispensable for developing new treatments. In this review, we summarize the
mechanisms of inflammatory mediators, divided among immune cells and molecules, on the prognosis of GC patients and EMT, which suggests that a combination of immunotherapy and anti-EMT treatments may be encouraging for the treatment of GC.

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INTRODUCTION

Gastric cancer (GC) was the fifth most common malignancy and the third leading cause of cancer worldwide in 2012. Almost one million new cases were estimated to have occurred annually. More than 70% of these occurred in developing countries, and approximately half of all cases worldwide (405000 cases) were diagnosed in China[1]. Two histologically distinct types of GC have described: diffuse-type, in which infiltrating neoplastic cells exists individually, and intestinal-type, which initiates from normal mucosa, transiting to chronic superficial gastritis, atrophic gastritis, intestinal metaplasia, and finally to dysplasia and adenocarcinoma[2]. In recent years, improvements in endoscopic detection and treatment strategies such as surgical resection and chemotherapy have contributed to 5-year survival rates of approximately 60% in Japan[3]. However, despite multimodal therapy, the average overall 5-year survival worldwide still remain at 40%-50%, while in the United States, the 5-year survival rate is only 26%-30%, and more than 60% of patients will develop local relapse or metastatic disease[4]. Therefore, investigating the mechanisms underlying the initiation and progression of GC will help improve early detection and treatment efficiency.

GC is the result of the accumulation of genomic damage that affects cellular functions essential for cancer development[7]. The major cause of GC is chronic infection with the Gram-negative bacterium Helicobacter pylori (H. pylori), which contributes to more than 75% of GC cases[8]. Although in the past, H. pylori infection has been regarded as a risk factor for GC and is categorized as a Group 1 carcinogen for humans[9-11], only a small number of infected individuals develop GC (approximately 2%-3% of the total infected individuals)[12], which makes H. pylori status an unclear predictor of GC prognosis. Some studies have yielded contrasting findings, showing that GC patients with positive H. pylori infection have better disease-free survival and overall survival, whereas negative H. pylori infection indicates poor prognosis in GC patients[13,14]. Recent meta-analyses further showed that instead of serving as a risk factor, H. pylori status could act as a protective factor in predicting GC progression[15], leading to further confusion. Another key factor leading to approximately 10% of GC cases is Epstein-Barr virus (EBV) infection[16]. A meta-analysis of 13 studies showed that EBV-positive patients have decreased survival, which indicates that EBV might serve as a predictive factor[17]. However, studies on the role of EBV are still in their infancy. Although the relationship between H. pylori or EBV and the prognosis of GC patients is unclear, the fact remains that these infections can induce physiological and morphological changes within the gastric epithelium, resulting in an increased risk of neoplastic transformations such as hypochlorhydria and gastric atrophy, which are precursors of GC. The induced inflammatory microenvironment recruits more immune cells that secrete aberrant factors such TGF-β, which may further lead to tumor cell metastasis, which is a major factor in the poor survival of GC patients[18].

METASTASIS AND EPITHELIAL-MESENCHYMAL TRANSITION

A key process in promoting tumor cells metastasis is the epithelial-mesenchymal transition (EMT), which is a process by which epithelial cells lose their epithelial attributes and acquire a mesenchymal cell phenotype[19,20]. During this process, epithelial tumor cells are endowed with three main changes. First, cell morphology changes from a cobblestone-like monolayer of epithelial cells with apical-basal polarity to spindle-shaped mesenchymal cells with migratory pseudopodalia or filopodia structures. Second, the cytoskeleton and intercellular junctions are reorganized with changes in differentiation markers such as the loss of E-cadherin and increased expression of Vimentin and Fibronectin. Third, functional changes are shown to potentiate angiogenesis and intratumor enhanced protease expression, allowing invasion through the extracellular matrix (ECM)[21,22]. EMT also increases resistance to apoptosis and contributes to the survival of circulating tumor cells[23]. Not all of these changes are invariably observed during EMT; however, the ability to migrate and invade the ECM as a single cell is regarded as marking the functional completion of the EMT program.

The development of EMT involves many different signaling pathways. Transforming growth factor-β (TGF-β) is recognized as a potent inducer of the EMT, acting at translational, post-translational, transcriptional and post-transcriptional levels[24]. After signal binds to TGF-β receptors, the EMT is initiated by either the phosphorylation of Smad2/3/4, which induces the transcription of Snail or Slug[25,26], or through non-Smad signaling pathways, including the PI3K/Akt-mTOR pathway[27,28], the RHO-GTPase pathway[29,30], and the ERK, p38 and JUN N-terminal kinase (JNK) MAPK pathways[31-33]. Aside from TGF-β receptors, receptor tyrosine kinases also contribute to
the initiation of the EMT through the activation of the PI3K/Akt and ERK signaling pathways, which promotes cell mobility and invasive behavior\(^\text{[34-36]}\). Some studies have also found that the frizzled receptor, Notch receptor, and patched (PTC) receptors as well as the IL-6 receptor can participate in EMT progression by activating the Wnt and STAT signaling, among other pathways\(^\text{[37-40]}\). To activate these pathways, ligands must first bind to membrane receptors, for example, cytokines found in the GC microenvironment, such as TGF-β1 and IL-1β. These inflammatory cytokines are thought to be released from recruited immune cells, endothelial cells and fibroblasts\(^\text{[41]}\), indicating that members of the microenvironment regulate EMT progression.

### INFLAMMATION AND EMT IN GC

The connection between inflammation and cancer has been studied for years, and chronic inflammation is thought to be a key contributor to tumor development\(^\text{[42]}\). Chronic inflammation is a protective response to damage to tissue homeostasis, inducing a prolonged, aberrant form called a “wound”\(^\text{[43]}\). The so-called “wound” continuously recruits immune cells and other protective cells and induces their secretion of inflammatory mediators. During this state, despite the excessive mediators, the damaged cells will amplify and divide frequently, leading the microenvironment to become oxidative and thus increasing the likelihood of DNA damage and mutations. Once the key damage or mutation occurs, the damaged cells start to secret pro-inflammatory cytokines to keep them active and revert themselves to tumor cells. Meanwhile, these cells manage to escape from immune surveillance and modify infiltrating immune cells into tumor-associated immune cells, which assists tumor progression rather than immune inhibition. These changes result in a “wound” that never heals and promote tumor initiation, progression and metastasis\(^\text{[44-47]}\). Given that more than 85% of GC is caused by infection, which induces inflammation, inflammation is accepted as a major driver of gastric carcinogenesis\(^\text{[48,49]}\).

The tumor-associated microenvironment is characterized by tumor infiltrating lymphocytes (TILs), the secretion of inflammatory mediators and angiogenesis. TILs interact with tumor cells via inflammatory molecules such as cytokines (TGF-β, TNF-α, IL-6, IL-1β), chemokines (CC- and CXC- receptors) and matrix metalloproteinases (MMPs), which form an inflammatory network\(^\text{[50]}\). Unfortunately, these molecules are also inducers of the EMT (Table 1), which may explain how inflammation contributes to GC cells metastasis. Upon infection by _H. pylori_, the level of soluble HB-EGF shedding is up-regulated, which further induces GC cells to undergo the EMT. This process partially relies on the expression of gastrin and MMP7\(^\text{[50,51]}\). GC EMT could also be induced by _H. pylori_ cytotoxin-associated gene A (CagA), which downregulates E-cadherin expression and increases the expression of vimentin and twist\(^\text{[52]}\). Eradication of _H. pylori_ reduces the expression of TGF-β1 while increasing E-cadherin expression, indicating that _H. pylori_ may trigger TGF-β1-induced EMT\(^\text{[53]}\). The development and metastasis of tumor cells may occur because GC cells escape immune surveillance or because immune cells become helpers for GC cells. Therefore, the tumor-related inflammatory microenvironment has an important role in regulating GC EMT, mainly through interactions with infiltrating immune cells.

### Immune cells and EMT

The major infiltrating functional immune cells in GC are T cells, macrophages, NK cells, DCs and MDSCs\(^\text{[54]}\). T cells are mainly divided into CD8\(^{+}\) cytotoxic T cells and CD4\(^{+}\) T helper cells\(^\text{[55]}\). CD8\(^{+}\) cytotoxic T cells (CTLs) exert active antitumor effects, and previous work has shown that GC patients with high CD8\(^{+}\) CTL infiltration display better prognoses\(^\text{[56]}\). However, other work has shown that higher CD8\(^{+}\)CTLs do not indicate good outcomes with metastasis due to the occurrence of adaptive immune resistance, such as the ratio of CD8\(^{+}\) CTLs with programmed death-ligand 1 (PD-L1)\(^\text{[57]}\). Meanwhile, CTLs can also produce IL-17 to promote inflammation and result in a poor prognosis\(^\text{[58]}\). EBV-specific CD8\(^{+}\) CTL injection significantly reduced tumor growth and metastasis in mouse models of GC\(^\text{[59]}\). Thus, treatment with autologous CD8\(^{+}\) CTL injection

### Table 1  Important inflammatory mediators involved in the EMT in GC

| Categories | Factors | Ref |
|------------|---------|-----|
| Cytokines  | TGF-β1  | [103,104] |
|            | TNF-α   | [99,100] |
|            | TGF-α   | [108] |
|            | IL-6     | [109,110] |
|            | IL-8     | [102] |
| Chemokines and receptors | CCL5 | [84,131] |
| Immune cells | CCL18 | [132,133] |
|             | CCR2    | [134] |
|             | CCR7    | [135] |
|             | CCL20-CCR6 | [136,137] |
|             | CXCR1   | [138,139] |
|             | CXCR3   | [140] |
|             | CXCL12-CXCR4 | [108,117] |
| MMPs       | Foxp3\(^{+}\)Tregs | [68,70] |
|            | Foxp3\(^{+}\)/CD8\(^{+}\) ratio | [71] |
|            | NK cells | [87,89] |
|            | TAMs    | [78,79] |
|            | DCs     | [93,95] |
|            | TAM/Foxp3\(^{+}\) ratio | [141] |
|            | MMP-2   | [125] |
|            | MMP-9   | [124-126,142] |
|            | MMP-7   | [51,127,128] |
for GC patients and patients with metastatic GC seems promising[60].

Naïve CD4+ T helper cells can differentiate into several subsets, including Th1, Th2, Treg, and Th17, by secreting various cytokines such as TGF-β, IL-10, and IFN-γ, which are also inducers of the EMT[55,61]. CD4+ T cell subsets are found at significantly lower levels in metastatic tumor draining lymph nodes (TDLNs) than in metastasis-free TDLNs, which indicates that metastasis is a consequence of the loss of CD4+ T cells[62]. Th1 (IFN-γ producing) and Th2 (IL-4 producing) cells play key roles in anti-tumor immunity. The balance between these two cell types can alter antitumor activity, as shown in human peripheral blood: a high Th1/Th2 ratio correlates with a better prognosis and less metastasis[63]. An expansion of Th17 cells is found in GC patients’ tissues and peripheral blood, especially in patients with metastasis. High levels of IL-1β, IL-21, IL-17 and TGF-β expression are also observed, which will induce macrophages to produce more IL-6 and IL-8 to activate the NF-κB pathway and might be a reason why metastasis occurs through the induction of the EMT[64-67]. Another important CD4+ T cell subset related to GC progression at CD4+ suppressor T lymphocytes, or Tregs, that express Foxp3. Higher Foxp3+ Treg infiltration is correlated with GC metastasis and poor prognosis[68-70]. Similar to Th1 and Th2, the ratio of Foxp3+/CD4+ and Foxp3-/CD8+ cells is very important for the suppression of metastasis[68,71].

Macrophages are among the most important immune cells that infiltrate the tumor microenvironment and include the following two phenotypes: M1 macrophages, which facilitate anti-tumor activity, and M2 macrophages, or tumor-associated macrophages (TAMs), which promote tumor progression[72]. Although macrophages can secrete cytokines such as IL-25 to hamper tumor growth and metastasis, large amounts of infiltration by TAMs disrupt this process[73]. TAM infiltration in GC can promote angiogenesis and lymphangiogenesis and predict poor overall survival[74-76], hence, TAMs are regarded as a promising therapeutic target[77]. When TAMs are cocultured with GC cells, the metastatic ability of GC increases, which might be the result of TGF-β1 secretion activating the TGF-β and NF-κB signaling pathways[78,79]. IL-8, which is secreted by surrounding TAMs, could also be an inducer of GC cell metastasis, especially under hypoxic conditions[80-82]. Meanwhile, chemokine factors can affect the relation between TAMs and GC cells. High CXCL12 expression on GC cells can recruit TAMs[83]. Recruited TAMs then secret CCL5, which activates the STAT3 signaling pathway, leading to tumor growth and invasion[84]. Activation of the NF-κB or STAT3 signaling pathway can elevate the expression of certain proteins related to mesenchymal phenotypes, such as Vimentin. In this way, GC cells start to undergo the EMT, which ultimately assists in metastasis[85,86].

NK cells play an important role in regulating GC development and metastasis by directly clearing tumor cells. Previous studies found that in GC patients, the expression of NKG2D, an activating receptor specifically expressed on NK cells, is higher compared with healthy controls, with the same trend observed when comparing GC patients with and without lymph node metastasis[87,88]. This NK cell dysfunction may be related to TGF-β1 levels[89]. These groups of immune cells are unable to inhibit GC progression mainly due to their loss or dysfunction.

DCs are the cells that process and present antigens to T cells[90]. However, their numbers still make a difference in controlling GC progression. Patients with lower DC infiltration have less lymph node metastasis and show a favorable prognosis[91-93]. This effect might due to the elevated IL-10 expression and decreased IL-10 expression produced by DCs through the activation of the NF-κB signaling pathway[94,95], which further affects the metastatic ability of GC cells. MDSCs are a relatively heterogeneous population of cells. Their expansion during cancer is associated with advanced GC stages and indicates poor prognosis[96,97]. However, studies of MDSC function in GC are still very limited.

**Inflammatory molecules and EMT**

Inflammatory mediators are factors that act directly on tumor cells and are secreted by both GC cells and infiltrating cells in the surrounding microenvironment. These mediators can be divided into three groups: cytokines, chemokines and MMPs.

Cytokines can be secreted by all constituents of the tumor microenvironment and appears to modify the EMT of GC cells, including TNF-α, IL-8, TGF-β, TGF-α, and IL-6[98]. TNF-α levels are increased by TNF-α-inducing protein (Tipα), which is released by H. pylori. The binding of Tipα to its membrane receptor activates the NF-κB signaling pathway, resulting in the transcription of TNF-α, which further increases the expression of N-cadherin and vimentin to enable GC cell migration and metastasis[99-101]. Increased of IL-8 levels promote the EMT in GC cells at early stages of GC progression through the activation of the NF-κB pathway[102]. TGFβ is the most potent and common inducer of the EMT. High TGF-β1 expression indicates poor prognosis in GC patients and is related to lymph node metastasis through the activation of the TGF-β signaling pathway[100,104]. Inhibition of this pathway can inhibit EMT-mediated migration and invasion[105-107]. TGF-α is involved in the EMT and is associated with poor OS in GC patients[108]. IL-6 can rescue GC cell resistance to anti-tumor drugs and EMT by activating the STAT3 pathway[109,110].

Chemokines are a group of secreted proteins that are produced in response to pro-inflammatory stimuli and most commonly participate in the chemotaxis...
of leukocyte trafficking and positioning. Current studies show that chemokines are also involved in tumor growth, angiogenesis, EMT, metastasis and immune evasion\[111-113\]. The two most important chemokine receptors in GC are CXCR4 and CCR7. CXCR4 expression is associated with aggressive tumor behaviors such as invasion and metastasis\[114\]. After binding its ligand CXCL12, actin polymerization is activated to induce cell motility and the EMT\[108,115,116\]. The CXCL12-CXCR4 axis alters the migratory and invasive ability of GC cells by upregulating the expression of MMP-2 and MMP-7 to assist EMT progression\[108,117\]. Meanwhile, CXCL12 can recruit myeloid-derived suppressor cells (MDSCs) into the tumor microenvironment to promote the progression of gastric cancer\[58\]. CCR7 is another important chemokine receptor in the progression of GC. CCR7 is associated with lymph node metastasis in GC patients\[70,118\]. Through the activation of CCR7 signaling or the TGF-β1 signaling pathway, GC cells initiate the EMT by altering the expression of E-cadherin, MMP-9, and Snail, which enable them to metastasize, and led by CCR7, they metastasize toward lymph vessels, which is why GC cells metastasize to lymph nodes\[119,120\].

After infection by pathogens such as H. pylori, the expression of matrix metalloproteinase (MMP) family is upregulated because the pathogens need to secrete proteins to assist their adherence to epithelial gastric cells\[121,122\]. The MMP family is among the most important inducers of the EMT through the degradation of the extracellular matrix (ECM) and basement membrane barriers\[123\]. Increased expression of MMP-2 and MMP-9 is reported to enhance the invasiveness of GC cells and correlates with metastatic GC\[124-126\]. Elevated MMP-7 levels can be used as a biomarker for H. pylori-related GC and potentially regulate the progression of GC through the EMT\[121,127,128\]. MMP7-infected mice infected with H. pylori show increased levels of M1 macrophages, which enhance the inflammatory response\[129,130\]. However, the precise mechanism of how MMPs regulate the EMT of GC needs to be clarified in the future.

CONCLUSION
The progression of GC is mainly caused by microbial pathogens and is closely related to host inflammatory factors. The inflammatory microenvironment enables the host immune system to not only combat pathogens but also to secrete cytokines to stimulate normal gastric epithelial cells to protect themselves. During this process, the altered microenvironment may cause random mutations to occur in gastric cells. Once these mutations accumulate to a certain level, the process will continue without restoring normal homeostasis. Thus, the infection starts to become an adenoma followed by a carcinoma. Meanwhile, in the gastric cancer microenvironment, the aberrant secretion by immune cells might lead to dysfunction and also stimulate GC cells to become resistant. In this way, GC cells are likely to gain the ability to continuously proliferate, become protected from apoptosis and escape immune surveillance. Through alterations in their signaling pathways, GC cells begin to translate more mesenchymal proteins such as MMP and vimentin, allowing them to migrate and invade into the blood and lymph vessels to metastasize, otherwise known as the EMT. Current studies mainly focus on the immune cells and GC prognosis and the effects on metastasis. However, studies on the mechanisms by which immune cells alter GC cells undergoing the EMT in the inflammatory microenvironment are still very limited. As long as GC metastasis is a major cause of death, targeting the EMT combined with immunotherapy shows promising results for the treatment of GC in the future.

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