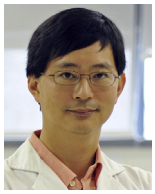
Gastroenterology 2015;149:1153–1162

Genetics and Molecular Pathogenesis of Gastric Adenocarcinoma



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Gastric cancer (GC) is globally the fifth most common cancer and third leading cause of cancer death. A complex disease arising from the interaction of environmental and host-associated factors, key contributors to GC's high mortality include its silent nature, late clinical presentation, and underlying biological and genetic heterogeneity. Achieving a detailed molecular understanding of the various genomic aberrations associated with GC will be critical to improving patient outcomes. The recent years has seen considerable progress in deciphering the genomic landscape of GC, identifying new molecular components such as *ARID1A* and *RHOA*, cellular pathways, and tissue populations associated with gastric malignancy and progression. The Cancer Genome Atlas (TCGA) project is a landmark in the molecular characterization of GC. Key challenges for the future will involve the translation of these molecular findings to clinical utility, by enabling novel strategies for early GC detection, and precision therapies for individual GC patients.

Keywords: Cancer Genetics; Cancer Genomics; Gastric Cancer.

Gastric cancer (GC) is currently the third leading cause of global cancer-related death, and particularly prevalent in Asia. Despite a steadily declining incidence, GC still causes more than 723,000 deaths a year.[1] Achieving a detailed molecular understanding of GC pathogenesis is pivotal to improving patient outcomes for this complex disease. This is clearly exemplified by the TOGA Phase III trial, where GC patients with *HER2/neu* receptor tyrosine kinase (RTK)-positive tumors experienced clinical benefit from chemotherapy plus trastuzumab (a HER2-targeting antibody) relative to chemotherapy alone.[2] In this review, we have attempted to capture the latest advances in GC molecular genetics. Special attention is paid to the recent landmark TCGA study, where almost 300 GCs were simultaneously profiled on multiple molecular platforms to identify 4 genomic subtypes: CIN (chromosomal instability), MSI (microsatellite instability), GS (genome stable), and EBV (Epstein-Barr virus).[3] The comprehensive nature of the TCGA study provides an invaluable resource upon which to interpret other related GC findings.

Gastric Premalignancy and the Critical Role of Inflammation

The human stomach consists of the fundus, corpus or body, and pyloric antrum. The gastric mucosa contains three main types of glands: cardiac glands (containing mucus-producing foveolar cells), oxyntic glands (parietal cells and chief cells producing hydrochloric acid and pepsinogen respectively), and pyloric glands with mucus–secreting cells and endocrine G cells secreting gastrin. Chronic atrophic gastritis and intestinal metaplasia (IM) involving the gastric mucosa are considered important steps in GC pathogenesis (Figure 1).[4] Mucosal atrophy is characterized by loss of glandular elements and replacement by metaplastic cells or fibrosis, with concomitant hypochlorhydria. IM is a preneoplastic lesion characterized by transformation of the gastric mucosa into an intestinal-like phenotype, replete with goblet cells and intestinal mucins. IM, associated with

Abbreviations used in this paper: **CIMP, CpG island methylation phenotype; CIN, Chromosomal instability; EBV, Epstein-Barr virus; EMT, epithelial-mesenchymal transition; GC, gastric cancer; GS, genome stable; *Helicobacter pylori*, *H pylori*; HDGC, hereditary diffuse gastric cancer; IM, intestinal metaplasia; lincRNAs, long intergenic noncoding RNAs; miRNAs, microRNAs; MSI, microsatellite instability; NGS, next-generation sequencing; sCNAs, somatic copy number alterations; TFs, transcription factors; TCGA, The Cancer Genome Atlas.**

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0016-5085
http://dx.doi.org/10.1053/j.gastro.2015.05.059

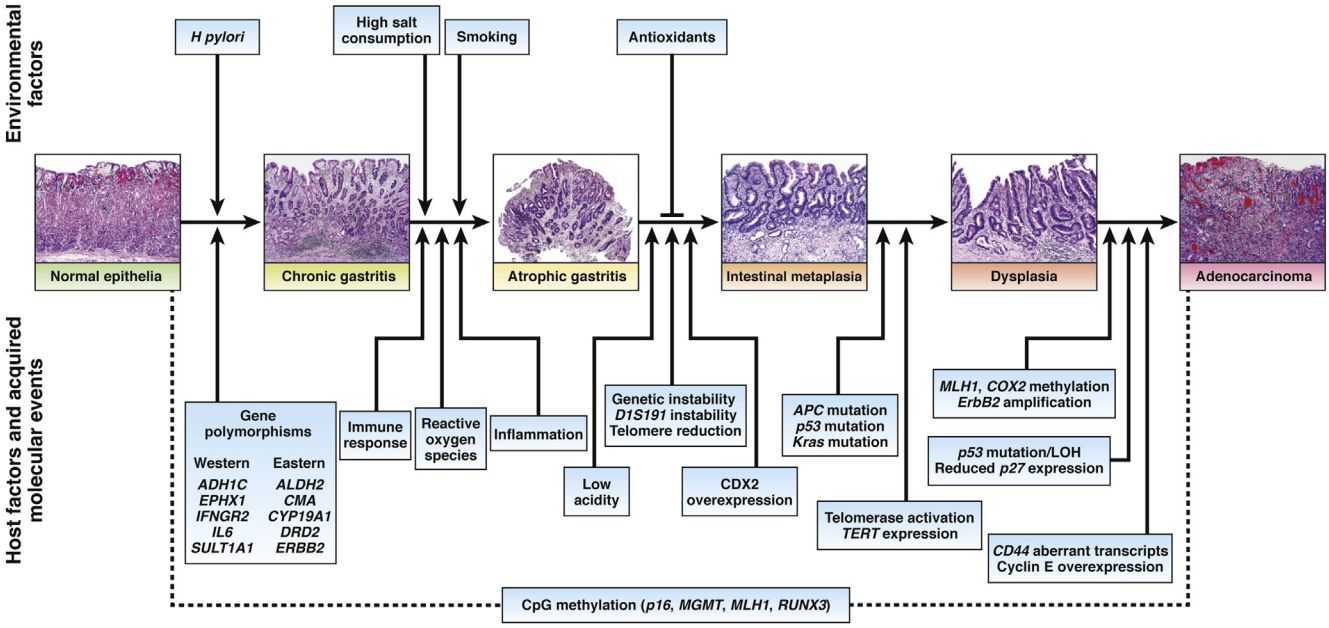

Figure 1. Cause and pathogenesis of intestinal-type GC. A summary of current knowledge of the cause and pathogenesis of intestinal type GC is shown, including host and environmental factors as well as acquired molecular events.[52,143–145] GC, gastric cancer.

over-expression of the homeobox transcription factor *CDX2*,[5] is currently classified into three subtypes: intestinal type, gastric type, and mixed gastric-intestinal type. The latter, also known as incomplete IM, is considered to confer the highest risk for GC development. Injury to the gastric mucosa has also been observed to cause metaplastic changes with spasmolytic peptide expression. This phenomena, termed spasmolytic peptide expressing metaplasia (SPEM) or trefoil factor family 2 (TFF2) expressing metaplasia, is induced after *Helicobacter pylori* (*H pylori*) infection and chronic gastritis.[6] Spasmolytic peptide expressing metaplasia has also been implicated as a precursor event in GC progression.[7]

In most patients, frank GC is often preceded by several decades of chronic gastric mucosal inflammation. Chronic inflammation activates the NF-κB transcription factor, a key mediator of tumor promotion.[8] Chronic inflammation also causes increased oxidative stress, due to reactive oxygen species and nitrosamines generated by leukocytes and macrophages which can damage proliferating cells. Moreover, the production of chemokines and cytokines may induce not only leukocyte migration but also promote carcinogenesis. Experimentally, mice with impaired immune systems such as severe combined immune deficiency (SCID) or recombinase activating gene (RAG2)-deficient mice are very susceptible to *H pylori* infection, but do not develop significant gastric disease.[9] Such data further supports an important functional role of the host immune system in GC pathogenesis.

Cause and Epidemiology of Gastric Cancer

Environmental factors play critical roles in GC pathogenesis, with major risk factors being *H pylori* infection, diet and smoking.[10] High salt intake, often due to traditional diets containing salted fish, is the best documented dietary risk factor for atrophic gastritis.[11] Recent data also suggests that iron deficiency may be a GC risk factor, as iron depletion can accelerate the progression of carcinogenesis by augmenting *H pylori* virulence.[12] EBV infection is recognized as an etiological agent in 5%–10% of GCs.[13,14]

H pylori is the most significant environmental risk factor for GC and is recognized as a class I carcinogen by the World Health Organization. Although more than 50% of the world population is infected with *H pylori*, only 1%–2% of infected people will develop GC in their lifetime.[15] A major *H pylori* virulence factor is the cytotoxin-associated gene A (*CagA*), within the bacterial cag pathogenicity island (cag-PAI) which is injected into the cytoplasm of gastric epithelial cells upon microbial colonization.[16] In transgenic mice, systemic expression of CagA has been shown to induce gastric epithelial hyperplasia, gastric polyps, gastric and intestinal adenocarcinomas.[17] Genetic variations in CagA, specifically present in Asian strains but not non-Asian strains, are also associated with increased chronic gastritis, gastric ulcer and gastric adenocarcinoma in human patients.[18] In gastric epithelial cells, CagA undergoes tyrosine phosphorylation by Src kinase and activates SHP-2 (Src homology 2- containing tyrosine phosphatase). Activated SHP-2 induces the Ras-ERK pathway, a key regulator of cell growth, migration, and adhesion.[19] CagA also disrupts tight junctions[20] and can target the PAR1/MARK kinase to alter apical-basolateral cell polarity, ultimately causing disorganization of the gastric mucosal architecture.[21] CagA also has tyrosine phosphorylation-independent functions, including interactions with the Met tyrosine kinase and E-cadherin. This latter interaction disrupts binding between E-cadherin and β-catenin, leading to nuclear accumulation of β-catenin