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Resolution of gastric cancer-promoting inflammation: a novel strategy for anti-cancer therapy

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Abstract

The connection between inflammation and cancer was initially recognized by Rudolf Virchow in the nineteenth century. During the last decades, a large body of evidence has provided support to his hypothesis, and now inflammation is recognized as one of the hallmarks of cancer, both in the etiopathogenesis and in ongoing tumor growth. Infection with the pathogen *Helicobacter pylori* is the primary causal factor in 90% of gastric cancer cases. As we increase our understanding of how chronic inflammation develops in the stomach and contributes to carcinogenesis, there is increasing interest in targeting cancer-promoting inflammation as a strategy to treat gastric cancer. Moreover, once cancer develops and anti-cancer immune responses are suppressed, there is evidence of a substantial shift in the microenvironment and new targets for immune therapy emerge. In this chapter, we provide insight into inflammation-related factors, including T lymphocytes, macrophages, pro-inflammatory chemokines and cytokines, which promote *H. pylori*-associated gastric cancer initiation and growth. While intervening with chronic inflammation is not a new practice in rheumatology or gastroenterology, this approach has not been fully explored for its potential to prevent carcinogenesis or to contribute to the treatment of gastric cancer. This review highlights current and possible strategies for therapeutic intervention including: i) targeting pro-inflammatory mediators, ii) targeting growth factors and pathways involved in angiogenesis in the gastric tumor microenvironment, and iii) enhancing anti-tumor immunity. In addition, we highlight a significant number of clinical trials and discuss the importance of individual tumor characterization towards offering personalized immune-related therapy.

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Keywords

immunotherapy; gastric cancer; *Helicobacter pylori*; inflammation; immune modulation

1 Introduction

The connection between inflammation and cancer was initially recognized by Rudolf Virchow in the nineteenth century (Virchow 1863). During the last decades, a large body of evidence has provided support to his hypothesis, and now inflammation is recognized as one of the hallmarks of cancer (Colotta et al. 2009). Many types of cancer are preceded by a chronic inflammatory process, mostly initiated by infections or exposure to environmental factors. It is estimated that about 15% of new cancer cases worldwide in 2012 were attributable to carcinogenic infections, with *H. pylori* being the most important, accounting for about 770,000 cases of gastric cancer (GC) annually (Plummer et al. 2016).

GC is the fifth most common malignancy worldwide and the third leading cause of cancer-related mortality (Ferlay et al. 2015). Incidence rates of GC differ widely across geographic regions, with the highest rates observed in Asia, Eastern Europe, and some Latin American countries. Most GCs are adenocarcinomas but are highly heterogeneous with respect to histological architecture and molecular features (Gullo et al. 2018; Cancer Genome Atlas Research 2014; Lee et al. 2016). Histological classification systems (Lauren 1965; Lauwers et al. 2010) are clinically impractical to guide patient management. Due to differences in etiological and epidemiological factors, GCs are classified anatomically as cardia (proximal) and non-cardia (distal). It is estimated that ~90% of cases of non-cardia cancer worldwide are caused by *H. pylori* infection (Plummer et al. 2015).

GC is a lethal disease, mainly due to the high rates of diagnosis at advanced stages. With the exception of Japan and Korea, where screening programs for early detection have been implemented, overall five-year survival rates after diagnosis are below 35% (Cancer Stat Facts: Stomach Cancer, SEER Cancer Statistics Review, 1975–2015 2018; Zeng et al. 2018). Early GC is limited to the mucosa and submucosa, regardless of lymph node involvement, and surgical resection is the only curative treatment. Only a minority of patients with advanced disease responds to current modalities of treatment, which, according to the stage, include a combination of adjuvant or neoadjuvant therapies with surgery (Van Cutsem et al. 2016). Recent advances in targeted therapy such as trastuzumab, an antibody against human epidermal growth factor receptor 2 (HER2), and ramucirumab, an antibody against VEGFR2 (Bang et al. 2010; Fuchs et al. 2014; Wilke et al. 2014), and immunotherapy modalities (Fuchs et al. 2018a) have produced encouraging results in the treatment of patients with certain subtypes of advanced GC.

Due to the wide heterogeneity of GCs, new strategies to treat this disease are a priority. Although most cancer research has focused on the molecular changes of the neoplastic cells, it is now recognized that non-tumoral cells in the tumor microenvironment, especially immune cells, proliferate with the tumor and provide essential support for its growth and invasion. The recognized protective effect of non-steroidal anti-inflammatory drugs against

GC and other gastrointestinal tumors (Abnet et al. 2009; Epplein et al. 2008; Kim et al. 2018) supports the role of chronic inflammation in carcinogenesis.

In this chapter, we provide insight into inflammation-related factors that promote *H. pylori*-associated GC initiation and growth, focusing on current and potential strategies for therapeutic intervention (Fig. 1). A section is dedicated to novel immunotherapy modalities, especially promising in certain subtypes of GC, such as Epstein-Barr virus (EBV)–associated and microsatellite instable (MSI) tumors. Of note, *H. pylori* is also the main etiologic factor of mucosa-associated lymphoid tissue lymphoma and will be discussed in chapter 4.

2 Inflammatory mediators of gastritis and the TME

2.1 Chronic inflammation in *H. pylori*

Chronic inflammation of the gastric mucosa, termed gastritis, is a hallmark of *H. pylori* infection. *H. pylori* colonization leads to gastritis in all infected persons, but not all persons will develop symptoms. Both innate and adaptive immune cells are present and active during chronic inflammation as discussed in chapters 8 and 9 of this volume. Immune cell migration to the stomach and production of chemokines and cytokines culminates in ongoing activation of anti-microbial responses and the generation of reactive oxygen and nitrogen species (ROS and RNS). The chronic inflammatory response is believed to be required for the development of a sequence of epithelial transformations called the Correa cascade, which includes multifocal atrophic gastritis, intestinal metaplasia, dysplasia, and cancer (Correa et al. 1975; Mera et al. 2005; Mera et al. 2018; Correa et al. 2010).

Characteristic of mucosal surfaces like the intestines, gastric epithelial cells respond to microbes in the environment. Gastric epithelial cells respond to *H. pylori* and produce a number of pro-inflammatory cytokines and chemokines, including interleukin (IL)-1β, IL-6, IL-8 and IL-18. The local cytokine responses in human subjects indicate that there is increased tissue expression of IL-1β, IL-6, IL-8 and tumor necrosis factor (TNF, also referred to as TNF-α) (Lindholm et al. 1998). It has been suggested that elevated levels of many of these cytokines including IL-1β, IL-8 and TNF can also serve as biomarkers for GC (Macri et al. 2006). These cytokines and chemokines impact recruitment of immune cells – particularly polymorphonuclear cells (PMNs) and macrophages. As the infection persists, these cytokine responses also chronically persist. Many of these cytokines converge on signaling through Janus kinase/signal transducer and activator of transcription proteins (JAK/STATs) and activating nuclear factor-kappa B (NF-κB), which leads to upregulation of transcription of anti-apoptotic proteins, pro-inflammatory cytokines and chemokines, adhesion molecules and increased expression of inducible nitric oxide synthase (NOS2) or NADPH oxidase enzyme isoforms (Gobert and Wilson 2017). These changes in the microenvironment contribute to the development of carcinoma, because they can lead to increased DNA damage, dysfunctional DNA repair enzymes and genetic instability. Moreover, many of these inflammatory cytokines, such as IL-1β, IL-6, and IL-8, play a pivotal role in mediating the interaction between cancer stem cells and the microenvironment.

In addition to innate immune cell infiltration, cells of the adaptive arm of the immune system, including T lymphocytes and B lymphocytes, migrate into the gastric tissue in response to *H. pylori* infection. The T lymphocytes are predominantly CD4+ T helper cells (T_H) and exhibit pro-inflammatory phenotypes (T_H 1 and T_H17) as they express interferon −gamma (IFNγ) and IL-17A, both pro-inflammatory cytokines associated with chronic inflammation. The differentiation of naïve T cells to activated T_H1 or T_H17 cells can be dictated by the innate cytokine environment. IL-1β, IL-6, IL-23 and transforming growth factor- beta (TGF-β) skew T cell response towards IL-17A producing cells while expression of IL-12 is likely to push naïve T cells towards IFNγ producing T cells. In humans (but not in mice), IL-23 also plays a role in T_H1 cell differentiation. Increased gene expression of IFNγ, IL-12p40, IL-17A and IL-23 has been reported in stomach biopsies from *H. pylori* infected adults and children (Bhuiyan et al. 2014; Staples et al. 2013) and expression of IL-17A is associated with disease severity (Arachchi et al. 2017). Interestingly, not all studies have the same cytokine signature, in a study which evaluated *H. pylori*-positive gastritis patients versus *H. pylori*-negative gastritis patients, IL-12 expression was significantly elevated only in the *H. pylori*-positive patients, whereas many other cytokines were elevated in both groups, including TNF, IL-1β, IL-6 and IL-8 (Bauditz et al. 1999).

IL-17A and IFNγ subsequently further activate epithelial cells and macrophages in the tissue and can amplify the PMN response. Animal models have successfully defined roles for IFNγ and IL-17A in activating the proper signals required for the development of gastritis but also in activating anti-microbial responses against *H. pylori* (Dixon et al. 2016; Algood et al. 2009; Sjokvist Ottsjo et al. 2015). In *H. pylori* infected individuals, the frequencies of IFNγ and IL-$17A^+$ cells were increased in the antrum (Luzza et al. 2000), particularly in patients with *H. pylori* induced gastric ulcers (Adamsson et al. 2017). Other T cell cytokines are also involved in the chronic inflammatory response including IL-21. Levels of IL-21 are increased in *H. pylori* infected samples from patients with gastritis (Caruso et al. 2007) and in *H. pylori* infected mice (Carbo et al. 2014). In human subjects, IL-21 expression correlates with activation of STAT3 and more severe gastritis (Bagheri et al. 2015). Mice deficient in IL-21 infected with *H. pylori* do not develop gastritis, but are colonized with a higher level of *H. pylori* than wild-type controls (Carbo et al. 2014). These data suggest again that IL-21 can drive inflammation but also that inflammation is necessary to bring anti-microbial responses to the stomach control *H. pylori* colonization.

Additional insight related to the role of macrophages in *H. pylori* immunopathogenesis and inflammation-associated cancer risk stems from studies related to polyamines. Polyamines are pleiotropic polycations that have many cellular functions, including regulation of gene transcription, protein translation, cell growth, proliferation, and differentiation (Hardbower et al. 2017; Pegg 2006, 2009). The production of the three major polyamines—putrescine, spermidine, and spermine—is tightly regulated and centers on the rate-limiting enzyme, ornithine decarboxylase (ODC1, hereafter referred to as ODC) (Asim et al. 2010). ODC uses the substrate, L-ornithine, to produce putrescine via a decarboxylation reaction (Asim et al. 2010). ODC has been implicated in several malignancies, including breast, colorectal, and gastric cancer. Most of the studies related to ODC have been focused on its role in epithelial cell function. However, ODC expression is upregulated in macrophages by *H. pylori* in vitro (Asim et al. 2010) and in infected gastritis tissues of mice and humans (Hardbower et al.

2017). Importantly, macrophage ODC is immunosuppressive, impairing M1-dependent host defense against *H. pylori*; mice with myeloid-specific deletion of *Odc* exhibited marked upregulation of M1 responses, including NOS2 expression/NO production; M1 gene signatures (*Nos2*, *Il1b*, *Tnf*, *Il6*, *Il12a*, *Il12b*) and M1 protein responses (IL-1β and TNF-α) as well as pro-inflammatory chemokines and IL-17A (Hardbower et al. 2017). In parallel, there was increased gastric inflammation (both acute and chronic) but a clear benefit of reduced *H. pylori* bacterial colonization levels. Another crucial observation was that the immunosuppressive effects of ODC activity were linked to the ability of putrescine to cause histone modifications (specific acetylation and methylation events) favoring suppression of gene transcription, thus blocking M1 response (Hardbower et al. 2017), suggesting that polyamines have a deleterious effect of restricting mucosal immune responses. These findings lead to the question of the potential role of ODC/polyamines in GC development induced by *H. pylori*; this is discussed in Section 4.2 below.

Many of these cytokines and signaling pathways likely contribute to the development of cancer. However, the microenvironment in the stomach of a patient with chronic gastritis likely differs from the tumor microenvironment.

2.2 The tumor microenvironment (TME) in gastric cancer

The TME is a complex network of tumor cells and numerous types of non-tumor cells, including lymphocytes, myeloid cells, endothelial cells, and fibroblasts. As a dynamic environment, the TME involves a large variety of molecules such as growth factors, cytokines, chemokines, antibodies, proteases, and metabolites as well as the extracellular matrix. Non-resolving inflammation derived from chronic infection with *H. pylori* is one of the characteristics of the TME in GC and is considered to play an essential role in tumor initiation and growth. In a long-term failed attempt to promote healing, this complex network of mediators in the gastric mucosa leads to the upregulation of pathways that increase cell survival, activate stem cells and promote epithelial proliferation.

Defined almost two decades ago, cancer immunoediting is the process by which the immune system can either restrain or promote cancer development, ultimately favoring the outgrowth of tumor cells with reduced immunogenicity (Shankaran et al. 2001; Schreiber et al. 2011). Mechanisms that lead to inhibition of anti-tumor immune responses involve multiple components within the TME. Tumor cells secrete cytokines and chemokines to recruit myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and tumor-associated macrophages (TAMs). These cells directly suppress the functions of natural killer (NK) cells and CD8+ T cells through the production and expression of various factors, ultimately favoring tumor growth and invasion (Kitamura et al. 2015).

The macrophage is a key player of the innate immune response that then modulates chronic inflammatory responses, therefore it plays an important role during *H. pylori* infection and carcinogenesis. Circulating monocytes are recruited across the vasculature into tumors by tumor-derived chemoattractants such as colony-stimulating factor 1 (CSF1), CC ligand 2 (CCL2), vascular endothelial growth factor A (VEGFA, commonly referred to as VEGF), or CXCL12 (Murdoch et al. 2008; Noy and Pollard 2014). In the tissues, macrophages adjust to the particular conditions of the environment, adopting either pro-inflammatory (M1) or anti-

inflammatory (M2) phenotypes (Mills 2012). M1 macrophages are activated by bacterial constituents and T_H1 cytokines (e.g., IFNγ) and show antitumor activity through high antigen-presenting capacity, phagocytosis and upregulation of pro-inflammatory T_H1 responses. In contrast, M2 macrophages are activated by T_H2 cytokines (e.g., TGF-β, IL-4, IL-10, and IL-13), leading to suppression of adaptive immunity and promotion of tissue remodeling, angiogenesis and tumor growth (Fig. 2) (Tiemessen et al. 2007; Mills 2012). Multiple characteristics of tumors, including hypoxia and abundant cell death, help direct macrophage function towards attempting a "homeostatic" restoration (Ruffell et al. 2012). Thus, it has been argued that most TAMs exhibit a predominantly M2 phenotype (Mantovani et al. 2002). However, the large variety of functions in which TAMs are engaged suggests that extreme forms of M1/M2 polarization may not exist in the TME (Qian and Pollard 2010). In any case, high densities of TAMs or M2 macrophages have been associated with worse overall survival in several malignancies, including GC (Zhang et al. 2012; Jiang et al. 2017).

TAMs promote the suppression of effective antitumor immunity via different pathways including production of anti-inflammatory cytokines (including IL-10 and TGF-β), prostaglandin E2 (PGE2), and expression of programmed death-ligand 1 (PD-L1) (Mantovani et al. 2014). In addition, TAMs regulate vascular programming of tumors by production of VEGF and other proangiogenic factors (Ruffell et al. 2012). Macrophage infiltration correlates significantly with tumor vascularity in human GC (Ohta et al. 2003). TAMs can also contribute to the invasiveness of tumor cells by remodeling the extracellular matrix and by opening the way to exit the tumor and colonize the surrounding tissues (Guiet et al. 2011). As the tumor progresses, hypoxic regions develop, caused by high metabolic and proliferative rates. Hypoxia is a potent inducer of VEGF, and this is mediated by the transcription factor hypoxia-inducible factor-1 (HIF-1) (Semenza 2003, 2012). In addition to the role in angiogenesis, VEGF that is secreted by tumor cells can function in an autocrine manner promoting proliferation, dedifferentiation and transition from an epithelial to mesenchymal phenotype, enhancing stromal invasion and tumor growth. This autocrine signaling, which is mediated by VEGFR2 and by neuropilins, could be necessary for the function of cancer stem cells because it seems to maintain the stem cell reserve and to sustain self-renewal (Goel and Mercurio 2013).

Recently, next-generation sequencing and large-scale genomics have led to new molecular classifications of GC (Cancer Genome Atlas Research 2014; Cristescu et al. 2015). The Cancer Genome Atlas (TCGA) project classified GC into four subtypes: EBV-positive, MSI), genomically stable, and chromosomally unstable tumors (Cancer Genome Atlas Research 2014). At the same time, advances in cancer immunotherapy have opened new frontiers for patient care across a variety of tumors. Among the GC subtypes, EBV and MSI are the most promising in this regard. Amplification of *CD274* and *PDCD1LG2*, which encode PD-L1 and PDCD1LG2 respectively, is often found in EBV-positive tumors with high levels of PD-L1 protein expression detected on tumor cells (Derks et al. 2016). The interaction of PD-L1 with its receptor PD-1 (commonly found on T cells) inhibits T lymphocyte migration, proliferation and secretion of cytotoxic mediators, ultimately favoring tumor escape from the immune response.

Tumor-immune interactions are increasingly recognized as drivers of the clinical outcome and as potential targets for therapy. Recently, Thorsson and co-workers (Thorsson et al. 2018) characterized the immune TME of 33 cancer types (more than 10,000 tumors) into six "immune subtypes": 1) wound healing, 2) IFNγ, 3) inflammatory, 4) lymphocyte depleted, 5) immunologically quiet, and 6) TGF-β dominant. About 80% of gastric adenocarcinomas were grouped within immune subtypes 1 (wound healing, characterized by elevated expression of angiogenic genes, a Th2 cell bias and high proliferating rate) and 2 (IFNγ dominant, with the highest M1/M2 polarization, a strong CD8 signal, but also a high proliferating rate). The best overall survival (combining all cancer sites) was observed in the immune subtype 3 (inflammatory, defined by elevated T_H17 and T_H1 genes and low/moderate tumor proliferation), while types 1 and 2 had less favorable outcomes despite having a substantial immune component (Thorsson et al. 2018). This study highlights the importance of the immune interactions within the TME on prognosis and the need for individual tumor characterization for effective personalized choice of immune-related therapies. Although the study by Thorsson and colleagues found that the immune subtype 3 TME (determined by immunogenetics) had the best overall survival of all cancer types, the situation may be different in the GC TME. A recent publication investigating the expression of several cytokines and their relationship with clinicopathological characteristics in GCs revealed that IL-17 expression (measured by immunohistochemistry) was associated with decreased survival (Kim et al. 2017). Taken together, these results indicate a need for a deeper understanding of T cell cytokines in the TME in GC.

3 Anti-cancer strategies targeting the pro-inflammatory mediators in the TME

3.1 Cell signaling inhibitors

One way to target several cytokines/inflammatory mediators is to inhibit the transcription factor NF-κB. Several drugs are available to modulate the NF-κB pathway and thereby reduce expression of IL-8 and other pro-inflammatory cytokines. Many of these drugs target NF-κB indirectly by reducing ROS production including resveratrol, anthocyanin, apigenin, and RK-1–123. Because resveratrol is a member of the polyphenol flavonoids class of antioxidants produced by a restricted number of plants it has received significant attention as a potential treatment/adjunct therapy for GC patients and several reviews have addressed it directly (Zulueta et al. 2015). Resveratrol has been shown to inhibit proliferation of a number of cancer cell lines, and it behaves as a chemo-preventive agent in assays that measure the three stages of carcinogenesis (Holian et al. 2002). While human pilot studies in patients with colorectal liver metastases have demonstrated that preoperative resveratrol reduced cancer cell proliferation (Patel et al. 2010) and increased apoptosis in resected tumor tissues (Howells et al. 2011), there have been no clinical trials with resveratrol in GC.

3.2 Cytokine antagonists (IL-1, IL-6, IL-18, TNF)

While many of these cytokines have been discussed in detail in other areas of this book (Chapters 8, 9, 12 and 13), here a review will be provided for cytokines that may be candidates for targeting during cancer therapy.

IL-1β is expressed by a number of different cell types *in vitro* in response to *H. pylori* and all of these cells may participate in the inflammatory response *in vivo*, including dendritic cells (DCs), monocytes/macrophages and gastric epithelial cells (Kim et al. 2013; Semper et al. 2014). IL-1β is a cytokine that has received significant attention because in several studies polymorphisms associated with increased expression of IL-1β are significantly associated with the development of GC (El-Omar et al. 2000; Camargo et al. 2006). Expression is notably correlated with clinical and pathological features of GC (Yin et al. 2016). Solid tumors in which IL-1β has been shown to be up-regulated include breast, colon, lung, head and neck cancers, and melanomas, and patients with IL-1β producing tumors have a generally poor prognosis. IL-1β inhibits acid secretion by downregulating H^+/K^+ATPase expression and gastrin expression (Smolka and Backert 2012). Moreover, transgenic expression of IL-1β in the stomach causes gastritis-associated GC with recruitment of MDSCs (Tu et al. 2008) and in human xenograph models, elevated levels of IL-1β are correlated with advanced metastatic disease (Lewis et al. 2006). There are several possibilities for targeting IL-1β including approved treatments already utilized to treat patients with rheumatoid arthritis (Nikfar et al. 2018). IL-1 receptor antagonist (IL-1RA, anakinra) is a naturally occurring protein has been shown to decrease tumor growth, angiogenesis, and metastases in murine xenograft models (Weinreich et al. 2003). This is the IL-1β blocking therapy that has received the most attention. Anakinra is well absorbed in humans, and its safety is well documented with few adverse reactions (Sota et al. 2018), making it a candidate to be tested in combination with standard chemotherapy in GC. Currently, there is only one clinical trial in the NCI database utilizing anakinra for treatment of cancer, and it is specifically focused on early stage multiple myeloma (clinicaltrials.gov ID# NCT02492750). In addition to the IL-1RA, there several other agents available to inhibit the inflammatory and tumor promoting effects of IL-1β including anti-interleukin-1 monoclonal antibodies, the soluble IL-1 receptor type II, IL-1β-converting enzyme inhibitors, and IL-1β cytokine traps.

IL-6 is another pleiotropic cytokine which impacts inflammatory T cell biology as well as tissue regeneration and carcinogenesis. While the findings on associations between IL-6 polymorphisms and risk of GC are controversial, there is increasing evidence that levels of IL-6 may be a prognostic marker for spread (Ashizawa et al. 2005). In inflammatory cells, IL-6 is well known for activating STAT3 signaling, which can induce a pro-carcinogenic, tumorigenic microenvironment. STAT3 signaling leads to activation of NF-κB in inflammatory cells and drives a positive feedback loop between immune cells and tumor cells that further stimulates the cancer stem cell components and may contribute to metastasis and resistance to cancer therapies. GC cell lines also express high levels of IL-6 receptor, and IL-6 activation of GC cells leads to STAT3 activation and VEGF production (Huang et al. 2004; Lee et al. 2010; Wang et al. 2013); moreover, in ex vivo assays this leads to human umbilical vein endothelial cell proliferation, tube formation and vascularization in a Matrigel plug assay (Huang et al. 2004). IL-6 also inhibits H_2O_2-induced apoptosis and blocks repair of oxidative DNA lesions in human GC cells through upregulation of anti-apoptotic gene, *MCL-1* (Lin et al. 2001). Again, methods targeting IL-6 have been developed for the treatment of IL-6-associated diseases, such as rheumatoid arthritis and Castleman disease, but not for cancers. These therapeutics include anti-IL-6 antibodies

(siltuximab and sirukumab), anti-IL-6 receptor antibodies (cilizumab and tocilizumab), soluble gp130 (also a receptor of IL-6, designed to inhibit IL-6 binding to IL-6R), and some selective small molecules which inhibit JAK/STAT signaling as described above. While the concept to inhibit IL-6 and/or IL-6 signaling is not new (Sansone and Bromberg 2012; Jones et al. 2011), few clinical trials have been performed with these therapeutics in solid tumors (Ruffell and Coussens 2015), and at the time of writing this chapter, no clinical trials were published utilizing these biological treatments in GC. Another way to block IL-6 indirectly is through the inhibition of STAT3. Napabucasin, an oral inhibitor of cancer stem cells through STAT3 signaling blocking, is being tested in many gastrointestinal tumors, either alone or in combination with standard chemotherapy. Currently there is one clinical trial evaluating the association between napabucasin and weekly paclitaxel (a first-line cytotoxic agent) as second-line therapy for patients with GC (NCT01278956). An interesting strategy in GC would be to investigate the efficacy and safety of napabucasin combined with an anti-IL-6 antagonist.

TNF is a pro-inflammatory cytokine, which was first recognized for its inhibitory effect in some tumors when present at high concentrations, but it is also key cytokine for orchestrating inflammation and the host immune response. TNF activated chemokine gradients recruit immune cells to the sites of infection/inflammation. TNF is induced during *H. pylori* infection (Lindholm et al. 1998). The level of TNF may dictate its functional consequences; for it is thought to be pro-angiogenic in tumors, but a potent anti-vascular cytokine at higher doses and can be used clinically to destroy tumor vasculature. Anti-TNF therapy is currently used for rheumatoid arthritis, Crohn's disease, and other inflammatory diseases (reviewed in (Udalova et al. 2016)), but targeting TNF as an anti-cancer therapy has led to some scrutiny. One can appreciate why there are two very different hypothesizes as to the effect of anti-TNF therapy on cancer. On one hand, anti-TNF therapy could inhibit cancer development by reducing chronic inflammation, but on the other hand, if TNF induces apoptosis or has suppressive effects on gene expression, anti-TNF therapies may enhance the development of certain tumors. There have been many studies to assess the possibility that existing anti-TNF treatments increase risk for cancer, but because of heterogeneity within these studies there has been no consensus (reviewed in (Solomon et al. 2012)). Interestingly, Fan and colleagues (Chen et al. 2009) investigated the opposing approach of delivering the TNF protein (not anti-TNF) to gastric tumors. They fused TNF with a peptide (GX-1) known to target the human GC vasculature and injected the construct into the circulation of *nude* mice containing tumors of human GC cells. This targeted approach of delivering TNF delayed tumor growth and was less toxic than TNF alone. But, administering TNF has not been tested in clinical trials.

As mentioned earlier, some chronic inflammation is driven by T cell-derived cytokines including IL-17A and IFNγ. Targeting IFNγ to reduce inflammation or treat cancer has not been strongly considered because it has such an important role for control of infections- both viral and bacterial. The level of immunosuppression created by inhibiting this pro-inflammatory pathway would be unacceptable. On the other hand, targeting IL-17A has been considered both in chronic inflammatory disease and in cancer. There is evidence of increased IL-17A expression in GC tissue compared to normal gastric tissue (Yamada et al. 2012) and this may contribute to an imbalance of T_H17/Treg cells (Li et al. 2013). On the

other hand, there is conflicting evidence as to whether T_H17 cells are increased in the peripheral blood of GC patients and good marker for tumor progression (Liu et al. 2012a; Zhang et al. 2008; Yamada et al. 2012). IL-17 inhibitors approved by the FDA include secukinumab and ixekizumab. These were designed to treat inflammatory disorders including psoriasis (Hueber et al. 2010; Sanford and McKeage 2015; Markham 2016), but they have not been used in a cancer setting and could be tested in patients with GC.

3.3 Non-steroidal anti-inflammatory drugs

Substantial evidence from epidemiological studies suggests that the use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) is protective against GC as well as other gastrointestinal tumors (Abnet et al. 2009; Epplein et al. 2009; Algra and Rothwell 2012; Huang et al. 2017; Kong et al. 2016; Rothwell et al. 2012; Zhang et al. 2014). Although the mechanisms by which NSAIDs protect GC are not completely understood, it is recognized that NSAIDs primarily reduce the production of prostaglandins (PGs) by inhibiting the activity of cyclooxygenase enzymes (Cox1 and/or Cox2). Cox1, encoded by *PTGS1*, is constitutively expressed and responsible for production of prostanoids during basal conditions in the gastrointestinal tract and other tissues. Cox2, encoded by *PTGS2*, is an inducible isoform upregulated at sites of inflammation and in some cancers, including GC (Ristimaki et al. 1997). Coxenzymes participate in the conversion of arachidonic acid into prostanoids, including PGs and thromboxane A2 (TxA_2) (Wang and DuBois 2018). Besides promoting inflammation, prostanoids may facilitate tumor progression by several mechanisms, including stimulation of proliferation and inhibition of apoptosis of cancer cells, stimulation of tumor invasion and angiogenesis, and suppression of immune responses. A comprehensive review on the role of prostanoids in gastrointestinal cancer was recently published (Wang and DuBois 2018). Among prostanoids, PGE2 is the most abundant in human GC (Uefuji et al. 2000), and the measurement of its metabolite (PGE-M) levels in urine has shown PGE-M could be used as a biomarker for predicting GC risk and prognosis (Wang et al. 2017).

In the context of colorectal cancer, a −Cox2 selective inhibitor, celecoxib, was the first approved agent for patients with familial adenomatous polyposis. However, due to the cardiovascular side effects (Bresalier et al. 2005), long-term use of Cox2-selective inhibitors for cancer chemoprevention is no longer recommended. In contrast, long-term regular use of aspirin has proven beneficial for prevention of both cancer and cardiovascular diseases. Based on the evidence suggesting that aspirin therapy reduces the incidence of colorectal cancer after 5 to 10 years of use, the U. S. Preventive Services Task Force now recommends low dose aspirin use for the primary prevention of colorectal cancer in adults aged 50 to 59 years who meet certain criteria (Bibbins-Domingo and Force 2016; Chubak et al. 2016). Regarding GC, the evidence on the role of aspirin on prevention has been more limited and there is no current recommendation as a chemopreventive agent. Consistent with previous evidence, however, a recent meta-analysis (Huang et al. 2017) and a longitudinal study covering the whole population of South Korea concluded that long-term aspirin use was associated with reduction in GC risk (Kim et al. 2018). In this high GC risk population, the protective effect was significant in those individuals with cumulative aspirin daily dose use for at least three years. The evidence on the use of non-aspirin NSAIDs has shown less

consistent results in protection against GC across studies (Kim et al. 2018; Abnet et al. 2009; Epplein et al. 2009; Huang et al. 2017). A recent study aimed to evaluate the protective effects of low-dose aspirin use after GC diagnosis found no association with GC-specific mortality after one year of follow-up (Spence et al. 2018). Currently, a phase III clinical trial assessing the long-term effects of regular aspirin use on recurrence and survival in various types of cancer is ongoing (Add-aspirin, NCT02804815). For the use of aspirin on GC prevention the well-known risks, including renal and platelet dysfunction, gastric ulceration and gastrointestinal bleeding (Lanas et al. 2011) should be considered. Nevertheless, the strength of the associations consistently seen in observational studies, along with the high GC mortality rate, supports the need for further research on the potential of NSAID chemoprevention trials, especially aspirin, among select high-risk populations.

Overall, blocking the inflammatory response in GC through the inhibition of pro-inflammatory cytokines comprises an attractive approach for clinical trials. A list of selected ongoing studies assessing therapeutic agents targeting cancer-promoting inflammation in patients with GC (excluding antiangiogenic agents) is presented in Table 1. However, it is unlikely that the blockade of a single cytokine would result in dramatic clinical effect. Rather, there is a good rationale to combine targeted agents directed to different cytokines in GC, including systemic chemotherapy. Yet, like most of the new clinical trials of advanced cancer, trials in GC should enroll molecularly-selected patients. In the context of cytokines, well-conducted studies should be undertaken to identify predictive biomarkers; with that information, patients would have their GC tissues tested for the biomarker in order to enroll into a specific “anti-inflammatory” trial.

4 Strategies targeting growth factors involved in angiogenesis

4.1 Growth Factors as target (VEGF/VEGFR2, CSF1/CSF1R, EGF/EGFR)

Vascular endothelial growth factor A (VEGFA, often referred to as VEGF), is a vascular permeability factor and the main regulator of tumor angiogenesis (Senger et al. 1983; Ferrara 2002). VEGF is a member of a family of growth factors and primarily binds to tyrosine kinase receptors VEGFR2 and VEGFR1 (Chung et al. 2010). VEGF is secreted by both tumor and non-tumor cells, such as macrophages, endothelial cells and fibroblasts (Goel and Mercurio 2013). VEGFR2 is mainly expressed by endothelial cells, but also by a variety of cells, including tumor cells. The binding of VEGF to VEGFR2 is considered critical for the regulation of tumor angiogenesis, by promoting the proliferation and migration of endothelial cells, as well as the degradation and remodeling of the extracellular matrix. Independent of the role of VEGF in tumor development, a large body of evidence supports a role for VEGF in the pathogenesis and maintenance of chronic inflammatory disorders. Notably, immune cells can express VEGF receptors, and the functions of these cells can be regulated by VEGF signaling. VEGF promotes the adherence of leukocytes to the vascular endothelium and the release of pro-inflammatory cytokines, such as IL-6 and TNF, which support tumor development in chronic inflammatory diseases (Waldner and Neurath 2012). The role of VEGF signaling in cancer-associated inflammation was demonstrated by Waldner and co-workers (Waldner et al. 2010). Patients with inflammatory bowel disease or with colitis-associated cancer showed increased expression of VEGFR2 on

intestinal epithelial cells. Results from in vivo and in vitro experiments demonstrated that chronic inflammation induces VEGFR2 expression on intestinal epithelial cells and that VEGFR2 signaling is necessary for tumor growth (Waldner et al. 2010). There is also significant evidence that VEGF/VEGFR2 signaling has an important role in GC pathogenesis (Lieto et al. 2008; Murukesh et al. 2010; Suzuki et al. 2010) and the inhibition of this interaction is the main target of anti-VEGF therapeutics (Ferrara 2009).

The monoclonal anti-VEGF antibody bevacizumab was the first agent developed targeting the VEGF pathway. Bevacizumab is now approved for first- and/or second-line treatment of a variety of tumors including colorectal cancer, but clinical trials in GC have not obtained encouraging results (Ohtsu et al. 2011; Shen et al. 2015). Ramucirumab, a human monoclonal antibody that targets VEGFR2 (Spratlin et al. 2010), is the first drug targeting angiogenesis that showed to prolong survival in patients with previously treated advanced GC or gastroesophageal junction carcinomas (GEJC) in phase III clinical trials (Fuchs et al. 2014; Wilke et al. 2014). Currently, ramucirumab is indicated as a single agent or in combination with paclitaxel, for the treatment of patients with advanced or metastatic, GC or GEJC with disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy (Ajani et al. 2016).

Apatinib, a selective VEGFR2 tyrosine kinase inhibitor, was tested in Asian patients with previously treated, advanced GC and showed prolonged overall and progression-free survival (Li et al. 2016). Apatinib was approved by the FDA in 2017 as a third-line therapy for refractory GC or GEJC. Experimental studies have suggested that apatinib not only has anti-angiogenesis effects but also possesses substantial angiogenesis-independent effects, inhibiting cell proliferation in vitro and delaying xenograph tumor growth in vivo (Lin et al. 2017). A large number of clinical trials including apatinib for patients with GC are currently underway, including phase III and IV trials (NCT03042611 and NCT02426034). Regorafenib, a multikinase inhibitor that targets VEGFR2 and is used for refractory colorectal cancer (Wilhelm et al. 2011; Riechelmann and Grothey 2017), is currently being tested in clinical trials for GC and has provided promising results (Pavlakis et al. 2016).

Colony-stimulating factor 1 (CSF1 or also known as MCSF) is a hematopoietic growth factor constitutively expressed by many cell types (Hamilton et al. 2016). CSF1 is the major lineage regulator of most populations of macrophages, but it is also a chemotactic factor for macrophages. CSF1 exerts its effects through a tyrosine kinase receptor (CSF1R), which is expressed on monocytes and macrophages, but also on other myeloid cells within the TME (Cannarile et al. 2017). In human GC, elevated expression of CSF1 or CSF1R significantly correlated with disease progression and also with poor overall survival and disease-free survival (Okugawa et al. 2018). Targeting TAMs by inhibition of CSF1/CSF1R has shown encouraging results in preclinical cancer models in a variety of tumors, not only decreasing the number of TAMs, but also reprogramming remaining TAMs to support antigen presentation and bolster T-cell activation (Ries et al. 2014; Zhu et al. 2014; Pyonteck et al. 2013; Quail et al. 2016; DeNardo et al. 2011). Experimental evidence has shown that macrophages can mediate chemotherapy resistance by providing survival factors or activating anti-apoptotic pathways in cancer cells. In a mouse model of breast cancer, cytotoxic therapy showed to induce CSF1-dependent macrophage recruitment (DeNardo et

al. 2011). In this model, blockade of macrophage recruitment with CSF1R-signaling antagonists, in combination with paclitaxel, showed promotion of T_H1 responses and improved mouse survival by reduction in primary and metastatic tumors.

In human tumors, the most promising evidence targeting the CSF1/CSF1R axis has been documented in patients with the diffuse type of tenosynovial giant cell tumor (TGCT). TGCT is a rare neoplasm associated with inflammation and joint destruction, in part due to infiltration of CSFR1-bearing macrophages (Gelhorn et al. 2016). Because TGCT is associated with overexpression of CSF1, therapies targeting the CSF1/CSF1R axis have been tested in patients with locally advanced or relapsed TGCT (Brahmi et al. 2016). Studies have shown significant clinical improvement with emactuzumab (RG-7155), a recombinant humanized monoclonal antibody targeting CSF1R (Ries et al. 2014; Cassier et al. 2015), and with the small molecule CSF1R inhibitor pexidartinib (PLX3397) (Tap et al. 2015). In the context of GC, a large number of clinical trials assessing the potential of various CSFR1 inhibitors (emactuzumab, pexidartinib, DCC-3014, and others) either as monotherapies or in combination with other therapeutic modalities are underway (see Table 1).

Additional recent studies have implicated several other potential master regulators of macrophage function and polarization in the context of *H. pylori* infection and gastric carcinogenesis. We recently reported (Hardbower et al. 2016) that epidermal growth factor receptor (EGFR) signaling is a crucial component of the response of macrophages to bacterial infections, with *H. pylori* a prototypical example. While EGFR signaling in gastric epithelial cells has been documented and related to both ligand-dependent (EGF) and independent (TNF) responses (Yan et al. 2009), the response of mouse and human macrophage cell lines and mouse bone marrow-derived primary macrophages was ligand-independent and involved both tyrosine 1068 and serine 1046/7 phosphorylation sites (Hardbower et al. 2016). Importantly, human gastric tissues exhibited marked phosphorylation of EGFR in gastric macrophages along the entire cascade from gastritis to gastric adenocarcinoma, and mice with myeloid specific deletion of *Egfr*, exhibited attenuated gastric inflammation scores, increased *H. pylori* colonization, and reduction of M1 macrophage and T_H1/T_H17 responses.

It should be noted that these studies were in a model of chronic infection, not cancer. However, in the azoxymethane-dextran sulfate sodium model of colitis-associated colon carcinogenesis, mice with myeloid deletion of *Egfr* showed a marked reduction of tumor development (Hardbower et al. 2017). Moreover, these findings were associated with attenuation of M2 responses and angiogenesis and associated signaling. Surprisingly, mice with epithelial deletion of *Egfr* did not show protection from colon tumorigenesis. There are a series of studies from other groups similarly showing that deletion of *Egfr* in myeloid cells reduces liver cancer (Lanaya et al. 2014) and other colon cancer models (Srivatsa et al. 2017). There are also studies related to pancreatic cancer implicating macrophage EGFR signaling in M2 macrophage polarization (Ma et al. 2016).

The addition of the EGFR inhibitor, gefitinib, was very effective in rodent models of gastric cancer (Sierra et al. 2018). Specifically when added to the diet, this agent significantly reduced development of dysplasia and intramucosal carcinoma in *H. pylori*-infected INS-

GAS mice and dysplasia and invasive gastric adenocarcinoma gastric cancer in infected gerbils. Gefitinib treatment reduced PMN infiltration and chemokine expression, as well as epithelial DNA damage in both rodent models. Gefitinib was effective if given as a pretreatment before infection or if administered after infection and inflammation was already established, and still had a benefit if given to animals after antibiotic eradication of the *H. pylori* (Sierra et al. 2018). It should be noted that the use of a pharmacologic approach does not distinguish the offending cellular source of EGFR signaling. To this end, the effect of gastric epithelial-specific deletion of *Egfr* was investigated; this resulted in less gastric inflammation, DNA damage and chemokine expression. Thus, the Wilson lab are generating mice with myeloid- and epithelial-specific deletion of *Egfr* on the cancer-prone FVB/N INS-GAS mouse and will be determining the effect on gastric carcinogenesis during *H. pylori* infection.

Despite the strong scientific rationale of antiangiogenic agents in GC and other solid tumors, the overall results of clinical trials with these agents have been quite modest, with survival improvements generally measured in weeks. Likewise, despite the promising preclinical data with anti-EGFR agents in GC, randomized trials with these agents, with the exception of trastuzumab for HER2-positive GC (Song et al. 2016), were not effective in patients with molecularly-unselected metastatic GC. Therefore, their future in the drug development process in GC is likely to be undermined by more innovative agents, such as immunotherapy.

4.2 Strategies inhibiting M1 to M2 transitions and promoting M1 phenotype

Besides the mentioned effects of targeting the CSF1/CSF1R axis on macrophage polarization, reprogramming TAMs into M1-phenotype macrophages can be achieved through a variety of other therapeutic modalities including chemotherapy, immunotherapy and radiotherapy (Ruffell et al. 2012; Genard et al. 2017). One of the modalities under investigation is based on the use of CD40 agonists. CD40 is a member of the TNF receptor superfamily that is present on a variety of immune cell types. CD40 activation plays a critical role in triggering T and B cell immunity, by activation of antigen-presenting cells, resulting in an enhanced anti-tumor immune response (Vonderheide 2018). By stimulating CD40, monoclonal antibodies against CD40 similarly have shown to reprogram TAMs from M2 phenotype to M1 macrophages. In a mouse model of pancreatic cancer, CD40-activated macrophages rapidly infiltrated tumors, showed anti-tumor properties, and facilitated the depletion of tumor stroma (Beatty et al. 2011). In addition, the activation of CD40 present on the surfaces of some solid tumor cells leads to direct tumor cell apoptosis and decreased tumor growth. In the context of GC, several clinical trials involving patients with a variety of advanced solid tumors are underway (Table 1). Some evidence has indicated that is also possible to re-educate TAMs by exposure to specific immunological mediators which may promote M1 macrophage development, such as IFNγ (Duluc et al. 2009; De Palma et al. 2008).

Having evidenced that loss of ODC enhances host defense against *H. pylori* (Hardbower et al. 2017), a related question is the potential to inhibit ODC *in vivo*. Efficacy of the pharmacologic agent α-difluoromethylornithine (DFMO), which blocks ODC activity, has

been demonstrated in clinical trials related to prevention of colon polyps (Meyskens et al. 2008; Zell et al. 2010), and has also been used for the treatment of neuroblastoma (Bassiri et al. 2015; Evageliou et al. 2016; Saulnier Sholler et al. 2015). The mechanism of action is unproven, but has been conceptually related to reduction of epithelial cell growth and DNA replication. The downstream enzyme, spermine oxidase (SMOX), which generates oxidative stress during the back-conversion of spermine to spermidine, is upregulated by *H. pylori* in both macrophages (Chaturvedi et al. 2004) and gastric epithelial cells (Chaturvedi et al. 2014; Chaturvedi et al. 2011). Moreover this generation of ROS leads to oxidative DNA damage in the gastric epithelium (Chaturvedi et al. 2014; Chaturvedi et al. 2011), which is especially notable in the presence of gastric intestinal metaplasia (Chaturvedi et al. 2015). Inhibition of ODC with DFMO or inhibition of SMOX reduces DNA damage and gastric cancer development in gerbils infected with a gerbil-adapted *H. pylori* strain derived from a patient with gastric dysplasia from the Andean mountain region of Colombia, where gastric cancer risk is high (Chaturvedi et al. 2015).

Based on these studies we are currently conducting a phase II clinical trial using DFMO (eflornithine, 500 mg po per day) versus placebo in Latin American sites (Honduras and Puerto Rico, NCT02794428) in patients with precancerous gastric lesions (i.e. intestinal metaplasia). The primary endpoint is DNA damage at 6 months of treatment, with secondary endpoints of DNA damage at 18 months and histopathology at 18 months. The trial is ongoing, but final results will not be expected until 2020. An additional goal of the study is to determine effects of DFMO on immune cells versus epithelial cells.

4.3 Inhibition of MDSCs

Myeloid-derived suppressor cells (MDSCs), a heterogeneous group of immature myeloid cells that inhibit the antitumor activity of T lymphocytes and NK cells and which are absent in physiologic conditions, make an important component of TME. Studies in mice have demonstrated that the depletion of MDSCs is associated with delayed tumor growth (Schroder et al. 2017; Davis et al. 2017). Based on such findings, MDSCs have been investigated as therapeutic targets in GC. The Dickkopf-related protein 1 (DKK-1), a Wnt regulator, promotes immunosuppression in TME through the stimulation of MDSCs (Moehler et al. 2018). Two DKK-1 directed antibodies (BHQ880 and DKN-01) are currently being tested in several tumor types; an ongoing phase I trial is testing a DKK-1 monoclonal antibody in monotherapy or in combination with paclitaxel or pembrolizumab for patients with heavily pre-treated GC or GEJC (NCT02013154). Another strategy to inhibit the functionality of MDSCs is through the blockade of the glucocorticoid-induced TNFR-related protein (GITR). This protein is expressed in normal monocytes, MDSCs and macrophages and its suppression has led to reduced tumor progression and increased T-cell infiltration in an animal model of pancreatic cancer (Moehler et al. 2018). Interestingly, the inhibition of GITR was associated with up regulation of cytotoxic T lymphocyte associated antigen 4 (CTLA4) on T cells and PD-L1 on tumor cells, proposing that a combination with checkpoint inhibitors may be required for this treatment to be effective.

4.4 Targeting chemokines and their receptors

The TME can also be targeted through the disruption of chemokines networks. Chemokines, small proteins normally involved in immune cell migration and lymphoid tissue expansion, are implicated in the TME immunosuppression through complex mechanisms, including the stimulation of MDSCs (Nagarsheth et al. 2017). Because chemokines and their receptors participate in major roles in inflammation and related-inflammatory diseases, research has been conducted to explore the modulation of certain chemokines as a form of cancer- (and TME-) directed therapy. Chemokine inhibitors, mostly in combination with immune checkpoint inhibitors, are undergoing clinical testing in different tumor types.

The overexpression of chemokine CCL2, the monocyte chemoattractant protein (MCP1), induces angiogenesis and tumorigenesis of GC in nude mice via macrophage recruitment (Kuroda et al. 2005). An elevated level of CCL2 has been reported in patients with GC, was correlated with lymph node metastasis, and was associated with lower overall survival rate (Tonouchi et al. 2002; Futagami et al. 2008; Tao et al. 2014). However, while the inhibition of the CCL2-CCR2 (CCL2 main receptor) signaling pathway represented an attractive approach in GC, clinical trials have shown disappointing results. Carlumab, also known as CNTO888, is a human $IgG1_k$ monoclonal antibody that binds CCL2 with high affinity and which has been tested in two different phase I trials in patients with solid tumors. In the first trial, carlumab was administered in monotherapy; it offered modest antitumor activity, with the best responses observed being tumor stabilization in ovarian cancer, ocular melanoma and neuroendocrine tumor (Sandhu et al. 2013). In a second phase I trial where carlumab was combined with different standard chemotherapeutic agents, only one out of 19 patients experienced a partial response (Brana et al. 2015). Another approach to CCL2/CCR2 interference is to inhibit the CCR2 receptor. A humanized IgG1 antibody, MLN1202, has been successful in several inflammation-related diseases such as multiple sclerosis and atherosclerosis. However, a phase II trial with this agent in patients with bone metastases did not show efficacy (Vela et al. 2015). Given the above results, further trials with CCL2/CCR2 inhibitors are on hold.

CXCR4 and CXCL12, its ligand, are immunohistochemically overexpressed in GC in comparison to normal gastric tissue and associated with survival, proliferation, angiogenesis, and migration of cancer cells. Studies have demonstrated that such chemokine expression patterns are prognostic factors for survival and metastases (Xue et al. 2017). Also, overexpression of CXCL12 in gastric mucosa contributes to carcinogenesis in the presence of inflammatory stimuli such as *H. pylori* (Shibata et al. 2013). CXCL12 also activates the PI3K/mTOR and MAPK/ERK signaling pathways (Rubie et al. 2016). The blockade of the CXCL12-CXCR4 axis is the target of drugs used to treat the human immunodeficiency virus (HIV) infection or to help with the mobilization and collection of CD34-positive hematopoietic stem cells for transplantation in patients with certain hematological malignancies. Recently several pre-clinical studies in different tumor types, including GC, report encouraging antitumor effects from this biological class (Xue et al. 2017). However, clinical trials with CXCL12-CXCR4 inhibitors have just begun. A phase I trial of LY2510924, a peptide antagonist, which blocks stromal cell–derived factor-1 from CXCR4 binding, was conducted in patients with advanced and refractory solid tumors (although

there were not any patients with GC in the study); while the safety profile was good, the best response observed was tumor stabilization in 20% of patients and the median duration of treatment was only 1.9 months (Galsky et al. 2014). Both randomized phase II trials in non-small cell lung cancer and renal cell carcinoma were negative for their primary endpoints of progression free survival (Salgia et al. 2017; Hainsworth et al. 2016). Despite these preliminary negative results, there are a number of ongoing clinical trials in multiple tumor types; but at the time of this publication, there are no trials in GC. An interesting approach in GC would be to combine CXCL12-CXCR4 inhibitors with other targeted agents that block the same pathways (e.g. mTOR inhibitors, MEK inhibitors) or with other chemokine inhibitors.

Interleukin-8 (IL-8) is a potent neutrophil chemotactic cytokine with potential impact on the tumor microenvironment. In chronic *H. pylori*-associated gastritis, gastric epithelial cells express increased levels of IL-8 within the lamina propria (Crabtree et al. 1994b). IL-8 is the single most up-regulated gene in whole genome profiling of *H. pylori* exposed gastric epithelial cells (Eftang et al. 2012). Moreover IL-8 expression is correlated with functional *cag*PAI status of *H. pylori* strains (Crabtree et al. 1994a; Crabtree et al. 1995), but IL-8 can also be strongly induced by IL-17 responses. The result of IL-8 expression is recruitment of PMNs to the tissue for higher degrees of PMN infiltration which is correlated with an increase in the secretion of TNF, IL-1β, IL-6 and IL-8 (Bauditz et al. 1999). In a study out of northern India, circulating levels of IL-8 were higher among patients with GC compared to healthy controls, but levels were comparable to patients with functional dyspepsia (Kumar et al. 2015). The expression of IL-8 directly correlates with a poor prognosis in GC (Yamada et al. 2013; Lee et al. 2004).

In addition to its potent neutrophilic chemotactic activity, IL-8 can induce proliferation and migration of cancer cells (Wilson et al. 1999; Brew et al. 2000). For this reason, there has been interest in targeting it as a cancer therapy. IL-8 increases the proliferation, migration and survival of endothelial cells, enhances epithelial-mesenchymal transition (EMT) and survival of cancer cells (Fernando et al. 2011). Moreover, there is evidence that IL-8 may enhance macrophage activity in tumors through activating VEGF expression, a potent angiogenic factor (Martin et al. 2009). IL-8 may modulate invasiveness and/or extracellular matrix remodeling through enhancement of matrix metalloprotease expression (MMP2/MMP9) (Li et al. 2005; Inoue et al. 2000; Kim et al. 2001). In addition to general mechanisms to block NF-κB signaling and IL-8 induction discussed above, small molecule inhibitors targeting IL-8 receptors (CXCR1 and CXCR2) have been developed. G31P and SCH-527123 were initially developed for use in prostate and colon cancers, respectively, with the intention of reducing cell migration and increasing apoptosis of cancer cells (Liu et al. 2012b; Ning et al. 2012). Repertaxin, another inhibitor of CXCR1 and CXCR2, has shown to decrease tumor proliferation in the GC cell lineMKN45 (Wang et al. 2016). These inhibitors have only been tested *in vitro* on GC cells and no clinical trials have been performed with them in GC.

Meanwhile there is also interest in directly blocking IL-8, especially since the findings that high serum IL-8 levels correlate with poor prognosis in various tumors (Sanmamed et al. 2014). Moreover, IL-8 was found to stimulate recruitment of MDSCs and promote EMT in

tumors conferring resistance to immune-mediated killing (reviewed in (David et al. 2016)). An IL-8-specific monoclonal antibody, known as HuMax-IL8, has been shown to reduce mesenchymal features in cancer cells leading to enhanced susceptibility to NK and T cell-mediated lysis and to decrease the frequency of granulocytic MDSCs in xenograft models (Collins et al. 2018). The HuMax-IL8 drug (BMS-986253) is also designed to inhibit IL-8 and thus far the only clinical trial utilizing this drug is to test it in combination with nivolumab in patients with advanced solid tumors, but no results have been published (NCT03400332).

5 Enhancing Anti-tumor Immunity (Therapy-induced inflammation)

Another form of targeting inflammation as an anti-cancer strategy is to modulate the immunosuppressive TME through therapies that stimulate the antitumor immune response. The immune checkpoint inhibitors, currently the monoclonal antibodies against PD-1/PD-L1 and CTLA4, represent a successful class and have been approved to treat numerous solid tumors and hematological malignancies. The use of immunotherapy in GC has just started and will be discussed below.

5.1 Checkpoint Inhibitors (anti-PD-1/L1, anti-CTLA4)

Currently, two immune checkpoint inhibitors (ICPi), pembrolizumab and nivolumab, have been approved in many countries for advanced/metastatic GC and both are anti-PD-1 monoclonal antibodies. The landmark phase II trial by Le D et al (Le et al. 2017) demonstrated dramatic tumor shrinkage and significantly prolonged progression free survival with pembrolizumab for patients with heavily pre-treated MSI solid tumors, mostly Lynch syndrome-associated colorectal cancer. These results led to the FDA's first ever site-agnostic approval. Given that tumor lymphocytic infiltration is one of the hallmarks of MSI tumors, it was conceived that ICPi would work mostly in "inflamed" tumors. This has proven to be true; larger magnitudes of benefit have been observed in inflammation-associated tumors with higher mutation burden, such as lung cancer, melanoma, and Merkel cell carcinoma. In GC, the overall benefit of immunotherapy has been modest. However, in specific subgroups where cancer-associated inflammation is present, i.e. MSI, higher response rates and prolonged disease control have been reported. While EBV-positive nasopharyngeal carcinoma patients are more likely to benefit from ICPi (Kao et al. 2015), clinical data in GC have not been published, but are eagerly awaited. Currently it is unknown whether concurrent or prior *H. pylori* infection predicts response and survival in GC.

In the KEYNOTE-059 multi-cohort trial, pembrolizumab was administered in different settings of patients with advanced GC or GEJC (Wainberg et al. 2017). Cohort 1 enrolled 259 patients with at least two prior lines of therapy and 57% of the patients had PD-L1 positive tumors (defined as positive immunohistochemistry expression in at least 1% in tumor cells); in this cohort, pembrolizumab monotherapy offered an overall objective response rate of 12% (16% in PD-L1 positive and 6% in PD-L1 negative, respectively), with 3% of patients achieving complete response, regardless of PD-L1 status. As expected, among the 4% of patients with MSI tumors, the objective response rate was 57.1% (Fuchs et al. 2017). This uncontrolled phase II trial led to the approval of this drug in the third line

setting of PD-L1-positive GC. Recently a phase III trial of pembrolizumab versus paclitaxel in second-line was negative for its primary endpoint, overall survival, for patients with combined positive score ≥ 1 tumors – the number of PD-L1 positive staining tumor, lymphocytes or macrophages divided by the total number of viable tumor cells and multiplied by 100 (Fuchs et al. 2018b). Interestingly, the study showed that the higher the combined positive score, the higher the benefit of pembrolizumab when compared to paclitaxel, reinforcing that the more intense the tumor inflammation, the higher the likelihood of anti-tumor activity from treatment with an ICPi.

In the phase III trial named ATTRACTION-2, 493 Asian patients with advanced GC or GEJC previously treated with chemotherapy were randomized to receive nivolumab or placebo until disease progression (Kang et al. 2017). Similar to the overall clinically irrelevant, albeit statistically significant, results with pembrolizumab, this trial demonstrated a modest gain (measured in days) in overall survival. In contrast to the pembrolizumab trial, PD-L1 expression was not predictive of a survival benefit with nivolumab. Based on these results, nivolumab was approved in Japan for GC.

Overall clinical trials in GC with anti-CTLA4 monoclonal antibodies have showed discouraging results, with limited efficacy signals (Bang et al. 2017; Ralph et al. 2010). Similarly, the results with the combination of anti-PD-L1 and anti-CTLA4 agents were disappointing. In two cohorts of the CheckMate 032 phase I/II trial where one-quarter to one-third of patients had PD-L1 positive tumors, nivolumab in combination with ipilimumab was delivered on two different dose schedules (Janjigian et al. 2017). These treatments led to overall objective response in 8% and 24% of patients, respectively, but with median overall survival times of only 6.9 and 4.8 months. These results clearly demonstrate that although immunotherapy is one of greatest advances in modern oncology, it does not work in molecularly unselected GC cancer patients. The molecularly distinct subtypes of GC (Cancer Genome Atlas Research 2014; Cristescu et al. 2015) should be explored for predictive biomarkers to ICPi responsiveness.

5.2 Other immunotherapies–immunoconjugates

A new class of immunotherapeutic agents, immunoconjugates, is being tested and demonstrating promising results in certain tumor types. A bispecific anti-carcinoembryonic antigen (CEA) anti-CD3 antibody carcinoembryonic antigen-T-cell bispecific antibody (CEA-TCB) has shown impressive results in phase I trials in colorectal cancer (Parkhurst et al. 2011). The CEA-TCB RO6958688 was given as monotherapy or in combination with atezolizumab, an anti-PD-L1 monoclonal antibody, to patients with advanced solid tumors, the majority with colorectal cancer, with positive immunohistochemistry expression of CEA (Tabernero et al. 2017); tumor inflammation was evidenced in computerized tomographies (CT) scans within a few days of administration in the higher dose levels cohorts, and after 4 weeks, metabolic response by 18-FDG PET scan was observed in 28% of patients in the monotherapy group and in 60% of those in the combination arm. Interestingly, the most common adverse events were inflammation-related, such as pyrexia (56.3%), and dose-limiting toxicities were associated with inflammation in metastatic lesions. Although preliminary, the CEA-TCB RO6958688 could be tested in a great variety of CEA+ tumors

(NCT02324257, NCT02650713). Indeed, phase III trials are planned in advanced colorectal and GC.

Conclusions

In this chapter, we have provided insights into inflammation-related factors that promote *H. pylori*-associated GC initiation and growth. Strategies for immune therapy could fall into 3 major classifications including: targeting pro-cancer inflammation and reprogramming or depleting immune cells in the TAM to increase anti-cancer immune responses. Some of these strategies will likely be most successful when therapy is provided as an adjunct to current chemotherapy, whereas, others may prove to be more effective as monotherapy. For example, anti-VEGF agents provide some benefit when combined with chemotherapy, but offer limited efficacy as monotherapy. On the other hand, immunoconjugates and immune checkpoint inhibitors seem to offer antitumor activity alone or combined among them, while the addition of chemotherapy does not appear to improve outcomes in GC. Moreover, because of the diversity of the microenvironments (gastritis to tumor) which have been reported and the array of potential targets, it is clear that immune subtyping and tumor characterization are crucial for the field to move to more successful immune-therapies to treat persons at risk of GC and/or to treat existing cancer. And lastly, the drug development process, including pharma and academia, should concentrate efforts to identify predictive biomarkers in GC and to design clinical trials with enriched populations so we can offer GC patients treatments that make a significant difference in their lives.

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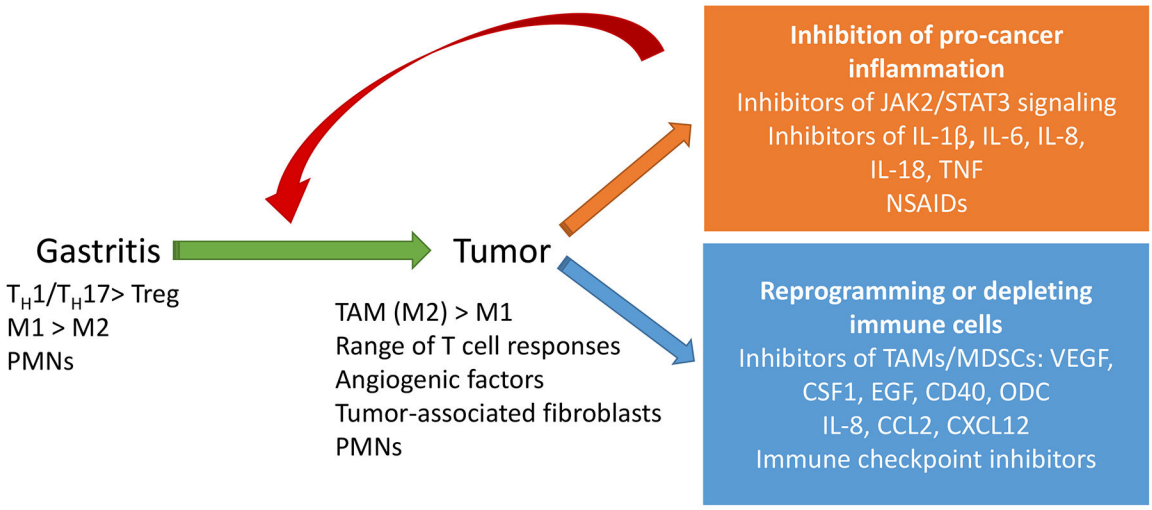

Figure 1. Resolution of gastric cancer-promoting inflammation: a novel strategy for anti-cancer therapy.

H. pylori infection leads to gastritis in infected persons, but only a subset will go on to develop GC. The microenvironment of the immune response during infection changes when a tumor develops. Immunotherapies could target several immune pathways. Some therapies could target the pro-inflammatory environment which drives the development of the tumor, while others would target the tumor microenvironment by reprogramming tumor infiltrating cells or inhibiting angiogenic factors.

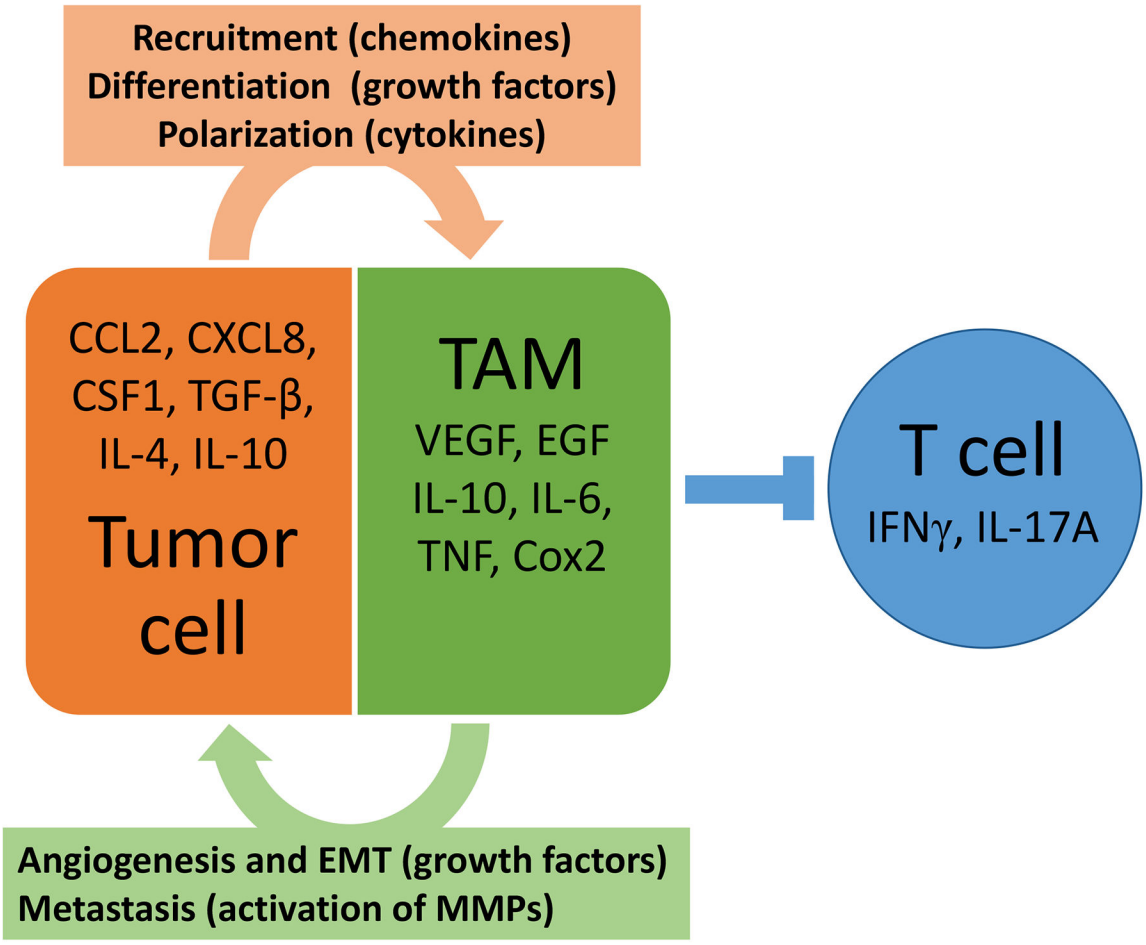

Figure 2. Tumor associated macrophages and their role in the tumor microenvironment.

Tumor cells can produce chemokines, cytokines and growth factors which drive recruitment, differentiation and polarization of TAMs. When the tumor associated macrophages enter the TME they can suppress anti-tumor T cell activity, contributes to angiogenesis of tumors cells through production of growth factors, and promote metastasis through activation of matrix metalloproteases.

Table 1.

Selected ongoing studies assessing therapeutic agents targeting cancer-promoting inflammation in patients with GC (excluding antiangiogenic agents)

Strategy	Agent	Target	Mode of action	Combination or comparator	Tumor types	Phase	ClinicalTrials.gov identifier
Blocking pro-inflammatory mediators	Napabucasin (BBI608)	STAT3	Inhibitor of cancer cell stemness; indirectly inhibits IL-6 through STAT3 inhibition	Napabucasin + paclitaxel	Metastatic or locally recurrent GC or GEJC	III	NCT01278956
	Aspirin	COX1/COX2	COX enzymes inhibition	Aspirin monotherapy	Non-metastatic solid tumors (adjuvant setting)	III	NCT02804815
Inhibiting recruitment of immune cells	Emactuzumab (RG7155)	CSFR1	Monoclonal antibody	Emactuzumab + atezolizumab (anti-PD-L1 mAB)	Locally advanced or metastatic solid tumors	IB	NCT02323191
				Emactuzumab + selicrelumab (CD40 agonist)[1]	Locally advanced or metastatic solid tumors	IA/IB	NCT02760797
	Pexidartinib (PLX3397)	CSFR1	Tyrosine kinase inhibitor	Pexidartinib + paclitaxel	Advanced, incurable solid tumors	IB	NCT01525602
	HuMax-IL8 (BMS-986253)	IL-8	Monoclonal antibody	HuMax-IL8 + nivolumab	Advanced, incurable solid tumors	I/II	NCT03400332
	DKN-01	DKK-1	Monoclonal antibody	DKN-01 + paclitaxel or pembrolizumab	Metastatic or locally recurrent GC or GEJC	I	NCT02013154
Reprogramming TAMs from M2 to M1	CDX-1140	CD40	Monoclonal antibody (CD40 agonist)	CDX-1140 + standard therapy	Advanced solid tumors	I	NCT03329950
	Selicrelumab (RO7009789)	CD40	Monoclonal antibody (CD40 agonist)	Selicrelumab + atezolizumab (anti-PD-L1 mAB)	Locally advanced or metastatic solid tumors	IB	NCT02304393
Immuno-conjugates	CEA-TCB antibody (RO6958688)	CEA expressed in tumor tissues	Bispecific anti-CEA anti-CD3 monoclonal antibody	Monotherapy	Advanced CEA-expressing solid tumors	I	NCT02324257

[1] This trial combines an inhibitor of immune cell recruitment and an agent to reprogram macrophages to M1 phenotype.

CD3: cluster of differentiation 3; CD40: cluster of differentiation 40; CEA: carcinoembrionic antigen; CEA-TCB: carcinoembryonic antigen T-cell bispecific; COX-1/COX-2: cyclooxygenases 1 and 2; CSF1R: colony-stimulating factor 1 receptor; DKK-1: Dickkopf-related protein 1; GC: gastric adenocarcinoma; GEJC: gastroesophageal adenocarcinoma; mAb: Monoclonal antibody; NCT: ClinicalTrials.gov identifier; PD-L1: programmed death-ligand 1; STAT3: Signal transducer and activator of transcription 3; TAMs: tumor-associated macrophages