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REVIEW

Gastrin and Gastric Cancer

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SUMMARY

The gastrointestinal peptide, gastrin, stimulates growth of gastric adenocarcinoma (gastric cancer) through the cholecystokinin-B receptors that are overexpressed in this malignancy. Serum gastrin levels may be increased secondary to chronic administration of proton pump inhibitors, atrophic gastritis, *Helicobacter pylori* infection, or from de novo gastrin expression from the gastric cancer epithelial cells. Strategies to interrupt the interaction of gastrin at the cholecystokinin-B receptor may provide a novel approach to the treatment of gastric cancer.

Gastric cancer is the third leading cause of cancer-related mortality worldwide. Despite progress in understanding its development, challenges with treatment remain. Gastrin, a peptide hormone, is trophic for normal gastrointestinal epithelium. Gastrin also has been shown to play an important role in the stimulation of growth of several gastrointestinal cancers including gastric cancer. We sought to review the role of gastrin and its pathway in gastric cancer and its potential as a therapeutic target in the management of gastric cancer. In the normal adult stomach, gastrin is synthesized in the G cells of the antrum; however, gastrin expression also is found in many gastric adenocarcinomas of the stomach corpus. Gastrin's actions are mediated through the G-protein–coupled receptor cholecystokinin-B (CCK-B) on parietal and enterochromaffin cells of the gastric body. Gastrin blood levels are increased in subjects with type A atrophic gastritis and in those taking high doses of daily proton pump inhibitors for acid reflux disease. In experimental models, proton pump inhibitor–induced hypergastrinemia and infection with *Helicobacter pylori* increase the risk of gastric cancer. Understanding the gastrin:CCK-B signaling pathway has led to therapeutic strategies to treat gastric cancer by either targeting the CCK-B receptor with small-molecule antagonists or targeting the peptide with immune-based therapies. In this review, we discuss the role of gastrin in gastric adenocarcinoma, and strategies to block its effects to treat those with unresectable gastric cancer. *(Cell Mol Gastroenterol Hepatol 2017;4:75–83; http://dx.doi.org/10.1016/j.jcmgh.2017.03.004)*

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Gastric adenocarcinoma (gastric cancer) is a common malignancy and is the world's second leading cause of cancer mortality worldwide.[1] Novel therapeutic targets desperately are needed. The meager improvement in the approximately 10% cure rate realized by adjunctive treatments to surgery is unacceptable because more than 50% of patients with localized gastric cancer die as a result of their disease.[2] The prognosis of those with advanced gastric cancer is poor, with a 5-year survival of only 20%–30%.[3,4] The only curative option in the treatment of gastric cancer is surgery, and for metastatic disease conventional chemotherapy has shown only a modest benefit, with an average survival of approximately 10 months.[5] Unfortunately, however only marginal improvements in patient outcomes have been achieved with chemotherapy despite extensive phase 3 testing.[6] The current standard of care for advanced gastric cancer in the first-line setting remains a combination of a fluoropyrimidine (eg, 5-fluorouracil) and a platinum (eg, cisplatinum)-containing chemotherapeutic agent. Targeted therapy may offer new possibilities for the treatment of gastric cancer. Because human epidermal growth factor receptor 2 (HER2) receptors are found in approximately 20% of gastric cancers, the addition of a HER2-receptor antibody to standard chemotherapy may be beneficial, as shown in the Trastuzumab for Gastric Cancer study, in which trastuzumab (Herceptin; Genentech, South San Francisco, CA) was beneficial in subjects with HER2-positive gastric cancer.[7] However, clinical trials studying the value of other targeted therapies, such as with epidermal growth factor receptor (EGFR) or vascular endothelial growth factor, yielded disappointing results.[8,9]

Histologic and Molecular Classifications of Gastric Cancer

In the West, most of those with gastric cancer typically present with advanced or metastatic disease, whereas in several Asian countries, gastric cancer usually is identified early and cure rates are higher.[10] Other regional differences in gastric cancer are readily identifiable; for example,

Abbreviations used in this paper: **CCK-BR, cholecystokinin-B receptor; ECL, enterochromaffin-like; EGFR, epidermal growth factor receptor; ERK, extracellular signal–regulated kinase; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PAS, polyclonal antibody stimulator; PPI, proton pump inhibitor; TCGA, The Cancer Genome Atlas.**

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proximal gastric cancers are more prevalent in Europe and the Americas than in Asia.[11] Histologically, gastric cancer has been categorized according to the Lauren[12] classification as either diffuse or intestinal-type. The intestinal-type is characterized by chronic *Helicobacter pylori* infection; is more prevalent in high-incidence areas such as Japan, Korea, and Eastern Europe[13]; and the more aggressive diffuse type has been associated with genetic variations (single nucleotide polymorphisms) of the prostate stem cell antigen.[14] The Cancer Genome Atlas (TCGA) Research Network described 4 groups of gastric cancer based on molecular classifications including Epstein–Barr virus, microsatellite instability, genomically stable, and chromosomal instability.[15] With the TCGA classification, 73% of the genomically stable were the diffuse type histologically according to Lauren's criteria and systematic differences in distribution were not observed between East Asian and those of Western origin. The Asian Cancer Research Group[16] further characterized the molecular classification with the incorporation of the tumor protein 53 activity and epithelial-to-mesenchymal transition and found some unique differences compared with the TCGA analysis.

Risk Factors for Gastric Cancer

Factors associated with an increased risk of gastric cancer include nutrition, such as high salt and nitrate intake, a diet low in vitamins A and C, the consumption of large amounts of smoked or cured foods, lack of refrigerated foods, and poor-quality drinking water.[17] Occupational exposure to rubber and coal also increase the risk.[18] Other risk factors that have been implicated include the following: cigarette smoking, *H pylori* infection, Epstein–Barr virus, radiation exposure, and prior gastric surgery for benign ulcer disease.[18] More recently, a number of investigators have shown that polymorphisms in inflammatory genes can be associated with gastric cancer risk.[19,20] Genetic risk factors include type A blood group, pernicious anemia, family history of gastric cancer, hereditary nonpolyposis colon cancer, and Li–Fraumeni syndrome.[18] Most cases of gastric cancer are sporadic, and gastric cancer associated with an inherited syndrome occurs in only a limited number of patients (1%–3%). E-cadherin mutations occur in approximately 25% of families with an autosomal-dominant hereditary form of diffuse gastric cancer.[21]

The gastrointestinal peptide gastrin is involved physiologically in secretion of gastric acid[22] and growth of the gastrointestinal tract.[23] Gastrin is an important growth factor for the developing[24] and adult[25] digestive system, and is trophic to the entire gastrointestinal tract.[26,27] Gastrin is released from G cells in the stomach antrum during normal physiologic digestion of food and serves as a major stimulator of gastric acid secretion from the stomach parietal cells (Figure 1).[28] In human beings the majority of gastrins are amidated and gastrin-17 is the most abundant circulating gastrin in the peripheral blood.[29] Proton pump inhibitors (PPIs) have been developed to facilitate healing of peptic ulcer disease and gastroesophageal reflux disease. Because this class of medications is very effective in suppressing acid, a consequence of long-term acid suppression can be the increase of serum gastrin levels[30,31] resulting from the interruption of the normal feedback mechanisms. One PPI, omeprazole, causes a 2- to 6-fold increase in serum gastrin levels in 80%–100% of patients receiving chronic therapy.[30,32,33] Up to 30% of patients on chronic PPI therapy may have gastrin blood levels greater than 500 ng/L or more than 6-fold greater than the upper limit of normal.[30,31,33] Even short-term administration of omeprazole has been shown to increase serum gastrin levels,[34] however, levels return to normal after discontinuation. Although raised as a potential issue at the time of their initial approval 25 years ago, the concern regarding PPI-induced hypergastrinemia has not disappeared completely.[35,36]

One concern in regard to hypergastrinemia and PPIs has been the potential relationship between gastrin and gastric cancer. When gastrin is administered in animal models, there is a marked increase in parietal cell mass and the enterochromaffin-like (ECL) cells of the stomach body.[37] Increased gastrin levels in rats[38] and human beings[39] have been associated with gastric carcinoid tumors arising from the ECL cells. In cell culture, gastrin has been shown to stimulate the growth of human gastric cancer cell lines.[40,41] Several reviews and meta-analyses have been performed concerning the association between PPI use and risk for gastrointestinal cancers without confirmatory results.[42,43] Ahn et al[44] reported a significantly increased risk of gastric cancer in a large systematic search with a cohort of nearly 6000 subjects; however, Lundell et al[45] did not find an increased risk in a cohort of 1920 subjects. Han et al[46] even suggested that PPI use may decrease the risk of gastric cancer by antagonizing the proliferative and anti-apoptotic effects of gastrin.[46]

Gastrin Mediates its Effects Through the Cholecystokinin-B Receptor

Gastrin mediates both its acid-releasing and growth properties on the gastrointestinal tract through a G-protein–coupled receptor called the cholecystokinin (CCK) or CCK-B receptor (CCK-BR).[47] After interacting with the CCK-BR on parietal or ECL-like cells, downstream signaling occurs through the activation of the phospholipase C–β/diacylglycerol/Ca^{2+}/protein kinase C cascade[48] (Figure 1). CCK-B receptors are overexpressed in gastric cancers,[40,49] and stimulation with exogenous gastrin promotes growth of this malignancy.[40] CCK receptors also induce other signaling pathways through tyrosine kinase receptors. CCK-BR signaling also has been shown to transactivate the EGFR[50] through Src and Matrix metalloproteinase releasing transforming growth factor-α from its precursor protein causing EGFR tyrosine phosphorylation.[50] The EGFR phosphorylates phosphoinositide 3-kinase, activating PDK1, Protein kinase B (PKB), and mammalian target of rapamycin. The EGFR interacts with adaptor proteins Grb2 and SOS, activating Ras and Raf, followed by phosphorylation of Mitogen-activated protein kinase/ERK and extracellular signal–regulated kinase (ERK). Gastrin also has been shown to mediate its actions by up-regulating phosphorylation of ERK