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TOPIC HIGHLIGHT

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Inflammation-related factors predicting prognosis of gastric cancer

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Abstract

Gastric cancer (GC), which is mainly induced by *Helicobacter pylori* (*H. pylori*) infection, is one of the leading causes of cancer-related death in the developing world. Active inflammation initiated by *H. pylori* infection and maintained by inherent immune disorders promotes carcinogenesis and postoperative recurrence. However, the presence with *H. pylori* in tumors has been linked to a better prognosis, possibly due to the induction of antitumor immunity. Tumor infiltrations of tumor-associated macrophages, myeloid-derived suppressor cells, neutrophils, $Foxp3^+$ regulatory T cells are correlated with poor prognosis. Tumor infiltrating $CD8^+$ cytotoxic T lymphocytes, dendritic cells, and CD45RO T cells are generally associated with good prognosis of GC, although some subsets of these immune cells have inverse prognosis prediction values. High ratios of $Foxp3^+/CD4^+$ and $Foxp3^+/CD8^+$ in tumors are associated with a poor prognosis; whereas high Th1/Th2 ratio in tumors predicts a good prognosis. High levels of interleukin (IL)-6, IL-10, IL-32, and chemokine C-C motif ligands (CCL)7 and CCL21 in circulation, high expression of CXC chemokine receptor 4, chemokine C-C motif receptor (CCR)3, CCR4, CCR5, CCR7, hypoxia-inducible factor-1α, signal transducer activator of transcription-3, cyclooxygenase-2, and orphan nuclear receptor 4A2 in tumors are associated with an unfavorable prognosis. Increased serum levels of matrix metalloproteinases (MMP)-3, MMP-7, and MMP-11 and increased levels of MMP-9, MMP-12, and MMP-21 in tumors are consistently associated with poor survival of GC. Further emphasis should be put on the integration of these biomarkers and validation in large cohorts for personalized prediction of GC postoperative prognosis.

Key words: Gastric cancer; Inflammation; Biomarker; Prognosis

Core tip: The prognosis of gastric cancer (GC) is not satisfactory, and is associated with *Helicobacter pylori* and/or Epstein-Barr virus infection, as well as host inflammation-related factors. In this article, we summarize the inflammation-related microbial and host factors that are reported to be associated with GC prognosis from different specimens and populations. So far, few simple panels have been clinically used for predicting GC prognosis. It is necessary to integrate different biomarkers with clinicopathological variables for personalized prediction of GC prognosis. The prognostic values of integrated predicators should be validated in large prospective cohorts before clinical application.

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INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer in men and the fifth in women worldwide. Almost one million new cases are diagnosed annually. More than 70% of new cases and deaths occur in developing countries[1]. To date, surgical resection remains the mainstay of curative treatment for GC. However, a subset of patients will develop local relapses and metachronous metastases after resection of the primary tumor. The overall 5-year survival rate of patients with GC in the United States is about 26%, while the rate improves to 63% if detected at an early stage. Similar low 5-year survival rates (≤ 30%) are also seen in European countries. However, higher 5-year survival rates (up to 50%) are reported from East Asia such as Japan, mainly due to its early detection and treatment services[2]. In addition, other measurable or unmeasurable factors including differences in proximal *versus* distal cancer incidences, environmental exposures, dominant pathological types, surgical factors, and neoadjuvant/adjuvant treatment protocols may also contribute to the differences in postoperative survival of GC patients. Because of the heterogeneity of GC prognosis, searching for more accurate predictors of GC prognosis has become a growing interest in GC research. Chronic infections of *Helicobacter pylori* (*H. pylori*) contribute to more than 75% of GC[3], and about 10% of GC may be caused by Epstein-Barr virus (EBV) infection[4]. Although a causal relationship of EBV infection with nasopharyngeal cancer has been identified, the association of EBV infection with GC has not been confirmed so far. Interestingly, *H. pylori* induce EBV reactivation in the gastric epithelium of GC patients latently infected with EBV[5]. A population-based intervention trial has demonstrated that a selective cyclooxygenase-2 (COX-2) inhibitor, celecoxib, or *H. pylori* eradication alone had beneficial effects on the regression of advanced gastric lesions[6]. Regular use of non-steroidal anti-inflammatory drugs in individuals with *H. pylori* infection can effectively reduce the risk of GC[7], indicating chronic inflammation following *H. pylori* infection contributes to the onset of GC. Accumulating evidence indicates that inflammation-related factors also play an important role in recurrence and metastasis of some types of cancers including GC. Both systemic inflammatory responses, such as primary or modified Glasgow prognostic score[8-11] and blood neutrophil-to-lymphocyte ratio[11-15], and local inflammatory responses such as the infiltration of various immune cells and their subsets in tumors (*e.g.*, infiltrating S100A9$^+$ inflammatory cells[16]) are associated with the prognosis of GC. Here, we review and summarize the inflammation-related microbial pathogen (Table 1) and host (Table 2) factors that have been shown to be associated with GC prognosis.

MICROBIAL PATHOGEN FACTORS

H. pylori

Chronic infection with *H. pylori* is the major cause of GC. It is well established that *H. pylori* infection contributes greatly to the carcinogenesis of GC. However, the role of *H. pylori* infection in predicting the survival of GC patients is less well understood. Interestingly, a prospective study has demonstrated that GC patients with positive *H. pylori* infection frequently showed better relapse-free survival and better overall survival (OS) after curative resection[17], which is contradictory to the notion that *H. pylori* acts as a risk factor of GC during the carcinogenesis process. Although this finding is in contrast to some studies[18,19], other studies[20,21] especially a recent meta-analysis containing 2454 cases[22] have demonstrated that *H. pylori* infection is an independent protective factor for GC progression. This protective effect is also consistent among different ethnic groups, using various *H. pylori* evaluation methods and quality assessment measures[22]. The suppressive effect of *H. pylori* on GC progression is possibly due to the induction of some antitumor immunity[17]. CagA, CagE, VacA and protein modifications (*e.g.*, CagA phosphorylation) of *H. pylori* have been associated with gastric carcinogenesis[23-26], but the association between these factors and GC prognosis is still unclear.

EBV

About 10% of GC cases are infected with EBV, while the prognostic value of EBV is poorly understood. Lymphoepithelioma-like carcinoma (LELC) is a special subtype of GC, and over 90% of LELC are EBV positive. LELC tends to have a lower frequency of lymph node metastasis and a better survival rate than other GC subtypes[27,28]. A recent meta-analysis including 4599 GC patients from 13 studies has shown that EBV positivity in tumors by *in situ* hybridization is associated with lower mortality (HR = 0.72; 95%CI: 0.61-0.86) and might serve as a valuable prognostic factor[29]. Furthermore, the protective effect is quite stable across patients or tumor types. However, these studies cannot clarify whether EBV infection itself or EBV-associated inflammatory responses and/or their interactions result in the protective effect. EBV-associated GC (EBV-GC) is a recently recognized entity defined by the presence of EBV in GC cells. After stratification of EBV-GC by host inflammatory response, it was found that EBV-GC patients with a Crohn's disease-like lymphocyte reaction had significantly longer OS and disease-free survival (DFS) than other EBV-GC patients, indicating that inflammation induced by EBV-GC could affect the prognosis of GC[28]. Mechanisms of the heterogeneity of induced inflammatory responses by EBV-GC need to be explored further.

HOST INFLAMMATION-RELATED FACTORS

There is a renaissance of research into the connection

Table 1 Important pathogens associated with the prognosis of gastric cancer

Factors	Source	Sample	Sample size	Cut-off value or characterization	Time of measurement	Prognostic role
H. pylori	Germany	Sera	166	Positivity	Prior to gastrectomy	Increased OS and RFS[17]
H. pylori	China	Tumor tissue	162	Positivity	At the time of surgery	Decreased OS and RFS[18]
H. pylori	Brazil	Tumor tissue	68	Positivity	At the time of surgery	No difference[19]
H. pylori	South Korea	Sera	274	Negativity	At the time of surgery and adjuvant chemotherapy	Decreased OS[20]
H. pylori	Italy	Sera and tumor tissue	297	Negativity	At the time of surgery	Decreased OS[21]
H. pylori	Brazilian, Asian and Caucasian	Sera	2454	Positivity	At the time of surgery	Increased OS and DFS[22]
EBV	Taiwan	Sera	150	Positivity	Prior to gastrectomy	Increased OS[27]
EBV	Korea	Sera	123	Expression	At the time of surgery	Increased OS and DFS[28]
EBV	Asia, Europe and Latin America	Sera	4599	Positivity	At the time of surgery	Increased OS[29]

DFS: Disease-free survival; EBV: Epstein-Barr virus; *H. pylori*: *Helicobacter pylori*; OS: Overall survival; RFS: Relapse-free survival.

Table 2 Important inflammation-related host factors with prognostic values for gastric cancer

Factors	Source	Sample size	Cut-off value or characterization	Time of measurement	Prognostic role
In peripheral blood					
MIF	China	97	> 6600 pg/mL	Prior to gastrectomy	Decreased 5-year survival rate[45]
Th1/Th2 ratio	Japan	157	High	After curative gastrectomy	Increased DFS[61]
Th17	China	51	High levels	Prior to gastrectomy	Decreased OS[62]
Th22	China	51	High levels	Prior to gastrectomy	Decreased OS[62]
$CD57^+$ T cells	Japan	48	⩾ 18%	At the time of gastrectomy	Decreased OS[68]
NLR	South Korea	775	> 3.79	Prior to gastrectomy	Decreased 5-year survival rate[12]
NLR	China	46	> 2.5	Prior to gastrectomy	Decreased PFS and OS[13]
TLR9	China	314	TLR9-1486C	Prior to gastrectomy	Decreased OS[73]
IL-1B + IL-1RN	Italy	123	IL-1B-511C/T and IL-1B-31T/C + Wide-type IL-1RN	Prior to gastrectomy	Decreased PFS and OS[76]
IL-6	Poland	99	> 288.7 pg/mL	At the time of gastrectomy	Increased overall complications and infective complications[83]
IL-2R	Japan	96	High expression	Prior to gastrectomy	Decreased OS[88]
IL-32	Japan	182	Positive expression	At the time of gastrectomy	Decreased OS[89]
VAP-1	Japan	107	Low levels	Prior to gastrectomy	Decreased OS[91]
MDSCs	United Kingdom	25	Increasing percentage	Prior to gastrectomy	Increased the risk of death[50]
MMP-11	China	86	Low levels at the 75^{th} percentile in the total group	After chemotherapy	Decreased median survival time and 1-year survival rate[104]
MMP-12	China	165	Positive expression	Prior to chemotherapy	Decreased OS[105]
In tumor					
TAM	Japan, Germany, Ukraine	449	Positive expression	Prior to chemotherapy	Decreased OS[44]
$CD68^+$ Mφ	Japan	111	High numbers	At the time of gastrectomy	Decreased OS[45]
Nitrotyrosine	China	66	Intermediate or high expressions	At the time of gastrectomy	Decreased 5-year survival rate[51]
$CD33^+$/p-$STAT^+$ cells	China	100	> 11 cells/HPF	After curative gastrectomy	Decreased 5-year survival rate[52]
DCs	Japan	174	High levels	At the time of gastrectomy	Increased 5-year survival rate[53]
DCs	Bulgaria	55	Low numbers	At the time of gastrectomy	Decreased 5-year survival rate[54]
$CD208^+$	Japan	128	High expression levels	At the time of gastrectomy	Decreased postoperative outcome[55]
$CD15^+$ TINs	Japan	115	< 21.60 cells/HPF	At the time of gastrectomy	Increased OS[56]
HIF-1α	Japan, China, South Korea, United Kingdom	1268	High expression	Prior to gastrectomy	Decreased OS[77]
HIF-1α	Japan, China, South Korea, United Kingdom	1555	High expression	Prior to gastrectomy	Decreased OS[78]
S100A9 protein	China	176	> 200 positive cells/HPF	At the time of gastrectomy	Increased OS[16]
Stroma $FoxP3^+$TILs	Germany	52	> 125.9/mm^2	At the time of gastrectomy	Increased NED-survival and OS[113]
Stroma $CD68^+$/$Foxp3^+$	Germany	52	High cell ratios	At the time of gastrectomy	Increased median survivals[113]
Tc17	China	103	Percentage ⩾ 2.75% or cell number ⩾ 484.37 per million	At the time of gastrectomy	Decreased DFS and OS[60]
$FOXP3^+$ Tregs	China	107	High numbers	At the time of gastrectomy	Increased OS[47]
$CD45RO^+$ T cells	Japan	101	High levels	At the time of gastrectomy	Increased OS and DFS[67]
$Foxp3^+/CD8^+$ ratio	China	133	High	At the time of gastrectomy	Decreased OS[65]

Foxp3$^+$/CD4$^+$ ratio	South Korea	180	High	At the time of gastrectomy	Loco-regional recurrence[66]
T-bet$^+$ TILs	China	152	High numbers	At the time of gastrectomy	Increased OS and DFS[69]
CD19$^+$ cells	China	846	> 7.91% ± 2.98%	At the time of gastrectomy	Increased DFS[70]
CD20$^+$ B cells	China	100	High density	Prior to gastrectomy	Increased OS and DFS[52]
Natural killer cells	Brazil	72	> 15 NK cells/10 HPF	At the time of gastrectomy	Increased OS and DFS[71]
COX-2	South Korea	457	Lack of expression	At the time of gastrectomy	Decreased OS and DFS[79]
STAT3	South Korea	100	> 10% stained cells	At the time of gastrectomy	Decreased OS and DFS[81]
NR4A2	China	245	Immunoreactive score ⩾ 3	At the time of gastrectomy	Decreased OS and DFS[85]
IL-12	Japan	85	High density	At the time of gastrectomy	Increased OS and DFS[86]
IL-10	Poland	136	> 10 pg/mL	At the time of gastrectomy	Decreased OS and DFS[87]
Annexin A1	Taiwan	118	High expression	At the time of gastrectomy	Decreased OS[90]
CCL7 and CCL21	China	194	Higher expression	At the time of gastrectomy	Decreased OS[92]
CXCR4	China	97	Higher expression	At the time of gastrectomy	Decreased OS[94]
HighCXCR4/high SDF-1α	South Korea	221	Expression	At the time of gastrectomy	Decreased 5-year survival rate[95]
CCR3	Japan	48	Positive expression	At the time of gastrectomy	Decreased OS[96]
CCR5	Japan	60	Positive expression	At the time of gastrectomy	Decreased OS[96]
CCR4	South Korea	753	Positive expression	At the time of gastrectomy	Decreased 5-year survival rate[97]
CCR7	Japan	224	> 10% positivity	At the time of gastrectomy	Decreased OS[98]
CX3CL1	Japan	158	High expression	At the time of gastrectomy	Decreased DFS[100]
CCL18	China	59	High expression	At the time of gastrectomy	Increased OS and DFS[48]
MMP-9	China, Finland, The Netherlands, Poland, Spain	1700	High expression	At the time of gastrectomy	Decreased DFS[102]
MMP-21	China	296	High expression	At the time of gastrectomy	Decreased OS[106]
MMP 14	China	205	Positive expression	Prior to chemotherapy	Decreased OS[107]
MT1-MMP, CD11b$^+$ immunocytes and LNR	China	184	MT1-MMP positive, low CD11b+ immunocytes and high LNR	At the time of gastrectomy	Increased OS[110]
Inflammation gene signature	Brazil	51	High expression pattern	At the time of gastrectomy	Decreased OS[112]

CCL: Chemokine (C-C motif) ligand; CCR: C-C chemokine receptor; CD: Cluster of differentiation; COX-2: Cyclooxygenase-2; CX3CL1: Chemokine (C-X3-C motif) ligand 1; CXCR4: C-X-C chemokine receptor 4; DFS: Disease-free survival; FOXP3: Forkhead box P3; HIF-1α: Hypoxia-inducible factors-1 α; HPF: High power field; IL: Interleukin; MDSCs: Myeloid-derived suppressor cells; MIF: Migration inhibitory factor; MMP: Matrix metalloproteinase; NLR: Neutrophil lymphocyte ratio; NR4A2: Nuclear receptor subfamily 4, group A, member 2; PFS: Progression-free survival; SDF-1α: Stromal cell-derived factor -1α; STAT: Signal transducers and activators of transcription; TAM: Tumor associated macrophages; Th1: T helper cell type 1; Th2: T helper cell type 2; Th17: T help cell type 17; Th22: T help cell type 22; TIL: Tumor infiltrating lymphocyte; TIN: Tumor infiltrating neutrophils; TLR: Toll-like receptors; Treg: Regulatory T cells; VAP-1: Vascular adhesion protein-1.

between inflammation and cancer[30-32]. Most current research support that acute inflammation triggered by tumor-infiltrating leukocytes does not exert normal immunoprotective mechanisms that lead to eradication of the evolving cancer (antitumor immunity). Excessively and chronically produced pro-inflammatory mediators may contribute to tumor promotion and progression[31-34]. Inadequate pathogen eradication, prolonged inflammatory signaling, and defects in anti-inflammatory mechanisms can lead to chronic inflammation and benefit tumor development[35]. In an inflammatory state, there is a high rate of cell turnover and the microenvironment is often highly oxidative and nitrosative, thus increasing the opportunities for DNA damage and somatic mutation. Chronic inflammation can promote an environment that is conducive to carcinogenesis, and it is involved in tumor initiation, promotion, and progression[31,36-39]. The tumor microenvironment is created by the tumor and dominated by tumor-induced interactions[40]. In the inflammatory microenvironment, there is a delicate balance between antitumor immunity and tumor-originated pro-inflammatory activity, which weakens antitumor immunity[33,41]. The tumor not only manages to escape from the host immune system (tumor escape), but it effectively contrives to benefit from infiltrating cells by modifying their functions to create the microenvironment favorable to tumor progression[40]. The net outcome of a persistent inflammatory microenvironment is enhanced tumor promotion, accelerated tumor progression, invasion of the surrounding tissues, angiogenesis, and often metastasis[31]. Cancer-associated inflammation is characterized by infiltration of immune cells including tumor infiltrating lymphocytes (TILs)[42], expression of cytokines and chemokines, tissue remodeling, and angiogenesis. The diverse cells communicate with each other by means of direct contact or through cytokines and chemokines, therefore exerting their functions of tumor promotion or suppression. Cancer cells can also release chemokines and recruit immune cells to constitute the inflammatory microenvironment. The inflammation-related molecules such as nuclear factor-κB (NF-κB) and signal transducer activator of transcription-3 (STAT3), primary inflammatory cytokines, secondary inflammatory cytokines, chemokines and matrix metalloproteinases (MMPs) form an inflammatory molecular network, playing an active role in maintaining tumor-promoting inflammation or antitumor immunity. Although tumor infiltrating immune cells and their interactions can reflect the host-tumor-pathogen immune response, immune cells and molecules in peripheral blood are also important for exploring the characteristics

of the complex tumor-related inflammation.

TIMs

TIMs are the major type of infiltrating inflammatory cells regulating antitumor immunity and are represented by mature cells such as macrophages, granulocytes, and dendritic cells (DCs), as well as by pathologically activated immature myeloid-derived suppressor cells (MDSCs)[43]. Macrophages, one of the most important components of the inflammatory infiltration in tumors, include M1-like and M2-like subtypes. M1-like macrophages facilitate anti-tumor immunity, while M2-like macrophages promote tumor progression. M2-like macrophages are strongly affected by the tumor microenvironment, and are also termed tumor-associated macrophages (TAMs). A meta-analysis of 55 studies with 8692 patients has shown that higher TAM infiltration is associated with worse OS in several cancers, including GC (RR = 0.52; 95%CI: 0.35-0.77)[44]. Thymidine phosphorylase (TP) expression is significantly correlated with the extent of infiltrating macrophages, and increased percentages of TP-positive macrophages and $CD68^+$ macrophages in tumors also indicate poor outcomes in patients with GC[45]. Macrophage migration inhibitory factor (MIF) can inactivate p53. Serum MIF positively correlates with MIF expression in GC, and increased serum MIF (> 6600 pg/mL) predicts a lower 5-year survival rate compared with those with lower serum MIF[46]. However, GC patients with high intratumoral macrophages and regulatory T cells (Tregs) have better 5-survival rates than those with low intratumoral macrophages and Tregs[47]. A high level of CCL18, mainly expressed in infiltrating macrophages that are preferentially located at the tumor invasion front, is also associated with favorable OS and DFS of GC patients[48]. The possible explanation for this inconsistency could be the presence of heterogenic subpopulations of macrophages in the tumor microenvironment.

MDSCs are a heterogeneous population of cells characterized by their myeloid origin, immature state and the ability to suppress T cell responses. The MDSC population expands rapidly during inflammation and cancer, which is associated with advanced GC stage and reduced survival[49,50]. Production of reactive oxygen species (ROS) and reactive nitrogen species is one of the major characteristics of all activated myeloid cells. Increased activity of free radical peroxynitrite is followed by ROS production, and peroxynitrite modification of chemokine (C-C motif) ligand 2 (CCL2) inhibits intratumoral migration of effector $CD8^+$ T cells. Nitrosylation, a marker of peroxynitrite activity, has been reported to be associated with poor survival of GC patients[51]. High $CD33^+$/p-$STAT^+$ cells representing a subset of MDSCs, are also associated with poor prognosis at stage ⅢⅠa GC[52].

The major functions of DCs are to process and present antigens for the activation of T cells. Maintaining enough density of mature DCs in tumors prolongs the survival of patients with advanced GC[53,54]. Contrary to the typical functions of DCs, intratumoral density of $CD208^+$ DCs has an inverse correlation with postoperative outcome in GC patients[55]. Among immune cells, neutrophils have a protumorigenic role by promoting neoangiogenesis and reducing antitumor immune response. In GC patients, tumor infiltrating neutrophils with positive CD15 are independently associated with an unfavorable OS[56]. S100A9, specifically expressed by inflammatory cells such as macrophages and neutrophils in early GC, is associated with a good prognosis[16]. In addition, S100A9 secreted into gastric fluid also has a prognostic monitoring value for GC[57].

TILs

TILs are another major component of infiltrating immune cells, and are represented by T cells, B cells, and natural killer (NK) cells. The subsets of T cells include $CD8^+$ cytotoxic T cell (CTL), $CD4^+$ T helper cell, CD45RO memory T cells, $FOXP3^+$ Tregs, and nature killer T cells. $CD8^+$ CTLs play an active role in directly killing tumor cells, indicating a favorable outcome[58,59]. However, $CD8^+$ T cells that produce interleukin (IL)-17 (Tc17 cells) promote the progression of inflammation and are possibly associated with poor prognosis[60]. $CD4^+$ lymphocytes include a group of heterogeneous T lymphocytes [*e.g.*, T helper (Th)1, Th2, Th3, Th17, Treg, T follicular helper, and Th22] which can secret diverse cytokines. Th1 cells (interferon γ-producing $CD4^+$ T cells) can activate CTLs, and Th2 cells (IL4-producing $CD4^+$ T cells) stimulate humeral immunity. Th1 activation is more effective than Th2 activation in inducing antitumor immunity. Consistently, high Th1/Th2 ratio in peripheral blood of GC significantly predicts a good postoperative prognosis[61]. High circulating Th17 and Th22 cells are associated with tumor progression and poor survival in GC[62]. $CD4^+$ Tregs suppress effector T lymphocytes, which are characterized with positive Foxp3 expression. High $Foxp3^+$ Tregs are correlated with GC progression and associated with a poor survival[63-65]. The balances between $Foxp3^+$ T cells and $CD4^+$ T cells as well as $Foxp3^+$ T cells and $CD8^+$ T cells are important for the suppression of metastasis, and higher $Foxp3^+/CD4^+$ ratio[66] and higher $Foxp3^+/CD8^+$ ratio[65] in resected tumor specimens are associated with a poor prognosis. High CD45RO T cell infiltration is significantly related to postoperative prognosis in advanced GC but not in early GC[67]. NK-like T cells comprising the subsets of $CD56^+$ cells and $CD57^+$ cells play an important role in modulating immune responses. In advanced GC, an increased proportion of $CD57^+$ cells in the circulation indicates a poor prognosis[68]. T-bet, a key master transcription factor for type 1 immune response, mainly expresses on $CD4^+$, $CD8^+$, and $CD56^+$ TILs. High T-bet TILs in tumor are associated with a better DFS and OS of GC patients[69]. The principal functions of B cells are to generate antibodies against antigens, but its functions related to tumor progression are less known. Recently, it has been reported that $CD19^+$ and $CD20^+$ B cells are associated with a favorable outcome in patients with GC[52,70]. NK

cells directly clear tumor cells, representing an antitumor immunity. GC patients with high density of NK cells in the tumors exhibit a higher survival rate when compared to those patients with low density of NK cells, especially for those at advanced stages[71].

TRANSCRIPTION FACTORS AND PRIMARY INFLAMMATORY CYTOKINES

In terms of cancer-related inflammation, a few molecules can serve as primary drivers (endogenous promoters), mainly including transcription factors such as NF-κB and STAT3 and primary inflammatory cytokines such as IL-1, IL-6, and tumor-necrosis factor (TNF)-α. NF-κB is a key orchestrator of innate inflammation and is aberrantly activated in many cancers. In GC, activated NF-κB is frequently identified in early-stage tumors and usually predicts a favorable prognosis[72]. The toll-like receptor (TLR)-MyD88 pathway and the primary inflammatory cytokines TNF-α and IL-1α can activate NF-κB. It has been reported that polymorphisms in NF-κB pathway genes such as *TLR9*, *IL-1β*, *IL-1Ra*, and *TNF*-α, are significantly associated with the prognosis of GC patients[73-76]. NF-κB can also be activated in response to hypoxia inducible factor (HIF)-1α. Accumulating evidence indicates that the interactions and compensations between NF-κB and HIF-1α relate to immunity in the hypoxic condition. Two meta-analyses both reported that HIF-1α expression was significantly correlated with poor prognosis of GC patients mainly from East Asian countries[77,78]. NF-κB induces the expression of inflammatory cytokines, adhesion molecules, and key enzymes in the prostaglandin synthase pathway such as COX-2. Immunohistochemical analysis has shown that COX-2 expression is an independent prognostic factor of DFS and OS of GC patients[79]. Along with NF-κB, STAT3 is a point of convergence for numerous oncogenic signaling pathways. In tumors, the maintenance of NF-κB activation requires STAT3[80]. STAT3 is constitutively activated both in cancer cells and immune cells, and higher STAT3 and STAT3 phosphorylation (Tyr705) in GCs indicate a poor prognosis[81,82]. IL-6 is mainly produced by TIMs under the regulation of the NF-κB signaling pathway. IL-6 is also linked with STAT3, and has multi-functions of growth-promoting and anti-apoptotic activities. Preoperative high IL-6 levels have been proposed as a poor prognostic factor for recurrence and OS of GC patients[83]. Nuclear receptor subfamily 4, group A, member 2 (NR4A2), a transcription factor belonging to the steroid orphan nuclear receptor superfamily, is also regulated by the NF-κB signaling pathway and COX-2 derived prostaglandin E2[84]. Expression of NR4A2 in GC cells confers chemoresistance of GC cell lines and predicts an unfavorable postoperative survival of GC patients, especially for those treated with postoperative chemotherapy[85].

Cytokines, chemokines, and matrix metalloproteinases

Cytokines including IL-1, IL-6, and TNF-α are regulators of host responses to infection and cancers, and play different roles in cancer-related inflammation network. Some cytokines facilitate the development of cancer-related inflammation, whereas others act as suppressors. T lymphocytes are a major source of cytokines. Cytokines produced by Th1 and Th2 are known as Th1-type cytokines (*e.g.*, TNF-α, IFN-γ, IL-12) and Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-10, IL-13), and are characterized by pro-inflammatory and anti-inflammatory roles, respectively. High IL-12-positive cell density in surgical specimens may be a significant independent predictor of better prognosis of advanced GC patients[86]. Conversely, an increased level of IL-10 is an independent unfavorable prognostic factor in patients with GC[87]. The relative balance between Th1 and Th2 cytokines appears important in cancer-related inflammation. A high circulating soluble IL-2 receptor level is associated with worse prognosis of GC patients[88]. IL-32 is a recently identified pro-inflammatory cytokine characterized by the induction of NF-κB activation, and the expression of IL-32 is associated with more severe metastatic conditions in GC[89]. Additionally, annexin A1 is a glucocorticoid-regulated anti-inflammatory protein. High tissue annexin A1 expression is an independent risk factor for poor OS in GC patients[90]. Vascular adhesion protein-1 (VAP-1) regulates leukocyte tissue infiltration. Serum soluble VAP-1 is a candidate prognostic marker in GC, and low levels of serum VAP-1 are associated with poor prognosis in GC patients[91].

Chemokines are 8-10 kDa secreted proteins with 20%-70% homology in structure, and share the common functional activity as being chemotactic for leucocytes. Over 40 chemokines have been identified so far. Although chemoattractants constitute a diverse array of molecules, they have to act together with a family of G protein-coupled receptors to communicate with leukocytes. Inflammatory chemokines are produced under pro-inflammatory stimuli (*e.g.*, IL-1, TNF-α, lipopolysaccharide, or pathogens) and determine the migration of inflammatory cells. CCL7 is a type of monocyte-specific chemokine, and CCL21 is a specific chemokine in DC cells and effecter T cells. Over-expressed CCL7 and CCL21 in GCs are related to lymph node metastasis and poor prognosis[92]. Stromal-derived-factor (SDF)-1 is strongly chemotactic for lymphocytes, and is found in GC metastasized to lymph nodes[93]. CXC chemokine receptor 4 (CXCR4) is a receptor specific to SDF-1. Interestingly, upregulated intratumoral CXCR4 expression is associated with poor OS in patients with GC[94], and high CXCR4/high SDF-1α expression indicates the worst prognosis in GC patients[95]. Chemokine (C-C motif) receptor 3 (CCR3), CCR4, CCR5, and CCR7 have been shown to have prognostic values for an unfavorable outcome in patients with GC[96-98]. Intratumoral high CXCR4, CCL3, CCR4, CCR5, and CCR7 are associated with unfavorable prognosis. IL-8 is a chemokine produced by macrophages and other cell types. It induces chemotaxis in neutrophils to migrate toward the site of inflammation. Polymorphism of *IL-8* is associated with prognosis

in patients with GC, and the *IL-8* 251 A/A genotype may indicate a poor prognosis in GC patients[99]. CX3CL1 is the only CX3C chemokine that can chemoattract NK cells, $CD8^+$ T cells, monocytes, and dendritic cells, and is one of the independent prognostic factors of DFS in GC patients[100].

An increased expression of the MMP family members is observed in almost every inflammation site. Studies in animal models have demonstrated that MMPs act broadly in the inflammation process, including regulation of inflammatory cytokine and chemokine activities, and generation of chemokine gradients. Pathogens such as *H. pylori* infection upregulate the expression of MMPs, which act on pro-inflammatory cytokines, chemokines and other proteins to regulate diverse aspects of inflammation. Elevated MMP-3 and MMP-7 in *H. pylori*-related GC can serve as biomarkers for a poor survival[101]. *MMP-9* gene expression is a predictor of outcome in patients with metastatic GC[102], which is further confirmed by a meta-analysis[103]. Serum levels of MMP-11 in Chinese patients with advanced GC are not associated with the response to front-line chemotherapy, but could play an important role in predicting lymph node metastasis and prognosis[104]. Increased MMP-12 and MMP-21 in tissues are associated with poor survival in patients with GC[105,106]. MMP-14 is a negative prognostic marker for patients with GC[107]. Although MMPs have been linked to GC prognosis, the precise mechanisms need to be clarified. It is possible that only some MMPs can truncate the inflammatory cytokines or chemokines and participate in the regulation of tumor-related inflammation.

CONCLUSION

The progression of GC after surgical resection is closely associated with microbial pathogens and host inflammatory factors. Positive *H. pylori* and/or positive EBV infection can serve as prognostic factors for a better survival of GC patients. Intratumoral TAMs, MDSCs, neutrophils, and Tregs are usually correlated with poor prognosis of GC. Tumor-infiltrating $CD8^+$ CTLs, DCs, CD45RO T cells are generally correlated with better prognosis of GC, although some subsets of these cells have inverse prognostic prediction values. A high NF-κB indicates a favorable prognosis, while high HIF-1α, STAT3, NR4A2, and preoperative high IL-6 predict a poor prognosis. Polymorphisms of *TNF-α*, *IL-1α*, and *TLR9*, which might affect the expression and/or function of these genes, are associated with the prognosis of GC patients. Increased IL-10, IL-32, CCL7, CCL21 and intratumoral high CXCR4, CCR3, CCR4, CCR5, and CCR7 are associated with unfavorable prognosis. Increased serum levels of MMP-3, MMP-7, MMP-11 and increased expression of MMP-9, MMP-12, and MMP-21 in tumors are consistently associated with poor GC survival.

In this article, we summarized the inflammatory factors associated with the prognosis of GC. As inflammation provides "fertile field" for the evolution of cancer-initiating cells, tumor growth-promoting molecules predominantly expressed in cancer-initiating cells also represent a cluster of prognosis-predicting biomarkers and/or therapeutic targets[108]. Since many studies are conducted in East Asian populations as summarized in Tables 1 and 2, the prognostic values of these molecules need to be tested in other populations. Furthermore, with the advancement of systems biology and vast amount of 'omics' data, it is of great importance to evaluate these data with clinical and pathological variables to more accurately predict cancer outcomes. Studies have already looked at combining gene expression data with clinicopathological data to better predict different types of cancer prognosis[109-111]. However, only a few studies have been conducted in the field of GC research[112,113]. Further emphases should be placed on the integration of diverse biomarkers and their validation in large cohorts for personalized prediction of GC postoperative prognosis.

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