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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)*

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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

Abbreviations used in this paper: **ATPase, adenosine triphosphatase; IFN, interferon; IL, interleukin; JAK, Janus-activated kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; SPEM, spasmolytic polypeptide-expressing metaplasia; STAT, signal transducer and activator of transcription; Th, T helper.**

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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.