Advances in the Mechanism of PI3K Signaling Pathway in Glioblastoma

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Abstract: Glioblastoma (GBM), classified as a WHO Group IV astrocytoma, is the most common highly malignant glioma in adults, accounting for 50% -55% of neuroectodermal-derived tumors. It is characterized by aggressive behavior, high recurrence rates, and extremely poor prognosis [1]. The phosphatidylinositol 3-kinase (PI3K) signaling pathway, functioning as a core regulatory network within cells, shows abnormal activation in 88% of GBM cases. This pathway plays a crucial role in tumor progression by regulating key biological processes including cell proliferation, metabolism, migration, and drug resistance [2]. Recent advancements in molecular biology have deepened our understanding of PI3K's mechanisms in GBM, particularly in subtype-specific functions, non-classical signaling pathways, and therapeutic target development. This systematic review examines the composition and activation modes of the PI3K signaling pathway, its core mechanisms in GBM, and recent progress in targeted therapies, aiming to provide theoretical foundations for precision treatment strategies in this challenging disease.

Keywords: Glioblastoma; PI3K Signaling Pathway; Therapeutic Target

1. Epidemiology and Targeted Therapy of Glioblastoma

1.1 Epidemiology of Glioblastoma

Gliomas are among the most common primary tumors in the centralnervoussystem (CNS), classified by the World Health Organization (WHO) into grades I (most benign) to IV (most aggressive) [3]. Approximately 50% of gliomas manifest as grade IV glioblastoma (GBM), the most aggressive form [4]. According to WHO, glioblastoma is defined as a diffuse astrocytic tumor with wild-type isocitratedehydrogenase (IDH) mutation, while astrocytomas (IDH mutant) grades II, III, or IV are now recognized as distinct categories. GBM accounts for about 15% of all brain tumors, primarily affecting adults aged 45-70. Breakthrough clinical studies show that the median survival with radiotherapy (RT) plus trivalent-methylazone (TMZ) is 14.6 months, compared to 12.1 months with RT alone [5]. The median overallsurvival (OS) is only 15 months, with just 7.2% of patients surviving beyond five years post-diagnosis. The International Case-Control Study on Gliomas reported that daily aspirin intake for over six months can reduce glioma risk by 38%. Another study evaluated the risk of glioma in 325 cases and 600 frequency-matched controls from the Houston metropolitan area (2001-2006), revealing that regular NSAID use was associated with a 33% reduction in glioma risk [6]. Additionally, epidemiological studies found gender differences in glioblastoma incidence, with male patients significantly outnumbering females at a ratio of approximately 1.5:1 [7]. These disparities may be linked to multiple factors including hormone levels, genetic susceptibility, and lifestyle. These findings provide new insights into the pathogenesis of glioblastoma and establish

a theoretical foundation for developing targeted treatment strategies

1.2 Targeted Therapy for Glioblastoma

As a highly vascular tumor, glioblastoma is characterized by excessive vascular endothelial growth factor (VEGF) expression. Bevacizumab, a monoclonal antibody targeting VEGF-A, has been studied in multiple large-scale clinical trials for glioblastoma, but research results confirmed no benefit for overall survival (OS) [8]. However, bevacizumab exhibits steroid-like anti-edema effects, reducing steroid dependence and thereby alleviating immunosuppression [9]. Administration of dexamethasone during vaccine initiation may induce systemic depletion of memory and initial CD4/CD8T cells, leading to treatment failure. In such cases, bevacizumab warrants re-evaluation, particularly given its potential to decrease reliance on immunosuppressive corticosteroids [10]. Given VEGF's status as an ideal target for glioblastoma, numerous trials have investigated VEGF or multi-kinase tyrosine kinase inhibitors (TKIs) targeting the tumor microenvironment (TME). Cediranib, an oral VEGF TKI, demonstrated no survival benefit in randomized Phase III trials, whether administered as monotherapy or in combination with lomustine for recurrent glioblastoma [11]. Trials of other agents like tivozanib, pazopanib, and sunitinib showed minimal efficacy, indicating limited effectiveness of VEGF monotherapy in unselected populations.

Recent Phase II trials of Rigosemib in recurrent glioblastoma settings have demonstrated survival advantages over Lomustine [12]. To validate these findings, Rigosemib is currently being evaluated in the Adaptive Global Innovative Learning Environment (AGILE) trial for glioblastoma [13]. The GBM AGILE is an international, seamless Phase II/III platform trial assessing multiple therapies for newly diagnosed and recurrent GBM, including: (a) the alkylating agent Val-083, which induces interstrand cross-linking at N7-guanine to act via p53-dependent or p53-independent mechanisms [14]; and Paxalisib (GDC-0084), a brain-penetrating phosphatidylinositol 3-kinase (PI3K)/mTOR inhibitor. PI3K/mTOR signaling is frequently dysregulated in glioblastoma, though prior trials targeting this pathway showed limited efficacy. For instance, buparlisib (a pan-PI3KTKI) demonstrated minimal monotherapy benefit in patients with recurrent PI3K-activated glioblastoma [15]. mTOR inhibitors such as Tislelizumab also failed to demonstrate therapeutic effects in Phase II trials [16]. This review comprehensively examines the safety of various rapalog-based therapies from existing clinical literature, discussing their potential mechanisms while considering established knowledge of mTOR-regulated biological pathways. To better prevent and manage mTORi-related side effects, it is necessary to identify changes in relevant biological pathways, which will help identify therapeutic targets.

Compared to epidermal growth factor receptor (EGFR) and VEGF, BRAFV600E activation mutations occur less frequently, affecting approximately 6% of glioblastomas, predominantly in epithelioid histological subtypes. Preliminary data from vemurafenib trials suggest its activity against BRAFV600E-mutated glioblastomas. However, combination therapies targeting BRAF/MEK (e.g., dabrafenib and trimebutine) may demonstrate greater therapeutic potential [17]. Gene fusions have also been identified in rare glioblastoma subpopulations, making neurotrophic tyrosine kinase (NTRK) tyrosine kinase inhibitors (TKIs) such as larotrectinib and entrectinib viable therapeutic options. Subgroup analyses indicate that NTRK inhibitors from these trials may benefit glioblastoma patients. Alterations in the cyclin D1-cell cycle-dependent kinase 4/6-retinoblastoma 1 (CDK4/6-RB1) pathway have emerged as a key therapeutic target for CDK4/6 inhibitors in glioblastoma. Studies report that over 78% of glioblastomas exhibit CDK4/6 and RB1 alterations, primarily observed in classical and mesenchymal subtypes [18]. Abemaciclib is currently being evaluated in the Innovative

Glioblastoma Therapy Individualized Screening Trial (INSIGhT).

2. Composition and Activation Mechanism of PI3K Signaling Pathway

2.1 Core Components of the Pathway

The PI3K family is classified into three categories (I, II, III) based on structural and functional differences, with Category I PI3K being the primary oncogene [19]. Category I PI3K forms an iso-dimeric structure composed of catalytic subunits (p110α, p110β, p110δ, p110γ) and regulatory subunits (p85α, p85β, etc.). Based on regulatory subunit variations, Category I PI3K is further divided into IA and IB subtypes: IA PI3K contains p110α, p110β, and p110δ, binding to p85 regulatory subunits; IB PI3K contains only p110γ, binding to p101 or p84 regulatory subunits. In glioblastoma (GBM), PI3Kβ (encoded by the PIK3CB gene) exhibits the highest expression level among all PI3K catalytic subunits, and this dominance remains unaffected by MGMT expression status, IDH mutation status, or tumor recurrence status, suggesting it serves as a core survival driver in GBM. Key downstream effector molecules include protein kinase B (AKT) and mammalian target of rapamycin (mTOR) [20]. As a central signaling molecule, AKT activates multiple substrates through phosphorylation, regulating cell proliferation and survival. mTOR forms two complexes (mTORC1 and mTORC2) that respectively regulate protein synthesis and AKT phosphorylation, forming a feedback regulation network within the pathway [21]. Furthermore, phosphatase and tensin homolog (PTEN), a key tumor suppressor gene, counteracts PI3K activity through dephosphorylation. Its functional loss is a major contributor to the abnormal activation of the PI3K pathway.

The PI3K/AKT signaling pathway is a widely recognized pathway in cancer, involved in biological processes such as cell proliferation, survival, migration, metabolism, and angiogenesis. Abnormal activation of this pathway is often associated with poor prognosis in glioblastoma patients [35-38]. TBXAS1 catalyzes the conversion of PGH2 into TXA2, an effective vasoconstrictor and platelet aggregation inducer. This enzyme plays a role in various pathophysiological processes including hemostasis, cardiovascular diseases, and stroke [39]. Additionally, it has been found that TBXAS1 can inhibit the expression of key proteins in the PI3K/AKT signaling pathway. TBXAS1 encodes different splice-transcript variants [40]. The PI3K/AKT signaling pathway promotes the progression of glioblastoma.

2.2 Pathway Activation Patterns

In the PI3K signaling pathway, mTOR serves both as a downstream effector and an upstream regulator. It exists in two complexes: the rapamycin-sensitive mTOR complex (mTORC1) and the rapamycin-insensitive mTOR complex (mTORC2). Activated Akt inhibits the activity of the tuberous sclerosis complex (TSC) 1/2, thereby initiating the mTORC1-mediated signaling pathway. This pathway participates in the phosphorylation of ribosomal protein S6 kinase (pS6k), eukaryotic initiation factor 4E (eIF4E), and eukaryotic initiation factor-binding protein 1 (4EBP1), which are involved in protein translation, ribosome biogenesis, and cell growth [22]. mTORC2 phosphorylates Akt at Ser-473, further contributing to cell survival, metabolism, proliferation, and cytoskeletal organization. Another crucial molecule in the PI3K pathway is PTEN. Clinical studies have shown that EGFR or PTEN mutations lead to persistent activation of the PI3K/Akt/mTOR signaling pathway, promoting tumor development and cancer treatment resistance [23]. The classical activation pathway of PI3K signaling primarily involves growth factor receptors. When ligands activate receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR) and platelet-derived growth factor

receptor (PDGFR), the tyrosine residues in their intracellular domains become phosphorylated, recruiting the PI3K heterodimer to the cell membrane. The regulatory subunit p85 binds to the receptor, triggering conformational changes that deactivate the catalytic subunit p110. This process converts phosphatidylinositol 4,5-diphosphate ($PI(4,5)P_2$) into phosphatidylinositol 3,4,5-triphosphate ($PI(3,4,5)P_3$) [24]. As a second messenger, $PI(3,4,5)P_3$ recruits AKT and PDK1 to the cell membrane. PDK1 phosphorylates AKT at T308, while mTORC2 phosphorylates AKT at S473, thereby fully activating AKT.

Recent studies have revealed a non-classical activation mechanism for PI3Kβ. Under high glucose conditions, hexokinase 1 (HK1) translocates from mitochondria to cytoplasm, phosphorylating the Y889 site of O-linked β-D-N-acetylglucosamine transferase (OGT). This phosphorylation facilitates p85α recruitment and mediates PI3Kβ binding to OGT, a process independent of the classical PI3K-AKT pathway's glycolytic regulation [25]. This discovery expands our understanding of PI3K activation mechanisms and highlights its functional diversity.

3. The Core Mechanism of PI3K Signaling Pathway in Glioblastoma

3.1 Regulating Tumor Cell Proliferation and Survival

Polarisomal glioblastoma multiforme (GBM) is the most common malignant glioma among all brain tumors, and currently lacks effective treatment options. GBM is frequently associated with overexpression and/or mutations of the epidermal growth factor receptor (EGFR), which subsequently activates multiple downstream signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/rapamycin-sensitive mTOR complex (mTOR) pathway [26]. The PI3K signaling pathway maintains the malignant proliferative phenotype of GBM cells through multiple mechanisms. In the classical pathway, activated AKT inhibits apoptosis-related proteins such as BAD and caspase-9 through phosphorylation, thereby reducing cell apoptosis. Simultaneously, it promotes protein synthesis by activating mTORC1, which facilitates phosphorylation of ribosomal protein S6 kinase (p70S6K) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), thereby accelerating protein synthesis and driving cell cycle progression [27].

Recent studies have revealed the pivotal role of PI3Kβ's non-classical protein kinase function in tumor proliferation [28]. PI3Kβ directly phosphorylates the T985 site of OGT, significantly enhancing its activity—a process independent of its conventional lipid kinase activity. Activated OGT promotes ACLY activity by glycosylating the T639 and S667 sites of ATP-citrate lyase (ACLY), thereby facilitating acetyl-CoA production. As a key precursor for fatty acid synthesis and histone acetylation, acetyl-CoA not only provides a material foundation for tumor cell proliferation but also regulates gene transcription through histone H3 acetylation, forming a "PI3Kβ-OGT-ACLY" signaling axis that drives glioblastoma (GBM) growth [29]. Clinical analyses confirmed that OGT phosphorylation levels at Y889 and T985 in GBM tissues are positively correlated with protein O-glycosylation and histone H3 acetylation levels, while inversely related to patient survival, validating the clinical significance of this signaling axis.

3.*2 Mediating Tumor Cell Migration and Invasion*

Glioblastoma (GBM) is one of the most common malignant tumors in the central nervous system. Characterized by high invasiveness and recurrence, GBM remains challenging to treat even with comprehensive therapies including surgical resection combined with radiotherapy, chemotherapy,

tumor electric field therapy, and targeted therapy [30]. Within the complex signaling network regulating GBM invasion, the PI3K signaling pathway plays an irreplaceable central role. Particularly, the PI3Kβ subtype (encoded by the PIK3CB gene) interacts with multiple signaling molecules, serving as a key node in modulating cellular motility.

Previous studies have established that PI3K β and c-Jun (JNK) collaborate through a synergistic mechanism, jointly modulating the FAK-vinculin signaling axis to regulate the dynamic equilibrium of adhesion plaque complexes. As critical structural connectors between cells and the extracellular matrix, the assembly and disassembly rates of adhesion plaques directly determine the formation and retraction efficiency of cell pseudopodia. FAK phosphorylation serves as the core activating signal for adhesion plaque maturation, while vinculin acts as a structural protein maintaining complex stability [31]. Research by Zhao Huafu's team at Shenzhen University demonstrated that PI3Kβ enhances FAK phosphorylation by activating downstream AKT signaling, while JNK directly regulates vinculin recruitment to adhesion plaque regions. This dual mechanism significantly accelerates adhesion plaque turnover, thereby inhibiting the formation and extension of plate-like pseudopodia and membrane folds in glioblastoma multiforme (GBM) cells, ultimately reducing their directional migration capacity [32]. Using total internal reflection fluorescence microscopy, the team observed that inhibiting PI3Kβ or JNK individually only mildly reduced adhesion plaque density, whereas combined inhibition decreased plaque density by over 40% and markedly slowed pseudopodia extension rates. Notably, this synergistic regulatory mechanism is PTEN-dependent: it shows stronger inhibitory effects in GBM cells with overexpressed wild-type PTEN, but diminished efficacy in PTEN-deficient cells, suggesting that pathway interactions are regulated by the status of tumor suppressor genes.

To enhance targeted therapy efficacy, researchers investigated upstream regulators of JNK and identified mixed-lineage kinase 3 (MLK3) as a key activator of both JNK and ERK pathways in glioblastoma (GBM) invasion regulation. Clinical analyses revealed distinct expression patterns, prognostic values, and molecular functions of MLK1, MLK2, and ZAK in gliomas. The study demonstrated significant differences in MLK1 and MLK2 expression between low-grade gliomas (LGGs) and high-grade gliomas (HGGs), with these variations correlating to patient prognosis [33]. In another study, preformed U87MG tumor spheres were cultured in collagen matrices containing or lacking EGF (100 ng/mL), CEP-1347 (400 nmol/L), or JNK inhibitor SP600125 (5 μmol/L). After 24 hours in serum-free medium, cells were stained with calcein-AM and imaged using confocal fluorescence microscopy. Quantitative analysis of dispersed cells at 24 hours revealed that MLK and JNK inhibitors blocked EGF-induced migration and invasion, suggesting their expression levels are closely associated with tumor progression and recurrence [34]. The 50 μm scale and 10× magnification showed MLK and JNK suppression effectively reduced EGF-mediated cell spread. Functional experiments confirmed that siRNA-mediated knockdown of MLK3 reduced GBM cell migration distance and invasive cell penetration, while significantly enhancing cell adhesion capacity. This demonstrates that MLK3 is essential for maintaining cellular motility.

Based on these findings, researchers proposed a combined therapeutic strategy targeting PI3Kβ and MLK3, aiming to block the invasive signaling network through the synergistic effects of PI3Kβ inhibitor AZD6482 and MLK3 inhibitor URMC-099 [35]. In vitro experiments demonstrated that this combination therapy inhibits adhesion plaque formation through multiple mechanisms, significantly reducing AKT (Ser473) and ERK (Thr202/Tyr204) phosphorylation levels while downregulating ROCK2 and zyxin phosphorylation activities—molecules involved in cytoskeletal remodeling and

adhesion plaque maturation, respectively [36]. The interaction between PI3Kβ and MLK3 forms a core signaling node regulating glioblastoma (GBM) invasion. MLK3 transduces signals to multiple downstream pathways, primarily c-Jun kinase (JNK) MAPK, extracellular signal-regulated kinase (ERK) MAPK, P38 MAPK, and NF-κB, thereby inducing transcriptional and post-translational regulation of various effector proteins. By integrating PI3K-AKT and MAPK signaling pathways, this mechanism precisely controls adhesion plaque dynamics and cellular motility, providing crucial theoretical and experimental foundations for developing targeted therapies against GBM invasion and recurrence.

3.3 Induced Chemotherapy Resistance

Temozolomide (TMZ) serves as a first-line chemotherapeutic agent for glioblastoma, demonstrating significant improvement in survival outcomes for glioblastoma patients. However, a subset of patients remain resistant to TMZ chemotherapy, resulting in treatment failure and tumor recurrence, with specific mechanisms yet to be fully elucidated [37]. The PI3K signaling pathway is identified as a key mechanism mediating TMZ resistance. Database analysis reveals that in MGMT-deficient GBM, PIK3CB mRNA expression levels are positively correlated with AKT phosphorylation levels ($r=0.35–0.42$, $P<0.05$). Furthermore, higher PIK3CB expression correlates with greater TMZ IC50 ($r=0.48$, $P=0.041$), confirming that elevated PI3Kβ expression is closely associated with TMZ resistance.

Mechanistic studies demonstrate that PI3Kβ mediates drug resistance by activating downstream AKT1 and AKT3 subtypes. In U87MG cells, ectopic expression of persistently activated Myr-AKT1 or Myr-AKT3 significantly diminishes the synergistic cytotoxic effects of PI3Kβ inhibitors TGX-221 and TMZ, whereas Myr-AKT2 shows no such effect, indicating that AKT1/3 are key effector molecules mediating PI3Kβ-mediated resistance [38]. Cell experiments confirm that in PI3Kβ-overexpressing SF295 cells, knockdown of PIK3CB alone enhances TMZ sensitivity, while PIK3CA or PIK3CD knockdown shows no significant effect, further validating the subtype-specific regulatory role of PI3Kβ in resistance [39].

3.4 Maintenance of Glioblastoma Stem Cell Dryness

Glioblastoma stem cells (GSCs) are the root cause of tumor recurrence and drug resistance, with the PI3K signaling pathway being indispensable in maintaining GSC stemness. Studies show that cancer cells develop resistance to therapies inducing apoptosis. Although multiple biomarkers have been developed, cancer remains a highly challenging disease due to persistent post-treatment decline. The PI3K/Akt/mTOR pathway interacts with signaling pathways like Wnt and Notch to jointly regulate GSCs' self-renewal, proliferation, and differentiation capabilities [40]. In VTC-103/GSCs with high PI3Kβ expression, the combination of PI3Kβ inhibitor AZD6482 and TMZ demonstrated significant synergistic inhibitory effects, while showing no obvious efficacy in PI3Kβ-low VTC-056/GSCs and normal neural stem cells. This suggests PI3Kβ serves as a precise target for GSC targeting. These findings provide new directions for eliminating GSCs and improving GBM prognosis.

4. Research Progress on Targeted Therapy of PI3K Signaling Pathway

4.1 Subtype-specific Inhibitors

Early pan-Pi3K inhibitors (e.g., BKM120) were limited in clinical use due to their excessive toxicity and poor efficacy from inhibiting multiple Pi3K subtypes. With deeper understanding of Pi3K

subtypes, subtype-specific inhibitors have become a research focus, with significant progress in developing Pi3Kβ inhibitors.

In vitro experiments demonstrated that the combination of TGX-221, a selective PI3Kβ inhibitor, and TMZ exhibited potent synergistic cytotoxic effects in PI3Kβ-exprising SF295 cells, while showing no significant synergy in PI3Kβ-low LN229 cells or normal astrocytes. The synergistic effect persisted even after reducing TMZ dosage, indicating strong tumor specificity [41]. Animal studies revealed that co-administration of TGX-221 and TMZ significantly reduced subcutaneous tumor volume in SCID/Beige mice, with tumor size remaining stable 11 days post-treatment, validating their in vivo synergistic efficacy [42]. Additionally, AZD6482, another PI3Kβ inhibitor, showed synergistic inhibition of glioblastoma cell proliferation, migration, and tumor growth when combined with MLK3 inhibitor URMC-099, providing a novel strategy to combat tumor invasion and recurrence.

4.2 Joint Therapeutic Strategy

Given the interactions between PI3K signaling pathways and other signaling networks, combination targeted therapy has become crucial for overcoming drug resistance. Beyond the combination of PI3Kβ inhibitors with TMZ in chemotherapy, dual-target inhibition of PI3Kβ and MLK3 can achieve stronger antitumor effects by simultaneously blocking proliferative and invasive signaling axes, while maintaining lower cytotoxicity to normal cells [43]. Additionally, inhibiting OGT or ACLY activity in PI3Kβ-mediated metabolic reprogramming pathways can block the "PI3Kβ-OGT-ACLY" signaling axis, reducing acetyl-CoA production and thereby suppressing tumor growth. This provides new insights for developing non-kinase-targeted drugs [44]. Current challenges in combination therapy include insufficient blood-brain barrier penetration efficiency, which affects drug accumulation in intracranial tumor tissues. Future efforts should focus on improving drug permeability through chemical modifications or targeted delivery systems (e.g., nanocarriers) to enhance intracranial efficacy. As a core driver of glioblastoma (GBM), PI3Kβ expression levels serve as prognostic indicators and therapeutic targets for MGMT-deficient GBM, providing a basis for patient stratification and precision treatment. The negative correlation between OGT phosphorylation levels and patient survival in clinical samples suggests the potential of the "PI3Kβ-OGT-ACLY" signaling axis as a molecular biomarker for efficacy monitoring and prognosis evaluation.

5. Conclusion

The PI3K signaling pathway plays a multifaceted regulatory role in the development of glioblastoma multiforme (GBM). Beyond modulating cell proliferation and survival through the classical PI3K-AKT-mTOR axis, it also mediates metabolic reprogramming and epigenetic modifications via PI3Kβ's kinase function. Furthermore, this pathway is crucial for tumor invasion, chemotherapy resistance, and the maintenance of glioblastoma stem cell (GSC) pluripotency. Recent studies have confirmed PI3Kβ as a core subtype target in GBM, with combination therapies using its specific inhibitors alongside chemotherapeutic agents or other signal molecule inhibitors demonstrating promising anti-tumor efficacy. Future research should focus on elucidating the interaction networks between PI3K subtypes and other signaling pathways to identify novel synergistic therapeutic targets. Developing PI3Kβ-specific inhibitors with enhanced blood-brain barrier penetration could improve intracranial drug concentration. Establishing a precision diagnosis and treatment system based on PI3K pathway biomarkers would enable personalized GBM therapy.

As mechanistic studies advance and drug development progresses, targeted therapy of the PI3K signaling pathway is poised to become a pivotal strategy for improving GBM prognosis.

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