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Targeting EGFR and PI3K/mTOR pathways in glioblastoma: innovative therapeutic approaches

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Abstract

Glioblastoma (GBM) stands as the most aggressive form of primary brain cancer in adults, characterized by its rapid growth, invasive nature, and a robust propensity to induce angiogenesis, forming new blood vessels to sustain its expansion. GBM arises from astrocytes, star-shaped glial cells, and despite significant progress in understanding its molecular mechanisms, its prognosis remains grim. It is frequently associated with mutations or overexpression of the epidermal growth factor receptor (EGFR), which initiates several downstream signaling pathways. Dysregulation of key signaling pathways, such as EGFR/PTEN/AKT/mTOR, drives tumorigenesis, promotes metastasis and leads to treatment resistance. The modest survival benefits of the conventional treatment of surgical resection followed by radiation and chemotherapy underscore the pressing need for innovative therapeutic approaches. In most the tumor, overexpression of EGFR is found associated with GBM and mutations in its several variants are important for promoting ongoing mitogenic signaling and tumor growth. This receptor inhibits apoptosis and promotes cell survival and proliferation by activating downstream PI3K/AKT/mTOR pathways. This route is typically blocked by PTEN, a crucial tumor suppressor, however, GBM frequently results in abnormalities in this protein. The aim of this review is to explore the molecular foundations of GBM, with a focus on the EGFR and PI3K/mTOR pathways and their impact on tumor behavior. Additionally, this review highlights EGFR and PI3K/AKT/mTOR inhibitors currently in clinical and preclinical trials, addressing treatment resistance, challenges, and future directions.

Keywords: Angiogenesis; EGRF; Glioblastoma; MTOR; PI3K; PTEN.