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REVIEW ARTICLE

Emerging Insights into the PI3K/AKT/mTOR Signaling Pathway and Non-Coding RNA-mediated Drug Resistance in Glioblastoma

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Abstract: Glioblastoma multiforme [GBM] is a highly aggressive grade IV central nervous system tumor with a dismal prognosis. Factors such as late detection, treatment limitations due to its aggressive nature, and, notably, drug resistance significantly affect clinical outcomes. Despite the effectiveness of Temozolomide [TMZ], a potent chemotherapy agent, the development of drug resistance remains a major challenge. Given the poor survival rates and chemoresistance, there is an urgent need for novel treatment strategies. Non-coding RNAs, particularly microRNAs [miRNAs], offer a promising approach to GBM diagnosis and treatment. These small non-coding RNAs play crucial roles in tumor progression, either suppressing or promoting oncogenic characteristics. The phosphoinositide-3 kinase [PI3K]/AKT/mTOR pathway, which regulates essential biological processes like proliferation and survival, is a key target of miRNAs in cancer. Studies have underscored the significance of PI3K/AKT/mTOR signaling in drug resistance development and its interplay with non-coding RNAs as mediators of tumorigenesis. This review aims to outline the involvement of PI3K/AKT/mTOR signaling in miRNA modulation and strategies to overcome chemoresistance in GBM.

Keywords: Glioblastoma, PI3K/AKT/mTOR, lncRNA, miRNAs, Temozolomide.

1. INTRODUCTION

Glioblastoma multiforme [GBM] is an adult-onset central nervous system [CNS] cancer with a significant and inevitable chance of recurrence even after the first-line standard of care. With an average survival rate of 5.5%, this incurable condition manifests in primary and secondary forms, each delineated by distinct genetic pathways, with primary GBM showing a higher incidence among the elderly compared to the secondary subtype [1]. Typical diagnostic and therapeutic approaches encompass imaging modalities like CT/MRI, surgical intervention, chemotherapy, and radiotherapy, respectively. Liquid biopsy, employing blood and CSF, shows the potential to enhance accuracy by assessing genetic markers like MGMT, IDH, and EGFR, thus guiding treatment decisions. Despite existing challenges, ongoing developments indicate the likelihood of its routine clinical integration [2, 3].

Given the complex nature of GBM, a thorough exploration of its molecular landscape is imperative to devise effective therapeutic strategies that could potentially improve patient outcomes. In light of this, the PI3K/AKT/mTOR signaling pathway and non-coding RNA [ncRNA] dynamic regulation were identified as major regulators of crucial cellular functions and intriguing therapeutic intervention targets [4, 5].

Targeted therapy strategies for GBM center around the PI3K/AKT/mTOR system, whose dysregulation fuels uncontrolled cell proliferation, resistance to apoptosis, invasiveness, and angiogenesis in GBM. Novel targeted therapies that aim to inhibit essential components of this pathway have shown promise in decreasing GBM cell proliferation, migration, and survival [6-8].

Furthermore, microRNAs [miRNAs], small RNA molecules intricately involved in gene expression regulation, exert profound effects on carcinogenesis and GBM pathogenesis, influencing key players like P53, RB, and the PI3K/AKT/mTOR pathway. They regulate treatment resistance, angiogenesis, proliferation, and cell cycle as oncogenes and tumor suppressors. Their expression profile may improve

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GBM diagnosis and prediction, and guide targeted therapies [9, 10].

Early clinical trials demonstrate that inhibitors targeting this system increase efficacy and reduce drug resistance [11, 12]. MiRNAs with therapeutic potential either imitate or inhibit essential components of the PI3K/AKT/mTOR pathway. Nanoparticle-based technologies, for example, improve miRNA dispersion, greatly increasing therapeutic efficacy [13]. Drug tolerance and complicated regulatory networks highlight the necessity of continuing to discover novel therapy targets [14, 15]. Through a comprehensive investigation of this pathway and ncRNA processes, it could be possible to substantially enhance the prognosis for GBM patients and advance closer to defeating this formidable disease.

2. GLIOBLASTOMA: A BRIEF OVERVIEW

Glioblastoma multiforme [GBM] represents 14.7% of all CNS tumors and is notorious for its aggressive nature, characterized by rapid growth, invasiveness, and resistance to treatment. WHO classification includes three subtypes of IDH mutant astrocytoma, IDH mutant oligodendroglioma with deletion of 1p/19q code, and IDH wild-type glioblastoma. Emerging from glial cells responsible for supporting and nourishing neurons, GBM poses surgical challenges due to its rapid growth and brain infiltration. Due to its fast development and brain infiltration, this entity is difficult to remove surgically [16]. Despite extensive research, the exact etiology of GBM remains elusive. It is considered that hereditary and environmental factors are not clearly implicated, and this condition is frequently categorized as sporadic. However, some studies have identified a correlation between GBM and particular single-nucleotide polymorphisms, genetics, and the consumption of anti-inflammatory medicines [17]. Despite its rarity, GBM garners significant public attention due to its dismal prognosis, with an average survival of around fourteen months post-diagnosis [17]. Clinically, GBM is categorized into primary [de novo] and secondary forms, with primary GBMs typically presenting a poorer prognosis. Primary form accounts for around 95% of GBM, which mostly affects the elderly. Unlike the preceding form, the secondary type is less prevalent and arises at a younger age. With an approximate 40% survival rate, men and Caucasians have a slightly higher prevalence and are often diagnosed around age 64. However, secondary GBM is prevalent in women. Alterations in molecular signaling pathways may give rise to these malignancies from neural stem cells [NSCs], oligodendrocyte progenitor cells [OPCs], and NSC-derived astrocytes, all of which contain similar characteristics to brain stem cells [18]. Within the many forms of GBM, the mesenchymal subtype has a higher vulnerability to invasion [17]. The most typical symptoms in these individuals are increasing neurological problems that occur within a few days. Additionally, patients frequently experience clinical manifestations, including seizures, headache, nausea, and vomiting, all of which are indicators of elevated intracranial pressure [19]. Commonly, non-invasive imaging techniques like CT scans and MRI can help identify subtypes of this illness; a biopsy is then performed to confirm the diagnosis. To identify active tumors, nuclear medicine methods such as single photon emission computed tomography [SPECT] and positron emission tomography [PET] are utilized currently [16]. The WHO classifies GBM as a grade IV malignancy, reflecting its formidable management challenges [20]. The identification of genetic irregularities as a consequence of molecular research, such as mutations affecting the epidermal growth factor receptor [EGFR], isocitrate dehydrogenase [IDH], and loss of tumor-suppressive genes TP53 and PTEN, can be a new step in discovering strategies for identifying and managing GBM [21]. Recent evidence suggests 'TP53's involvement in tumor initiation, particularly evident in high-grade astrocytoma. Moreover, an investigation into grade II and III astrocytic tumors revealed a potential correlation between its mutations and chromosome 17p allelic loss, extending beyond GBM to encompass lower-grade astrocytomas [22].

The word GBM refers to alterations in the cellular and extracellular matrix caused by the presence of a large number of polymorphic biochemical forms [23]. The current standard of care for GBM consists of surgical resection, radiation therapy [RT], and chemotherapy. Although these treatments are initially recommended, they carry the risk of complications, including neurological impairments, recurrence of the tumor due to RT resistance, and drug resistance to temozolomide [TMZ], respectively [24]. Continual investigations into the molecular pathways underlying GBM and the evaluation of unique therapeutic strategies, such as gene therapy, targeted therapies, and immunotherapy, provide hope for improved projections [25]. However, developing effective therapeutic therapies for GBM remains a considerable issue.

3. PI3K/AKT/mTOR SIGNALING PATHWAYS IN GLIOBLASTOMA

The complex PI3K/AKT/mTOR pathway regulates critical biological functions like cell growth, survival, metabolism, and protein synthesis. It is strictly regulated in normal conditions but overactivated in GBM and other tumors, causing uncontrolled cell proliferation, apoptosis escape, angiogenesis, and treatment resistance [26].

Relevant genes, including EGFR, PI3K, AKT, and mTOR, are vulnerable to PI3K pathway aberrations in GBM. The activation of PTEN, pivotal in around 70% of GBMs, often diminishes due to PTEN loss or amplification of EGFR, VEGFR, or PDGFRalpha [27]. Overactivation of the PI3K/AKT/mTOR has been related to enhanced cell proliferation, reduced apoptosis, increased invasiveness, and angiogenesis in GBM. AKT, vital to the pathway, fosters cell survival and proliferation by inhibiting pro-apoptotic molecules and activating anti-apoptotic proteins, fueling cancer cell growth. Furthermore, the growth factor mutation in

GBM wild-type IDH contributes to the facilitation of cell division and the improvement of the glioma invasion pathway through the influence of cyclin D1[13]. Moreover, PI3K isoforms p110α and p110δ facilitate cell migration, potentially fueling the aggressive GBM phenotype [28]. Changes in class IA PI3K p110α, the primary isoform, are evident in GBM. Inhibitors targeting AKT phosphorylation, like KP-372-1, KP-372-2, and A-443654, effectively curb cell proliferation, directly impacting GBM. [13]. Yet, AKT activation suppresses PTEN and alters the PI3K pathway in uterine, GBM, prostate, lung, and melanoma cancers [29, 30]. Furthermore, re-expressing PTEN enhances P53 protein activity, leading to increased cell cycle arrest and chemosensitivity to etoposide [31].

Meanwhile, mTOR functions as a pivotal checkpoint of cellular proliferation by regulating protein synthesis and cell metabolism, thereby permitting the uncontrolled proliferation of tumor cells [32]. It controls cytoskeletal dynamics through mTORC2 and cell size/growth in response to nutrition through mTORC1. Aging, neurological diseases, and numerous human malignancies are linked to its prolonged activation by mTOR or upstream target mutations. Targeting mTORC1 and mTORC2, which may inhibit cell proliferation and motility, is a potent approach to treating GBM [33]. Additionally, PI3K/AKT/mTOR signaling and critical regulators like VEGF and FGF are crucial to brain tumor angiogenesis. Its significance in the development of GBM has led to its emergence as a potentially effective therapeutic goal. In preclinical and clinical trials, many inhibitors targeting distinct components of this system are being investigated [13]. However, difficulties remain, such as inhibitor resistance and the necessity for patient classification to identify individuals who would benefit. Due to the complexity of this pathway and its interactions with other signaling networks, extensive research is required to develop effective combination therapies and overcome resistance mechanisms. In brief, modulation of the PI3K/AKT/mTOR signaling pathway facilitates the progression and initiation of GBM, aggressive behavior, and resistance to standard therapeutic approaches.

4. miRNAs IN GLIOBLASTOMA

MicroRNAs [miRNAs], RNA molecules comprising fewer than 25 nucleotides, play a vital role in human gene regulation, with over 1400 miRNA types identified to date. Functional miRNAs develop from primary transcripts [Pri-miRNAs] through RNase III [34, 35]. Mature miRNAs interact with mRNA to suppress genes and modulate essential biological processes, rendering them critical for comprehending normal biological activities and cancers [36, 37]. Comprising between 1% and 3% of the human genome, they play a pivotal role in gene regulation. Approximately 40% of microRNA genes are embedded inside other genes, suggesting a role in gene regulation [38]. The discovery of the first miRNAs in the 1990s linked them to numerous diseases and disorders, notably cancer. They regulate protein maturation, which controls cell survival, proliferation, and cell cycle control. Alterations in miRNA levels induced by genetic or epigenetic factors may drive tumor formation and progression [37]. Researchers in the 2000s highlighted the role of microRNAs in GBM and other brain tumors. Brain tumors may result from unbalanced miRNAs, which are essential for brain cell growth. Their functions in the determination of cell identity and differentiation of brain stem cells are significant [39]. Normal and tumor tissue have different miRNA expression patterns during brain development, suggesting a role in CNS tumor formation and progression [40]. MiRNAs contribute to tumorigenesis by increasing proliferation, promoting angiogenesis, and facilitating metastasis through mutated genetic pathways, including P53, RB, and PI3K/AKT/mTOR. On the whole, they are classified as tumor suppressors or oncogenes [41]. However, the specific functions of these may vary depending on the tumor's tissue and type. For instance, the inhibitory type includes miR-7, miR-34a, and miR-128, whereas the oncogene class comprises miR-10b, miR-21, and miR-93 [39]. In contrast, miR-218 and miR-451 decrease tumor development by increasing apoptosis and lowering cellular proliferation [40]. Regarding angiogenesis, angiomiRs, such as miR-125b and miR-296, exert a substantial effect on this process in GBM. They influence the behavior of endothelial cells and contribute to vascularization [41]. Drug resistance is affected by miRNAs such as miR-195 and miR-328, which affect GBM cell response to TMZ and mitoxantrone [42]. Stemness-related miRNAs such as miR-128, miR-124, miR-137, miR-34a, miR-326, and miR-145 regulate GBM stem cells and determine their capacity for self-regeneration, differentiation, and carcinogenesis (Table **1**). These miRNAs' control is crucial in altering key GSC properties [43]. The following part will focus on the regulation of the PI3K/AKT/mTOR signaling pathway by microRNAs in GBM.

5. ROLE OF miRNAs IN MODULATING PI3K/AKT/mTOR SIGNALING PATHWAY IN GLIOBLASTOMA

miRNA profiles differ dynamically with tumor development, indicating disease stage and therapy possibilities [70]. Some can be analyzed in blood and cerebrospinal fluid [CSF] to predict GBM [71, 72]. As previously stated, miRNAs have a dual effect on GBM and perform an important part in treatment resistance, angiogenesis, cell proliferation, and cell cycle regulation [40, 74, 75]. Understanding their expression profile may help with GBM diagnosis and prediction. However, the underlying mechanisms of miRNA-mediated cellular control and their therapeutic potential remain unknown. Specific miRNA dysregulation promotes glial cell transition and cancer development [76-84]. The correlation between miRNA and GBM was initially established in the micro-oncogene and anti-apoptotic agent miR-21, which also disclosed its involvement in the malignant phenotype [40].

Table.1 MicroRNA involvement in GBM.

microRNA	Type	Regulatory Molecule	Expression	Outcome	References
miR-34a/miR-125B	In vitro: C6 and U87 cell	spirulina	Tumor suppressor	Spi reduced C6 and U87 cell growth and triggered cell death in a GBM model	(44)
MiR-590-3p	In vivo: Normal brain tissues and glioma tissues	EMAP-II and TMZ	Oncogene	Co-administration of TMZ and EMAP-II resulted in the inhibition of GSC viability, migration, and invasion.	(45)
miR-125b	Primary GSC	miR-125b inhibitor	Tumor suppressor	Through inhibition of the Wnt/-catenin signaling, PI3K and miR-125b inhibitors induce TMZ resistance to GBM.	(46)
miR-223-3p	In vitro: Human GBM cell lines (H4, A172, SHG44, and LN229) normal cell line (HEB) in vivo: human embryonic kidney 293 T (HEK-293 T)	PITPNA-AS1	Tumor suppressor	PITPNA-AS1 activates the PI3K/AKT signaling cascade by regulating EGFR expression via mir-223-3p.	(47)
MiR-223	in vivo: Human tissue: 26 paired GBM tissues peritumoral brain edema	paired box 6 (PAX6)	Tumor suppressor	TMZ-induced cell survival was enhanced by exogenous miR-223.	(48)
miR-155	In vitro: U87-MG cells	miR-155 mimic/ miR-155 inhibitor	Oncogene	miR-155 modulates U87-MG cell proliferation, migration, and invasion via PI3K/AKT signaling.	(49)
miR-548x and miR-4698	In vitro: A-172 and U251 cells	pCDH plasmid	Tumor suppressor	miR-548x and miR-4698 may decrease GBM via regulating the PI3K/AKT pathway.	(50)
miR-6071	In vitro: A172, U251, U87 and LN229), and normal human astrocyte In vivo: Thirty GBM tissue samples and 10 pair-matched normal brain tissues	ULBP2	Tumor suppressor	miR-6071 may limit GBM cell growth, migration, and invasion.	(51)
miR-770-5p	In vitro: T98G, LN229, U138, SHG44, A172, U251 and human umbilical vein endothelial cell line GBM tissues: stage I + II (N = 19), stage III (N = 26), and normal brain tissues (N = 45)/ Five-week-old BALB/c nude mice	circABCC3	Tumor suppressor	CircABCC3 controlled GBM's miR-770-5p/SOX2 axis via PI3K/AKT.	(52)
miR-181a	In vitro: U373 and U87MG	carmustine	Tumor suppressor	Replacement of miR-181a may increase GBM chemotherapy response.	(53)
Anti-miR-21 and miR-124	In vitro: U87MG cells/in vivo: nude mice	Angiopep-2	Oncogene/ tumor suppressor	The co-administration of anti-miR-21 and miR-124 modulated the mutant RAS/PI3K/PTEN/AKT signaling pathway in tumor cells concurrently.	(54)
miR-205	In vitro: GBM stem-like cells	ERBB3	Tumor supressor	ERBB3 upregulation is maintained through the inactivation of miR-205.	(55)

(Table 1) Contd….

microRNA	Type	Regulatory Molecule	Expression	Outcome	References
miR-7-5p	In vitro: Human glioma cell lines (U251, U87, SHG44, T98G, GOS-3, TJ905, U373) and normal cells (HEB) In vivo: 106 glioma tissues and 23 normal brain tissues	LPP-AS2	Tumor supressor	GBM tumorigenesis was facilitated by LPP-AS2 via a feedback loop involving miR-7-5p/EGFR/PI3K/AKT/c-MYC.	(56)
	In vitro: U87MG, LN229, A172 and T98G	2-DG		The signaling pathway involving miR-7-5p and TFF3 is crucial in GBM cell lines treated with 2-DG.	(57)
miR-32	In vitro: U87 and human monocytic cell line THP1	PTEN	Oncogene	MiR-32 stimulates M2 macrophage polarization via PI3K/AKT signaling.	(58)
miR-126	In vitro: U87MG, U251, U343, Hs683, LN215, and A17224 and primary normal human astrocytes HA1800	lncRNA-XIST	Tumor suppressor	LncRNA-XIST performed as a miR-126 competing endogenous RNA, regulating the IRS1/PI3K/AKT pathway in GBM.	(59)
miR-579	In vitro: A-172, U251, and human embryonic kidney (HEK293T) cells	PTEN mutant cell lines	Tumor suppressor	miR-579 regulates the PI3K/AKT signaling pathway, acting as a new tumor suppressor gene in GBM.	(60)
miR-210	In vivo: Fifty samples of human GBM Grade IV, eight samples of anaplastic astrocytoma Grade III and six samples of diffuse astrocytoma	NeuroD2	Tumor suppressor	NeuroD2 is tightly controlled by p53 and miR-210 as a tumor suppressor and prognostic biomarker in GBM.	(61)
miRNA-641	In vitro: HEK 293 cells	AKT2	Tumor suppressor	Intronic miRNAs may protect cells against host pathway overactivation related to tumor growth.	(62)
miR-92b	In vitro: U251, U87, LN229 and T98G	E3 ubiquitin ligase CHIP	Tumor suppressor	The CHIP/miR-92b/PTEN axis forms a novel mechanism that underlies the development of GBM.	(63)
miR-124-3p	In vitro: U251 and U87	neuropilin-1	Tumor suppressor	miR-124-3p acts as the upstream suppressor of NRP-1 which promotes GBM cell development and growth by PI3K/AKT/NF-B pathway in GBM cells.	(64)
miR-326	Human samples: 56 GBM samples and 14 control brain samples	ARRB1	Tumor suppressor	miR-326 is a glioma cell tumor suppressor microRNA.	(65)
miR-302/367	In vitro: HEK-293T, the U87MG and U373	–	Tumor suppressor	U87MG cells show suppression of transformation-related genes caused by the miR-303/367 cluster.	(66)
miR-203	In vitro: U251, U373, and T98G MG cells and normal human astrocytes	radiation sensitivity	Tumor suppressor	In order to overcome the radiation resistance of GBM, miR-203 might be a viable target.	(67)
MiR-449a	In vitro: U87 and U251 In vivo: nude mice	Podoplanin	Tumor suppressor	Through temporal inhibition of the PI3K/AKT pathway, miR-449a regulates myc-associated zinc-finger (MAZ) protein.	(68)
miR-608	In vitro: U87 and U251 /In vivo: Clinical specimens	Human macrophage migration inhibitory factor (MIF)	Tumor suppressor	MiR-608 upregulation decreased GSC proliferation, migration, invasion, and apoptosis in U87 and U251 cell lines via targeting MIF, JNK, and PI3K/AKT.	(69)

In light of the high mortality rate and limited treatment options associated with GBM, recent research has emphasized the significance of miRNAs in regulating the PI3K/AKT/mTOR pathway [72]. Disruption of this mechanism may promote GBM formation and progression [26]. Several miRNAs, notably miR-7, miR-21, miR-34a, miR-124, and miR-137, function as regulators of the PI3K/AKT/mTOR pathway in GBM [84-87]. Furthermore, miR-128 and miR-218 directly target and inhibit PI3K activity, whereas miR-101 and miR-199a have been shown to target mTOR, a downstream effector of this pathway [71, 88]. By modulating pathway activity, these microRNAs hold

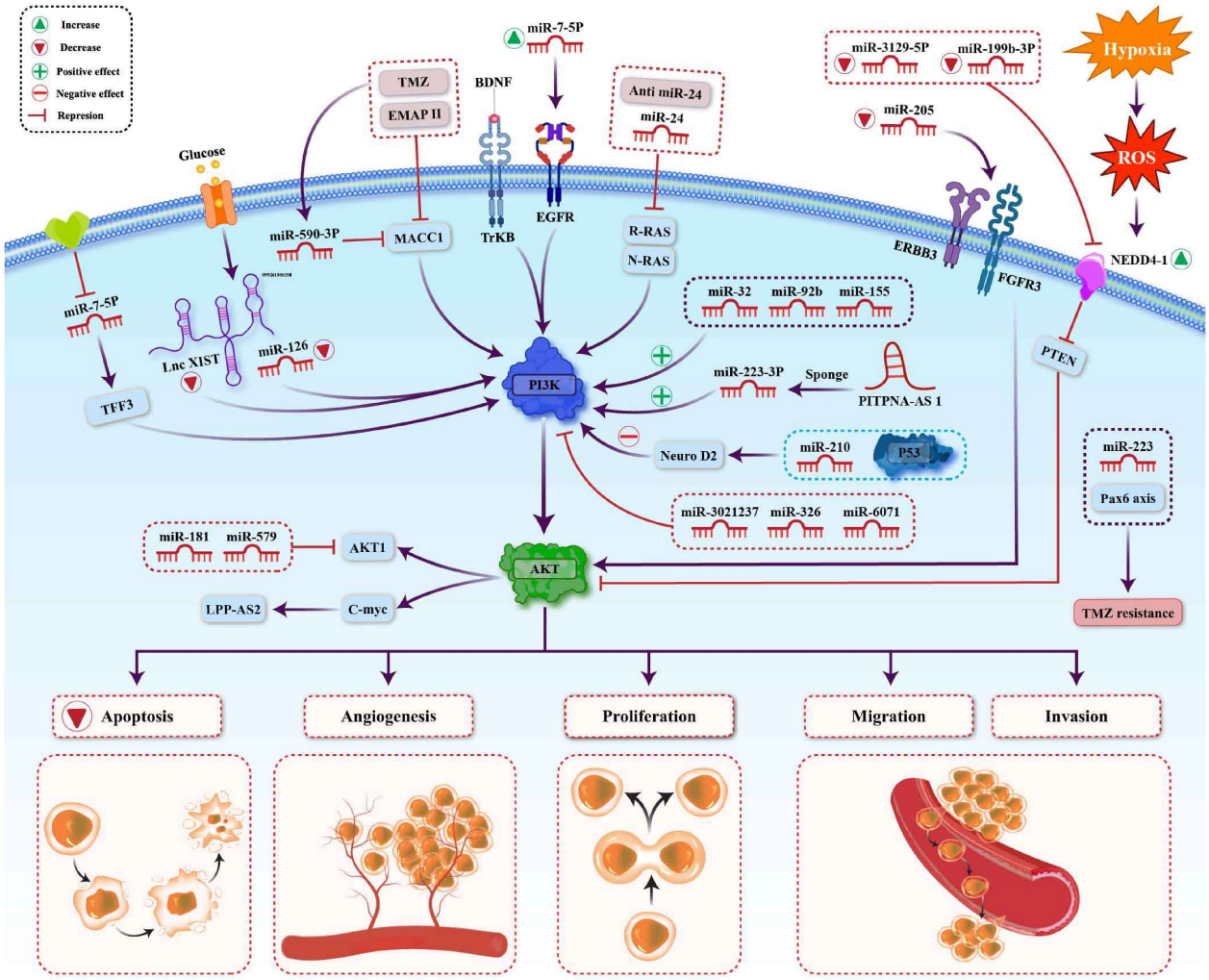

Fig. (1). The interaction between microRNAs and the PI3K/AKT/mTOR in GBM. This figure illustrates the regulatory roles of several miRNAs that target different sections of the pathway, highlighting their importance in the evolution of glioblastoma, resistance to therapy, and possible therapeutic approaches. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

promise as effective therapeutic targets for GBM (Fig. **1**).

A microalga recognized for its antioxidant and anti-inflammatory effects has been found to inhibit cell growth, promote cell death, and enhance the activity of miR-34a and miR-125b, both of which are implicated in the PI3K/AKT/mTOR pathway [44]. Additionally, it has been shown that the combined administration of TMZ and endothelial-monocyte-activating polypeptide II [EMAP-II] can influence the miR-590-3p/MACC1 axis by inducing autophagy [45]. Furthermore, inhibitors of PI3K and miR-125b are crucial for GBM stem cell resistance to TMZ [46].

Additionally, it has been found that PITPNA-AS1, a long non-coding RNA [LncRNA], acts as an oncogenic regulator in GBM by modulating the expression of EGFR via the regulation of miR-223-3p, thereby activating the PI3K/AKT pathway [47]. Moreover, miR-155 has been demonstrated to prevent apoptosis while also controlling U87-MG glioma cell invasion and migration [49]. Additionally, Kalhori et al. observed that miR-548x and miR-4698 upregulation resulted in cell cycle arrest and a reduction in AKT1 protein levels, in addition to inhibiting cell proliferation [50]. Concerning UL16 binding protein 2 [ULBP2] in counteracting the suppressive effect of miR-6071 on GBM, Zhou et al. assert that miR-6071 impedes apoptosis and cell migration through the PI3K/AKT pathway [51]. Similarly, Zhang et al. demonstrated that CircABCC3 knockdown decreases GBM cell malignancy via modifying the miR-770-5p/SOX2 axis through the PI3K/AKT signaling pathway [52]. Moreover, miR-181a and carmustine, a chemotherapy drug, inhibited U373 cell proliferation by decreasing AKT1 [53]. As an alternative treatment, targeted polymeric nanoparticles coated with angiopep-2 peptide could present anti-miR-21 and miR-124 to GBM tissue via the RAS/PI3K/PTEN/AKT pathway [54]. Furthermore, Mooij et al. demonstrated that extracellular vesicles expelled by GBM cells can regulate tumor growth through the

transfer of oncogene components, including miR-21-5p, let-7b-5p, miR-3182, and miR-4448 [89]. Moreover, ERBB3 overexpression in GBM enhances FGF sensitivity, metabolic activation, and target sensitivity by repressing miR-205 [55]. Moreover, miR-489-3p's BDNF-mediated targeting of the PI3K/AKT pathway offers novel opportunities for GBM therapeutic therapy [90]. Zhang et al. described the function of LncRNA LPP-AS2 in facilitating tumor growth via a feedback loop involving miR-7-5p/EGFR/PI3K/AKT/c-MYC [56]. By negatively modulating PTEN, miR-32 can enhance the polarization of M2 macrophages; by stimulating PI3K/AKT, it can also enhance the growth and development of tumor cells [58]. Based on the existing body of literature concerning LncRNA-XIST and miR-126, glioma cells exhibit an elevated glucose metabolism mediated by the IRS1/PI3K/AKT pathway [59]. According to a comprehensive investigation by Kalhori [2019], miR-579 acts as a tumor suppressor in GBM by directly targeting PDK1, Rheb, and mTOR [60]. Overexpression of neurogenic differentiation factor [NeuroD2] was discovered to operate as a tumor suppressor, controlled by p53 and miR-210 under hypoxic environments, and critical for promoting cell migration and proliferation through the PI3K/AKT pathway [61]. Experiments with 2-Deoxy-d-glucose [2-DG] demonstrated that silencing miR-7-5p increased cell invasion by activating PI3K/AKT Trefoil Factor 3 [TFF3] signaling [57]. Notably, it has been suggested that the miR-223/PAX6 axis controls the PI3K/AKT signaling pathway, which in turn controls the proliferation, invasion, and chemoresistance to TMZ [48]. The correlation between AKT2 and endogenous miR-641 has been widely reported in research. Based on the findings, miR-641 changes AKT2's functional state by influencing the kinases needed to activate it [62]. According to Xu et al., overexpression of miR-92b in T98G and LN229 cells decreased PTEN and noticeably reversed CHIP knockdown cell glioma development [63]. In line with earlier studies, miR-124-3p inhibits tumor development via the PI3K/AKT/NFB pathway by suppressing NRP-1's 3'UTR [64]. Similarly, miR-326 expression demonstrated a positive and substantial connection with ARRB1, with an anticancer impact that reduced migration and colony formation [65]. In line with this, miR-302/367 suppressed transformation-related proteins such OCT3/4, SOX2, and PI3K/AKT signaling [66]. Shifting the focus to DNA damage repair, Chang et al. demonstrated that miR-203 overexpression enhanced radiosensitivity [67]. It was also shown that mice expressing miR-449a had a higher survival rate and smaller tumors linked with Myc-associated zinc finger protein [MAZ] [68]. According to Wang et al., miR-608 reduces the macrophage migration inhibitory factor [MIF], thereby deactivating the PI3K/AKT and JNK pathways [69].

6. PI3K/AKT/mTOR REVERSES DRUG RESISTANCE IN GLIOBLASTOMA

The challenge of drug resistance in cancer is similar to the highly aggressive elements present in infectious diseases [91, 92]. This issue, together with the disease's recurrence, obscured chemotherapy's early achievements. As the initial therapeutic option, the combination of chemotherapy medications with diverse mechanisms has shown to be effective in malignancies such as breast, testicles, etc. Nonetheless, novel treatments, such as immunological strategies and targeted therapies aimed at molecular targets, are being developed [93, 94].

The PI3K/AKT/mTOR pathway has become a prominent candidate for managing drug resistance due to its involvement with multiple malignancies [95]. The alteration of this signaling system in breast cancer chemoresistance has been extensively studied [96]. This paper offers a review of current findings on the function of this pathway in the reversal of drug resistance in GBM.

The accumulation of untreatable cancer stem cells [CSCs], frequently caused by PTEN loss and mTOR pathway activation, complicates GBM treatment challenges. In a major breakthrough in 2023, Uniyal et al. investigated how inhibition of the mTOR pathway with different inhibitors, such as rapamycin and LY294002, affects GBM CSCs. The results proved that Torin2 prevented self-renewal and eliminated tumor cells [97]. A 2022 study on reversing TMZ resistance with Tubeimoside-I [TBMS1] showed that TBMS1, combined with TMZ, induced apoptosis by inhibiting the PI3K/Akt/mTOR/NF-kB signaling pathway [98]. In a study by Guo et al. [99], the analysis of NDC80 kinetochore complex [NUF2] in TMZ resistance revealed that NUF2 knockdown inhibited tumor growth by attenuating malignant phenotypes through Fox transcription factor M1 [FOXM1]. A phase I clinical trial discovered that combining vistusertib, a mTORC1/2 inhibitor, with TMZ was safe and efficacious in GBM patients experiencing their first relapse [100]. CoCl2-induced autophagic apoptosis, mediated by hypoxia, appears to modulate the PI3K/AKT/mTOR pathway, suggesting a promising approach [101]. Tutak et al.'s research on PI3K/AKT/mTOR suppression with Voxtalisib [Vox] and low-intensity pulsed ultrasound [LIPUS] demonstrated greater efficacy in targeted GBM and GBMCSCs [102]. Hao Yu Chuang et al. highlights NEDD4-1, an E3 ligase, as a key regulator of the PTEN/PI3K/AKT/mTOR axis and the oxidative stress response. The expression of NEDD4-1 is upregulated in TMZ-resistant cells due to dysregulated miRNAs such as miR-3129-5p and miR-199b-3p[103]. Furthermore, in T98G cells, the anticancer potential of LY294002 [a PI3K inhibitor] and TMZ sensitizes glioma cells via ER stress regulation, whereas Hsp27 helps them survive apoptosis [11]. CRNDE is currently believed to modify autophagy along the PI3K/Akt/mTOR and ABCG2 expression [104], making it a possible indicator for TMZ therapy response in GBM. TMZ resistance is also associated with calcineurin-NFAT pathway YZ129 inhibitors. YZ129 directly decreased HSP90's calcineurin functionality and NFAT nuclear translocation. Hypoxia, glycolysis, and PI3K/AKT/mTOR signaling were also inhibited. These results suggest that targeting the HSP90 chaperone network could manage GBM [105]. In immunodeficient

mice models of patient-derived subcutaneous xenograft [PDX] GBM, Alcaniz et al. found that TMZ resistance is linked to hypoxia-related gene sets and mTORC1 signaling, whereas mTOR inhibitor sensitivity is connected to reactive oxygen species and angiogenesis [106]. In the context of rapamycin monotherapy resistance induced by PTEN mutation, Xia et al. indicated that combination treatment of Smurf1 silencing together with rapamycin inhibitors may perform an important role in drug resistance by decreasing tumor development [107]. Since the majority of GBM patients have high levels of DHX33 expression, Wang et al. concluded that upregulating the wild-type DHX33 protein confers resistance to mTOR inhibitors. Hence, it presumably functions as a pivotal regulator in facilitating the progression of GBM [108]. Furthermore, berberine and solid lipid curcumin particles have been demonstrated to be more effective than single therapies at inhibiting this pathway [109]. Computer models of critical cancer pathways, including PI3K/AKT/MTOR, are being used to simulate patient-specific data. Based on FDA-approved kinase inhibitor simulations, GBM responds better to combination treatment than monotherapy due to tumor heterogeneity and adaptive resistance [110]. Moreover, since cPLA2 is linked to chemoresistance, reducing it modestly reduces GBM growth and survival while dramatically increasing the vulnerability of chemoresistant GBM cells to drug therapies [111]. On the other hand, double hydroxide nanoparticles coated with etoposide have been employed to overcome chemoresistance in destroying GBM stem cells [112].

In brief, diverse strategies that target pathways implicated in drug resistance in GBM indicate an optimistic progression in the ongoing attempt for enhanced therapeutic approaches to this intimidating disorder.

7. THERAPEUTIC IMPLICATIONS AND FUTURE PERSPECTIVES

Throughout several clinical studies with different treatments for GBM, none have shown to be as beneficial as TMZ for malignant glioma. It is indisputable that drug resistance to it will develop throughout therapy. Understanding the reasons for resistance and developing novel therapeutic strategies to reverse chemical resistance is thus a critical step in the treatment of GBM patients [113].

In general, two approaches can be employed to combat drug resistance: laboratory research and clinical trials. A comprehensive analysis of these approaches is going to be presented in the next section [114].

7.1. *In vitro* Models

The development of laboratory models is critical for advancing medicinal techniques. They are extremely useful for screening cells for drug sensitivity and discovering biomarkers associated with drug resistance [114]. In recent years, 3D cell culture models have become increasingly popular since they resemble in vivo cultures more and provide higher drug resistance [115, 116]. Moreover, in terms of tumor heterogeneity and distinctive properties, patient-derived cultured cells detect genetic features and treatment resistance information by developing immortal cancer cell lines [117]. Furthermore, considering the significance of the tumor microenvironment, it is critical to investigate the arrangement of non-neoblastic astrocytes and tumor-associated macrophages in the manner of drug resistance and immunosuppressive environment in GBM [118]. The medication dose and period of exposure have an important impact on drug resistance. Consequently, high drug concentrations are crucial for the selection of resistant clones, whereas a progressive increase in drug dose is required to induce acquired resistance [119]. Standardization of drug resistance mechanisms in GBM models remains a significant challenge in the contemporary era, notwithstanding the availability of multiple approaches [114].

In light of this, the development of consistent and standard methods for comprehending the issue of chemoresistance in GBM is critical.

7.2. Clinical Approaches

The clinical field proposes three approaches to drug resistance: early detection of malignancy, enhancement of therapeutic response, and adaptive interventions implemented during continuous monitoring [93]. Even though early identification and monitoring of cancer is one of the best ways of tumor eradication and medication resistance prevention, it is difficult due to the necessity of greater biomarker screening. Furthermore, CSF can be employed as a less invasive approach to diagnosis in the early stages of GBM, which needs proven standards [120, 121]. In the second strategy, the appropriate therapy for the person is anticipated by optimizing the prediction of chemical sensitivity [122]. The third strategy is to continuously evaluate the treatment response according to the discovery of resistance development, which may be done using biological biomarkers. Therapy response biomarkers such as MGMT, miR-128, miR-342, miR-205, and others were discovered in blood samples. Meanwhile, CSF samples revealed several microRNAs, such as miR125b, miR-223, miR-451, miR-711, and more [121]. Accelerating tumor identification is critical for improving the efficacy of GBM therapy. Emerging research in breakthrough therapies, such as tumor growth inhibitors and immunotherapy, is evolving. Personalized therapy may potentially hold promise for early detection and treatment of GBM [123].

As our knowledge of intrinsic and acquired chemoresistance pathways continues to expand, it is anticipated that novel therapeutic approaches for GBM will emerge in the coming years.

CONCLUSION

In light of its aggressiveness and lack of treatment options, GBM has a challenging worldwide perspective. MiRNAs with dual activities as tumor suppressors and oncogenes have emerged as critical regulators in GBM pathophysiology. Important cellular processes are also regulated by signaling cascades, including PI3K/AKT and mTOR. Disruption of this pathway promotes GBM development by increasing uncontrolled proliferation, evasion of apoptosis, and resistance to treatment. Mutations in critical genes such as EGFR, PTEN, and mTOR, in particular, contribute considerably to the advancement of cancer. Multiple studies have highlighted the importance of understanding the miRNA-PI3K/AKT/mTOR pathway interaction. Moreover, several studies have shown that miRNA-mediated treatments can reduce pathway activity and sensitize GBM cells to therapy, reversing drug resistance.

Drug resistance remains a key concern in the treatment of malignancies, including GBM, necessitating novel approaches. mTOR inhibitors, combination therapy, and new medicines such as TBMS1 or NEDD4-1 inhibitors, which have shown promising outcomes in preclinical and clinical studies, are among the experimental interventions addressing this resistance. Furthermore, modern approaches such as 3D cell cultures and patient-derived models increase platforms for interpreting resistance mechanisms and measuring therapy responses, hence improving precision medicine initiatives.

Looking ahead, prospects are dependent on the development of immunotherapeutic techniques, improvement of early detection methods, the use of biomarkers for specific treatments, and the use of biomarkers for personalized therapies. Novel therapeutics that target particular miRNA pathway interactions, as well as novel drug delivery technologies, have the potential to change GBM treatment. While challenges persist, collaborative efforts to combine multi-omic analyses and clinical trials are opening the way for more effective and customized medicines, as well as hope for better outcomes and higher survival rates in GBM patients.

AUTHORS' CONTRIBUTIONS

MA and MR wrote the article; MS prepared the figures and tables; BY and MM designed and revised the article. All the authors studied and approved the final manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

CONSENT FOR PUBLICATION

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