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Opinion

How Can Gastric Cancer Molecular Profiling Guide Future Therapies?

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Gastric cancer is the third greatest global cause of cancer-related deaths. Despite its high prevalence, only recently have comprehensive genomic surveys shed light on its molecular alterations. As surgery is the only curative treatment strategy and chemotherapy has shown limited efficacy, new treatments are urgently needed. Many molecular therapies for gastric cancer have entered clinical trials but–apart from Trastuzumab and Ramucirumab–all have failed. We analyze the current knowledge of the genetic 'landscape' of gastric cancers, elaborating on novel, preclinical approaches. We posit that this knowledge lays the basis for identifying *bona fide* molecular targets and developing solid therapeutic approaches, requiring accurate patient selection and taking advantage of preclinical models to assist clinical development of novel combination strategies.

Pathological Classifications of Gastric Carcinomas

In spite of decreasing incidence and mortality in the past decades, gastric cancer still remains one of the most common causes of cancer-related death [1]. Globally, gastric cancer accounts for 989 600 new cases and 738 000 deaths each year, with a case fatality ratio of 0.75 [2]. Incidence is strongly influenced by ethnic and geographical factors: it is higher in Eastern Asia, Eastern Europe, and South America, while North America and Africa show the lowest rates [3]. In Europe, stomach cancer is the fifth most common cancer with 159 900 new cases and 118 200 deaths reported in 2006 [4].

Epidemiologically, dietary factors and ***Helicobacter pylori*** (see Glossary) infection are among the major risk factors for the development of distal tumors, while those for proximal cancers include gastroesophageal reflux disease and obesity [5].

Proximal/gastroesophageal junction tumors are usually associated with inflammation due to chronic gastric acid/bile reflux. Inflammation is characteristically absent in the development of gastric cancer resulting from germline mutations in the human cadherin 1 gene (*CDH1*) [6]. A role for the **Epstein–Barr virus** (**EBV**; whose genome can be identified in tumor cells) has also been demonstrated [7] (Box 1). Approximately 80–90% of gastric carcinomas develop in a sporadic setting, and the remaining show familial clustering, with approximately 1–3% exhibiting a clear inherited genetic susceptibility [6].

Two main classifications are used to define gastric adenocarcinomas: (i) the World Health Organization (WHO) classification recognizes four histological subtypes (papillary, tubular, mucinous, and poorly cohesive) and (ii) the Lauren classification identifies intestinal, diffuse, or mixed subtypes [8]. Neither the WHO nor the Lauren classification systems are particularly clinically useful, as their prognostic and predictive capabilities cannot adequately guide patient management. Therefore, at present, the histopathological, anatomical, and epidemiological

Trends

Gastric cancer is the third leading cause of cancer mortality worldwide. Surgery is the only curative treatment strategy and conventional chemotherapy has shown limited efficacy, with a median overall survival of 10 months.

Trastuzumab and Ramucirumab (targeting HER2 and VEGFR, respectively) are currently the only gastric cancer approved targeted therapies; hence, new treatments are urgently needed.

Despite the high prevalence of gastric cancer, very few comprehensive genomic surveys have been performed to date.

Recently, the Cancer Genome Atlas (TCGA) Research Network and the Asian Cancer Research Group (ACRG) separately reported two Gastric Cancer whole genome molecular profiling analyses, proposing two new molecular classifications for gastric malignancies.

Given that the use of targeted therapies in gastric tumors is much less common than in other cancers, the reported data represent a critical starting point to design more appropriate clinical trials based on the principles of precision medicine.

Starting from available molecular data, recent preclinical models (tumor-derived cell lines, organoids, and PDXs) should complement clinical investigations, so as to facilitate the development of targeted therapeutic approaches.

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Box 1. Role of Epstein–Barr Virus in Epithelial Tumors

EBV-associated epithelial cancer (characterized by the presence of an integrated EBV genome) represents approximately 80% of EBV-associated neoplasms [55]. The most frequent neoplasms are nasopharyngeal carcinoma (89%) and gastric cancer (10%). EBV is not sufficient to induce the full malignant transformation but is believed to impart the first 'hit' to the process. In fact, the presence of a clonal EBV genome in tumor cells indicates that viral infection takes place at the beginning of the tumorigenic process. P16 inactivation (commonly found in EBV+ tumors) is required to allow persistent EBV inactivation in epithelial cells, eliciting clonal expansion of EBV-infected cells [56]. Another common event in EBV+ tumors is PDL1/2 overexpression that underlines the role of immune evasion for progression of these tumors. Finally, EBV + tumors are rarely associated with p53 mutations, which are otherwise very common in EBV– tumors of the same histotype [11].

distinctions are not taken into account in the clinical management of the disease, either initially for potentially curative treatment, or, palliatively, for advanced disease.

While the identification of specific molecular phenotypes in other epithelial malignancies has had profound implications for treatment strategies, this has had a much lower impact on gastric cancer. As molecular alterations of drug-targeted genes are fairly frequent [9,10], research performed in preclinical models could help identify actual tumor drivers along with the best therapeutic options.

TCGA (The Cancer Genome Atlas) Molecular Characterization of Gastric Adenocarcinomas

Recently, owing to new technological platforms, molecular landscapes of gastric cancer have been explored and two new classifications have been proposed [11]. The **TCGA** Research Network has characterized 295 primary gastric adenocarcinomas using six molecular platforms (evaluating somatic copy number alterations, whole exome sequencing, mRNA and miRNA sequencing, DNA methylation analysis, and phosphoproteomics). Their integrated analysis has allowed the identification of four molecularly distinct subtypes (Figure 1).

The first group (9% of gastric adenocarcinomas) was significantly enriched in EBV burden and was characterized by extensive DNA promoter hypermethylation (typically associated with silencing of specific genes). Interestingly, the methylation profile was different from that observed in the **microsatellite instability** (**MSI**) subtype, with several genes differentially silenced [e.g., *MLH1* (MutI homolog 1), a key component of the DNA mismatch repair system, which is hypermethylated in MSI tumors but not in EBV+ tumors]. Interestingly, the EBV subtype showed the highest frequency of *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α) mutations (80% of cases), dispersed along the sequence and common to those present in the TCGA dataset or in the **COSMIC** (**Catalogue Of Somatic Mutations In Cancer**) repository, in 68% of the cases [11]. Other common alterations or mutations were found in *ARID1A* (AT-rich interaction domain 1A gene, 55%) and in *BCOR* (BCL6 corepressor gene, 23%), plus the amplification of a locus containing JAK2 (Janus kinase) and PDL1/2 (Programmed cell death 1 ligand 1 and 2; **inhibitory immune checkpoint**) genes (15%). This latter observation can be functionally coupled with the finding that strong IL-12 mediated signaling molecular signatures were identified, suggestive of a robust presence and/or communication/with immune cells in these biopsies. Consequently, targeting PI3K and inhibitory immune checkpoints may indeed yield important therapeutic targeting options.

The second group was enriched for MSI (22% of gastric adenocarcinomas), presenting elevated mutation rate and hypermethylation [11]. Mutations of kinases such as *EGFR* (5%), *HER2* (5%), *HER3* (14%), *JAK2* (11%), *FGFR2* (2%), *MET* (3%), and *PIK3CA* (42%) were present. Interestingly, MSI tumors revealed common alterations in major histocompatibility complex class I genes, such as *B2M* and *HLA-B*, potentially suggesting reduced tumor antigen presentation to cells of the immune system.