REVIEW

Regulation of Gastric Carcinogenesis by Inflammatory Cytokines

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SUMMARY

Chronic atrophic gastritis and gastric cancer are strongly linked. Immune cytokines produced during chronic inflammation are capable of acting on both immune and epithelial cells to impact disease progression, but the pathophysiologic roles of many cytokines remain undefined.

Chronic inflammation caused by infection with *Helicobacter pylori* and autoimmune gastritis increases an individual's risk of developing gastric cancer. More than 90% of gastric cancers are adenocarcinomas, which originate from epithelial cells in the chronically inflamed gastric mucosa. However, only a small subset of chronic gastritis patients develops gastric cancer, implying a role for genetic and environmental factors in cancer development. A number of DNA polymorphisms that increase gastric cancer risk have mapped to genes encoding cytokines. Many different cytokines secreted by immune cells and epithelial cells during chronic gastritis have been identified, but a better understanding of how cytokines regulate the severity of gastritis, epithelial cell changes, and neoplastic transformation is needed. This review summarizes studies in both human and mouse models, describing a number of different findings that implicate various cytokines in regulating the development of gastric cancer. *(Cell Mol Gastroenterol Hepatol 2017;4:47–53; http://dx.doi.org/ 10.1016/j.jcmgh.2017.03.005)*

Despite recent declines in both incidence and mortality in the United States, gastric cancer remains the fifth most common cancer and the third leading cause of cancer-related death worldwide.[1] Many factors influence likelihood of gastric cancer, but chronic atrophic gastritis is strongly associated.[2] However, there is a lack of mechanistic insight into why chronic gastritis advances to gastric cancer in a subset of individuals. Cytokines are secreted or membrane-bound signaling molecules that are major components of the inflammatory response, and polymorphisms in a number of cytokine genes influence the risk of developing gastric cancer. Cytokines have pleiotropic effects on various cell types and regulate death, proliferation, differentiation, and migration. We review the limited human data, extensive murine *Helicobacter* infection models, and noninfectious murine models of gastric metaplasia to summarize the current understanding of the role of cytokines in regulating gastric cancer development.

Inflammation and Gastric Carcinogenesis

H pylori and autoimmune gastritis are the most common etiologic lesions that create an environment conducive to gastric inflammation, and both conditions increase gastric cancer risk. The Correa pathway describes the progression from inflammation to atrophic gastritis (loss of parietal cells), metaplasia, dysplasia, and ultimately to adenocarcinoma.[3,4] Gastric atrophy is a key step, because studies of resected stomachs from patients with intestinal-type gastric cancer have shown gastric atrophy in every case.[5] Atrophy, metaplasia[4] (including spasmolytic polypeptide-expressing metaplasia [SPEM], thought to be a precursor lesion to gastric cancer), dysplasia, and neoplastic transformation all occur in a setting of inflammation and a complex milieu of cytokines.[6–8] A better understanding of how cytokines regulate the degree of inflammation and the extent of epithelial cell changes is needed to better understand gastric carcinogenesis.

Cytokine Signaling

The immune system is essentially a network that uses cytokines to facilitate communication between cells. Cytokines signal similarly to growth factors, in that they are secreted or membrane-bound proteins that bind to specific receptors on target cells. Many cytokines were first characterized by immunologists as proteins made by leukocytes that also act on leukocytes (hence many are called interleukins). However, cytokines can act on a broad range of cell types including gastrointestinal epithelium.[9–11] When a cytokine binds its cognate receptor, an intracellular signal is transduced by second messengers that ultimately leads to the activation of transcription factors. Many cytokines activate Janus-activated kinases (JAKs), signaling molecules that

phosphorylate and activate signal transducers and activators of transcription (STATs), which dimerize when activated and translocate to the nucleus and regulate transcription. Not all cytokines activate JAK-STAT signaling, and different signal transduction pathways can be used that ultimately activate transcription factors such as activator protein 1, mitogen-activated protein kinases (MAPKs), and nuclear factor kappa B (NF-κB).[12–15] In addition to their ability to act on immune cells and regulate the type and degree of inflammation, cytokines also act on epithelial cells and other cell types to regulate secretion,[9,16] proliferation,[16,17] and differentiation.[18–20] Because of their broad and pleiotropic effects on immune and epithelial cells, cytokines are an obvious candidate for analysis as gastric cancer risk factors. Many questions remain concerning the levels and types of cytokines that regulate gastric cancer development and progression. The answers to these questions will likely advance our understanding of the link between chronic inflammation and gastric cancer.

Human Studies

In 1994, the World Health Organization officially announced that *H pylori* was a risk factor leading to gastric cancer. Since then, studies have found correlations between increases in inflammatory cytokines in *H pylori*–infected individuals with increased gastric cancer risk. One study found increased risk in *H pylori*–infected individuals with a particular genotype in the inflammatory cytokine interleukin (IL) 1β (*IL1B*) that led to increased production.[21] Similarly, studies have associated increased levels of IL8, a cytokine that attracts neutrophils and activates inflammatory genes, and an increased risk of atrophic gastritis and diffuse gastric cancer.[22–24] Genotypes of *TNF*, *IL10*, *IL1B*, and *IL1RN* are also reported to confer greater risk of gastric cancer.[25–27] Overall the evidence indicates that the types and amounts of cytokines made in response to *H pylori* infection have a significant impact on the risk of developing gastric cancer. *H pylori* infects the lumen of the stomach, where immune cells do not normally traffic. As a result, in most cases the immune response is unable to clear *H pylori* from the stomach, and inflammation becomes chronic. It is likely that the greater the inflammatory response, the greater the tissue damage, including parietal cell atrophy, and greater atrophy leads to metaplasia and dysplasia and increases gastric cancer risk.

The type of immune response to chronic gastritis also likely influences cancer risk. For example, risk may depend on the types of cytokines made by different subsets of differentiated CD4+ helper T cells responding to *H pylori* or self-antigens such as H+/K+ adenosine triphosphatase (ATPase) in the case of autoimmune gastritis. The major T helper (Th) cells and the signature cytokines secreted by each include Th1 cells that secrete interferon (IFN)-γ, Th2 cells that secrete IL4, Th17 cells that secrete IL17A and IL22,[28] and Th22 cells that secrete IL22. Th1 responses and Th17 responses are the predominant responses during cases of *H pylori* infection and autoimmune gastritis. Several reports correlate IL17A production with more severe

disease and poor prognosis, suggesting IL17A promotes tumorigenesis.[29–31] Studies have reported the following:

- tumor-infiltrating CD4+ Th17 cells produce IL17 in the tumor microenvironment and promote tumor progression in human gastric cancer[32];
- there are increased Th17 cells infiltrating tumors in patients with advanced gastric cancer[33];
- gastric cancer patients have higher levels of IL17 in serum and in cancer tissues[34]; and
- genetic data indicate that IL17A and IL17F polymorphisms increase gastric cancer risk.[35]

IL17A is not only expressed by CD4+ Th17 cells but can be made by natural killer cells, CD8+ T cells, and other cell types. Furthermore, the IL17 family of cytokines includes 6 members (IL17A, IL17B, IL17C, IL17D, IL17E, and IL17F). Whether any of the additional members of the cytokine family influence immune and/or epithelial cells during the progression from gastritis to gastric cancer remains to be determined.

In 2009, a distinct subset of CD4+ Th cells that secretes the cytokine IL22, called Th22 cells, was identified.[36] Since then, reports have implicated a pathophysiologic role for IL22 in gastric cancer. IL22 produced by cancer-associated fibroblasts was reported to promote gastric cancer cell invasion through STAT3 and extracellular signal-regulated kinase activation. IL22 receptors are expressed in gastric cancer tumor cells, with expression significantly related to lymphatic invasion and poor prognosis.[37] These new findings are important because MAPK signaling has been implicated in invasion and metastasis of gastric cancer.[38]

In addition, cytokines in the IL12 family (IL12, IL23, IL27, IL35), particularly IL23, are also upregulated in gastric cancer cell lines and in tissue from *H pylori*–infected individuals.[39] Two of these cytokines signal through the gp130 receptor, which is also used by several members of the IL6 family of cytokines (IL6, IL11, oncostatin M, and others). This is relevant because gp130 signaling is often dysregulated in gastric cancer.[40] IL6, IL11, and other cytokines that signal through the gp130 receptors activate STAT3, and STAT3 is reported to be overactivated in gastric cancer and gastric cancer stem cells, indicating poor prognosis.[41,42]

Several additional cytokines are reported to be expressed in the inflamed gastric mucosa, including IL10, IL32, and IL33.[43–45] Additional information is needed to understand how the complex milieu of cytokines that are present in an individual with chronic gastritis influences the risk of gastric cancer (Table 1). There is much to learn, such as which cytokine receptors are expressed by various immune and gastric epithelial cells, which signaling pathways are activated and/or suppressed, and how different combinations and levels of cytokines might promote gastric oncogenesis and/or metastasis. Studies in mouse models have provided valuable insight into some of these questions. Some of the models and cytokines studied are briefly reviewed below.

Table 1. Human Studies and Cytokines Implicated in Gastric Cancer Progression

Data source	Cytokines implicated
Genetic associations	IL1β, IL8, tumor necrosis factor-α, IL10, IL17A, IL17F
Biological data	IL10, IL17A, IL22, IL23, IL32, IL33

Mouse Studies

Murine Helicobacter Infection Models

Inbred mouse strains can differ significantly in their response to identical infectious agents. For example, in response to infection with *Leishmania*, C57BL/6 mice preferentially expand Th1 CD4+ cells that produce IFN-γ, whereas the response in BALB/c mice is dominated by Th2 cells that produce IL4. This differential cytokine production has significant consequences, with BALB/c mice being much more susceptible to infection and death.[46,47] This dichotomy is also seen in murine models of *Helicobacter* infection. Th2-skewed BALB/c mice were shown to clear bacteria more efficiently and develop less gastric pathology than C57BL/6 mice with a predominantly Th1 immune response.[48] These early studies demonstrated that changes in the cytokine milieu significantly affect gastric pathology resulting from infection, and this has been supported by evidence from both humans and mouse models that concurrent infection with helminthes is capable of ameliorating the pathologic Th1 response by promoting a competing Th2 response.[49,50]

Additional studies have demonstrated the importance of cytokines for disease progression. Although mice lacking CD4+ T cells do not develop gastritis in response to *Helicobacter*,[51] IFN-γ treatment in the absence of infection was sufficient for the development of gastritis, and IL4 treatment before infection was capable of preventing inflammation.[52] These studies suggest that although CD4+ T cells are important initiators of the inflammatory response to infection, composition of the cytokine milieu is also relevant to disease progression, regardless of cellular origin. It is also worth noting that although many studies have addressed the Th1/Th2 dichotomy, discovery of additional CD4+ Th subsets such as Th9, Th17, and Th22 warrant further investigation. IL17A, the defining cytokine for the Th17 lineage, has been implicated in the inflammatory response to *Helicobacter* colonization in humans.[53] It is also associated with more severe pathology in infected mice; one recent study observed that IL17A-deficient mice develop less severe gastritis in response to infection.[54] Thus, it is unlikely that any one cytokine is responsible for all changes in epithelial cells that predispose to gastric pathology. It is most likely that cytokines can enhance and oppose each other's effects on the gastric epithelium, either promoting or preventing disease progression.

The regulation of the immune response by ILs and other cytokines is well-documented, and the difference in pathology caused by *Helicobacter* is due in part to regulatory effects on the immune system. For instance, IL4-deficient mice have more severe gastritis during infection that is correlated with higher levels of IFN-γ production, and IFN-γ–deficient mice have less severe gastritis with greater proportions of IL4 producing cells.[55] T-cell transfer studies into immunodeficient mice demonstrated that IL10 expression by regulatory CD4+ T cells is required for their ability to suppress T-cell–mediated gastritis caused by *H pylori* infection.[56]

Direct signaling by cytokines into gastric epithelial cells is also important to disease progression, which is evident by the fact that dysregulated gp130 signaling in the gastric epithelium is common in chronic infection and gastric cancer in humans.[40] This signaling pathway has been further implicated in *Helicobacter*-mediated gastritis by studies showing that IL11, which is one of many cytokines that signal through gp130, is upregulated in infected mice, and treatment with IL11 causes epithelial cell changes similar to chronic atrophic gastritis.[57] In addition, a mouse model with defective transforming growth factor-β receptor signaling localized to the gastric epithelium had higher incidence of gastric pre-neoplasia after infection, and downstream signaling molecules for transforming growth factor-β receptor such as Smad3 and Smad4 have also been implicated as important repressors of gastric tumorigenesis.[58–60] Other signaling pathways are also involved; it was recently shown that *Helicobacter* induced the stem cell marker SOX9 in metaplastic gastric epithelial cells in an IL1 receptor–dependent manner.[61] Cytokines produced by the gastric epithelium are also capable of regulating the nature of the inflammatory response; gastrokine-2, a secreted protein normally produced by the gastric mucosa, was shown to restrain Th1 responses but have no effect on Th2, Th17, or regulatory CD4+ T cells cytokines.[62]

Overall, murine *Helicobacter* models have increased our understanding of how cytokines made in response to infection can influence gastric cancer risk. These studies have revealed a complex series of relationships in which cytokines from a multitude of sources regulate the type and degree of the immune response, influence epithelial cell changes, and affect the degree of bacterial colonization.

Noninfectious Murine Models of Gastric Metaplasia

Mouse models have been developed to study the influence of cytokines on gastritis and gastric epithelial cell changes that do not involve *Helicobacter*. Although none of these models develop adenocarcinoma, several interesting findings have shown that cytokines can act on immune cells to regulate the type and degree of inflammation and on gastric epithelial cells to regulate atrophy, hyperplasia, metaplasia, and tumor formation. The studies discussed below describe a number of different cytokines that likely contribute to inflammation, atrophy, and metaplasia in the stomach.

Cytokines Produced by the Immune System

IFN-γ is the signature cytokine made by Th1 cells, but its exact role(s) in regulating epithelial cell changes is

unknown. One study showed that infusing IFN-γ into mice for 2 weeks caused mucous neck cell hyperplasia.[63] The same group used a Huntington interacting protein 1 related knockout (Hip1r–/–) mouse model of gastric metaplasia and showed that IFN-γ deficiency selectively reduced the extent of mucous neck cell hyperplasia but did not affect the expansion of surface mucous cells, loss of parietal cells, or loss of zymogenic cells.[64] More recently Petersen et al[65] showed that IFN-γ expression was not required for metaplasia (SPEM) to develop in an acute model of parietal cell atrophy resulting from the administration of L635 to deplete parietal cells. Collectively these 3 studies showed that IFN-γ expression was not necessary for atrophy or metaplasia (SPEM) in these models. However, when IFN-γ was expressed in mice under the control of a parietal cell specific promoter (H⁺/K⁺ ATPase promoter), mice spontaneously developed inflammation, loss of parietal and chief cells, metaplasia (SPEM), and dysplasia.[66] To further complicate interpretation, another group generated IFN-γ expressing mice using the same H⁺/K⁺ ATPase promoter and found that IFN-γ played a role in suppressing inflammation and epithelial cell changes.[67] These studies highlight the complexity of studying pleiotropic cytokines such as IFN-γ on gastric epithelial cell changes in various models. However, it is important to note that in the context of chronic atrophic gastritis, the cell types and relative levels of IFN-γ production may vary, and inflammation may also affect responsiveness of different epithelial cells to IFN-γ and other cytokines.

The cytokine receptor gp130 is a ubiquitously expressed, signal transducing receptor that heterodimerizes with a number of different co-receptors that bind: IL6, IL27, IL35, leukemia inhibitor factor, oncostatin M, ciliary neutrophic factor, and cardiotrophin 1.[68] The importance of this cytokine receptor in gastric cancer was identified in mice that express a transgene with a mutation in the suppressor of cytokine signaling 3 binding site of gp130 that leads to constitutive activation. These mice rapidly developed gastritis, atrophy, and progressed to metaplasia and dysplasia.[69] The cytokines IL6 are believed to drive gastric tumorigenesis in these mice, in part through their ability to activate STAT3, a known driver of inflammation-associated tumorigenesis.[70,71] Findings in this model importantly identify gp130 as a cytokine receptor that directly regulates gastric epithelial cell changes associated with cancer. Other cytokines influence gastric cancer by influencing immune cells. For example, IL1β was shown to induce severe gastric dysplasia when expressed under the control of H⁺/K⁺ ATPase promoter, in part because of the recruitment of myeloid-derived suppressor cells.[72] Future challenges will be identifying which of the many cytokines present in chronic inflammation promote or inhibit tumors, and whether these activities are due to their ability to regulate immune or epithelial cell biology.

Autoimmune gastritis is one of the most common autoimmune conditions in humans. Recent studies have reported that patients with severe autoimmune gastritis (pernicious anemia) are up to 4 times more likely to develop gastric cancer than individuals who do not have disease.[73,74] Mouse models of autoimmune gastritis can provide insight into the link between gastritis and gastric cancer. McHugh et al[75] cloned a T-cell receptor from a mouse that had developed autoimmune gastritis. The T-cell receptor was specific for a peptide from H⁺/K⁺ ATPase, and expressing this T-cell receptor as a transgene in BALB/c mice (called TxA23) caused autoimmune gastritis to develop spontaneously and with complete penetrance. It was recently shown that TxA23 mice develop gastritis, oxyntic atrophy, metaplasia (SPEM), and several other features associated with human gastric carcinogenesis.[76] Despite the fact that these mice are on a BALB/c background, inflammation is predominantly mediated by IFN-γ producing CD4+ T cells (Th1) and IL17 producing CD4+ T cells (Th17).[76,77] These mice have been used to study the importance of CD4+ regulatory T cells in suppressing cytokines and reducing the severity of gastritis and oxyntic atrophy[78,79] and to show that CD4+ T cells that produce IFN-γ (Th1), IL17 (Th17), and IL4 (Th2) are all capable of inducing gastritis and oxyntic atrophy, although with varying degrees and types of gastric pathology.[80,81] Other models of autoimmune gastritis have shown that neutralizing the cytokines IL21 and tumor necrosis factor suppressed disease development.[82] Future studies in these mice will provide valuable insight into the cytokines that promote and suppress inflammation and epithelial cell biology in a setting of chronic inflammation.

Cytokines Produced by Epithelial Cells

Epithelial cells are also a source of cytokines that may regulate gastritis and gastric cancer. Recently, IL33 was reported to be highly expressed in gastric epithelium, particularly by surface mucous cells.[45] IL33 is a member of the IL1 family of cytokines that binds to ST2 (IL1RL1) and IL1 receptor accessory protein IL1RAP and activates NF-κB and MAPK signaling. Administering IL33 in large doses to mice induced inflammation, atrophy, and metaplasia in the fundus, induced IL6 and IL9 expression, and promoted the expansion of myeloid-derived immune cells in the stomach.[45] Recently, IL33 was shown to be important for SPEM development via an IL13-dependent mechanism in a model in which parietal cells are depleted with L635.[83] IL11 is expressed by epithelial cells in the fundic mucosa, especially by parietal cells. Like IL6, IL11 binds to gp130 in combination with another receptor subunit, IL11 receptor alpha, to activate JAK-STAT signaling pathways. Injecting mice with IL11 was shown to induce atrophic gastritis.[57] These recent findings have added IL33 and IL11 to list of cytokines (Table 2) that require additional investigation to increase understanding of the regulation of inflammation and epithelial cell changes in the stomach.

Summary

Studies in humans and mouse models of gastritis and gastric cancer are identifying important roles for cytokines in regulating oxyntic atrophy, hyperplasia, metaplasia, and progression to gastric cancer, but more information on cytokines that influence gastric cancer development is needed.

Table 2. Mouse Studies and Cytokines Implicated in Precancerous Changes

Epithelial change	Associated cytokines/cytokine receptors
Parietal cell atrophy	IL4, IL6, IL11, IL33, IFN-γ, gp130 receptor
Neck cell hyperplasia	IL1, IL6, IFN-γ, gp130 receptor
Metaplasia	IL1β, IL6, IL11, IL13, IL33, IFN-γ, gp130 receptor, transforming growth factor-β

Furthermore, these cytokines' functions (pro- vs anti-tumorigenic) and cellular targets (immune vs epithelial) will enhance understanding of how inflammation and cytokines influence gastric cancer risk. As new biologics are developed to target specific cytokines and cytokine pathways to treat a number of different inflammatory diseases, a better understanding of which cytokines promote gastric cancer development and progression may be used to develop additional therapeutic options for patients with chronic atrophic gastritis and gastric cancer.

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