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Harnessing the role of aberrant cell signaling pathways in glioblastoma multiforme: a prospect towards the targeted therapy

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Abstract

Glioblastoma Multiforme (GBM), designated as grade IV by the World Health Organization, is the most aggressive and challenging brain tumor within the central nervous system. Around 80% of GBM patients have a poor prognosis, with a median survival of 12-15 months. Approximately 90% of GBM cases originate from normal glial cells via oncogenic processes, while the remainder arise from low-grade tumors. GBM is notorious for its heterogeneity, high recurrence rates, invasiveness, and aggressive behavior. Its malignancy is driven by increased invasive migration, proliferation, angiogenesis, and reduced apoptosis. Throughout various stages of central nervous system (CNS) development, pivotal signaling pathways, including Wnt/β-catenin, Sonic hedgehog signaling (Shh), PI3K/AKT/mTOR, Ras/Raf/MAPK/ERK, STAT3, NF-KB, TGF-β, and Notch signaling, orchestrate the growth, proliferation, differentiation, and migration of neural progenitor cells in the brain. Numerous upstream and downstream regulators within these signaling pathways have been identified as significant contributors to the development of human malignancies. Disruptions or aberrant activations in these pathways are linked to gliomagenesis, enhancing the invasiveness, progression, and aggressiveness of GBM, along with epithelial to mesenchymal transition (EMT) and the presence of glioma stem cells (GSCs). Traditional GBM treatment involves surgery, radiotherapy, and chemotherapy with Temozolomide (TMZ). However, most patients experience tumor recurrence, leading to low survival rates. This review provides an overview of the major cell signaling pathways involved in gliomagenesis. Furthermore, we explore the signaling pathways leading to therapy resistance and target key molecules within these signaling pathways, paving the way for the development of novel therapeutic approaches.

Keywords: Cell signaling pathways; Glioblastoma Multiforme; Notch; PI3K; TGF-β; Targeted therapy; Wnt/β-catenin.