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Unraveling the Complexity of Gastric Cancer through TCGA Subtypes

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ABSTRACT

Gastric cancer remains a significant global health burden, characterized by high heterogeneity. The Cancer Genome Atlas (TCGA) has been pivotal in classifying gastric cancer into distinct molecular subtypes, providing profound insights into its pathogenesis, prognosis, and potential therapeutic strategies. This review comprehensively explores the four TCGA - defined subtypes of gastric cancer: Epstein - Barr Virus (EBV) - positive, Microsatellite unstable (MSI), Genomically Stable (GS), and Chromosomally Unstable (CIN). By dissecting the unique molecular, genetic, and clinical features of each subtype, we aim to elucidate how this classification can enhance our understanding of gastric cancer and drive the development of more personalized treatment approaches.

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Introduction

Gastric cancer ranks among the leading causes of cancer-related deaths worldwide, with a complex etiology influenced by genetic, environmental, and infectious factors. Traditional classification systems, such as the Lauren classification (intestinal and diffuse types) and the World Health Organization's histological classification, have limitations in predicting disease behavior and guiding treatment. The advent of high - throughput genomic technologies, facilitated by initiatives like TCGA, has revolutionized our understanding of gastric cancer heterogeneity at the molecular level. Identifying distinct molecular subtypes not only deepens our knowledge of the underlying biology but also offers the promise of more targeted and effective therapies.

TCGA - Defined Subtypes of Gastric Cancer

EBV - Positive Subtype

Molecular Features

The EBV - positive subtype accounts for approximately 9% of gastric cancers. These tumors are characterized by a high frequency of phosphatidylinositol 3 - kinase, catalytic subunit alpha (PIK3CA) mutations, with non - silent mutations present in about 80% of cases [1,2]. There is also extreme DNA hypermethylation, particularly in CpG island methylator phenotype (CIMP), and amplification of genes such as Janus kinase 2 (JAK2), programmed death ligand 1 (PD - L1, encoded by CD274), and programmed death ligand 2 (PD - L2, encoded by PDCD1LG2). In contrast, mutations in the tumor suppressor gene TP53 are rare in this subtype [3,4].

Clinical Implications

EBV - positive gastric cancers are more common in males and often occur in the gastric fundus and body. They tend to have a better prognosis compared to some other subtypes, potentially due to their unique molecular profile and distinct tumor - immune microenvironment. The overexpression of PD - L1 and PD - L2 suggests that these tumors may be sensitive to immune checkpoint inhibitor therapies, which are designed to block the immunosuppressive signals and enhance the anti - tumor immune response. Several ongoing clinical trials are exploring the efficacy of PD - L1/PD - L2 antagonists in treating EBV - positive gastric cancer patients [5,6].

MSI Subtype

Molecular Features

The MSI subtype represents around 22% of gastric cancers. It is characterized by a high mutation rate, especially in genes encoding oncogenic signaling proteins. Mutations in PIK3CA, ERBB2, ERBB3, and Epidermal Growth Factor Receptor (EGFR) are frequently observed. The underlying cause of MSI is often the hypermethylation of the MLH1 gene promoter, leading to the silencing of the MLH1 mismatch - repair protein. This results in the accumulation of mutations in repetitive DNA sequences throughout the genome.

Clinical Implications

MSI - positive gastric cancers are more prevalent in elderly females and are often located in the gastric antrum or pylorus. The high mutation burden in these tumors generates a large number of neoantigens, making them highly immunogenic. Immunotherapy, particularly immune checkpoint blockade, has shown promising results in treating MSI - high cancers across various tumor types, including gastric cancer [7,8]. However, not all MSI - positive gastric cancer patients respond equally to immunotherapy, and further research is needed to identify biomarkers that can predict treatment response.

GS Subtype

Molecular Features

The GS subtype, accounting for about 20% of gastric cancers, is enriched for the diffuse histological variant. It is characterized by mutations in the Ras Homolog Gene Family, Member A (RHOA) or fusions involving RHO - family GTPase - activating proteins (GAP), such as the CLDN18 - ARHGAP fusion. Mutations in CDH1, which encodes E - cadherin and is crucial for cell - cell adhesion, are also relatively common in this subtype. The RHOA signaling pathway, which regulates actomyosin dynamics and cell functions like adhesion, proliferation, and survival, is dysregulated in GS tumors [9].

Clinical Implications

GS - type gastric cancers often present at a younger age compared to other subtypes. Due to the lack of highly targetable driver mutations and relatively low immunogenicity, these tumors have been challenging to treat. Traditional cytotoxic chemotherapy has been the mainstay of treatment, but the prognosis for GS - subtype patients remains poor. However, ongoing research is exploring novel therapeutic strategies, such as targeting the RHOA pathway or combining chemotherapy with emerging targeted agents [10].

CIN Subtype

Molecular Features

The CIN subtype is the most common, comprising approximately 50% of gastric cancers. It is characterized by significant aneuploidy and focal amplification of receptor tyrosine kinases, including Vascular Endothelial Growth Factor A (VEGFA), EGFR, ERBB2, ERBB3, and c - met. Mutations in the TP53 gene are highly prevalent, occurring in about 73% of cases. Additionally, genes related to cell - cycle regulation, such as CCNE1, CCND1, and CDK6, are often amplified.

Clinical Implications

CIN - subtype gastric cancers are frequently found in the gastroesophageal junction and cardia and are more common in the elderly. The amplification of VEGFA and other receptor tyrosine kinases makes these tumors potential candidates for targeted therapies. For example, anti - VEGFR2 monoclonal antibodies, such as ramucirumab, have shown some efficacy in treating CIN-subtype gastric cancer patients, especially in combination with chemotherapy. However, the development of resistance to these targeted agents remains a major challenge [11].

Prognostic Significance of TCGA Subtypes

The TCGA - defined subtypes have distinct prognostic implications. EBV - positive tumors generally have a better prognosis, potentially due to the immunogenicity associated with EBV infection and the potential sensitivity to immunotherapy. MSI - positive tumors also tend to have a relatively favorable prognosis compared to some other subtypes, mainly attributed to their high immunogenicity and response to immune checkpoint blockade. In contrast, the GS subtype has a poor prognosis, likely due to the lack of effective targeted therapies and its aggressive biological behavior. The prognosis of the CIN subtype is variable, with some patients responding well to chemotherapy and targeted therapies, while others experience rapid disease progression. Understanding these prognostic differences can help clinicians in counseling patients and tailoring treatment plans [12].

Therapeutic Implications

Immunotherapy

The identification of EBV - positive and MSI - high subtypes has opened new avenues for immunotherapy in gastric cancer. Immunotherapy drugs, such as anti - PD - 1 and anti - PD - L1 antibodies, have shown promising results in treating these subtypes. For EBV - positive tumors, the overexpression of PD - L1 and PD - L2 makes them prime candidates for immune checkpoint blockade. In MSI - high gastric cancers, the high mutation burden leads to the generation of neoantigens, which can be recognized by the immune system, making immunotherapy an effective treatment option. However, challenges remain, including the identification of predictive biomarkers to select patients who are most likely to respond to immunotherapy and the management of immune - related adverse events [13].

Targeted Therapies

For the CIN subtype, the amplification of receptor tyrosine kinases provides potential targets for targeted therapies. Drugs like ramucirumab, which targets VEGFR2, and trastuzumab, which targets HER2 (ERBB2), have been used in the treatment of CIN - subtype gastric cancers with HER2 amplification. In the GS subtype, although currently there are no standard targeted therapies, ongoing research is exploring the targeting of the RHOA pathway. Inhibitors that can disrupt the abnormal RHOA signaling may hold promise for treating GS - subtype tumors.

Challenges and Future Directions

Heterogeneity within Subtypes

Despite the classification into four subtypes, there is still significant heterogeneity within each subtype. For example, not all EBV - positive tumors respond equally to immunotherapy, and there may be differences in the molecular profiles and treatment responses even within the same subtype. Further research is needed to identify sub - subgroups within the TCGA - defined subtypes to better understand this heterogeneity and develop more personalized treatment strategies.

Biomarker Discovery

The identification of reliable biomarkers that can predict treatment response and prognosis for each subtype is crucial. Currently, while PD - L1 expression is used as a biomarker for immunotherapy in some cases, it is not a perfect predictor. New biomarkers, such as tumor - Infiltrating Lymphocyte (TIL) counts, neoantigen load, and gene expression signatures, are being investigated to improve patient selection for different treatment modalities.

Combination Therapies

Combining different treatment modalities, such as immunotherapy with chemotherapy, targeted therapy, or radiotherapy, may enhance treatment efficacy. For example, in CIN - subtype gastric cancers, combining anti - VEGFR2 therapy with chemotherapy has shown improved outcomes. Future research should focus on optimizing combination therapies for each TCGA subtype to improve patient survival and quality of life.

Conclusion

The TCGA - defined molecular subtypes of gastric cancer have significantly advanced our understanding of the disease. By recognizing the unique molecular, genetic, and clinical characteristics of the EBV - positive, MSI, GS, and CIN subtypes, we can develop more personalized treatment strategies. Immunotherapy and targeted therapies, tailored to the specific features of each subtype, hold great promise for improving the prognosis of gastric cancer patients. However, challenges related to heterogeneity, biomarker discovery, and treatment resistance need to be overcome. Continued research in this area is essential to translate the knowledge of TCGA subtypes into improved clinical outcomes for gastric cancer patients.

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