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Editorial

TCGA divides gastric cancer into four molecular subtypes: implications for individualized therapeutics

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Abstract

Gastric cancer is a leading cause of cancer deaths in the world. The treatment of gastric cancer is challenging because of its highly heterogeneous etiology and clinical characteristics. Recent genomic and molecular characterization of gastric cancer, especially the findings reported by the Cancer Genome Atlas (TCGA), have shed light on the heterogeneity and potential targeted therapeutics for four different subtypes of gastric cancer.

Gastric cancer caused 723,000 deaths in 2012 and is ranked as the third leading cause of cancer deaths. Many of the deaths happened in Asian countries, including China[1]. The incidence of gastric cancer is also rising in western countries. Gastric adenocarcinoma is a very heterogeneous cancer type and has traditionally been classified into intestinal and diffuse types according to the Lauren classification, or classified by alternative system, proposed by the World Health Organization. However, these traditional classification systems have demonstrated little clinical utility. The Cancer Genome Atlas (TCGA) network, funded by the United States National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), has undertaken gastric adenocarcinoma as one of the 25 major cancer types to be comprehensively characterized by state-of-the-art genomic platforms. Results from the impressive efforts of hundreds of multidisciplinary researchers were published online in *Nature* on July 23rd, 2014[2].

Using six genomic and molecular platforms including genome/exome/methylome DNA sequencing, RNA sequencing, and protein arrays and sophisticated statistical and informatics analyses of data from 295 tumors, the TCGA network classified gastric cancer into four subtypes: Epstein-Barr virus (EBV)-positive tumors, microsatellite instable (MSI) tumors, genomically stable (GS) tumors, and tumors with chromosomal instability (CIN). There will be a number of clinical impacts from this new classification[3].

The EBV subtype highlights the viral etiology of gastric cancer; the TCGA characterization of this subtype suggests potential therapeutic targets for this group of tumors. EBV was discovered 50 years ago from Burkitt's lymphoma. EBV is carried in the blood circulation without symptoms by 90% of the adult population. However, for reasons yet-to-be identified, EBV may affect epithelial cells and become carcinogenic. It is estimated that EBV is associated with 2% of all human tumors including nasopharyngeal carcinoma, another major cancer type that is unique for Chinese population especially in the southern areas of China such as Guangdong Province. In recent years, it has been increasingly recognized that the majority of gastric cancers are associated with infectious agents, including *H. pylori* and EBV. EBV is found within malignant epithelial cells in 9% of gastric cancers. The TCGA network reported that the EBV-positive gastric tumors cluster together and exhibit a higher prevalence of DNA hypermethylation [i.e., CpG island methylator phenotype (CIMP)] than any other cancers (e.g., colorectal cancer, endometrial cancer, and glioblastoma) reported by TCGA before[4-6]. Of therapeutic importance, there is a strong predilection for phosphatidylinositol 3-kinase, catalytic subunit alpha (*PIK3CA*) mutation in EBV-positive gastric cancers, with non-silent *PIK3CA* mutations found in 80% of this subgroup ($P < 0.001$). In contrast, tumors in other subtypes displayed fewer *PIK3CA* mutations (range from 3% to 42%). *PIK3CA* mutations in EBV-negative gastric cancers are mostly localized in the kinase domain (exon 20), but were more dispersed in EBV-positive gastric cancers. It will be very important for future work to evaluate how EBV-positive and -negative gastric cancers respond to the available PI3K inhibitors actively developed by pharmaceutical companies. TCGA analysis also showed that immunosuppressant proteins currently being evaluated as targets to augment antitumor immune response, such as programmed death ligand 1/2 (PD-L1/2), were elevated in

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EBV-positive tumors, suggesting that PD-L1/2 antagonists represent new therapeutic options for the EBV subtype of gastric cancer.

GS gastric cancers, another special subtype, are enriched for the diffuse histological variant. This subtype is characterized by mutations in the ras homolog gene family, member A (*RHOA*) gene or fusions involving Rho-family GTPase-activating proteins (GAP). The Rho family of GTPases regulates actomyosin dynamics and other cell functions, including adhesion, proliferation, and survival. Furthermore, the RhoA signaling pathway is strongly associated with the ability of tumor cells to invade and successfully establish metastases. TCGA network identified *RHOA* mutation in 16 cases of gastric cancer, and these were significantly enriched in the GS subtype. RhoA, when in the active guanosine triphosphate (GTP)-bound form, acts through a variety of effectors, including rho-associated coiled-coil-containing protein kinase 1 (ROCK1), mDia, and protein kinase N, to control actin-myosin-dependent cell contractility and cellular motility and to activate signal transducer and activator of transcription 3 (STAT3) to promote tumorigenesis. Structural mapping of *RHOA* mutations showed that the mutations were clustered in two adjacent amino-terminal regions that are predicted to be at the interface of RhoA with ROCK1 and other effectors. The mutations found in this study may act to activate downstream signaling of RhoA, a hypothesis validated by two recently published studies in *Nature Genetics*[7,8]. The importance of RhoA pathway in gastric cancer was further implicated by the discovery of recurrent structural genomic alterations. Whole genome sequencing of 107 tumors revealed numerous structural rearrangements, including 74 changes predicted to produce in-frame gene fusions. The *Nature* paper reports two cases with an interchromosomal translocation between CLDN18 and Rho GTPase activating protein 26 [ARHGAP26; also known as GTPase regulator associated with focal adhesion kinase (GRAF)], a GAP that facilitates conversion of Rho GTPases to the GDP state to enhance cellular motility. CLDN18 is a protein involved in cell-cell tight junction adhesion. RNA sequencing data from tumors identified CLDN18-ARHGAP26 fusion in nine additional tumors, and two of these tumors showed CLDN18-ARHGAP26 fusion. Realization of the key mutations and gene fusions in this subtype is important information for future drug development to counter this group of cancers.

TCGA revealed interesting findings from the MSI subtype of gastric cancer as well. In contrast to what was found in MSI colorectal cancer, *BRAF V600E* mutations were not found. However, targetable mutations in *PIK3CA*, *ERBB3*, *ERBB2,* and epidermal growth factor receptor (*EGFR*) were identified. In the CIN subtype of gastric cancer, TCGA network identified genomic amplifications of receptor tyrosine kinases (RTKs), many of which are targetable. Angiogenesis may be highly relevant to CIN subtype based on the recurrent amplification of vascular endothelial growth factor A (*VEGFA*) gene. The VEGFR2 targeting antibody ramucirumab has shown antitumor effects on gastric cancer[9]. It will be interesting to investigate whether the response to ramucirumab is predicted by the *VEGFA* amplification.

Clinicians should be highly encouraged by the four major genomic subtypes defined by TCGA that show distinct salient genomic features, providing a guide to targeted agents that should be evaluated in clinical trials for distinct populations of gastric cancer patients. It should also be noted that much work is needed to fully understand the clinical impact of this new classification and the mutations found in different subtypes of gastric cancer. A major unfulfilled task is to determine the clinical associations of the molecular signatures because most cases in the TCGA cohort lacked sufficient clinical follow-up data; thus the important survival analysis and chemotherapy response analysis could not be done by the network. Another issue for Chinese doctors is that the TCGA cohort is mainly from non-Asian population. How the TCGA findings impact the clinical practice in China needs investigations on Chinese patients with gastric cancers, which may have unique etiology. Nevertheless, the TCGA report is expected to provide valuable foundation and motivation to explore and refine molecular classification and tailored therapies to significantly decrease mortality and improve survival of patients with gastric cancers. The fact that *RHOA* mutations were also found in Asian populations with gastric cancer, reported by two recent *Nature Genetics* papers[7,8], is a reason for such an optimistic outlook.

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