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Short Communication

Molecular Mechanisms and Genetic Alterations in Glioblastoma

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DESCRIPTION

Glioblastoma represents a highly aggressive form of brain tumour with a complex molecular landscape that contributes to its rapid progression and resistance to therapy. At the core of its biology are genetic and epigenetic alterations that disrupt normal cellular regulatory mechanisms, allowing uncontrolled growth, invasion into surrounding tissue and evasion of cell death pathways. Understanding these molecular mechanisms is critical for the development of more effective therapies and for tailoring treatment strategies based on individual tumour profiles. One of the most common genetic changes in glioblastoma involves amplification or mutation of the Epidermal Growth Factor Receptor (EGFR) gene. EGFR signalling plays a central role in regulating cell proliferation, survival and migration. Alterations in this pathway lead to persistent activation of downstream signalling cascades, including the PI3K/AKT/mTOR and RAS/MAPK pathways, which support tumour cell survival and resistance to apoptosis. In addition, Epidermal Growth Factor Receptor Variant III (EGFRvIII), a variant resulting from a deletion in the extracellular domain of the receptor, is frequently observed in glioblastoma and contributes to aggressive growth and therapeutic resistance [1-3].

Mutations in tumour suppressor genes such as Tumor Suppressor Gene (TP53) and Phosphatase and Tensin Homolog deleted on Chromosome 10 (PTEN) are also critical in glioblastoma pathogenesis. TP53 encodes a protein that monitors DNA integrity and induces apoptosis in cells with genetic damage. Loss or inactivation of *TP53* allows the accumulation of mutations, promoting tumour progression. PTEN is a negative regulator of the *PI3K/AKT* pathway and its loss results in hyper activation of proliferative signalling, enhancing cell survival and contributing to therapeutic resistance. Additional alterations in genes such as *RB1*, *NF1* and *CDKN2A* further disrupt cell cycle control, promoting unregulated proliferation. Epigenetic changes, including DNA methylation and histone modification, play an important role in glioblastoma biology. Methylation of the O (6)-Methyl Guanine-DNA-Methyl Transferase (MGMT) gene promoter reduces the expression of the DNA repair enzyme O6-methylguanine-DNA methyl transferase, increasing tumour sensitivity to alkylating agents such as temozolomide. Conversely, methylated MGMT is associated with reduced treatment response and poorer prognosis. Global patterns of DNA methylation also influence gene expression networks that regulate stemness, differentiation and invasive behavior. Histone modifications contribute to chromatin remodelling, further altering transcriptional programs and supporting the malignant phenotype [4-7].

Glioblastomas exhibit substantial intratumoral heterogeneity, with subpopulations of cells showing distinct genetic and molecular profiles. This heterogeneity underlies variable responses to therapy and contributes to recurrence following treatment. Tumour stem-like cells, identified by specific molecular markers, possess the ability to self-renew and repopulate the tumour after cytotoxic therapy, making them a major obstacle to long-term disease control. These cells often reside in hypoxic niches, where micro environmental factors support their survival and resistance to conventional therapies. Recent research has highlighted the role of non-coding RNAs, including microRNAs and long non-coding RNAs, in regulating glioblastoma biology. These molecules modulate gene expression post-transcriptionally, influencing pathways involved in proliferation, invasion, angiogenesis and immune evasion. Altered microRNA expression can contribute to tumour progression and some non-coding RNAs have emerged as potential biomarkers for diagnosis, prognosis and therapeutic targeting. Angiogenesis is another defining feature of glioblastoma. Tumour cells secrete Vascular Endothelial Growth Factor (VEGF) and other pro-angiogenic factors to stimulate the growth of new blood vessels, ensuring an adequate supply of oxygen and nutrients to support rapid growth. The resulting vascular network is often abnormal, with leaky vessels contributing to edema and elevated intracranial pressure. Anti-angiogenic therapies targeting VEGF pathways have been explored as treatment options, although resistance frequently develops due to compensatory mechanisms within the tumour microenvironment. Molecular profiling has enabled the

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classification of glioblastoma into subtypes based on gene expression patterns, including classical, mesenchymal, proneural and neural. Each subtype exhibits distinct molecular alterations and clinical behavior. The proneural subtype, often observed in younger patients, is associated with mutations in PDGFRA and IDH1 and may have a more favorable prognosis, while the mesenchymal subtype demonstrates increased invasiveness, inflammatory signalling and poorer outcomes. Understanding these subtypes helps refine therapeutic strategies and informs clinical decision-making [8].

In summary, glioblastoma is driven by a network of genetic, epigenetic and micro environmental factors that collectively support uncontrolled growth, invasion and resistance to therapy. Mutations in oncogenes and tumour suppressor genes, epigenetic alterations and angiogenic signalling converge to create a highly aggressive and heterogeneous tumour. Advances in molecular characterization provide insight into disease mechanisms, enable subtype classification and offer potential avenues for targeted therapies. Continued investigation into these pathways is essential to develop more effective treatments and improve outcomes for patients affected by this formidable brain tumour [9,10].

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