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REVIEW

Gastric Cancer Genomics: Advances and Future Directions

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SUMMARY

Improved sequencing technology has led to better understanding of the complex genomic landscape of gastric cancer. Herein, we review the recent advances in gastric cancer genomics and their potential to directly impact the diagnosis and treatment of this cancer.

Advancement in the field of cancer genomics is revolutionizing the molecular characterization of a wide variety of different cancers. Recent application of large-scale, next-generation sequencing technology to gastric cancer, which remains a major source of morbidity and mortality throughout the world, has helped better define the complex genomic landscape of this cancer. These studies also have led to the development of novel genomically based molecular classification systems for gastric cancer, reinforced the importance of classic driver mutations in gastric cancer pathogenesis, and led to the discovery of new driver gene mutations that previously were not known to be associated with gastric cancer. This wealth of genomic data has significant potential to impact the future management of this disease, and the challenge remains to effectively translate this genomic data into better treatment paradigms for gastric cancer. *(Cell Mol Gastroenterol Hepatol 2017;3:211–217; http://dx.doi.org/10.1016/j.jcmgh.2017.01.003)*

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Gastric cancer continues to remain a major source of morbidity and mortality throughout the world. Recent estimates have indicated that more 950,000 new cases of gastric cancer will be diagnosed per year, with more than 720,000 deaths, making gastric cancer the fifth most common cancer in the world and the third most common cause of cancer-related mortality.[1] Currently, the primary method for classification of gastric cancer is based on its histologic subtype.[2] Lauren's[3] criteria, the most commonly accepted histologic classification of gastric cancer, separates gastric cancer into 2 major subtypes: intestinal and diffuse. The World Health Organization produced an additional histologic classification for gastric cancer, separating these tumors into categories including tubular, papillary, mucinous, and poorly cohesive/signet ring.[4] Despite the ability to classify gastric cancer successfully using these histologic classifications, this information has not led to the development of histologic subtype-specific treatment options.

Over the past decade there have been countless advances in cancer therapy, and many of these gains are related to the development of more personalized therapies for cancer treatment. However, in gastric cancer, although some treatment studies have been successful, such as showing that postoperative chemoradiotherapy is more effective than surgery alone,[5] most of the efforts to develop more personalized therapies have proven unsuccessful.[6,7] Currently, the only widely used personalized therapy for gastric cancer involves treatment of metastatic human epidermal growth factor receptor 2 (HER2)-positive tumors with the HER2 antibody trastuzumab, the efficacy of which was shown in the Trastuzumab for Gastric Cancer study.[8] In this study, patients with metastatic HER2-overexpressing gastric cancers showed increased median overall survival when treated with trastuzumab plus standard chemotherapy compared with standard chemotherapy alone, which led to the approval of trastuzumab for the treatment of metastatic HER2-positive gastric cancer in 2013. Although the use of trastuzumab showed the potential for personalized therapy in gastric cancer, there certainly is room for improved therapeutic options. One way to potentially improve and personalize treatment paradigms for gastric cancer is to better understand the genomics of this disease.

Use of Next-Generation Sequencing to Better Define Gastric Cancer Genomics

Recently, genomic sequencing has become far less expensive, and also has become more efficient, developing even faster than comparable computer technology as predicted by Moore's Law.[9] This has led to next-generation sequencing (NGS) being increasingly used to study nearly all types of malignancies, and gastric cancer is no exception.[10] There have been 2 recent seminal reports that used NGS to

Abbreviations used in this paper: **ACRG, Asian Cancer Research Group; CIN, chromosomal instability; EBV, Epstein–Barr virus; EMT, epithelial-to-mesenchymal transition; GS, genomic stability; MSI, microsatellite instability; MSS, microsatellite stable; NGS, next-generation sequencing; PD-L, programmed death-ligand; RTK, receptor tyrosine kinase; TCGA, The Cancer Genome Atlas.**

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sequence large sets of gastric cancer samples to better characterize the genomics of gastric cancer, including a report from The Cancer Genome Atlas (TCGA)[11] as well as a separate study from the Asian Cancer Research Group (ACRG).[12] The TCGA study evaluated 295 treatment-naive primary gastric adenocarcinomas from multiple participating centers, where analysis included whole-exome sequencing, copy number analysis, DNA methylation and RNA analysis, microsatellite instability testing, and, on a select group of tumors, whole-genome sequencing.[11] The study from the ACRG examined 300 primary gastric adenocarcinomas from a single center in Seoul, South Korea.[12] This study used 49 gastric adenocarcinomas that previously underwent study with whole-genome sequencing[13] combined with 251 additional specimens, and then used a combination of gene expression profiling, targeted sequencing of genes of interest, as well as genome-wide copy number microarrays.[12] In addition to these 2 large studies, there also have been multiple smaller studies that have used NGS to better characterize the genomics of gastric cancer.[14–18] The plethora of data obtained from these recent NGS studies has helped define the genetic landscape of gastric cancer, has led to a contemporary approach to the development of genomically based molecular subtypes of gastric cancer, and has elucidated novel gastric cancer driver mutations, which all may lead to new perspectives on therapeutics.

Development of Genomically Based Molecular Classification Systems for Gastric Cancer

Genomic data have been used to develop molecular classification systems for many types of cancer including colorectal cancer[19] and pancreatic cancer.[20] Although classic classification criteria for gastric cancer has been histologically based (eg, Lauren's[3] and World Health Organization),[4] recent use of genomic data also has led to the development of novel molecular classification schemes for gastric cancer (Figure 1). First, the TCGA Research Network proposed a classification system that divides gastric cancers into 4 distinct subtypes: Epstein–Barr virus (EBV) positive, microsatellite instability (MSI), genomic stability (GS), and chromosomal instability (CIN).[11] EBV-positive tumors, which represented 9% of the tumors sequenced, showed significant CpG island methylator phenotype, as well as the highest levels of DNA hypermethylation.[11] This observed DNA hypermethylation was consistent with previous reports linking EBV-positive gastric cancers to DNA hypermethylation.[21] All tumors from this class showed *CDKN2A* (p16INK4A) promoter hypermethylation, but lacked hypermethylation of *MLH1*.[11] These tumors also had the highest rate (80%) of *PIK3CA* mutations, showed a high rate of *ARID1A* mutations (55%), and very infrequently showed any mutations in *TP53*. Another important characteristic of this group, for therapeutic purposes, was overexpression of programmed death-ligand (PD-L)1/2 in combination with increased immune cell signaling signatures. The second group included tumors with MSI, which resulted in significantly hypermutated tumors.[11] This group of tumors accounted for 22% of the total samples, and showed significant CpG island methylator phenotype, including hypermethylation of the *MLH1* promoter. Mutational analysis in this group identified a total of 37 significantly mutated genes including *TP53*, *KRAS*, *PIK3A*, and *ARID1A*, whereas there were only 25 significantly mutated genes in the non-MSI cancers. The remaining 69% of tumors from the TCGA group were divided based on the presence of extensive somatic copy number aberrations.[11] By using this branch point, the third group defined by the TCGA data is the GS group, which comprised 20% of the total samples.[11] This group of tumors comprised the majority of gastric cancers with diffuse histology, and also had the largest percentage of *CDH1* mutations consistent with the abundance of diffuse histology in this group. GS tumors also showed an increase in *RHOA* mutations and CLDN18–ARHGAP fusions, and increased expression of cell-adhesion pathway genes. Finally, comprising the remaining 50% of the tumors was the CIN group. This group showed marked aneuploidy as well as amplifications of receptor tyrosine kinases (RTKs). This

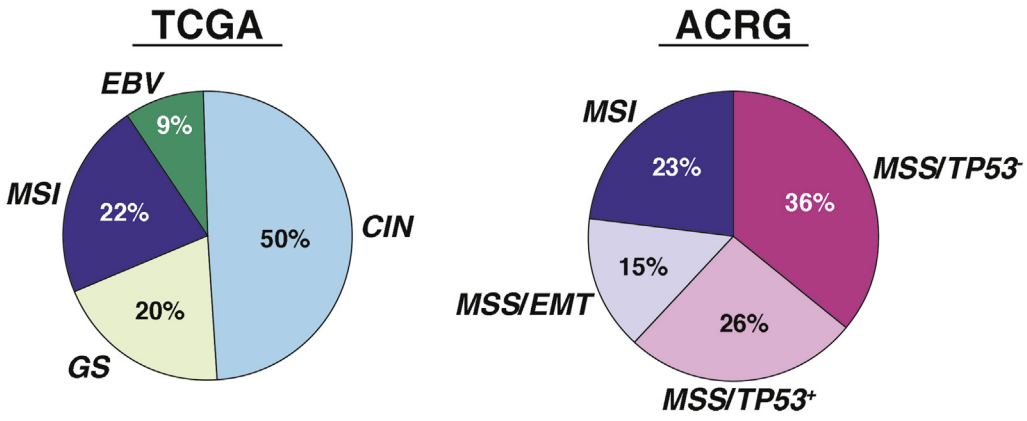

Figure 1. Molecular classifications of gastric cancers. TCGA molecular subtypes including EBV positive, MSI, GS, and CIN. ACRG molecular subtypes including MSI and MSS tumors with either MSS/EMT, *TP53* activity (MSS/TP53^{+}), or *TP53* inactivity (MSS/TP53^{-}). Percentages represent the fraction of molecularly characterized gastric cancer samples belonging to each subtype.