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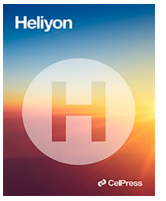

Review article

Research progress of drug resistance mechanism of temozolomide in the treatment of glioblastoma

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ABSTRACT

Glioblastoma, the most malignant primary brain tumor among gliomas, is characterized by a low cure rate, high recurrence rate, and invasive growth. Without chemotherapy, the median survival of patients is only 12.1 months. The standard treatment for glioblastoma primarily involves surgical resection, complemented by radiotherapy. Temozolomide (TMZ), a new oral alkylating agent, is currently used as the first-line chemotherapy drug for glioma. However, TMZ treatment only improves median survival by 2 months, largely because of the tumor's ability to develop resistance to the drug. The main mechanism underlying this resistance involves DNA repair processes, such as the action of O6-methylguanine DNA methyltransferase (MGMT), which repairs the DNA damage caused by TMZ, and other DNA repair mechanisms including mismatch repair and base excision repair. These mechanisms can effectively repair the DNA damage caused by TMZ, thereby reducing the sensitivity of tumor cells to the drug. This study summarized the recent research progress of TMZ resistance mechanism in glioblastoma, aiming to provide a theoretical basis for the development of new therapies. The mechanisms of glioma resistance to TMZ mainly involves DNA damage repair (as mentioned above), abnormal cell signaling pathways (p53-mediated signaling, reactive oxygen species-mediated signaling, endoplasmic reticulum stress and autophagy-related signaling, receptor tyrosine kinase-related signaling, transforming growth factors, β-mediated signaling pathway, Wnt/β-Catenin signaling pathway), glioma stem cells, tumor microenvironment (hypoxic microenvironment, nano-drug delivery system), epidermal growth factor receptor, and microRNAs.

1. Introduction

Gliomas are primary tumors of the central nervous system that originate from the brain's intrinsic cells and [1]account for 40%–50 % of all intracranial tumors. Glioblastomas (GBM) represent approximately 80 % of primary malignant tumors in the central nervous system [2]. According to the Central Brain Tumor Registry of the United States, the annual incidence of glioma is approximately 6.4/100,000 [3], and the onset peak occurs after the age of 70 years. Moreover, the 5-year survival rate has a normal distribution trend with increasing age [4].Glioblastoma (IDH-wildtype,Genes/Molecular Profiles Characteristically Altered:IDH-wildtype,TERT promoter, chromosomes7/10,EGFR) is classified into grades 4 according to the 2021 WHO Classification of Tumors of the Central Nervous System grading standards [5]. GBM is the most advanced form of glioma [3,4]. Owing to its heterogeneity and permeability, response of GBM to most treatment modalities is unpredictable, and the complexity of the disease is a major barrier to the development of

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effective treatments.

Currently, the conventional comprehensive standard treatment for glioma is mainly surgical resection, complemented by radiotherapy and chemotherapy. Nevertheless, the prognosis of patients with conventional treatment is poor. Owing to the invasive growth pattern of gliomas, surgical resection can only be performed within the visible area. However, the brain's fine structure necessitates removing as much of the glioma as possible without excessively expanding the resection area. Additionally, radiotherapy often causes adverse reactions, such as nausea, vomiting, hair loss, seriously affecting patient health. Moreover, TMZ is a commonly used chemotherapy drug for glioma treatment, but its therapeutic effect is limited by acquired resistance, and the therapeutic mechanism involved remains elusive. This study aimed to provide a theoretical basis for better selection of chemotherapeutic drugs and enhancing GBM treatment by analyzing the drug resistance mechanisms in glioma.

2. Mechanism of action of commonly used chemotherapy drugs

In recent years, in clinical and scientific research, many drugs have been developed for glioma treatment, among which the most common alkylating agents include dacarbazine, carmustine, lomustine (comustine), and TMZ. These drugs, or their active forms, produce electrophilic methyldiazonium ions that act as nucleophiles and react with intracellular DNA to form various adducts. The distribution, half-life, properties, and cellular characteristics of these adducts determine the degree of cytotoxicity and the potential for drug resistance [6].

TMZ was the first U.S. FDA-approved (1995) alkylated drug for clinical treatment of glioma, which does not hydrolyze at normal stomach acid levels and remains stable. However, TMZ hydrolyzes at physiological pH to form 5-(3-methyltriazole-1-imidazole-4-carboxamide[5-(3-methyltriazol-1-yl)imidazole-4-carboxamide) (MTIC). MTIC is further hydrolyzed into 5-aminoimidazole-4-carboxamide and methyl diazole, which then reacts with DNA, transferring methyl groups to DNA bases. Among these, guanine N7 (N7MeG) and adenine N3 (N3MeA) sites are the most common methyl adducts, accounting for 70 % and 10 % of the total alkyl adducts, respectively [7]. Although the guanine O6 site (O6MeG) constitutes only 5 % of the total DNA methyl adduct, it is highly pre-mutagenic and pre-toxic. Therefore, the damage it causes to DNA is the most severe.

3. DNA repair damage mechanism

After TMZ damages the DNA of GBM cells, it can trigger various drug resistance mechanisms, with DNA repair playing a key role owing to its activation in response to chemotherapy. DNA repair pathways involved include direct repair, mismatch repair, and base excision repair (Fig. 1).

3.1. Direct repair

One of the main mechanisms of TMZ in the treatment of glioma is to induce the methylation of guanine O6, resulting in glioma cell death. O6-methyl guanine DNA methyltransferase (MGMT) is a DNA repair enzyme that directly removes methyl groups from the O6 position of guanine, repairing lesions caused by TMZ; MGMT is often overexpressed in cancer cells. It is also associated with the

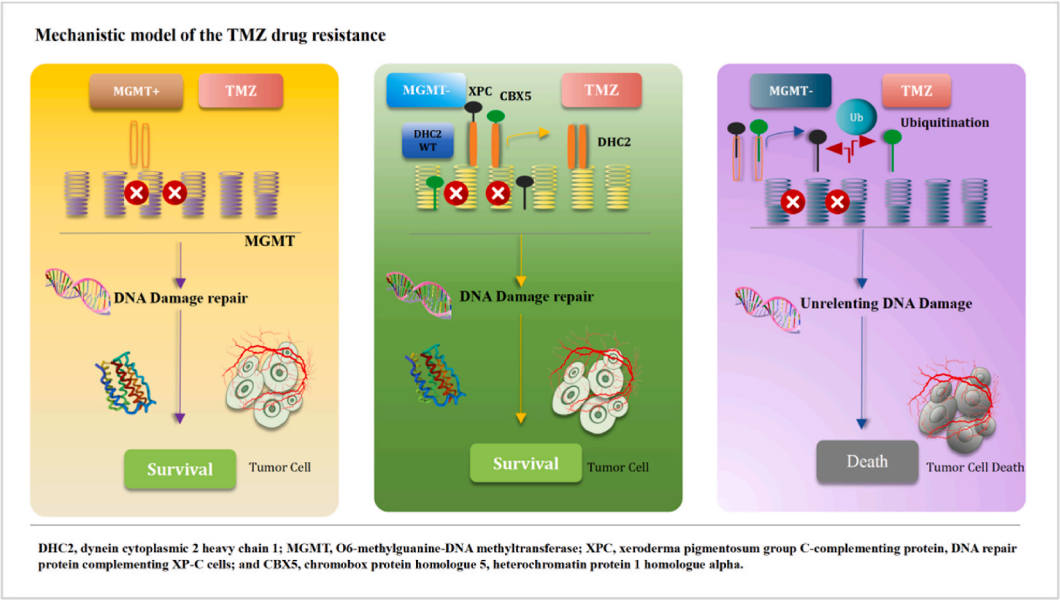

Fig. 1. Mechanistic of the TMZ drug resistance.

development of chemotherapy resistance in glioma. In addition, MGMT, a protein with a relative molecular mass of 22 kDa, can transfer the alkylated adduct at the O6 site to the cysteine residue in the autocatalytic pouch during the alkylation transfer reaction, thus allowing DNA recovery and inactivation of the functioning MGMT with the alkyl adduct, which may be ubiquitinated [8,9] and then degraded by the proteasome mechanism [10]. As one MGMT molecule can only repair one alkyl adduct, the total number of MGMT molecules in each cell and the rate at which the cell resyntheses MGMT are the rate-limiting steps for the cell in removing DNA O6-alkylguanine adducts. Therefore, DNA repair after chemotherapy-induced damage is dependent on the continuous expression of MGMT. Most MGMT are located in the cytoplasm and are transferred to the nucleus through alkylation after DNA alkylation damage; however, their specific mechanism remains unclear [11].

MGMT expression levels of varies significantly among different organs. The expression level of MGMT is relatively low in the brain tissue and highest in the liver. Tumors often exhibit higher expression levels than their tissues of origin [12]. MGMT promoter methylation is feasible in GBM and is associated with a good clinical response to TMZ [13]. Furthermore, Changes in MGMT protein are caused by activation of various signaling pathways after treatment with TMZ, such as induction of MGMT expression by activation of typical Wnt/β-catenin signal cascade. Conversely, inhibition of Wnt signal can enhance the effect of alkylating drugs and restore chemical sensitivity of different cancers [14]. Transcriptional activation of MGMT in rat hepatocellular carcinoma cells occurs 12–24 h after radiation or treatment with alkylating agents [15]. In HeLa S3 cells, MGMT expression level increases 3–5 times after treatment with various protein kinase C activators [16]. The MGMT promoter has two AP-1 binding sites, and their absence weakens the activation of the MGMT promoter by PMA and TPA [16]. In addition, p53 is required for the induction of MGMT genes by ionizing radiation. If MGMT levels determine tumor susceptibility, it would be advantageous to develop predictive MGMT analysis. Because it is possible to reduce MGMT activity in tumors, MGMT-based therapies are anticipated to expand to various solid and hematopoietic tumors. However, MGMT inhibitors such as O6-benzylguanine, a synthetic derivative of guanine, are limited by blood toxicity and inefficiency [17]; therefore, combination treatment options are being considered. A decrease in Bcl-2 levels is a marker of apoptosis triggered by the p53 mutant O6MeG [18], and it has been experimentally confirmed that the simultaneous use of MGMT and Bcl-2 inhibitors is a feasible strategy [19]. In gliomas, O6MeG triggers apoptosis by activating mitochondrial and p53-controlled Fas-dependent pathways in tumors with p53 mutations [18]. As MGMT can significantly inhibit apoptosis and increase the p53 response in gliomas, MGMT and p53 are considered predictors of O6AA resistance in this tumor entity [20]. MGMT promoter methylation is predictive of the response to chemotherapy with alkylating agents in GBM [21] (Fig. 2).

3.2. Base excision repair

The methylation levels of N_7MeG and N_3MeA account for more than 80 % of the total methylation levels of TMZ [7]. Conversely, base excision repair can be repaired quickly, thus promoting the survival of GBM, thereby playing an important role in the mechanism of TMZ resistance. The base excision repair system is composed of multiple catalytic reactions of DNA glycosylase, endonuclease, polymerase, and DNA ligase. Mutations in one or more of these components can impair the ability of DNA damage repair, contributing to the cytotoxicity of TMZ in GBM. Unlike N7 lesions, N3 lesions can be fatal if not repaired. Base excision repair is initiated by DNA glycosylase recognition and excision of modified bases [21], followed by repair synthesis to restore the DNA sequence. N-Methylpurine-DNA glycosylase (MPG) is responsible for the repair and removal of N3MeA, N7MeG, and N3Me [22]. Consequently,

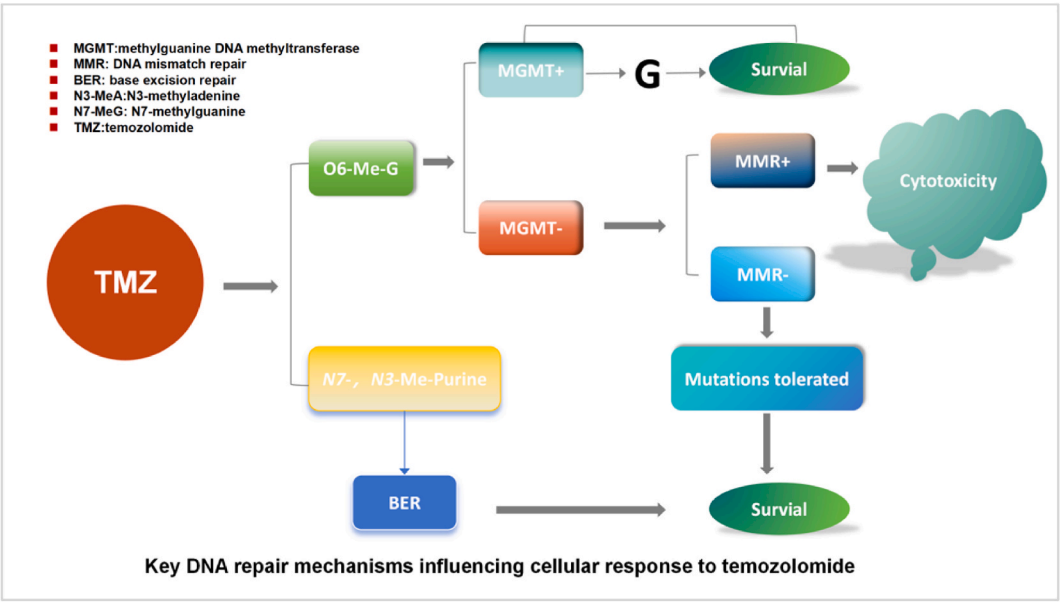

Fig. 2. DNA repair mechanisms.

MPG-knockout mice exhibit higher survival rates [23]. Among base excision repair components, poly (ADP-ribose) polymerase-1 (PARP-1) is an important enzyme with dual roles. The inhibition of PARP-1 leads to the accumulation of broken DNA in cells, which in turn leads to cell death. Overactivation of PARP-1 due to DNA damage leads to the depletion of nicotinamide adenine dinucleotide and adenosine triphosphate (ATP), which in turn leads to cell death. The tyrosine kinase inhibitor dovetinib can downregulate HMGA2, base excision repair, and other members of GBM cells, thereby increasing TMZ sensitivity [24]. The combination of TMZ and the PARP1 inhibitor velipanil plays a synergistic role in GBM cells exhibiting high TMZ resistance [25]. Another important protein involved in base excision repair is PARP-1. In response to DNA damage induced by alkylating agents, PARP-1 binds to DNA single-stranded breaks to form auto-polymerized ADP-ribosylation, which enables it to interact with other proteins such as polymerase [26] and XRCC1 [27]. PARP-1 interacts with FEN-1 to enhance strand replacement and DNA repair synthesis via polymerase, thereby promoting long-patch base excision repair [28]. In addition, PARP-1 mediates XRCC1 recruitment to single-stranded breaks [29] and protects DNA repair intermediates from nuclease attack [30].

3.3. Mismatch repair

The mismatch repair mechanism prevents mismatches caused by replication errors and incorrect insertions. It consists of two parts: MutS and MutL. MutS protein is a mismatch recognition factor, and MutL mediates the crosstalk between MutS and other members of the repair complex, such as exonucleases, helicases, and polymerases. The mismatch repair system is highly conserved in eukaryotes and performs multiple functions. However, in higher organisms, this function is more complex, and six MutS and multiple MutL homologues, also known as MLH or PMS, have been identified thus far because of their association with post-meiosis separation in yeast.

In mammals, MSH2 and MSH6 heterodimers recognize base mismatches [31], whereas another heterodimer pair consisting of MLH1 and PMS2 is recruited to the repair site to regulate this process. Unrepaired O6MeG pairs with thymine instead of cytosine, allowing the O6MEG-T complex to be recognized by the mismatch repair system. This process removes the thymine from the newly synthesized DNA strand without affecting the O6MeG. In the next replication cycle, a mismatch occurs again, and the repair cycle is repeated. This ineffective mismatch repair cycle causes the replication fork to stop, and the cell attempts to divide, resulting in a double-strand break, and these double-stranded breaks are cytotoxic to cells. Thus, O6MeG-induced cytotoxicity requires cells to express mismatch repair activity [32]. In the absence of mismatch repair, the O6MeG mismatch is not recognized, leading to chemical resistance. Mutated mismatch repair components in GBM have rarely been reported. However, in recurrent GBM, this mutation in MSH6 leads to decreased expression, further confirming that TMZ can inactivate mismatch repair activity, thereby rendering GBM cells resistant to the drug. EGFRvIII + increases sensitivity of GBM to TMZ by upregulating DNA mismatch repair, leading to an increased number of DNA double-stranded breaks and significant S/G2 phase arrest after TMZ treatment [33] (Fig. 3).

4. Drug efflux transporters and TMZ resistance mechanism

In cancer therapy, overexpression of drug efflux transporters is often associated with multidrug resistance. One of the reasons for cancer chemotherapy failure is that drug efflux transporters reduce intracellular drug levels by increasing chemotherapeutic drug

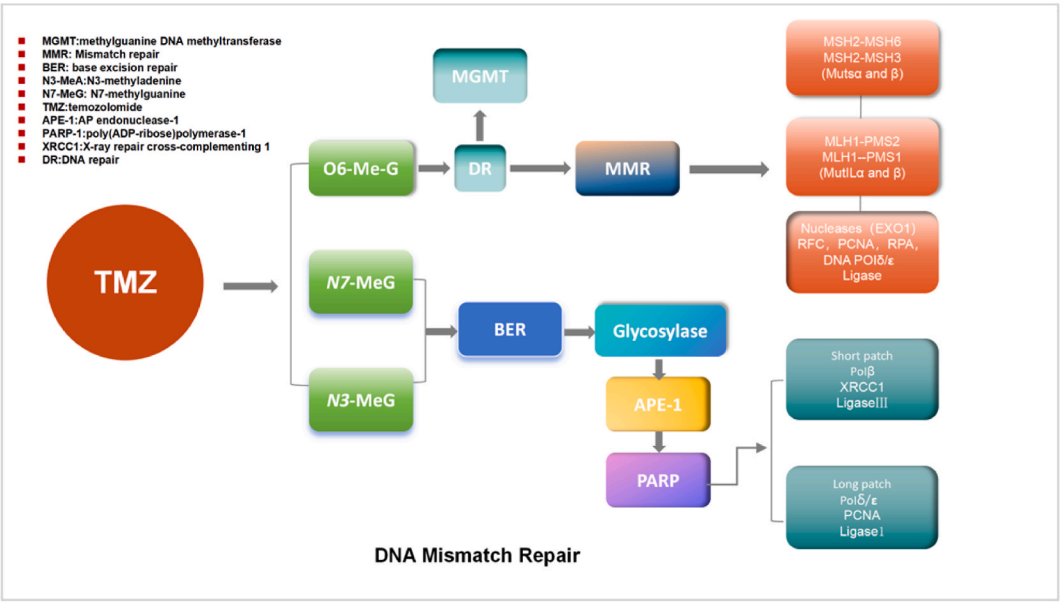

Fig. 3. Summary of proteins involved in DNA repair pathways activated by TMZ-induced DNA lesions.

efflux, which in turn leads to tumor insensitivity to drugs, and the drug efflux transporter mechanism is usually effective against multiple chemotherapy drugs. The mechanism of multiple drug resistance (MDR) involves the high expression of ATP-binding cassette (ABC) transporter superfamily members; there are three major drug effector transporters—ABCB1 (also known as MDR1 or p-glycoprotein; the most studied), ABCC1 (MRP1), and ABCG2.

Studies have confirmed the clinical relevance of ABCB1 in several cancers; however, the clinical relevance of other transporters remains unclear. Destruction of ABCB1 gene can lead to increased drug levels in many tissues [34]. MDR1 is located on the cell membrane and consists of two structurally similar regions, each containing a transmembrane domain with six hydrophobic helices and a highly conserved nucleotide-binding domain (NBD). MDR1 hydrolyzes ATP to release energy by binding ATP to its upper two NBDS, facilitating the transport of intracellular substances to the extracellular space. Inhibition of any ATP-binding site on MDR1 affects its efflux function. High MDR1 expression usually in tumor cells in response to stimulation by antitumor drugs. To protect themselves, tumor cells stimulate high expression of MDR1 mRNA, leading to increased drug efflux. The expression level of ABCB1 is closely related to vascular invasion [35]. ABCB1 expression is the highest in the largest and most aggressive soft tissue sarcomas [36]. In addition, MDR1 can inhibit apoptosis of tumor cells by regulating endogenous and exogenous apoptotic pathways, thereby reducing the efficacy of antitumor drugs. Therefore, overcoming drug resistance through inhibition of ABC transporters remains the focus of research, and the development of ABC transporter inhibitors is clearly an extremely attractive potential chemotherapy adjuvant; however, the development of third-generation ABC transporter inhibitors has not been effective in clinical trials.

ABCB1 belongs to a superfamily of membrane transporters that export various endogenous compounds and drugs from the cells via ATP hydrolysis. Cancer cells upregulate ABCB1 expression as an adaptive response to escape chemotherapy-mediated cell death. However, some studies have highlighted an epigenetic regulatory role of ABCB1. Promoter methylation of ABCB1 has been found to occur in several tumor types, including gliomas, but its role as a biomarker has not been fully established. One study analyzed the methylation of ABCB1 promoters in tumor tissues from 50 glioma patients to assess its incidence and to semi-quantitatively measure the level of ABCB1 methylation, evaluating its usefulness as a potential biomarker. This study showed that ABCB1 methylation levels in samples from different grades of gliomas have high inter-individual variability. In addition, a positive correlation has been observed between ABCB1 methylation, WHO tumor grade, and IDH1 wild-type status. Therefore, ABCB1 methylation can be considered a potential diagnostic or prognostic biomarker for glioma patients, indicating that the tumor is more aggressive. ABCB1 is frequently methylated in high-grade gliomas and may serve as a diagnostic biomarker of more aggressive tumors [36].

5. Drug resistance mechanism mediated by abnormal cell signaling pathway

5.1. p53-mediated signaling pathway

p53 is a tumor suppressor protein encoded by TP53 gene. A series of DNA damage responses triggered by TMZ treatment in glioma can eventually activate p53, allowing it to function as a tumor suppressor. Mouse twin-micro2 homology (MDM2) is an E3 ubiquitin protein ligase whose expression is upregulated by protein kinase B (Akt). Akt, which acts downstream of receptor tyrosine kinase (RTK) activation, negatively regulates p53 protein expression. Direct genetic alteration of p53 or interaction between p53 and MDM2 are two mechanisms of p53 functional inactivation; MDM2 and MDMX are ring domain proteins that exert their carcinogenic effects primarily by inhibiting the tumor suppressor protein p53 [37].

The tumor suppressor p14ARF can competitively bind to MDM2, block the interaction between p53 and MDM2, and upregulate p53 expression. The tumor suppressor enzyme PTEN can inhibit MDM2 transcription to prevent p53 degradation and inactivation and can enhance the transcriptional activity of the TP53 gene. Moreover, its mutation leads to enhanced proliferation of tumor cells. The association between PTEN and p53 can increase the sensitivity of tumor cells to TMZ [38].

Galactonagglutinin (Gal1) belongs to the lectin family, and its expression is increased by hypoxic stimulation. Gal1 can regulate and modify the biological function of p53, as well as act on RAS-related pathways, leading to chemotherapy resistance. These results indicate that the p53-MDM2 axis plays a role in DNA damage-mediated drug resistance. TP53 gene mutation leads to the promotion of tumor cell growth and TMZ resistance, and the inhibition of pathway-related associations may become a target for future drug resistance [39].

5.2. Reactive oxygen species (ROS)-mediated signaling pathway

In cancer cells, the REDOX status plays a crucial role in the signaling pathways that regulate cell death and survival [40]. Various anticancer drugs currently used in cancer chemotherapy can stimulate the production of ROS [41]. Chemotherapy resistance of GBM cells to TMZ is associated with reduced ROS production. Combining TMZ with drugs that increase ROS levels can enhance its cytotoxicity in GBM cells [42,43]. TMZ produces intracellular ROS through the oxidation of peroxisomes, microsomes, and mitochondria, and secondary ROS are produced by DNA double-stranded breaks induced by TMZ. ROS can activate multiple stress response signaling pathways and directly or indirectly disrupt the physiological functions of proteins, lipids, nucleic acids, and other substances in cells, which is the pathological basis of many diseases. Glioma cells may produce ROS to protect against TMZ-induced cell death, leading to the development of drug resistance. When TMZ mediates cell death signals, ROS initially activates c-JUN amino-terminal kinase (JNK). JNK activation can strongly induce MGMT expression and subsequent protein activation in glioma cells, promoting DNA repair and cell invasion. The ROS-mediated signaling pathway plays a critical role TMZ drug resistance. Combining TMZ with related drugs can improve the therapeutic effect in glioma treatment to a certain extent [44].

5.3. Endoplasmic reticulum stress and autophagy related signaling pathways

In addition to classical targeted DNA damage, TMZ also causes off-target effects, namely, the endoplasmic reticulum stress response (ERSR), which regulates GBM chemical sensitivity. TMZ mediates ROS production and induces glioma cell ERSR [45].

When ERSR is activated, it triggers the activation of protein kinase R-like endoplasmic reticulum kinase, which in turn promotes glioma cell growth. In mild ERSR, multiple cytoprotective effects can lead to TMZ resistance in glioma cells, while in persistent and severe ERSR, cell homeostasis cannot be restored, leading to the activation of various pathways. ERSR has a crucial downstream target: autophagy. Autophagy regulates key proteins involved in the mitochondrial apoptosis pathway and death receptor apoptosis pathway. It plays a role in promoting tumor cell survival by providing metabolic substrates and contributing to chemotherapy resistance [46]. In clinical treatment, the inhibition of autophagy can significantly increase TMZ-induced apoptosis.

5.4. RTK-related signal path

Carcinogenic activation of RTK is a key signal for maintaining the carcinogenicity of glioma cells. In normal cells, RTK bind to specific extracellular ligands and self-dimerize in the plasma membrane, thereby inducing self-phosphorylation of the C-terminal intracellular kinase domain of RTK. Furthermore, the phosphorylated RTK activates various downstream cell signaling molecules and induces cell proliferation and invasion [47].

RTK are an important family of proteins involved in many signaling pathways, including proliferation, cell survival, transcription, and cell cycle regulation. Their roles and involvement in cancer cell survival have been extensively described in the literature and are often associated with overexpression and/or overactivity in cancer pathology. Owing to these characteristics, RTK are relevant targets against cancer. Over the past decade, numerous studies have highlighted the role of RTK signaling in regulating DNA repair, providing evidence of a relationship between RTK and the proteins involved in the repair pathway. Some researchers have summarized RTK as a potential modulator of double-stranded DNA repair pathways and proposed new research directions aimed at implementing new therapeutic strategies targeting DNA repair and RTK-mediated signaling pathways [48,49].

Phosphatase plays an important role in regulating RTK-mediated signaling, while PTEN affects downstream signaling by inhibiting phosphoinositol 3-kinase (PI3K). In addition to PTEN, the protein phosphatase 2A (PP2A) is known to play a role in regulating RTK-mediated signaling by blocking Akt, ERK1/2, and other signaling molecules, such as c-Myc, through dephosphorylation. PP2A is widely recognized as a tumor suppressor [50]. It is a serine/threonine phosphatase that plays a key regulatory role in apoptosis, mitosis, and DNA damage response. PP2A typically acts as a tumor suppressor gene. However, inhibiting PP2A activity in tumor cells may be a viable way to enhance tumor sensitivity to chemoradiotherapy, because this inhibition may cause cells to enter a state of mitotic disorder, making them more susceptible to death. In fact, there is evidence that inhibiting PP2A can slow tumor growth after radiation therapy in a range of cancer types, including ovarian, liver, glioma, pancreatic, and nasopharyngeal cancers. In this review, we discussed the current understanding of the role of PP2A in tumor radiotherapy and the potential mechanisms by which it may influence this process [51].

Abnormal activation of glioma RTK and their downstream pathways can lead to TMZ resistance.

The three main pathways are summarized below.

5.5. RTK-Ras-Raf-MEK-ERK signal path

Extracellular signals stimulate proto-oncogene Ras to bind guanosine triphosphate and become activated. This activation leads to the phosphorylation of Raf, which in turn activates mitogen-activated protein kinase (MEK). MEK then phosphorylates and activates ERK, ultimately driving gene expression [52]. Activated ERK catalyzes the phosphorylation of several cytoplasmic effectors and nuclear transcription factors, thereby promoting cell survival, migration, and proliferation [53]. Inhibition of the abnormal activation of this pathway can effectively inhibit the proliferation of glioma cells and improve TMZ resistance.

5.6. RTK-PI3K-Akt-mTOR signaling pathway

PI3K, an activated RTK, converts phosphatidylinositol-4,5-diphosphate to phosphatidylinositol-3,4, 5-triphosphate (PIP3). PIP3 recruits 3-phosphoinositol-dependent protein kinase-1 (PDK1) and protein kinase B (Akt) to the plasma membrane. PDK1 then phosphorylates Akt, leading to its activation. Activated Akt stimulates the mammalian target protein complex 1, a major regulator of energy and REDOX reactions, which contributes to the carcinogenic properties of glioma cells 18]. This pathway promotes tumor angiogenesis, autophagy, and tumor proliferation and migration, contributing to tumor cell resistance to TMZ [54].

5.7. Tyrosine kinase Janus kinase (JAK)-Activator of transcription (STAT) signaling pathway

After RTK activation, JAK is phosphorylated by tyrosine, and STAT is recruited to the phosphotyrosine residue of the RTK cytoplasmic domain. Tyrosine phosphorylates STAT and releases it into the cytoplasm by forming homolog dimers or heterodimers with other STATs. The oligomerized STAT is further phosphorylated by ERK1/2. Activated Akt then translocates to the nucleus, where it binds to the promoter of target genes and initiates transcription, ultimately leading to increased cell proliferation and migration [55].

JAK also binds to tyrosine-phosphorylated adaptor proteins and activates RAS-mediated pathways through RTK activation. STAT3 activation is increased in TMZ-resistant gliomas, and targeting STAT3 in these gliomas overcomes TMZ resistance. The carcinogenic

activation of STAT in gliomas is primarily triggered by the overactivation of RTK-related mechanisms, which can complicate glioma treatment [56].

5.8. Transforming growth factor-β (TGF-β)

TGF-β-mediated signaling is one of the important regulatory mechanisms in glioma biology. In healthy cells and early cancer cells, the TGF-β pathway has tumor suppressor functions, including promoting cell cycle arrest and apoptosis; additionally, its activation in advanced cancers can promote tumorigenesis, including metastasis and chemical resistance. Epithelial-mesenchymal transformation (EMT) reduces intercellular adhesion in various cancers, is associated with TMZ resistance, and can be activated by TGF-β. The TGF-β signaling pathway is activated when TGF-β binds to TGF-β receptor II, which then recruits and phosphorylates TGF-β receptor I. This activation subsequently triggers the SMAD signaling pathway and leads to carcinogenic mutations through the activation of the PI3K/AKT and RAS/MAPK pathways, thereby selectively resisting the cell growth inhibition of TGF-β or the p53 pathway. Connective tissue growth factor (CTGF) is a secreted protein belonging to the CCN family. TGF-β regulates CTGF through the SMAD and ERK1/2 signaling pathways. CTGF contributes to TMZ resistance by promoting the expression of anti-apoptotic survival proteins and transformase inhibitor proteins, or by inhibiting the expression of the pro-apoptotic PARP. Targeting the TGF-β/CTGF signaling axis may provide new strategies for overcoming TMZ resistance [57].

5.9. Wnt/β-Catenin signaling pathway

The Wnt signaling pathway plays a crucial role in different stages of central nervous system development, and its activation can lead to TMZ resistance. miR-505 acts as a tumor suppressor to inhibit tumorigenesis in GBM. TMZ can increase the level of miR-505, and the combination of pri-miR-505 and TMZ can promote miR-505 mediated inhibition of GBM cells. miR-505 inactivates the Wnt/β-catenin signaling pathway by directly targeting and inhibiting WNT7B. The induction of miR-505 combined with TMZ therapy may be an effective therapeutic strategy for GBM inhibition [58].

Additionally, mannose inhibits MGMT, enhances the sensitivity of glioma cells to TMZ, and participates in Wnt/β-catenin pathway. Mannose may be a potential innovative drug for improving the treatment of gliomas, especially TMZ-resistant gliomas with high MGMT [59].

GBM is characterized by high incidence, treatment tolerance, and recurrence. However, the molecular events controlling the chemotherapeutic resistance to TMZ remain elusive. The WNT signal is amplified by TMZ and mediates the drug response of GBM. MGMT redundancy contributes to WNT-mediated chemotherapy resistance and is highly correlated with p53 mutation status. In p53 mutated GBM, the loss of p53 function downregulates miR-34a expression. miR-34a normally inhibits WNT ligand 6 (WNT6) transcription by binding directly to the 3′ UTR of WNT6 mRNA. The reduction of miR-34a leads to the activation of WNT signaling and contributes to WNT-mediated TMZ resistance. Combining TMZ with WNT inhibitors or miR-34a mimics enhances drug sensitivity in p53-mutant GBM cells and prolongs survival in xenografted mice. The results of this study provide insights into the molecular mechanisms underlying the chemoresistance of GBM to TMZ and facilitate the development of novel therapeutic strategies for p53-mutant GBM by targeting the miR-34a/WNT6 axis [60].

6. Mechanism of drug resistance involving glioma stem cells (GSC)

GSC can self-renew, continuously differentiate, and proliferate indefinitely, which is considered one of the reasons for glioma progression and drug resistance. Sex-determining region Y (RY)-box9 protein (SOX9) is a transcription factor expressed in most solid tumors. SOX9 overexpression inhibits apoptosis and promotes cell proliferation, invasion, and migration. Moreover, SOX9 knockdown in GBM cell lines significantly inhibits stem-like properties, including stem cell marker expression and glioma cell globule formation, suggesting that SOX9 regulates GSC self-renewal [61].

Pyruvate dehydrogenase kinase 1 (PDK1) is the downstream target of SOX9. PDK1 activity impacts the self-renewal of GSCs in GBM; its inactivation inhibits glioma cell sphere formation and significantly sensitizes these spheres to TMZ. PDK1 activity regulates the level of phosphorylated AKT, which also affects TMZ resistance. In conclusion, the SOX9-PDK1 axis is a key regulatory pathway of GSC self-renewal and plays an important role in TMZ resistance [62].

LINC00174 downregulation reduces the chemotherapeutic resistance of human glioma cells to TMZ by modulating the miR-138-5p/SOX9 axis. TMZ is one of the most commonly used drugs in glioma chemotherapy; however, it usually has a limited therapeutic effect on gliomas owing to its resistance. Long non-coding RNAs (lncRNAs) play key regulatory roles in various physiological and pathological processes. LINC00174 can promote the growth of colorectal cancer cells; however, the function and potential therapeutic modalities of LINC00174 in gliomas remain unclear. The results indicate that LINC00174 is highly expressed in glioma tissues, and its downregulation can significantly inhibit cell proliferation and promote apoptosis in both normal and TMZ-resistant glioma cells. Mechanistic studies have shown that LINC00174 can sponge microRNA-138-5p (miR-138-5p) and downregulate its expression, thereby upregulating the target of miR-138-5p and the level of SOX9 protein. In addition, in vivo studies have shown that LINC00174 shRNA exerts tumor-suppressive effects by downregulating SOX9 expression in gliomas. A previous study systematically investigated the newly established LINC00174/miR-138-5p/SOX9 axis regulatory pathway, which may offer a new approach for glioma treatment [63].

The dysregulation of transcription factors is a common issue in human cancers. SOX9 is a key transcription factor that is involved in many diseases, including cancer. The expression of SOX9 is regulated by microRNA (miRNA), methylation, phosphorylation, and

acetylation. Interestingly, SOX9 acts as a proto-oncogene or tumor suppressor, depending on the type of cancer. Recent studies have reported the key role of SOX9 in the regulation of the tumor microenvironment (TME). Furthermore, the activation of SOX9 signaling and the pathways it regulates play crucial roles in cancer onset and progression. There is also growing evidence that SOX9 acquires stem cell characteristics to induce EMT. In recent decades, SOX9 has been extensively studied in cancer stem cells (CSC) and the EMT. However, the link between SOX9 and cancer resistance was not discovered until recently. In addition, its differential expression may serve as a potential biomarker for tumor prognosis and progression. This review discussed the various biological implications of SOX9 in cancer progression and resistance and elucidated its signaling networks, which may be potential targets for the design of novel anticancer drugs [64].

7. Mechanism of drug resistance involving TME

7.1. Low oxygen microenvironment

Hypoxia is considered the main feature of EMT and can activate EMT-related signaling pathways through various mechanisms, such as the upregulated expression of EMT-related transcription factors and repressors. Under hypoxia conditions, the NF-**κ**B and Notch signaling pathways that directly trigger EMT are activated. Hypoxia also increases ROS levels, promoting cell proliferation and inducing EMT through the TGF-β signaling pathway [65].

Hypoxia is considered a major feature of the TME and a potential factor in the CSC phenotype and enhanced tumor ability. The acidic microenvironment surrounding hypoxic cells is associated with the activation of proteases that promote metastasis. Owing to abnormal angiogenesis and their inaccessible location, hypoxic cells are less likely to accumulate therapeutic concentrations of chemotherapeutic drugs, resulting in therapeutic resistance. Therefore, targeting the hypoxic CSC niche in combination with chemotherapy may be a promising strategy for eradicating CSC [66].

Hypoxia-inducing factor (HIF) is the most important transcription factor related to hypoxia, and HIF-1α can promote the malignant progression of GBM under hypoxia conditions. The combination of HIF targeted therapy and TMZ reduces the occurrence of tumors and significantly improves the sensitivity to chemotherapy. The HIF-1α/HIF-2α/miR210-3p network promotes the malignant progression of GBM through a positive feedback loop with epidermal growth factor and induces GBM cells to generate GSCs. HIF knockdown can inhibit cell cycle arrest and promote cell proliferation, thus enhancing chemotherapy sensitization in GBM [67]. A hypoxic microenvironment can mediate resistance to chemotherapy, which is of great significance in the treatment of GBM.

HIF1α promotes the malignant progression of GBM under hypoxia conditions, leading to poor prognosis of GBM patients. However, none of the treatments targeting HIF1α in GBM have successfully eradicated the tumor. Researchers found that targeting both HIF1α and HIF2α increased tumor volume. However, combining HIF1α/HIF2α targeted therapy with TMZ reduced tumorigenicity and significantly increased chemotherapy sensitivity. In addition, miR-210-3p induces the expression of HIF1α and inhibits the expression of HIF2α, suggesting that miR-210-3p regulates the expression of HIF1α/HIF2α. Epidermal growth factor (EGF) can upregulate the expression of HIF1α under hypoxia. However, one study reported that in addition to the previously mentioned signaling pathways, the upstream proteins HIF1α and HIF2α induce EGF expression by binding to the sequences AGGCGTGG and GGGCGTGG. In summary, within the hypoxic microenvironment, the HIF1α/HIF2α-miR210-3p network promotes the malignant progression of GBM through a positive feedback loop with EGF. Moreover, under hypoxic conditions, differentiated GBM cells further differentiate into glioma stem cells. Knocking out HIF1α and HIF2α inhibits cell cycle arrest, promotes cell proliferation, reduces dryness, and enhances chemical sensitization of GBM cells. Thus, both HIF1α and HIF2α regulate the proliferation, differentiation, and chemotherapy resistance of GBM cells through specific pathways, which is of great significance for the treatment of GBM [68].

HIF1 is the main factor in hypoxia activation and is an important driver of tumor progression in GBM patients. HIF-1α is a transcription factor regulated by the presence or absence of O2. HIF-1 expression is associated with high-grade glioma and aggressive tumor behavior. HIF-1 promotes tumor progression by activating angiogenesis, immunosuppression and metabolic reprogramming, as well as promoting cell invasion and survival. Furthermore, in GBM, HIF-1 is regulated not only by oxygen but also by carcinogenic signaling pathways such as MAPK/ERK, p53, and PI3K/PTEN. Therefore, inhibition of the hypoxic pathway may be an important therapeutic option for diseases with limited treatment options. This article reviewed the role of HIF-1 in the progression of GBM and the inhibitors studied to date, with the aim of advancing our understanding of this challenging disease [69].

8. Mechanism of drug resistance involving EGFR

EGFR is a protein kinase that can promote tumor growth, invasion, angiogenesis, and chemical resistance, as well as plays a significant role in the occurrence and development of tumors. Binding of EGFR to ligands can activate the Ras/Raf/ERK or PI3K/AKT/mTOR pathways, inhibiting autophagy and apoptosis, thereby resulting in a decline in TMZ efficiency. Decreased EGFR expression and inhibition of its pathway can help overcome TMZ resistance [70].

9. Mechanism of drug resistance involving miRNA

miRNAs play important roles in biological processes, such as cell proliferation and differentiation, by targeting protein-coding mRNA at the post-transcriptional level [71]. miRNAs are key regulatory factors in the mechanism of MDR, as they regulate the expression of target genes [72]. It is estimated that miRNAs control the translation of more than 50 % of the human genome. Thus, a specific target gene can be controlled by multiple miRNAs, and an miRNA can also be involved in the regulation of various target

mRNAs [73]. Several studies have highlighted the roles of miRNAs in carcinogenesis. Interestingly, the same miRNA molecules may act as suppressor genes and/or oncogenes, depending on the organ or tissue [74]. Dysregulated miRNAs have been found to alter cancer characteristics, including the evasion of growth suppressors; activation of invasion, metastasis, angiogenesis; and resistance to cell death. By injecting large amounts of cytotoxic chemotherapy drugs into the extracellular space, miRNAs play a crucial role in regulating MDR in glioblastoma by influencing the expression levels of MDR transporters. ABCG2 is a major member of the ABC transporter family and is highly expressed in GBM [75]. miR-328 targets and inhibits ABCG2 in GBM cells, thereby increasing their sensitivity to chemotherapy drugs [76]. Additionally, upregulation of miR-9 has been reported to inhibit ABC transporters, including MDR1, ABCC3, and ABCC6, thereby reversing MDR in GBM cells. MiR-381 is a common tumor-suppressing miRNA that is downregulated in GBM, and overexpression of miR-381 can effectively sensitize GBM U251 cells to TMZ by targeting multiple ABC transporters such as ABCG2, ABCC3, and ABCC5 [77].

MiR-1268a is another tumor suppressor miRNA that is downregulated in GBM. Li et al. reported that miR-1268a levels decrease after treating GBM cells with TMZ. They found that the overexpression of miR-1268a inhibits the protein translation of ABCC1 and reverses TMZ-induced upregulation of ABCC1. Conversely, downregulation of miR-1268a increases ABCC1 protein levels and enhances the upregulation of ABCC1 under TMZ treatment [78]. miR-10a, miR-195, and miR-455-3p are upregulated in TMZ-resistant GBM cells, while miR-181b and miR-181c are downregulated in TMZ-resistant GBM patients [79]. Nie et al. reported that miR-198 is downregulated in GBM patients. Patients with downregulated miRNA expression have a poor prognosis. In addition, in vitro and in vivo studies have shown that miR-198 overexpression is associated with increased chemical sensitivity to TMZ. This is achieved by targeting MGMT directly with miR-198 and inhibiting its protein translation. Therefore, miR-198 induces chemical sensitivity of GBM to TMZ by targeting MGMT [80]. Another study by Gao et al. found that transfection of TMZ-resistant GBM cells with miR-370-3p downregulates GBM and enhances cell sensitivity to anticancer drugs by inhibiting the DNA repair abilities of tumor cells. According to these findings, MGMT is a direct target of miR-370-3p and plays a key role in the miRNA-mediated reversal of MDR in GBM [81].

There are various types of miRNAs, and their regulatory networks are very complex. Mutations and abnormal miRNA expression can lead to drug resistance. miR-126-3p inactivates the Wnt/β-catenin signaling pathway by targeting SOX2, making GBM cells sensitive to TMZ. The expression of miR-126-3p is decreased in TMZ-resistant GBM tissues and cells. High levels of miR-126-3p enhance TMZ sensitivity by inhibiting cell viability, reducing colony formation potential, and inducing apoptosis. In addition, SOX2 is identified as a downstream target of miR-126-3p. Conversely, SOX2 overexpression conferred resistance to TMZ in GBM cells. Moreover, mir-126-3p-mediated TMZ sensitivity was reversed by increased SOX2 expression. Furthermore, mir-126-3p-induced inactivation of Wnt/β-catenin signaling was substantially eliminated by SOX2 upregulation [82].

The abnormal expression of specificity protein1 (Sp1) is involved in GBM development and metastasis. Sp1 expression is upregulated in GBM cell lines, while miR-130a-3p expression is downregulated; Sp1 is a confirmed target of miR-130a-3p. Elevated levels of miR-130a-3p inhibit the proliferation, migration, and TMZ resistance of GBM cells. However, Sp1 overexpression disrupts the inhibition of miR-130a-3p. The functional interaction between miR-130a-3p and Sp1 in GBM initiation and progression suggests potential therapeutic targets for this disease [83].

10. Nano-delivery systems can improve drug resistance

Nanomedicine therapy aims to overcome cancer drug resistance by offering alternative drug delivery methods. This emerging approach improves therapeutic outcomes while reducing harmful side effects on normal tissues. Cancer drug resistance is a complex process involving multiple mechanisms. Flexible, rapid drug design, and production capabilities of novel nanomedicine based on tumor gene profiles can be created, making drug selection for individual patient treatment more intensive and effective. With the emergence of advanced design and alternative drug delivery mechanisms for different nanomedical drugs, including liposomes, polymer couplings, micelles, dendrites, and carbon-based and metal nanoparticles, overcoming various forms of multidrug resistance shows promise and opens new horizons for cancer therapy [84].

The activation of RTK proteins is often observed in the malignant progression of gliomas. A study showed that crosstalk activation of EGFR and mesenchymal epithelial transformation factor signaling pathways contributes to TMZ resistance, leading to poor prognosis in GBM patients. In order to simultaneously reduce the activation of EGFR and MET, researchers conjugated herbin3 and cMBP to the surface of MPC nanoparticles modified with NHS-PEG8-Mal, creating a bi-functional brain-targeting nano-inhibitor, BIP-MPC-NP. In TMZ-resistant gliomas, DNA damage repair is weakened and TMZ sensitivity is enhanced through TTP-mediated downregulation of E2F1 in the presence of BIP-MPC-NP. In vivo magnetic resonance imaging showed that BIP-MPC-NP and TMZ injections significantly inhibited tumor growth and prolonged survival time. These results suggest that this nano-inhibitor holds promise as a viable strategy for overcomingto overcome TMZ resistance in gliomas [85].

To overcome the limitations of treatment, studies have shown that the nanoapproach is a suitable solution for enhancing drug accumulation in brain tumor tissues while reducing systemic toxicity. The drug delivery system used to overcome MGMT-mediated GBM resistance primarily delivers MGMT inhibitors and gene therapy to regulate MGMT gene expression [86].

11. Expectation

A clear understanding of the mechanism of TMZ resistance is of great significance in improving the postoperative prognosis of GBM patients, but clinical practice has shown that about 50 % of patients show resistance to TMZ. The mechanism of GBM resistance against TMZ suggests that the tumor-specific DNA repair vulnerability of GBM can be targeted, and the combination of inhibitors with specific drug resistance targets may improve the sensitivity of GBM to TMZ. For example, the combination of MGMT inhibitors and base

excision repair site inhibitors (such as PARP-1) in the treatment of GBM patients is completely feasible in theory, but clinical practice has shown that when PARP-1 inhibitors are used together with drugs inducing DNA damage, bone marrow suppression is induced, limiting its promotion and application. Although, the drug resistance of TMZ is the most intractable problem. Thus, new drugs urgently need to be developed for GBM treatment or combined therapies.The study found that the second-generation small molecule multiCDK inhibitor AT7519 is a potential drug for GBM treatment according to high-throughput screening.Furthermore, AT7519 also inhibited thephosphorylation of CDK1/2 and arrested the cell cycle at the G1-S and G2-M phases. More importantly, AT7519 induced intrinsicapoptosis and pyroptosis via caspase-3-mediated cleavage of gasdermin E. The results shown tumor volume was significantly reduced after treatment with AT7519 [87].Now, Nicotinamide phosphoribosyltransferase (NAMPT) has become a new target for many diseases, especially cancer including GBM. Therefore, varieties of NAMPT inhibitors have been researched, dual-targeted being one. However, most NAMPT inhibitors possess some limitations, such as toxicity and poor pharmacokinetic properties.Recentl, research on discovering more efficient and less toxic dual-targeted NAMPT inhibitors with desirable pharmacokinetic properties has drawn attention [88].Recently, several novel activators and inhibitors of NAMPT for neuroprotection and anti-cancer have been researched, respectively.However, NAMPT activators are still in basic research, and only a few NAMPT inhibitors have entered the clinical stage. Novel drug design strategies such as proteolytic targeting chimera (PROTAC), antibody-drug conjugate (ADC), and dual-targeted inhibitors also offer new directions for the development of NAMPT inhibitors [89]. A research reported a novel way for the treatment of NAPRT-silenced GBMs using nanoparticle (NP)-encapsulated NAMPTis administered by convection-enhanced delivery (CED). Researchers demonstrated that GMX1778 (a NAMPTi) can be formulated in degradable polymer NPs with retention of potency for NAMPT inhibition and anticancer activity in vitro, plus sustained drug release in vitro and in vivo. Meanwhile, The result shown that CED of NP-encapsulated GMX1778 to NAPRT-silenced intracranial GBM xenografts in mice exhibit significant tumor growth delay and extends survival [90]. Activation of Nrf2 is regarded as a potential preventive and therapeutic strategy. However, aberrant hyperactivation of Nrf2 is found in a variety of cancers and promotes cancer progression and metastasis. Moreover, constitutive activation of Nrf2 confers cancer cells resistance to chemo- and radio-therapy. Thus, inhibiting Nrf2 could be a new therapeutic strategy for cancer [91]. A variety of inhibitors have been gradually reported, including PARP/PARG inhibitors, Akt inhibitors and so on.Therefore, the identification of GBM-related molecular biomarkers and an in-depth understanding of the regulation of signaling pathways are of great significance, suggesting that the use of active but safe drug combinations will effectively treat GBM. The mechanism underlying TMZ resistance in GBM is relatively complex. In addition to the drug resistance mechanism, there are other mechanisms such as GBM stem cells that promote drug resistance, autophagy, mRNA, and lncRNA interactions to reduce the therapeutic effect of chemotherapy drugs. Moreover, there may be other underlying mechanisms that are still unclear. Further research will identify additional methods to overcome drug resistance and enhance efficacy, improving the therapeutic effect on GBM and benefiting more patients.

CRediT authorship contribution statement

Hao Wu: Writing – review & editing, Writing – original draft, Visualization, Supervision. **Wenwen Gao:** Methodology. **Peng Chen:** Data curation. **Yao Wei:** Formal analysis. **Haikang Zhao:** Resources. **Fenglu Wang:** Investigation.

Declaration of competing interest

The author reports no conflicts of interest in this work.

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