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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Gastric Cancer in the Era of Precision Medicine

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SUMMARY

The following pages provide a summary of current knowledge regarding the genomics of gastric cancer (GC), with a particular emphasis on how new genomic knowledge informs precision medicine and personalized therapies.

Gastric cancer (GC) remains the third most common cause of cancer death worldwide, with limited therapeutic strategies available. With the advent of next-generation sequencing and new preclinical model technologies, our understanding of its pathogenesis and molecular alterations continues to be revolutionized. Recently, the genomic landscape of GC has been delineated. Molecular characterization and novel therapeutic targets of each molecular subtype have been identified. At the same time, patient-derived tumor xenografts and organoids now comprise effective tools for genetic evolution studies, biomarker identification, drug screening, and preclinical evaluation of personalized medicine strategies for GC patients. These advances are making it feasible to integrate clinical, genome-based and phenotype-based diagnostic and therapeutic methods and apply them to individual GC patients in the era of precision medicine. *(Cell Mol Gastroenterol Hepatol 2017;3:348–358; http://dx.doi.org/10.1016/j.jcmgh.2017.02.003)*

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Gastric cancer (GC) is the fifth most common cancer worldwide and the third leading cause of cancer death in developed countries, with 984,000 new cases and 841,000 deaths occurring globally in 2013.[1] The incidence and mortality of GC are declining, in part because of improved *Helicobacter pylori* eradication and cancer screening. However, adenocarcinoma of the gastric cardia is increasing in North America and Europe,[2,3] and the incidence of non-cardia GC among whites aged 25–39 years has increased 1.67-fold in the United States during the past 2 decades.[4] Moreover, most GC cases are diagnosed at advanced stages, with consequent poor outcome; treatment is mostly restricted to cytotoxic chemotherapy. Thus, there is an urgent need to improve our understanding of the pathogenesis of GC and to identify more effective, less toxic therapeutic strategies. GC is multifactorial, with complex host genetic and environmental factors contributing to its development. GC is also highly heterogeneous; it is customarily divided into 2 main histologic subtypes, intestinal and diffuse, which are based on the Lauren classification.[5] However, the use of anti–human epidermal growth factor receptor-2 monoclonal antibody, trastuzumab, and anti–vascular endothelial growth factor receptor-2 monoclonal antibody, ramucirumab, has shifted the previous histopathologic paradigm to incorporate new genetic and molecular features.[6,7] Recently, remarkable advances in next-generation sequencing (NGS) technologies have defined the genomic landscape of GC[8–10]; studies of microRNAs (miRNAs) and long noncoding RNAs (lncRNAs)[11,12] as well as novel preclinical models (such as patient-derived tumor xenografts [PDX] and patient-derived organoids) have largely filled the gap between cancer genetics and phenotype.[13–17] These advances have made it possible to integrate traditional, genome-based and phenotype-based diagnostic and therapeutic methods with application to individual GC patients in the era of precision medicine.

Etiologic Factors in Gastric Carcinogenesis

Environmental Factors

Among clinical risk factors for GC, which include smoking, high-salt diet, high intake of meats, and bile reflux, infection with *H pylori* is a leading factor, especially in distal GC.[18–21] On the basis of improved estimates from prospective studies, 89% of new non-cardia GC cases are attributable to *H pylori* worldwide.[22] *H pylori*–mediated gastric carcinogenesis involves several mechanisms: cytotoxin-associated gene A, vacuolating cytotoxin A–induced chronic inflammation, oxidative damage, genomic instability, and epigenetic changes in gastric epithelial cells.[18,23–26] Interestingly, an

Abbreviations used in this paper: **CIMP, CpG island methylator phenotype; CIN, chromosomally unstable/chromosomal instability; EBV, Epstein-Barr virus; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; GC, gastric cancer; GTPase, guanosine triphosphatase; HDGC, hereditary diffuse gastric cancer; hPSC, human pluripotent stem cell; lncRNA, long noncoding RNA; LOH, loss of heterozygosity; miRNA, microRNA; MSI, microsatellite unstable/instability; MSI-H, high microsatellite instability; MSS/EMT, microsatellite stable with epithelial-to-mesenchymal transition features; NGS, next-generation sequencing; PDX, patient-derived tumor xenografts; TCGA, The Cancer Genome Atlas; TGF, transforming growth factor.**

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inverse relation between *H pylori* infection and the risk of proximal GC has been observed in Western countries.[27]

Epstein-Barr virus (EBV) occurs in 2%–20% of GC, with a worldwide average of 10%.[28] In EBV-associated GC, latent membrane protein 2A activates DNA methyltransferase 1 by inducing phosphorylation of STAT3, thereby causing CpG island hypermethylation of the PTEN promoter.[29] Specific EBV transcripts, including latent genes and viral miRNAs, also have oncogenic properties such as increased cell proliferation and motility, impairment of apoptosis, and increased chemoresistance.[30]

Host Factors

Hereditary cancer syndromes linked to 1%–3% of GC consist of 3 principal syndromes: hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and familial intestinal GC.[31] Germline mutations in *CDH1*, *CTNNA1,* and other tumor suppressor genes, including *BRCA2*, *STK11,* and *SDHB*, have been identified in HDGC.[32] *CDH1* mutations are prognostic genetic markers in HDGC. GAPPS is characterized by autosomal dominant transmission of fundic gland polyposis restricted to the proximal stomach, without evidence of colorectal or duodenal polyposis or other hereditary gastrointestinal cancer syndromes.[33] GC is also increased in other heritable syndromes, such as Li-Fraumeni syndrome with germline mutation of *TP53*, Peutz-Jeghers syndrome with frameshift mutation in *STK11*, hereditary nonpolyposis colorectal cancer with germline DNA mismatch repair gene mutation, and familial adenomatous polyposis with germline *APC* mutation.[31,34]

From Histologic to Molecular Classification

GC has long been categorized by using histomorphologic classification systems. According to the Lauren classification, GCs are divided into 2 main subtypes, intestinal and diffuse.[5] However, these histologic classifications are not sufficient to reflect the molecular and genetic characteristics of GC or to develop personalized treatment strategies in the era of precision medicine.

Recently, advances in genomic technology and high-throughput analysis have helped reveal the molecular genetic landscape of GC (Figure 1). Several molecular classification systems have been proposed, and distinct molecular subtypes have been identified.[8–10,35–37] In 2014, a landmark study by The Cancer Genome Atlas (TCGA) proposed 4 subtypes: (1) EBV-positive (8.8%), (2) microsatellite unstable/instability (MSI, 21.7%), (3) genomically stable (19.7%), and (4) chromosomally unstable/chromosomal instability (CIN, 49.8%).[8] Most EBV-positive tumors occurred in male patients and in the gastric fundus or body, displaying extreme DNA hypermethylation and amplification of *JAK2* and *PD-L1/2*, with 80% harboring non-silent *PIK3CA* mutations. All EBV-positive GCs displayed *CDKN2A* promoter hypermethylation, while lacking the *MLH1* hypermethylation characteristic of the MSI-associated CpG island methylator phenotype (CIMP).[8,38] Strong interleukin-12–mediated signaling signatures suggested a robust immune cell presence in this subtype. In contrast, MSI-subtype tumors tended to occur in female patients, diagnosed at advanced ages, and characterized by elevated mutation rates, including mutations of genes encoding targetable oncogenic signaling proteins. The genomically stable subtype lacked numerous molecular alterations, correlated well with the Lauren diffuse histologic variant, but harbored mutations of *RHOA* or fusions involving RHO-family guanosine triphosphatase (GTPase)–activating proteins. The active GTP-bound form of *RHOA* activates *STAT3* to promote tumorigenesis.[39] Finally, CIN subtype tumors were frequent at the gastroesophageal junction/cardia, correlated well with the Lauren intestinal histologic variant, showed marked aneuploidy, and harbored focal amplifications of

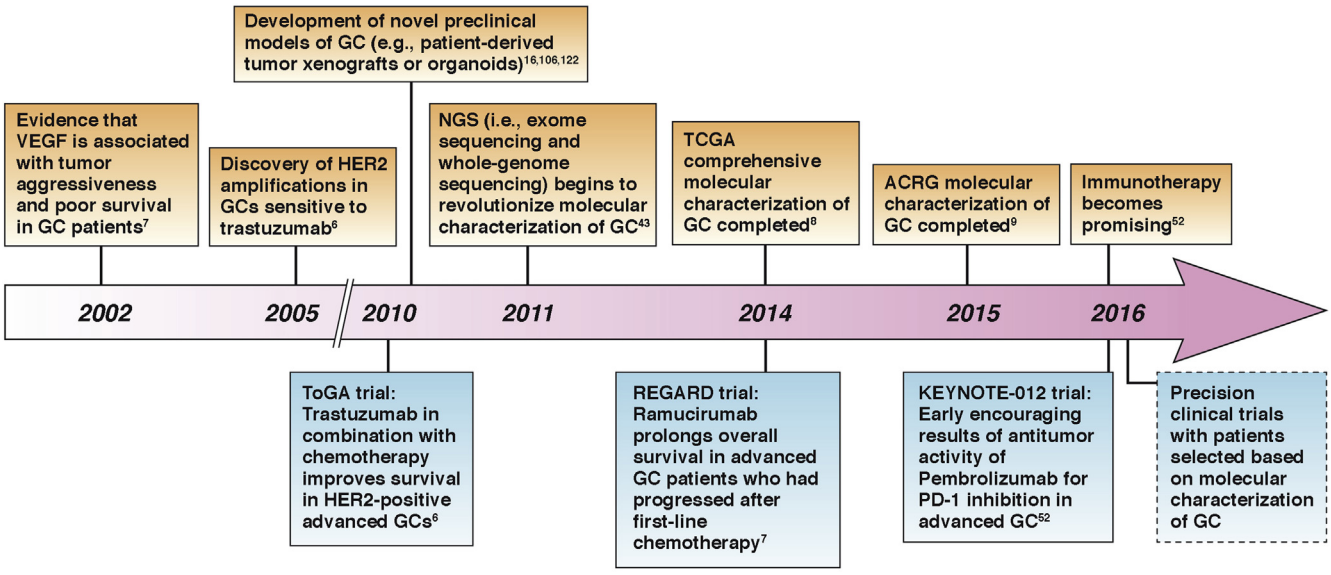

Figure 1. Timeline of selected major developments in GC (*above arrow*) and related clinical trials (*below arrow*) in recent years.