Genetic and molecular pathogenesis of glioblastoma multiforme.

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Introduction

Glioblastoma multiforme (GBM) is an aggressive and highly malignant brain tumor that affects thousands of individuals worldwide. Despite significant advances in cancer research, GBM remains one of the most challenging cancers to treat, with a median survival of around 15 months. Understanding the genetic and molecular pathogenesis of GBM is crucial for developing effective therapies and improving patient outcomes. In this article, we delve into the intricate world of GBM's genetic and molecular landscape, shedding light on its underlying complexity.

Genetic alterations in glioblastoma multiforme

Genomic studies have revealed a wide range of genetic alterations in GBM, highlighting the heterogeneity and complexity of this disease. The most common genetic alterations observed in GBM involve tumor suppressor genes, oncogenes, and epigenetic modifications. The tumor suppressor gene TP53, which regulates cell division and prevents the formation of tumors, is frequently mutated in GBM, leading to uncontrolled cell growth and tumor development. Another tumor suppressor gene, PTEN, is often inactivated or deleted in GBM, resulting in increased cell proliferation and reduced cell death [1].

Oncogenes such as EGFR (epidermal growth factor receptor) play a critical role in GBM pathogenesis. Amplification and mutation of EGFR are commonly observed in GBM, leading to excessive activation of downstream signaling pathways that promote cell survival, proliferation, and invasion. Additionally, mutations in other oncogenes, such as PIK3CA and PDGFRA, are also prevalent in GBM, further contributing to tumor growth and progression.

Epigenetic modifications

In addition to genetic alterations, epigenetic modifications play a crucial role in GBM development. Epigenetics refers to changes in gene expression that occur without alterations to the underlying DNA sequence. DNA methylation, histone modifications, and non-coding RNA molecules are key players in the epigenetic regulation of gene expression. Promoter methylation of tumor suppressor genes, such as MGMT (O6-methylguanine-DNA methyltransferase), is a frequent epigenetic alteration in GBM. Methylation of the MGMT promoter reduces the expression of this DNA repair enzyme, making tumor cells more susceptible to DNA damage caused by chemotherapy agents like temozolomide. Other genes involved in cell cycle control, DNA repair, and apoptosis are also commonly affected by DNA methylation in GBM [2].

Histone modifications, including acetylation, methylation, and phosphorylation, dynamically regulate gene expression. Aberrant histone modifications have been observed in GBM, leading to altered chromatin structure and gene dysregulation. For instance, the histone methyltransferase EZH2, which catalyzes the addition of methyl groups to histones, is often overexpressed in GBM, contributing to the silencing of tumor suppressor genes and promoting tumor growth. Non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as critical regulators of gene expression. Dysregulation of miRNAs in GBM affects various signaling pathways involved in cell proliferation, invasion, and apoptosis. Similarly, lncRNAs play diverse roles in GBM pathogenesis, acting as oncogenes or tumor suppressors depending on their targets and functions [3].

Molecular signaling pathways

Multiple molecular signaling pathways are dysregulated in GBM, contributing to its aggressive nature. The phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR pathway is frequently activated in GBM, promoting cell growth, survival, and angiogenesis. The Ras/Raf /MEK/ERK pathway, another key signaling cascade, is also commonly altered in GBM. Activation of this pathway leads to increased cell proliferation, survival, and invasion. The Notch signaling pathway plays a crucial role in normal brain development but is often dysregulated in GBM. Aberrant Notch signaling promotes the self-renewal of cancer stem-like cells, contributing to tumor initiation, recurrence, and therapy resistance. Similarly, the Wnt/β-catenin pathway, which regulates cell fate and proliferation, is frequently activated in GBM, driving tumor growth and invasion. The tumor microenvironment also plays a significant role in GBM pathogenesis. Interactions between tumor cells and various cellular components, such as immune cells, endothelial cells, and stromal cells, shape the tumor microenvironment and influence tumor progression. In GBM, immune evasion mechanisms and an immunosuppressive microenvironment hinder effective antitumor immune responses, allowing tumor cells to escape immune surveillance and promote tumor growth [4].

Emerging therapeutic strategies

Understanding the genetic and molecular pathogenesis of GBM has paved the way for the development of targeted therapies aimed at specific alterations in tumor cells. Targeted

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therapies focus on inhibiting or modulating the activity of specific molecules or pathways critical for tumor growth and survival. For example, inhibitors targeting EGFR, such as erlotinib and gefitinib, have been explored in clinical trials for GBM treatment. However, the efficacy of single-agent targeted therapies has been limited, partly due to the extensive heterogeneity and redundant signaling networks in GBM [5].

Conclusion

The genetic and molecular pathogenesis of GBM is a complex and multifaceted process involving a wide array of genetic alterations, epigenetic modifications, and dysregulated signaling pathways. The heterogeneity and plasticity of GBM tumors pose significant challenges for effective treatment strategies. However, advancements in genomic profiling, molecular characterization, and targeted therapies offer hope for improved patient outcomes.

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