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REVIEW ARTICLE

# Novel sights on therapeutic, prognostic, and diagnostics aspects of non-coding RNAs in glioblastoma multiforme

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## Abstract

Glioblastoma Multiforme (GBM) is the primary brain tumor and accounts for 200,000 deaths each year worldwide. The standard therapy includes surgical resection followed by temozolomide (TMZ)-based chemotherapy and radiotherapy. The survival period of GBM patients is only 12–15 months. Therefore, novel treatment modalities for GBM treatment are urgently needed. Mounting evidence reveals that non-coding RNAs (ncRNAs) were involved in regulating gene expression, the pathophysiology of GBM, and enhancing therapeutic outcomes. The combinatory use of ncRNAs, chemotherapeutic drugs, and tumor suppressor gene expression induction might provide an innovative, alternative therapeutic approach for managing GBM. Studies have highlighted the role of Long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) in prognosis and diagnosis. Dysregulation of ncRNAs is observed in virtually all tumor types, including GBMs. Studies have also indicated the blood–brain barrier (BBB) as a crucial factor that hinders chemotherapy. Although several nanoparticle-mediated drug deliveries were degrading effectively against GBM in vitro conditions. However, the potential to cross the BBB and optimum delivery of oligonucleotide RNA into GBM cells in the brain is currently under intense clinical trials. Despite several advances in molecular pathogenesis, GBM remains resistant to chemo and radiotherapy. Targeted therapies have less clinical benefit due to high genetic heterogeneity and activation of alternative pathways. Thus, identifying GBM-specific prognostic pathways, essential genes, and genomic aberrations provide several potential benefits as subtypes of GBM. Also, these approaches will provide insights into new strategies to overcome the heterogenous nature of GBM, which will eventually lead to successful therapeutic interventions toward precision medicine and precision oncology.

**Keywords** GBM · LncRNA · miRNA · Nanoparticles · Prognosis

## Introduction

Brain cancer accounts for 1.2% of the various cancers, with 17,000 new cases yearly, especially in the USA. The Central Nervous System consists of the brain and spinal cord and aids in giving motor signals by processing sensory information. They control processes such as thoughts, hormone secretion, movement, heartbeats, and respiration (Controlled by the Brain stem). The various cancers found in the brain in children are Astrocytoma, Ependymoma, Diffuse Intrinsic Pontine Glioma (DIPG), Germ cell Tumors, and Medulloblastoma (Packer et al. 2008; Warren 2012). In adults, along with the above types, additional benign tumors like Oligodendroglial tumors in the temporal or frontal lobe, mixed gliomas, Pineal Parenchymal tumors in the pineal region, Craniopharyngioma, a rare type found at the anterior end of the brain just above the pituitary gland, and Meningeal tumors in the surrounding layers of the brain and spinal cord called meninges have been detected. (Farwell et al. 1977; Jeuken et al. 2004; Lutterbach et al. 2002). In GBM, Grades I-II belong to lower-grade gliomas (LGG) [angiocentric glioma and diffuse astrocytoma], and high-grade glioma (grade III-IV) include mesenchymal astrocytoma and GBM (Louis et al. 2007, 2016). The classification is based on isocitrate dehydrogenase (IDH1), alpha-thalassemia/mental retardation, X-linked (ATRX), tumor suppressor protein (TP53), and 1p/19 (Yang et al. 2016; Han et al. 2018). Most primary

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GBM cancers are wild-type IDH, while secondary GBM develops from lower-grade glioma and carries mutations in IDH. (Ohgaki and Kleihues 2013).

Intense research and investigations on palliative care remain essential during various stages of GBM. Emerging studies have identified the potential use of TMZ in $O^6$-methylguanine-DNA-methyltransferase (MGMT) methylated genetic background and anaplastic glioma. Emerging studies have revealed BBB and tumor microenvironment (TME) as significant challenges for disease therapy (Tan et al. 2020). Bioinformatics analysis identified overexpression of a few genes such as Cell Adhesion Associated, Oncogene Regulated (BOC), Elongation of very long chain fatty acids protein 6 (ELOVL6), Vascular endothelial growth factor C (VEGFC), etc. The molecular aberrations in GBM include mutations in the p53 gene, Retinoblastoma, PI3K-Akt signaling, EGFR signaling, Neurogenic locus STAT homolog protein 1 (NOTCH 1), and NOTCH 2 signaling, etc. (Brennan et al. 2013). The essential gene that dictates a patient's survival and responsiveness towards TMZ is MGMT. Methylation of MGMT promoter results in an increased survival rate when compared with the hypomethylated state. MGMT repairs the $N^7$ and $O^6$ positions of guanine, alkylated by TMZ. Kato et al. 2010 have reported that small interfering RNA (siRNA) targeting MGMT can enhance the ability of TMZ-induced cytotoxic effects.

Interestingly, $O^6$-Benzylguanine ($O^6$-BG) and $O^6$-(4-Bromothenyl) guanine ($O^6$-4-BTG) can access pseudo substrates and inhibit the catalytic activity of MGMT protein (10 q26.3). In addition, miRNAs such as miR-142, miR-181d, miR-221, miR-222, miR-603, and miR-767-3p bind to 3' untranslated region (3'UTR) of MGMT and lead to degrade the mRNA. Studies by Matthew H. Kulke et al. 2009, have shown that the therapeutic efficiency of TMZ was enhanced during lower levels of MGMT (Yu et al. 2020). Identifying the molecular targets of GBM involved in disease pathogenesis and developing small molecules is essential to anticancer therapy. The nervous system cancers include astrocytoma, ependymoma, glioma, meningioma, medulloblastoma, and neuroblastoma. Chemotherapy has a role in treating almost all newly diagnosed diffuse gliomas (WHO I-IV). Emerging studies have identified potential benefits using TMZ for grade IV GBM, Procarbazole, and Vincristine for grade II and grade III cancers. Several alternatives for GBM care include systemic therapies and combined modality therapy. Furthermore, there are several factors, such as tumor size and Karnofsky's performance score (KPS). Interestingly, the tumor-treating fields (TTFields) with TMZ represent an effective therapeutic strategy for GBM therapy (Hottinger et al. 2016). In GBM cancers and GBM cancer stem cells (GSCs), several chromosomal alternations such as recurrent copy number changes, polysomy (chromosome 7), monosomy (chromosome 10), loss of chromosome 10 q, and deletions in 9p21, as well as cancer stemness markers such as CD15, CD31, CD34, CD45, CD133, CD90 lead to genomic instability and cancer stemness (Pesenti et al. 2019). The other genomic alterations include amplification of epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR), aberrations in RTK/Ras/PI3K signaling pathways, frequent mutations including alterations in Neurofibromatosis type 1 (NF1), Phosphatase and Tensin Homolog (PTEN), Mouse double minute 2 homolog (FGF), and telomerase reverse transcriptase (hTERT) (Reifenberger et al. 1993; Verhaak et al. 2010; Heidenreich et al. 2015). ncRNAs, a significant portion of the transcriptome that do not appear to have protein-coding functions, are crucial in various biological processes, including disease development (Sun and Chen 2020). ncRNAs are junk transcriptional products that regulate various cellular processes such as chromatin remodeling, transcription, post-transcription, and cancer signaling pathways. These pathways were broadly classified into oncogenic and tumor suppressive in nature. (Wang et al. 2019). Completing an understanding of ncRNAs will provide useful insights for better therapy against various diseases including cancer. LncRNAs, small interfering RNA (siRNA), enhancer RNA (eRNA), circular RNA (circRNA), Y RNA, miRNA, and piwi-interacting RNA (piRNA) are classified as regulatory ncRNAs. In contrast, ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), telomerase RNA (TERC), tRNA-derived stress-induced RNAs (tiRNA), tRNA-Derived Fragments (tRF), and Small nucleolar RNA (snoRNA) classified as housekeeping ncRNAs (Zhang et al. 2019) rRNAs and tRNAs play a role in protein translation and that lncRNAs and miRNAs can control the expression of genes (Decoding noncoding RNAs). Targeting many transcripts that encode regulators of cell-cycle progression, migration, invasion, and metastasis (Ma et al. 2010; Kim et al. 2016; El Fatimy et al. 2017). miRNAs and lncRNAs are effective biomarkers for predicting treatment outcomes or monitoring therapeutic responses. Additionally, ncRNAs function as a nuclear receptor response element mimic for glucocorticoid receptor (GR), which reduces the expression of oncogenic miRNA and increases apoptosis while reducing proliferation, invasion, and migration (Zhang et al. 2013; Zhao et al. 2015). ncRNAs reduce the production of genes that improve lipid synthesis (SCAP, SREBP-1), proliferation (CDK6), and apoptosis (MCL-1), as well as B cell proliferation (Garzon et al. 2009; Santanam et al. 2010; Ru et al. 2016). The present review focuses on the emerging aspects of therapeutic, prognostic, and diagnostic aspects, as well as drug delivery approaches against GBM cancer. The regulation of

various genes involved in cancer cell proliferation by miRNA and lnc RNA.

## Drugs and importance

GBM patients have a survival period of 12–15 months. Most therapeutic drugs in clinical trials impair pathological processes of glioma formation and thus improve quality of life. Recent high-through-hit identification (hit-ID) strategies such as high throughput screening, DNA encoded library screening, and fragment-based drug identification led to drug discovery (Silvestri and Colbon 2021). Also, emerging trends have indicated that Drug repurposing is a novel concept for effectively treating cancers and many other health disorders. Also, drug repurposing saves time and is cost-effective (Tan et al. 2018). TMZ is the standard drug with 100% bioavailability and lipophilicity in GBM cancer therapy. In several GBM cases, the high expression of MGMT resulting unresponsiveness to chemotherapeutic drugs and enhancement in the GSCs. This indicates the need to focus on identifying effective therapeutic drugs against GBM cancers (William et al. 2018). To date, Food and Drug Administration (FDA) has approved several drugs such as Lomustine, Carmustine, Bevacizumab, carmustine wafer implants, Dabrafenib, Trametinib, Afinitor, Belzutifan, Danyelza, Welireg, and Tafinlar (Hadjipanayis and Stummer 2019; Odogwu et al. 2018; Novartis 2016; Fallah et al. 2022; Mullard 2021) (Fig. 1). Also, it is imperative to identify the specific, and effective drug molecules that specifically target the GBM cancer tissue and BBB, cancer stem cells, etc. The GBM anticancer drugs ideally possess less than 500 Da. The effective entry of drugs can be prevented by various proteins such as organic anion transporting polypeptide 1A2 (OATP1A2/SLCO1A2), organic anion transporter 3 (OAT3/SLC22AB), p-glycoprotein (P-gp), multi-drug resistance-associated protein 4 (MRP4/ABCC4), monocarboxylate transporter 1 (MCT1/SLC16A1) (Urquhart and Kim 2009).

Recent drug developments have suggested using high throughput (HTS), microwave-assisted organic synthesis (MAOS), combinatorial chemistry, and medicinal chemistry for drug discovery. The genomic-wide association studies (GWAS) about metabolic modeling, transcriptomic data, as well as system biology data have indicated that GBM patients with low survival periods have upregulated glycine (cytosol), methionine (cytosol), L-methionyl-tRNA (met)

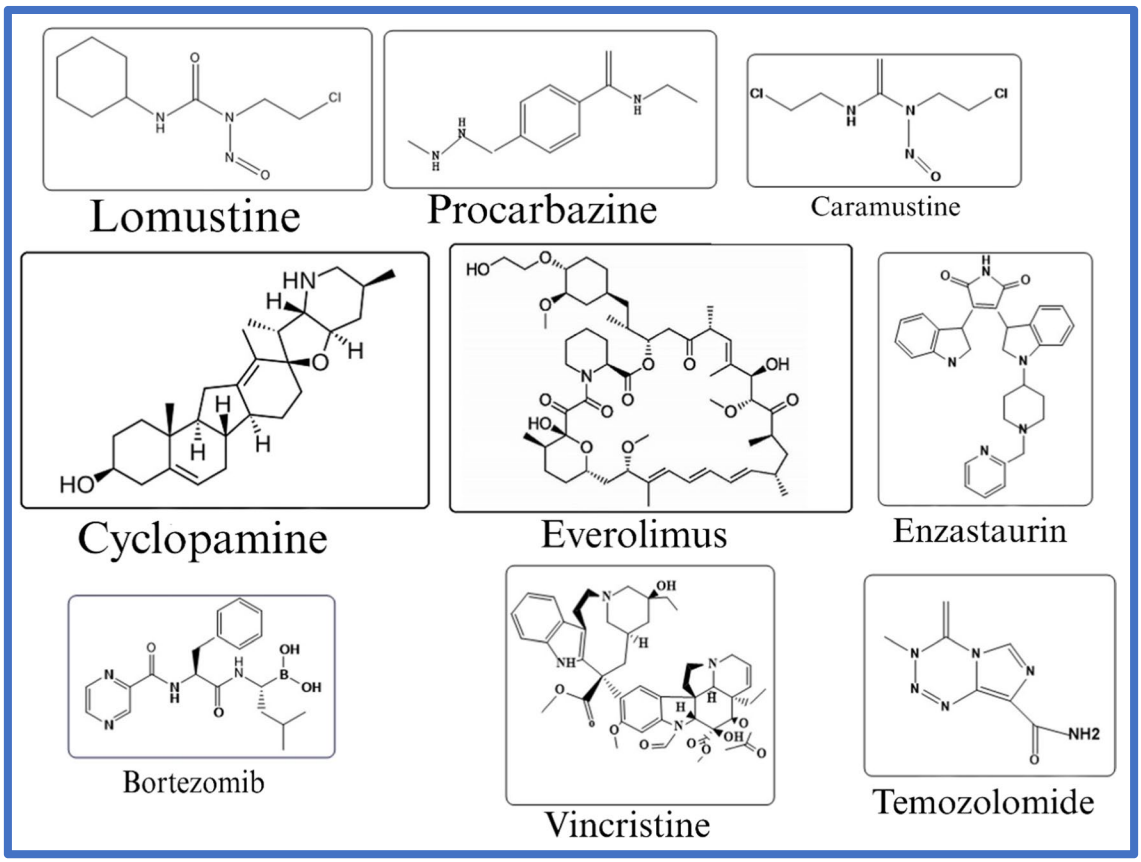


**Fig. 1** Chemotherapeutic molecules employed in GBM therapy

(cytosol), formate (mitochondria) and low levels of heparin sulfate precursor 14 (Golgi apparatus), taurine ( extracellular), trichloroacetate ( cytosol), etc. (Larsson et al. 2020).

## Drugs in clinical trials and their importance

Drugs involved in clinical trial II against GBM are multikinase inhibitors, Poly ADP-Ribose Polymerase Inhibitor, proteasome inhibitors, Stromal Cell-Derived Factor Chemokine Receptor Type-4 (CXCR-4) Inhibitors, G-protein coupled receptor antagonists, BRAF inhibitors, etc. (Wang et al. 2021b). To date, only one drug that has reached clinical trial phase III is Bevacizumab, which is presently approved for GBM cancer therapy. Emerging studies have indicated that various drugs such as Tyrosine kinase inhibitors inhibit various tyrosine kinases such as Vascular endothelial growth factor receptor 1 (VEGFR1), Fibroblast growth factor receptor (FGFR), PDGFR, etc., and were found to inhibit tumor angiogenesis (Wilhelm et al. 2011). Several proteasome inhibitors disrupt the cell cycle and are also known to inhibit the proteasomal degradation of several proteins (Yin et al. 2005). Bortezomib inhibits angiogenesis and cytokine signaling and enhances chemotherapy by enhancing apoptosis (Yin et al. 2005). Iniparib (4-iodo-3-nitrobenzamide) (i.e., prodrug) and PARP inhibitor were used to treat breast cancer, pancreatic cancer, and GBM. Researchers have identified that Iniparib facilitates the release of the radical nitro ion that binds to selenium protein and thus enhances redox condition and cellular cytotoxicity (Fogelman et al. 2011; O'Shaughnessy et al. 2011). In addition, BRAF belongs to the serine-threonine kinase family and is an oncogene participating in the RAS-RAF-MEK-ERK pathway. Interestingly, mutation BRAFV600E was observed in 50% of anaplastic ganglions, xanthoastrocytomas, and high-grade gliomas (Chi et al. 2013; Brennan et al. 2013; Schindler et al. 2011). The most important drugs that are useful for treating GBM are presented below.

### Lomustine (CCNU)

Chemotherapeutic drugs are also considered primary therapeutic agents to treat GBM. Lomustine was an approved drug for treating recurrent high-grade glioma (HGG). CCNU is an alkylating agent that crosslinks DNA as well as RNA in dividing cells, thereby inducing apoptosis in tumor cells. In GBM patients, CCNU is administered orally at 80–110 mg/$m^2$ every 6 weeks (Wirsching et al. 2014; Wick et al. 2017). Wick et al. conducted a randomized clinical trial (RCT) with CCNU in combination with Bevacizumab, which improved overall survival (Weller and Rhun 2020). Common toxicities of chemotherapeutics were hematologic toxicity (49.7%) (Weller and Rhun 2020). CCNU was a critical factor in PCV (P: procarbazine, C: Lomustine, V: Vincristine) regimen against HGG (Lassen et al. 2014).

### Carmustine: (BCNU; bis-chloroethyl nitrosourea)

The FDA approved Carmustine to treat HGGs (Hadjipanayis and Stummer 2019). Walker et al. conducted an RCT that reported a median overall survival (O.S.) of 11.75 months (Walker et al. 1978). Currently, BCNU is only FDA-approved to treat recurrent GBM. Surprisingly, Carmustine induces several nonspecific effects on normal lung and eye cells and pulmonary and ocular toxicity.

### Carmustine wafer implants

The FDA approved carmustine wafer implants for recurrent HGGs 2003 (Hadjipanayis and Stummer 2019).

### Bevacizumab

Bevacizumab (BVZ) is FDA-approved drug as a monotherapy and combined with Irinotecan (Cohen et al. 2013; Vredenburgh et al. 2007). In several clinical trials, combining Etoposide and Carboplatin with Bevacizumab has exhibited potential benefits against recurrent GBM (Carrillo et al. 2014; Mrugala et al. 2012) (Fig. 1; Table 1).

### Temozolomide

TMZ, an oral alkylating agent, is the first-line treatment for GBM, resistance to TMZ is a significant hurdle in GBM patients. The combination of TMZ, difluoromethylornithine (DFMO), an inhibitor of ornithine decarboxylase, and radiation in GBM cell lines resulted in consistently higher suppression of proliferation, causing cell-cycle arrest in the G2/M phase and caspase-8 activity (Alexiou et al. 2019).

## Nanoparticle-mediated drug delivery in GBM

Emerging studies have emphasized using nanoparticles to deliver chemotherapeutic drugs or agents specific to the tumor site. Thus, the application of nanoparticle-mediated drugs and siRNA delivery has enormous potential in drug discovery. These nanoparticles were classified as organic or inorganic (Bukhari et al. 2021). Throughout the body, the blood vessels supply nutrients and oxygen to various types of cells. It comprises endothelial cells, neurons, astrocytes, and pericytes (Keaney and Campbell 2015). BBB facilitates the movement of molecules with only molecular weight molecules of less than 500 Da. Nanoparticles carry small molecules such as siRNAs, miRNAs, and drugs into various

**Table 1** Drugs in clinical trials against GBM

| S.No | Drug | Clinical trial | Reference |
|---|---|---|---|
| 1 | TMZ | TMZ, an oral alkylating agent. The exposure to TMZ depletes the DNA-repair enzyme MGMT | Newlands et al. 1997; Stupp et al. 2001; Yung et al. 2000; Brock et al. 1998; Tolcher et al. 2003 |
| 2 | TMZ with tumor treating field (TTF) | Treatment with TMZ and alternating electric fields at 200 kHz (i.e., Optune™ therapy) inhibits mitotic spindle formation and cell division | Stupp et al. 2012, 2015, 2017; Tuszynski et al. 2016; Helekar et al. 2018; 2020; Helekar and Voss 2016; Hambarde et al. 2020 |
| 3 | Bortezomib | Bortezomib and 24 cycles of TMZ treatment caused an effective decrease in tumor volume | Tang et al. 2015; Stupp et al. 2005; Gilbert et al. 2014; Chinot et al. 2014 |
| 4 | TMZ with micellarized CYP (MCyp) | Cyclopamine (Cyp) is a Sonic Hedgehog (Shh) antagonist, Combined use of MCyp with TMZ causes a block in the Shh pathway and eliminates neurosphere formation | Liu et al. 2017 |
| 5 | TMZ with Nimotuzumab | Nimotuzumab, an anti-EGFR antibody in combination with TMZ, inhibited the tumor expressing the EGFRvIII when injected subcutaneously or in intracerebral mode | Nitta et al. 2016 |
| 6 | Enzastaurin and Lomustine combination | Inhibit the GBM tumor growth | Wick et al. 2010 |
| 7 | Lomustine and Bevacizumab | GBM Patients, when given Lomustine plus Bevacizumab (BEV), exhibit positive results in eliminating cancer | Wick et al. 2017 |
| 8 | PCV with Radiotherapy | 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU or Carmustine), Procarbazine, and Vincristine improve the survival time in patients suffering from GBM | Yang et al. 2007 |
| 9 | Nivolumab | Kills GBM cancer cells effectively | Reardon et al. 2020 |
| 11 | Lomustine | Lomustine is used against recurrent GBM and is employed to treat the anaplastic oligodendroglioma with 1p/19q co-deletion | Batchelor et al. 2013; Ren et al. 2021; Wirsching et al. 2014 |
| 12 | Glidael Wafers | Gliadel® 06-benzyl guanine (06-BG) wafer implantation increases survival benefits without added toxicity | Quinn et al. 2009 |

cells and tissues. Thus, it aids in preventing cancer, cardiac diseases, and diabetes. Recently, several attempts were made to effectively deliver siRNA and miRNA to inhibit RNA-dependent RNA polymerase (RdRP) and viral replication against COVID-19. Organic nanoparticles, including dendrimers, chitosan, etc., and inorganic, iron, zinc oxide, etc., were found to have future therapeutic utility against various cancers. The most important property of an ideal nanoparticle is biodegradability, biostability, ease of synthesis, and multiple modifications (Kozielski et al. 2019). Multiple nanoparticle modifications will allow the incorporation of small molecules, siRNAs, and antibodies in multiple systems for targeting cancer (Pourgholi et al. 2016). Most of these nanoparticles are in clinical trials.

Further, exploring nanoparticles provides better results for effective stabilization in the bloodstream or circulating system. These nanoparticles have considerable advantages in the future therapy of GBM cancer. Nanoparticles that deliver siRNA have amino groups on the outer surface (Weber et al. 2000). siRNA easily binds with the amino group. For example, the PAMAM nanoparticle has 64 amino groups, but the potential application of the PAMAM nanoparticle was limited due to heavy cytotoxic effects on normal cells (Wu et al. 2013). The other types of PAMAM dendrimer modifications include hydroxy, carboxy, etc. In addition, Magnetic nanoparticles were also utilized for the miRNA delivery, which will be further tracked in vivo animal model systems using the magnetic resonance analytic technique.

Nano-formulations generally have a lesser particle size, bulky surface area, reactivity, and several active sites with sufficient adsorption ability. The key advantages of the nanoparticle are increased drug absorption, bioavailability, and prolonged circulating time (Yin et al. 2020). SGT-p53 comprises wild-type p53 plasmid DNA in a cationic liposome containing transferrin receptor and single-chain antibody. This nano-complex crosses the BBB and sensitizes the TMZ resistant GBM (Kim et al. 2015). It was found that SGT-p53 reverses TMZ resistance via abrogation of MGMT and enhances the TMZ-induced cytotoxic effect in TMZ-resistant GBM (Kim et al. 2016). The various nanoparticles employed for GBM cancer therapy are liposomes, polymers, magnetic nanoparticles, etc. Further, the inhibitors used in nanoparticle-mediated drug delivery in GBM are interferon β (IFN β), Signal transducer, and activator of Transcription 3 (STAT3) inhibitor, etc. (Yoshino et al. 2009; Koh Saka et al. 2012; Bobustuc et al. 2010; Hirose et al. 2001). A mutant form of p53 was observed in both primary and secondary GBM, and thus improving wild-type p53 has a beneficial effect (Steele and Lane 2005; ShChors et al. 2013). Transferrin receptor (TfR) is a receptor that was widely expressed in BBB and GBM cells (Ramalho et al. 2022; Voth et al. 2015). Interestingly, Transferrin receptor 1 was found to control the rate of iron uptake by fine-tuning the amount of iron delivered to the cells to meet metabolic needs (Cazolari et al. 2007). Recent studies have identified the critical hurdles in GBM therapy, such as the inability to cross BBB and ineffective penetration in the BBB.

### Liposome (Yang et al. 2012)

The initiation, progression, of GBM cancer was dysregulation due to differential changes in miRNAs. Thus, targeting dysregulated miRNA with various oligonucleotides has clinical limitations, including poor RNA stability, off-target effects, and inefficiency in crossing the BBB. The BBB was found to prevent many small molecule drugs from entering the brain tumor environment. However, focused ultrasound (FUS) combined with intravenous microbubbles (MBs) have shown a promising result and enhanced the BBB permeability. Interestingly, modified liposomes (i.e., liposomal-doxorubicin) targeting Interleukin-4 (IL4) receptor has exhibited promising result in nonobese diabetic-severe combined immunodeficiency (NOD-scid) mice. Both drug delivery, and survival of NOD Mice of GBM cancer was enhanced.

### Polymers

Several copolymers include polyethylene glycol (PEG), polypropylene glycol (PPG), and poly(L-lysine). These copolymers have properties such as self-assembly, siRNA binding, particle size, surface potential, the architecture of the complexes, and siRNA delivery. Silencing of green fluorescent protein (GFP) using copolymer to deliver GFP-specific siRNA to Neuro-2a cells expressing GFP was almost as effective as using Lipofectamine 2000, with minimal cytotoxicity. Thus, the copolymer platform for siRNA delivery exhibited improved siRNA delivery in vitro and in vivo (Dai et al. 2014). Recent studies have identified that specifically designed siRNA bind and induce post-transcriptional silencing of target genes (mRNA).

### Magnetic hyperthermia therapy

Magnetic Hyperthermia Therapy (MHT) is a modern, advanced therapeutic option for treating GBM. Hyperthermia therapy (H.T.) involves exposure of a body region to elevated temperatures to achieve and potential anticancer effect. This includes radiofrequency, ultrasound, microwave, laser, and magnetic nanoparticles (MNPs) (Mahmoudi et al. 2018).

## Gold nanoparticle

Emerging studies have revealed that the surface reactivity of gold nanoparticles (AuNPs) has gained attention as a radiation therapy radiosensitizer for cancer cells and as a drug carrier to target cells. This calf thymus DNA with HAuCl4 solution as a radiosensitizer of human glioma cells with cancer stem cell (CSC)-like properties (e.g., U251MG-P1), to reduce their survival. The radiosensitivity of the AuNP-associated cells is significantly enhanced. Also, the generation of reactive oxygen species (ROS), apoptosis induction, or DNA damage was enhanced (Kunoh et al. 2019). In vivo, 1.9 nm nanoparticles were found to be toxic following intracerebral delivery in rats bearing glioma, while no toxicity was observed using 15 nm nanoparticles at the same concentration (50 mg/mL). Survival of rats that had received the combination of treatments (AuNPs:50 mg/mL, 15 Gy) was significantly increased compared with the survival of rats that had received irradiation alone (Bobyk et al. 2013). Gold-iron oxide nanoparticles (polyGIONs) surface loaded with therapeutic miRNAs (miR-100 and antimiR-21) inhibit GBM cancer cell proliferation and enhance apoptosis (Sukumar et al. 2019).

## Dendrimers

2,2-bis(methylol)propionic acid (Bis-MPA) as "nonviral vectors" for transfection of siRNA in cell cultures. The study encompassed dendrimers of generation one to four (G1–G4), modified to bear 6–48 amino end-groups, where the G2–G4 proved capable of siRNA complexation and protection against RNase-mediated degradation. The G2 dendrimers were nontoxic to astrocytes, glioma (C6), and GBM cancer cells (U87), while G3 and G4 dendrimers exhibited concentration-dependent toxicity towards primary neurons (Stenström et al. 2018). Specific properties in cancer cells compared to normal cells, such as overexpression of various receptors and differences in biological conditions like pH, temperature, and redox of tumor microenvironment, cause an increase in site-specific targeting efficiency. Thus, modifications of dendrimers through the attachment of lipids, amino acids, proteins/peptides, aptamers, vitamins, antibody were effective against GBM (Ghaffari et al. 2018). Studies also proved that Poly (amidoamine) (PAMAM) dendrimers are well-defined, highly branched macromolecules with numerous active amine groups on the surface. These N.P.s carry drugs and genes (pDNA, siRNA) and deliver them to cancer cells.

## Inorganic nanoparticles

Titanium dioxide nanoparticles ($TiO_2$NPs) have attracted interest due to their use in various applications. $TiO_2$NPs can enter the brain; toxicity was assessed at different levels: mitochondrial function (by MTT), membrane integrity, and cell morphology (by calcein AM/PI staining) after acute exposure at various doses ranging from 1.5 to 250 µg/ml for 7–10 days at sub-toxic concentrations (from 0.05 to 31 µg/ml). Prolonged exposure has revealed that the proliferative capacity (colony size) was compromised at the shallow $TiO_2$NP doses, such as 1.5 µg/ml and 0.1 µg/ml, respectively, for D384 and SH-SY5Y (Coccini et al. 2015).

## Polymicelles

Polymeric micelles are core–shell-type nanoparticles that act as promising nanoparticles due to their size, stability, and drug incorporation efficiency and release rate (Nishiyama et al. 2016).

## Quantum dots

Quantum dots (Q.D.) nano-transporters are Carbon quantum dots (CQDs) that were successfully functionalized with Mal-PEG-NHS linked RGERPPR. They exhibit double functions of both tissue imaging and targeting train gliomas (Devi et al. 2022).

## Nanogels

Nanogels are unique local tailorable drug delivery systems and consist of a three-dimensional polymeric network formed via physical or chemical assembly. Nanogel delivery systems (DPPC) with cell-penetrating peptides (CPP) are introduced into the astrocyte. DPPC is around 300 nm, the potential is about 0–5 Mv. The DPPC is verified as the `biocompatible carrier for further application by cell viability tests. The in vitro- constructed BBB model proves that Dipalmitoyl phosphatidylcholine (DPPC) can efficiently penetrate the BBB, attributed to both the temperature-sensitive passive targeting and the active cell-penetrating peptides (CPP) penetration. This indicates that the use of these nanoparticles acts effectively against glioma.

## Graphene

Graphene, graphene oxide, and reduced graphene oxide were considered promising for industrial and biomedical applications due to their high mechanical stiffness and strength. Synthesized techniques, such as liquid phase exfoliation and wet chemical oxidation, often require toxic organic solvents, surfactants, strong acids, and oxidants for exfoliating graphite flakes. The residual contaminants cause of graphene-induced toxicity in biological cells. Pooresmaeil and co-workers developed the pH-responsive magnetic (Fe3O4 NPs)/G.O. hybrids to deliver doxorubicin. Approximately

65% drug release was observed at 40 °C and pH 5.0 in cancer cells, which was 22% in normal cells (37 °C and pH 7.4) (Borandeh et al. 2021). Liu et al. 2012 fabricated electrically responsive rGO / poly (vinyl alcohol) (PVA) membranes for the delivery of lidocaine hydrochloride (Liu et al. 2012). The G.O. nanocarrier system has more advantages such as anti–tumor drug delivery systems, like liposomes, ① good blood compatibility and optimal dispersibility in the liquid environment of the human body (Daniyal et al. 2020); ② sizeable specific surface area facilitating multi-functional modification by biomolecules and small molecules, such as proteins and single–stranded DNA bases (Shahmoradi et al. 2018). (Wang et al. 2022).

### Nanopeptide-drug combination

Studies have indicated that platinum pro drug (Pt IV) was effectively transported into GBM tissue by M13 peptide, A cell-penetrating peptide transporter 10, that can deliver the drugs to the tumor site and inhibit the growth of the tumor**.** Emerging studies have identified the tumor homing peptide, also known as tumor-promoting peptides such as TT1 and its linear form Lin TT1 (AKRGARSTA), bind to cell surface receptors expressed on GBM cancer cells and follow the process of tumor accumulation and penetration. These peptides will process and generate the c-terminally expose a C-end rule motif RXXR/K-OH in TT1, which will further bind to another receptor neutrophilic-1 (NRP-1) which eventually results in endocytic/exocytic transcytosis, extravasation, and tumor penetration (Teesalu et al. 2013; Sugahara et al. 2009; Teesalu et al. 2009; Sharma et al. 2017). Recent studies have also indicated that Iron oxide nano worms (N.W.s) coated with LinTT1, a nanocarrier system optimized for peptide-mediated tumor targeting (Park et al. 2008, 2009, 2010; Agemy et al. 2011; Roth et al. 2012).

## Signaling pathways in GBM cancer

GBM (grade IV cancer) has poor patient survival. GBM cancers are primarily primary and are up to 90% in incidence. The majority of patients are in the elderly category. Secondary-grade GBM cancers are low-grade astrocytomas. The critical genetic alterations and pathway alterations in GBM were found to be p53, EGFR, PDGFR, PTEN, MDM2, phosphatidyl inositol-3-kinase PI3K/ Akt/ mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), nuclear factor-kappa beta (NF-kB), Wnt, STAT-3, and NOTCH pathway. Understanding the complex disease biology and the signaling provides effective therapeutic strategies and improves the prognostic and diagnostic aspects of GBM pathogenesis and prevention.

### $P^{53}$pathway

The p53 gene is a regulator and a critical tumor suppressor that induces cell-cycle arrest and apoptosis (Huang et al. 2007; Huse and Holland 2010), many of which are involved in tumor development and invasion. GBMs are divided into primary and secondary subtypes. Primary GBMs develop quickly and robustly, while secondary GBMs develop progressively from low-grade astrocytoma. p53 mutations are the most common development of secondary GBMs, whereas mutations in the p53 pathway are also detected in primary gliomas at a lesser frequency (St Louis et al. 1999; Ohgaki and Kleihues 2013). PTEN mutations were found to be widely mutated in high-grade gliomas (Lespagnard et al. 1999; Fulci et al. 2000). The chromosomal regions (chro 9p, chro 10q23.3, and chro10q25.26) that encompass genes such as CDK2A cyclin-dependent kinase 2A), CDK2B (cyclin-dependent kinase 2B), ARF, MDM2, EGFR, and PTEN were also found to be mutated or deleted. p53 protein expression was associated with significantly longer survival rates, as observed in univariate analysis. Also, it was found that in multivariate analysis of overall survival (Cox regression), only postoperative Karnofsky performance status remained as an independent prognostic factor (Birner et al. 2002). Inactivation of *p53* can result in resistance to apoptosis, a critical mechanism in treatment failure during DNA-damaging agents (Nieder et al. 2000). Mutations of the p53 gene on (exons 5 to 8) were found in many primary tumors and to a lesser extent in oligodendroglia, 1 oligoastrocytoma). (Reifenberger et al. 1996).

### pRB-CDK2-CDK4 axis in GBM pathogenesis

Retinoblastoma (R.b) is located at the chromosome location 13q14.1-q14.2 and was found to be involved in the cancer progression of astrocytomas (Henson et al. 1994). Mutations in R.B. are detected in more than 20% of high-grade gliomas. Interestingly loss of 13q was associated with the transition from low- to intermediate-grade gliomas (Henson et al. 1994; Bahuau et al. 1998). CDKN2B, i.e., (p15), a CDK inhibitor commonly inactivated in GBM, forms a complex with CDK4 or CDK6, thus preventing the activation of CDKs leading to the inhibition of cell growth and the cell-cycle arrest at G1 phase.

### PI3K-PTEN-Akt-mTOR pathway

The PI3K-PTEN-Akt-mTOR pathway regulates normal cellular functions and plays a critical regulatory role in cancer cell migration and metabolism. It was found that the PI3K pathway is altered in about 70% of GBMs, due to various biological aspects such as deletion of PTEN or amplification of EGFR and vascular endothelial growth factor

receptor (VEGFR)/ platelet-derived growth factor receptor α (PDGFRα) (Zhi et al. 2009). Overexpression of EGFR, which is one of the most frequent signaling mutations in GBM, and its amplification leads to increased activation of the PI3K pathway (Peraud et al. 1997; Watanabe et al. 1996).

### RAS/MAPK pathway

Human RAS genes (Rat Sarcoma) transform oncogenes, including H-Ras, N-Ras, and K-Ras. K-RAS belongs to the G protein family. The activation and deactivation of RAS are controlled by its binding to guanosine triphosphate (GTP) or guanosine diphosphate (GDP), respectively (Lu et al. 2005; Hurley et al. 1984). Activated RAS further activates RAF kinase through direct binding, regulating downstream signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway (Moodie et al. 1993; Thomas et al. 1992). RAS also regulates the activities of other pathways, such as the PI3K pathway, and consequently, RAS regulates cancer cell proliferation, differentiation, signal transduction, apoptosis, and tumorigenesis.

### STAT3 and zinc importer 4 (ZIP4) pathway

Signal transducer and activators of transcription (STAT) protein complexes are a family of cytoplasmic proteins with Scr Homology-2 (SH2) domains that functions as cytokines and transduce signals from the cytoplasm to the nucleus. Interestingly, these proteins acted as transcription factors and were found to regulate various biological processes related to cancer cells, such as proliferation, and migration (Abal et al. 2006; Rahaman et al. 2002). Interestingly, STAT3 was once thought to possess only oncogenic properties, but emerging studies have identified both the suppressive and oncogenic roles in GBM, depending on the genetic profile of the tumor (de la Iglesia et al. 2008).

### WNT pathway

Wnt signaling is overexpressed GBM. Activation of the Wnt pathway in these tumors is associated with mutations in, Adenomatous polyposis coli (APC), β-catenin, AXIN, and transcription factor 4 (TCF4). Mutations in Wnt signaling genes were extensively characterized in colorectal cancers. Mutations in Wnt signaling components were observed in β-catenin, APC, and AXIN1 of colon cancer and medulloblastoma, hepatocellular carcinoma. In contrast, aberration of the key components of the Wnt pathway is not of common occurrence in GBM, and gastric cancers (Nageret al. 2012; Morris et al. 2013). Recent reports from a small cohort have reported the existence of APC mutations observed in 13% of GBM (Tang et al. 2015). Overexpression of leucine-rich protein 1 (PELP1) was observed in almost all GBM samples (Sareddy et al. 2019). Studies have identified the pivotal role of epigenetic modifications regulating the Wnt pathway. Further, Gene Expression Omnibus miRNARNA profiling of GBM versus the normal brain found that miR-138–2-3p and miR-770-5p were differentially expressed.

The mammalian homologs of the *Drosophila melanogaster* protein Van Gogh (VANGL). VANGL1, VANGL2, and frizzled protein 7 (FZD7) are transcriptionally upregulated in glioma and correlate with poor patient outcomes. Consequently, knocking down of VANGL1 suppresses the motility of GBM cell lines, restoration of Neuregulin receptor degradation protein-*1* (NRDP1), a RING finger type E3 ubiquitin ligase whose decreased expression in GBM correlates with poor prognosis, reduces GBM cell migration, and invasiveness by suppressing Planar Cell Polarity (PCP) signaling. These findings revealed an essential mechanistic role for this pathway in GBM malignancy (Wald et al. 2017). In addition, receptor-like tyrosine kinase (RYK), a typical member of the receptor tyrosine kinase (RTK) family involved in the control of neuronal differentiation (Lyu et al. 2008), resulted in being essential for WNT5a-dependent invasiveness in glioma. (Hirano et al. 2014). MuTSigCV has indicated that in GBM cancer, the mutation of genes such as PTEN, EGFR, p53 (Lawrence et al. 2013). In addition, loss of chromosome 10q, alterations of p53, amplification of EGFR and PDGFR, and aberrant tyrosine kinase (RTK/Ras) signaling contributes to GBM cancer. Interestingly, studies have shown the differential expression of transforming growth factor beta 1 (TGFβ1) induced and SRY box 4 (SOX4) were also considered as therapeutic drug targets (Qiu et al. 2018). Furthermore, genes such as nucleolar and spindle-associated protein 1 (NUSAP1) and G-protein coupled receptor 65 (GPR65) were considered survival biomarkers.

## Gene expression patterns in GBM cancer

In GBM cancer, three genes TP53, PTEN, and EGFR are the most significantly mutated genes (SMG) as observed by MuTSigCV (Lawrence et al. 2013). The loss of chromosome 10q, alteration of p53, R.B., amplification of EGFR, PDGFR, and aberrations in receptor tyrosine kinase (RTK/Ras) signaling. Other frequent alterations include NF1 and MDM2. Differentially expressed genes such as transforming growth factor beta-induced (TGFβ1) and SRY box 4 (SOX4) were also considered therapeutic target genes. Further, in survival analysis, nucleolar and spindle-associated protein 1 (NUSAP1) and G-protein coupled receptor 65 (GPR65) were significant genes.

Dynein, cytoplasmic 1, intermediate chain 1 (DYNC1I1) was down-regulated in glioma. The lower expression of DYNC1I1 was correlated with poor patient survival. The epigenetic mark H3K27me3 on lysine 4 was found in the promoter region, revealing the active transcription region. The SEMA3C is another essential gene with multiple mutations observed in GBM cancer. Telomerase reverse transcriptase (TERT) gene -124 bp (hg19chr5:1; 295, 228 C > T; -146 bp (hg 19 chr5, 1, 295, 250 C > T (Heidenreich et al. 2015). The homeobox gene 5 DLX5, distal-less homeobox 5, affects glioma cell motility via PAX6/DLX5-WNT5A axis (Hu et al. 2016; Cell; 167:1281–1295). Among GBM and ISL1 are. 90% of GBM cases belong to the IDH-WT type ( high grade), and 10% of cases IDH mutant type ( lower grade). The other vital mutations are protein tyrosine phosphatase receptor type Z1 (PTPRZ1 and promoter methylation in MGMT. Thus, it is imperative to investigate the mutations, methylation, and other epigenetic changes to identify the prognostic and diagnostic markers and therapeutic response.

## Prognostic and diagnostic markers

Glioma cells can invade the neighboring tissues beyond detection leading to tumor relapse. This leads to an inevitably critical recurrence even after the surgical removal of GBM tissue (Jacobs et al. 2011; Stylli et al. 2005).

### IDH

IDH mutation was prognostic of more prolonged survival in low-grade Glioma (Leu et al. 2013; Sabha et al. 2014; Metellus et al. 2010; Gorovets et al. 2012). IDH mutations were most common in cases of oligodendroglioma (94%) and little lesser extent in cases of astrocytoma or mixed tumors (Leu et al. 2013). Metabolic mapping and image analysis on GBM cancer samples revealed the occurrence of IDH1 (R132) mutation. NADP + -dependent IDH activity and other NADPH-producing dehydrogenases, glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, malate dehydrogenase, and hexose-6-phosphate dehydrogenase. Mutation of Isocitrate dehydrogenase (IDH) gains oncogenic function. It converts alpha-ketoglutarate to the oncometabolite 2-hydroxyglutarate (2-HG), ultimately leading to genome-wide methylation change in GBM patients, leading to altered gene expression (Najafi et al. 2022). Heterozygous mutations of isocitrate dehydrogenase-1 (IDH1) dominantly inhibit wild-type IDH in GBM cancer. Studies have revealed that IDH1 activity results in the inactivation of enzymes. Interestingly, forced expression of a mutant form of IDH1 in cultured cells decreased alpha-ketoglutarate (alpha-KG) and thus enhances hypoxia-inducible factor subunit HIF-1 alpha (HIF-α) that facilitates tumor growth during low oxygen availability. Thus, HIF-1α levels were higher in tumors with mutant IDH than in wild-type tumors (Zhao et al. 2009). Interestingly, IDH mutation was observed to be associated with enhanced DNA methylation, called Glioma CpG island methylation phenotype (G-CIMP) (Noushmehr et al. 2010). It was observed that in secondary GBMs, IDH mutation and G-CIMP phenotype exist exclusively (Cohen et al. 2013). The key IDH mutations include those associated with R132 (CGT): 12R132H (C•G → T•A) and 1 R132G (C•G → G•C) that functions as a homodimer. The mutant IDH1 protein acts as a dominant negative by combining with the wild-type (W.T.) allele product to afford a dysfunctional heterodimer of the wild-type and mutant (Zhang et al. 2019).

### MGMT

MGMT was known to play an essential role in chemoresistance to TMZ. Thus, MGMT is considered a promising target in GBM treatment (Yu et al. 2020). GBM patients with MGMT methylation were associated with more prolonged overall survival but not progression-free survival (PFS) (Binabaj et al. 2018). It was also established that methylation of MGMT promoter is a crucial predictor of alkylating agents' ability to kill glioma cells. The methylation sites and rich CpG islands vary in MGMT-deficient GBM cancer cells. However, the change in the methylation status of the MGMT promoter after chemotherapy, radiotherapy, or both still need to be fully explored. Several studies have demonstrated that chemotherapy can induce MGMT expression in gliomas. Thus, researchers have employed several strategies that have been pursued to improve the anti-tumor effects of TMZ which include the synthesis of analogs of $O^6$-methylguanine ($O^6$-meG) such as $O^6$-benzylguanine ($O^6$-BG) and $O^6$-(4-bromothenyl) guanine ($O^6$-BTG), RNA interference (RNAi), and viral proteins (Yu et al. 2020). The expression level of MGMT in glioma has no relation with gender, age, tumor size, surgical approach, and Karnofsky Performance status (KPS) score. MGMT has shown a profound influence on cancer cell survival and proliferation during the treatment with O6-alkylating agents such as TMZ, Carmustine, Lomustine, etc. In addition, to these drugs, MGMT deficiency causes O6-methylguanine lesions to mispair with thymine, which leads to mismatch repair (MMR) mediated apoptosis in gliomas. Thus, MGMT, MMR, and DNA replication were found to be crucial factors in cell resistance (Li et al. 2017a, b). In general, as a part of diagnostics as well as prognostics, the methylation of MGMT promoter was detected by methylation-specific PCR, and bisulfite sequencing (BiSEQ). EGFR amplification was detected by fluorescence in situ hybridization (FISH) or next-generation sequencing was co-related (Goldstein et al. 2019). Studies have indicated that optimal assessment of

MGMT status function as a prognostic biomarker for patients with newly diagnosed GBM treated with chemo-radiation requires determination of both promoter methylation and immunohistochemistry (IHC) protein expression (Lalezari et al. 2013). Interestingly concordant MGMT methylation and lack of protein expression result in a response in TMZ therapy-treated patient subgroups with HR of 2.02 and 0.76 ($p < 0.05$) (Pandith et al. 2018; Uno et al. 2011).

### 3.P[53]

Expression of the neoplastic phenotype in GBM cells was inhibited when rat cells were transfected with the murine wild-type *p53* gene, mutant *p53* gene, and other oncogenes (Finlay et al. 1989). Moreover, the short arm of chromosome 17 is often deleted in human tumors. In colorectal cancers, deletion of 17pl3.1 (Baker et al. 1989); harbors the *p53* gene. In general, *p53* gene mutations are clustered in four 'hot spots' that coincide with highly conserved regions. DNA sequence analysis has revealed that p53 mutations were rare in primary GBMs (11%), whereas secondary GBMs were characterized by a high number of p53 mutations (67%). The incidence of p53 protein accumulation (nuclear immunoreactivity to PAb 1801) was also lower in primary (37%) than in secondary GBMs (97%) (Watanabe et al. 1996). Progression of low-grade astrocytomas to anaplastic astrocytoma or GBM occurred at an equal frequency (Watanabe et al. 1997).

### PTEN

PTEN deleted on chromosome 10 is a tumor suppressor gene that regulates various biological processes such as proliferation, survival, genomic stability, and cell motility (Bazzichetto et al. 2019). Regulation of PTEN function involves genetic, transcriptional, post-transcriptional, and post-translational events (Yang et al. 2017a, b). Recent meta-analysis studies indicated that PTEN mutation is associated with poor prognosis and shorter survival time (Han et al. 2016a, b; Sasaki et al. 2001). (Han et al. 2016a, b). Mutation of PTEN is the second common oncogenic mutation in GBM, occurring in 30% of the tumors (Gao et al. 2013; Cerami et al. 2012). PTEN mutation and mutations in EGFR are critical prognostic factors in anaplastic astrocytoma with GBM (Smith et al. 2001). PTEN on chromosome 10q23.3 regulates the Akt signaling pathway and thus modulates cell growth and apoptosis. It was found that the PTEN gene is mutated in 20–40% of GBM. Very few GBMs showed loss of PTEN. PTEN methylation frequently occurs in GBMs leading to loss of PTEN expression. Loss of Heterozygosity (LOH) at the PTEN locus and loss of PTEN protein expression was inconsistent. (Baeza et al. 2003). The novel chromatin-associated function of PTEN in complex with the histone chaperone death domain associated protein (DAXX) and the histone variant H3.3. Interestingly, PTEN interacts with DAXX and, regulates oncogene expression by modulating DAXX-H3.3 association on the chromatin, independently of PTEN enzymatic activity. DAXX inhibition inhibits tumor growth explicitly and improves the survival of orthotopically engrafted mice implanted with human PTEN-deficient glioma samples, associated with global H3.3 genomic distribution changes leading to upregulation of tumor suppressor genes and downregulation of oncogenes.

### EGFR & CDKN2A

EGFR gene amplification and overexpression are striking features of GBM in up to 40% of tumors (Hatanpaa et al. 2010). It was found that the Median survival was longer in the high-amplifier group (Hobbs et al. 2012). Overexpression of EGFR was an indicator of poor prognosis in overall survival in glioma patients (Li et al. 2018a, b). The serum levels of EGFR are enhanced many folds in patients with malignant Glioma, suggesting poor survival (Quaranta et al. 2007; Li et al. 2018a, b). The highly oncogenic mutant is produced by the deletion of exons 2 to 7 of the EGFR causing a loss of 267 amino acids from the receptor's external domain. Since EGFRvIII cannot attach a ligand, it signals automatically. EGFRvIII shares the same signaling domain as the wild-type EGFR, but it appears to produce a unique set of downstream signals that may boost tumorigenicity. EGFR and Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) alterations and determine the prognostic significance in lower-grade glioma (LGG).

### Neurofibromin 1 (NF-1)

NF1 is a tumor suppressor gene and a RAS-GTPase. Dysregulated NF1 expression activates cancer cell proliferation, migration, and invasion. Loss of NF1 expression in GBM was associated with increased tumor aggressiveness. The neurofibromin protein contains at least four significant domains. The leucine-rich domain (LRD) of neurofibromin inhibits the invasion of human GBM cells without affecting their proliferation. NF1-LRD fails to hydrolyze Ras-GTP to Ras-GDP. Thus, NF1-LRD inhibits glioma invasion (Fadhlullah et al. 2019).

### MDM2

Whole transcriptome analysis has identified MDM2 as associated with sensitivity and resistance to the chemotherapeutic drugs against GBM. MDM2 amplification occurred in 2 primary (7%) GBMs but none of the secondary GBMs. Only one out of 15 primary GBMs overexpressing MDM2 contained a p53 mutation (Biernat et al. 1997).

### MALAT1

MALAT1 is a prognostic factor in GBMs that induces chemoresistance to TMZ via suppression of miR-203, thereby promoting thymidylate synthase (TS) expression. MALAT1 knockdown reversed TMZ resistance in GBM cells. In contrast, MALAT1 overexpression induced chemoresistance by suppressing miR-203, promoting TS expression. (Chen et al. 2017).

### HOTAIR

HOTAIR is an adverse prognostic factor overexpressed in multiple human cancers.

HOTAIR has overexpressed in GBM. HOTAIR was frequently co-expressed with HOXA9 in high-grade gliomas. Integrated into silico analyses, chromatin immunoprecipitation (chIP) and quantitative RT-PCR (qPCR) data showed. GBM patients with high HOTAIR expression have a significantly reduced overall survival, (Xavier-Magalhães et al. 2018).

### Maternally Expressed Gene 3 (MEG 3)

MEG3 expression, when observed in studies, was significantly downregulated in GBM cancer, and negatively correlated with WHO grade in glioma patients. Low MEG3 expression was associated with the advanced WHO grade. This indicates the role of MEG3 in glioma cell proliferation, apoptosis, and autophagy (Zhao et al. 2018).

### Plasmacytoma Variant Translocation 1 (PVT1)

The expression of lncRNA PVT1 oncogene (PVT1) in Glioma and its clinical samples of gliomas have shown that its level is positively related to WHO glioma grade and prognosis of gliomas.

### Urothelial Carcinoembryonic Antigen 1 (UCA 1)

Urothelial carcinoembryonic antigen 1 (UCA1), overexpressing glioma cell lines. LncRNA UCA1 can promote glioma cells' proliferation by upregulating cyclin D1 transcription. Thus, UCA1 may serve as a prognostic indicator (Zhao et al. 2017).

## The epigenetic mechanism, genetics, and epigenetics in GBM cancer

LncRNA is an epigenetic player of the size of more than 200 nucleotides in length. Studies have identified that a delicate balance between genetic and epigenetic alterations drives tumor recurrence and chemoresistance. The Cancer Genome Atlas (TCGA) has identified the involvement of a considerable number of lncRNAs which can specifically be expressed in low-grade glioma (LGG) subtypes (IDH1/2 wt, IDH1/2 mut, and IDH mut 1p19q co-deletion), as well as classical, mesenchymal, neural, and pro-neural types of GBM (Reon et al. 2016). Microarray analysis has shown few lncRNA, such as ACo16745.3, XL0C_001711, and RP11-128A17.1 were involved in glioma recurrence. The critical target of ACo16745.3 is fork-head box protein D4- like1 (FOXD L1). Higher expression of FOXDL1 correlates with higher expression of lncRNA. LncRNA (up to 50,000) and miRNA (up to 3,000) broadly and profoundly regulate gene expression. Like in other cancers, the expression status of various lncRNAs in GBM cancer can be used as diagnostic and prognostic markers. Frequent deregulation of lncRNAs was observed in cancer cells which regulate several aspects of malignancy, including tumor cell proliferation, survival, invasion, and migration, as well as cancer stemness, angiogenesis, tumor immune responses, therapy resistance, and microenvironment (Fig. 2A-D). Lnc RNA participates in the differentiation and maintenance of pluripotency of stem cells. Chromatin RNA In situ reverse transcription sequencing (CRIST-seq) has emphasized that the lncRNA interacts with promoters of Oct4, and Sox-2 dictates the fate of stem cells (Chen et al. 2020).

Nuclear RNAs interact with various RNA types, such as transcription factors, chromatin modifying factors, and several RNA binding factors to regulate gene expression. The lncRNA Gm15055 was found to be induced by Oct4 and regulated the HOX gene expression by interacting with PRC2, which was involved in the maintenance of H3K27me3 (Liu et al. 2016). Mechanistically, lncRNA, which is p53-regulated and ESC-associated 1 (lncPRESS1), interacts with SIRT6. Inhibiting SIRT6 decreases the histone H3K56 and H3K9 acetylation levels to safeguard human embryonic stem cell (hESC) pluripotency (Jain et al. 2016). P53 inhibits the lncPRESS1, and the knockdown of lncPRESS1 result in the differentiation of hESC by increased expression of HOXA2, HOXB1, and FOXA2 and decreased expression of c-Myc, oct-4, and Nanog, etc. (Jain et al. 2016).

LncRNAs were involved in various cancers, including hepatocellular carcinoma and ovarian cancers. RNA sequencing analysis has identified vital lncRNA SOX2OT, and its nearby Sex determining region Y-box 2 (SOX2) was upregulated in TMZ -resistant cancer cells (Shahryari et al. 2015). SOX2 activates the Wnt / β-catenin pathway and induces cisplatin-resistance of lung adenocarcinoma (He et al. 2017). SOX2OT can regulate SOX2 to promote cancer cell growth and proliferation via regulating the miRNAs such as miR-195-5p and miR-122 in glioma cells (Su et al. 2017). SOX2OT is positively regulated with tumor grade, and the level of SOX2OT is higher in relapsed GBM patients than in primary GBM patients. Cancer stem cell-associated distal enhancer of SOX2 (CASCADES) functions

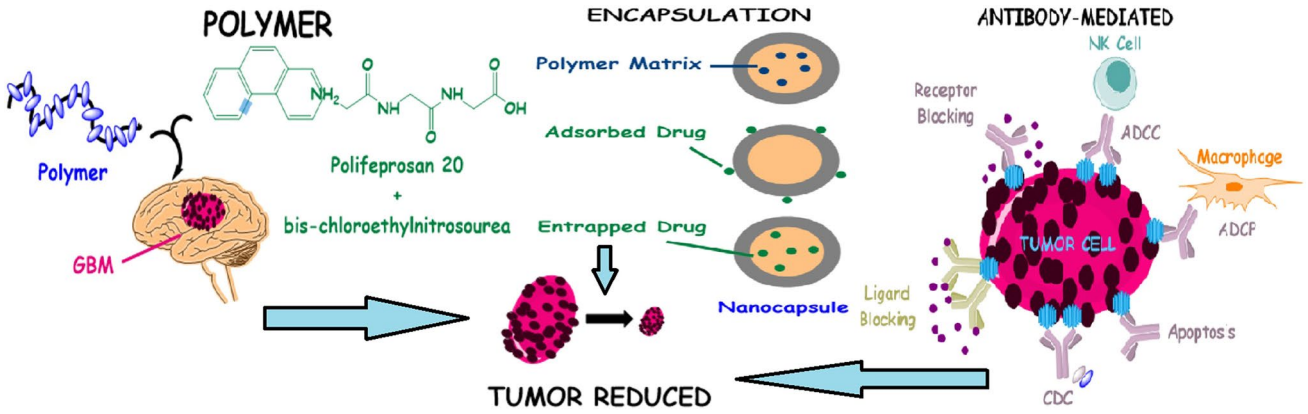


**Fig. 2** Various ways of killing GBM cancer cells. **A** Magnetic effect by using helmet **B**. Nano-particle mediated drug delivery **C**. Antibody induced cell death **D**. Polymer based drug delivery

as an epigenetic regulator, and the knockdown of CASCADE in GSCs results in the differentiation of neurons (Shahzad et al. 2020). Another essential lncRNA MATN-AS1 and its regulation of RELA genes, such as p65, p50, p52, c-Rel, and RelB, is involved in GBM cancer stem cell proliferation (Han et al. 2019) (Fig. 3; Table 2).ncRNAs such as TALC, MALAT1, OIPS-AS1, HOXD-AS1, H19, UCA1, NEAT1, and HOTAIR regulate several miRNAs that can regulate several genes involved in carcinogenesis.

## RNA-guided RNA modification in GBM diagnosis

RNA–protein complexes involved in the RNA-dependent modifications. In human RNAs, approximately 200 types of 2′-O-methylations and pseudouridylations are introduced by two RNA-guided RNA modification systems, such as box C/D and H/ACA RNA–protein complexes (RNPs) (Table 3). A distinct guide RNA belongs to each complex

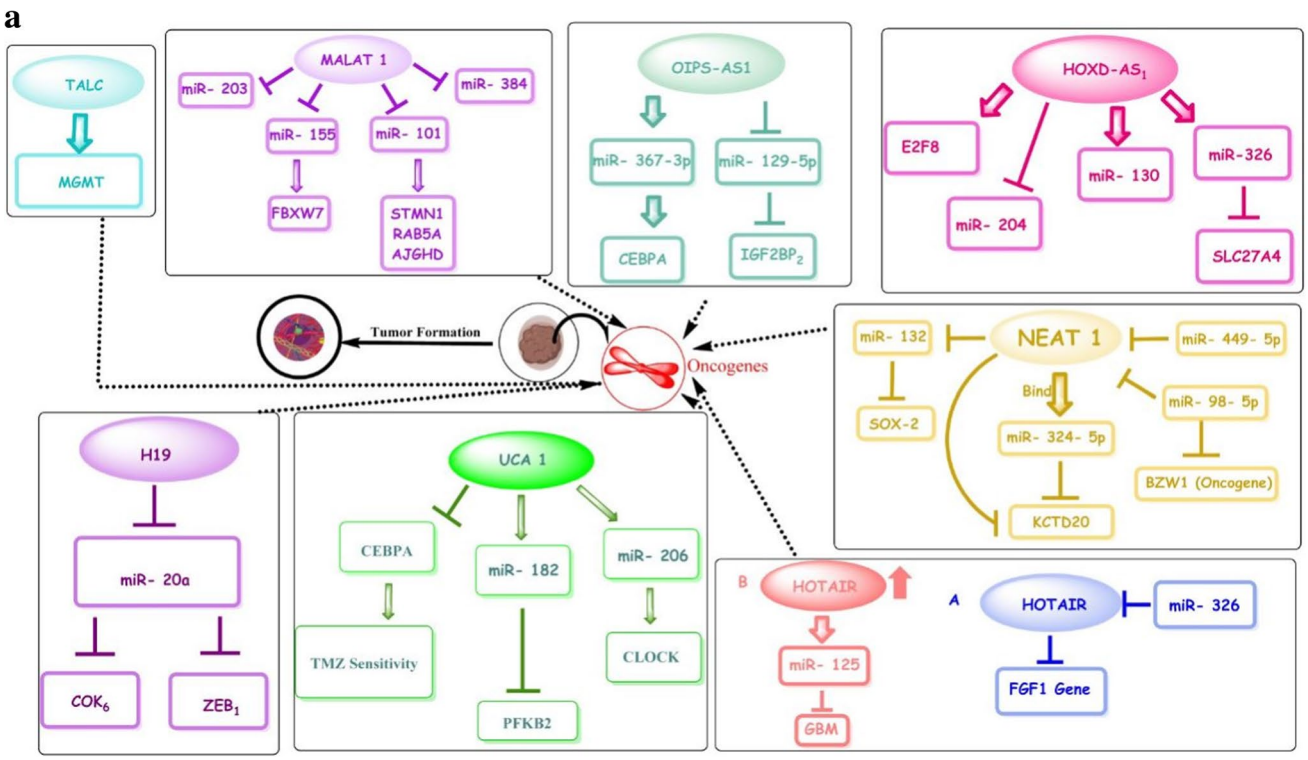


**Fig. 3** A The oncogenic role of ncRNAs in GBM. Figure 3b. The role of tumor suppressor ncRNAs in GBM. Non-coding RNAs such as CASC-2, MEG-3, PVT1, and XIST regulate several miRNAs involved in the expression of several genes, such as PTEN, involved in tumor suppression

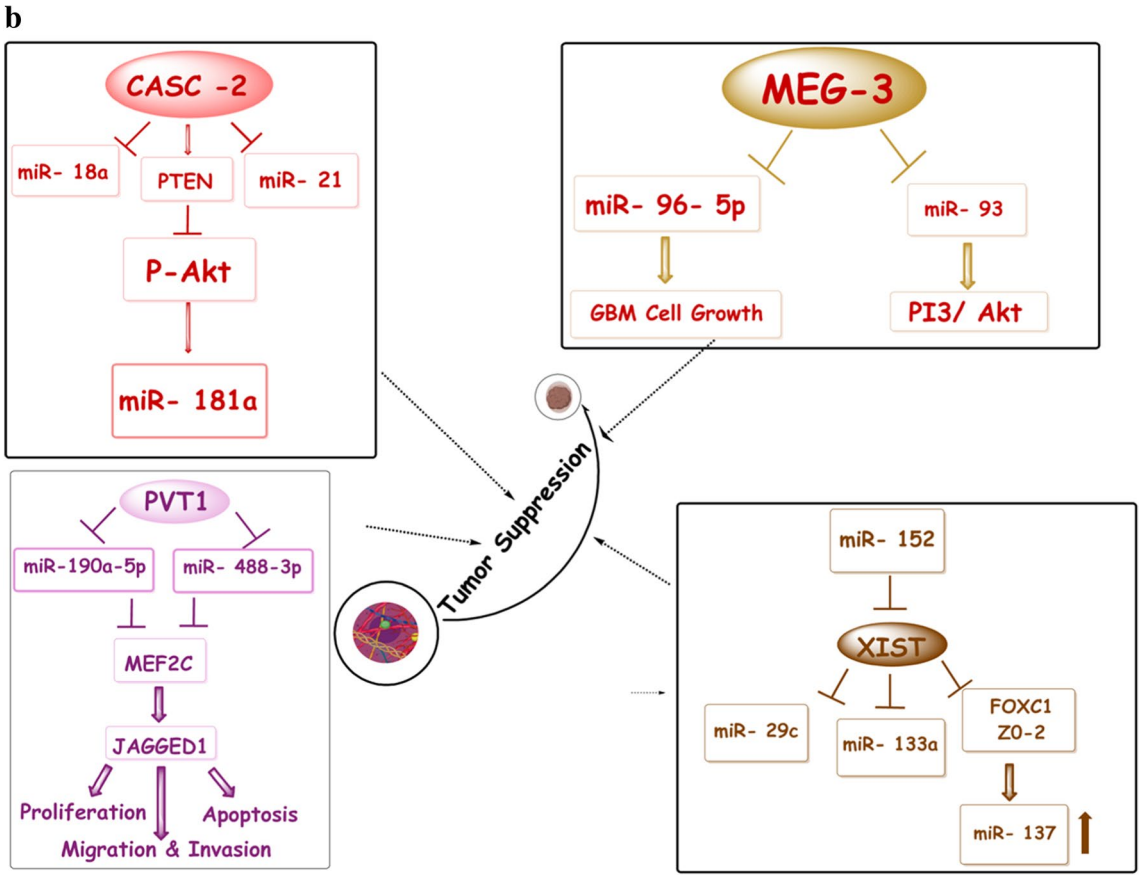


**Fig. 3** (continued)

for determining the target RNAs and binding to their complementary regions. Similarly, a group of proteins with the modifying enzyme (2′-O-methylase or pseudouridylase) belongs to each complex (Ye et al. 2009). For example, snoRNPs, a small nucleolar ribonucleoprotein complex, are involved in RNA-guided RNA modification. Box C/ An RNA-guided RNA modification system carries out alteration of the primary sequence and modulation of the function of target RNAs, including rRNAs, snRNAs, tRNAs, and perhaps mRNAs. From various eukaryotic RNAs, uridines are converted to pseudouridines with the help of H/ACA RNPs. The functional H/ACA RNP complex consists of a guide RNA and four proteins such as Cbf5, Gar1, L7Ae, and Nop10. L7Ae and Cbf5 interact with guide RNA. Cbf5 catalyzes the modification via explicitly identifying and binding to H/ACA guide RNAs. Guide RNAs help modify specific ribonucleotides by base pair with target RNAs (Baker et al. 2005).

D guide RNAs involved in the 2′-O-methylation of specific nucleotides. C/D RNAs are the methylation guide RNAs with a C (RUGAUAG, R is purine) and D (CUGA) box near the 5′ end and 3′ end, respectively. A bipartite C/D RNA functional enzyme complex consists of a guide RNA and three different proteins: methyltransferase fibrillarin, Nop5 (Nop56/58), and L7Ae. In the eukaryotic complex, a single Nop5 protein is replaced by paralogs Nop56 and Nop58 and a 15.5-kDa protein instead of L7Ae. Fibrillarin catalyzes the transfer of a methyl group to the ribose 2′-OH group from the unbound SAM. A scaffold protein, Nop5 consists of three domains, (i) a coiled-coil domain for self-dimerization; (ii) an N-terminal domain (NTD) for binds to fibrillarin; (iii) a C-terminal domain (CTD) for binding to the L7Ae–RNA complex. L7Ae–C/D RNA complex formation is the initial step, followed by Nop5 association with the preassembled L7Ae–C/D RNP in the C/D RNP assembly process. Finally, fibrillarin is recruited into the assembly by its interaction with Nop5. The activity of this complex is dependent mainly upon the integrity of the symmetric structure (Ye et al. 2009) (Table 3).

## Conclusion

GBM is the most malignant and aggressive type of Glioma. Understanding GBM progression and epigenetic regulation by ncRNA will help in future diagnostic tools and

**Table 2** LncRNA-miR interactions in GBM

| S.NO | LncRNA | mRNA | FUNCTION | GENE TARGET of miR | REFERENCES |
|---|---|---|---|---|---|
| 1. a | HOX transcript antisense RNA Oncogene (HOTAIR) | miR-219 | The upregulated RNA expression level of HOTAIR, the miR-219, increased miR-219 | NA | Li and Guan 2020a, b |
| 1. b | | miR-326 | HOTAIR was upregulated in glioma. miR – 326 targets lncRNA HOTAIR. miR – 326 targets Fibroblast growth factor -1 (FGF-1) | FGF-1 | Ke et al. 2015 |
| 1. c | | miR-125 | HOTAIR regulates Hexokinase 2 (HK2) by targeting miR-125, further suppressing the GBM cell proliferation and enhancing TMZ-induced apoptosis | HK-2 | Zhang et al. 2020 |
| 2. a | Nuclear Enriched abundant transcript 1 Oncogene (NEAT 1) | miR-449b5p | NEAT1, an essential lncRNA for forming nuclear body paraspeckles. NEAT1 was upregulated in GBM cancer more than in noncancerous brain tissues | | Zhen et al. 2016 |
| 2. b | | miR-985p | NEAT1 expression was correlated with miR-98-5p in glioma tissues. NEAT1 knockdown inhibited glioma cell proliferation | BZW1 | Li and Guan 2020a, b |
| 2.c | | miR-324-5p | NEAT1 contributes to cancer growth by affecting cell proliferation, migration, invasion, and drug resistance. It is expressed higher in glioma tissues than in adjacent normal brain tissues | KCTD20 | Zhang et al. 2021 |
| 2.d | | miR-132 | NEAT1 promoted glioma development by promoting SOX2 expression by suppressing miR-132 | SOX2 | Zhou et al. 2018 |
| 3. a | Urothelial carcinoma associated 1 Oncogene (UCA 1) | miR-182 | lncRNA UCA1/miR-182 axis as a nodal driver of glioma invasion that occurs via GBM-associated stromal cells (GASCs) | CXCL 14@PKFB2 | He et al. 2018 |
| 3.b | | miR-206 | Bio information was analyzed to predict the association between UCA1 and miR-206 | - | Huang et al. 2019 |
| 3. c | | miR-182-5p | MGMT is responsible for repairing DNA alkylation damage caused by TMZ | MGMT | |
| 4. a | Cancer Susceptibility Candidate 2 -Tumor Suppressor (CASC 2) | miR-181 | CASC2 could inhibit the miR-181a expression by direct targeting in TMZ-resistant GBM | PTEN, Akt | Liao et al. 2017 |
| 4. b | | miR-21 | CASC2 was less expressed in glioma tissues and U251 and U87 glioma cell lines. CASC2 inhibits glioma via negative regulation of miR-21 | - | Wang et al. 2015a, b |
| 4.c | | miR-18a | CASC 2 inhibits metastasis | - | Wang et al. 2020 |
| 5.a | H19 – (Oncogene) | miR-130a-3p | H19 was overexpressed in glioma tissues | N-cadherin and Vimentin | Hu et al. 2018 |
| 5.b | | miR-200a | Up-regulation of H19 promoted the proliferation of glioma cells by targeting miR-200a. Up-regulation of miR-200a leads to a reduction of CDK6 expression and inhibits GBM | CDK6 | Chen et al. 2021 |

**Table 2** (continued)

| S.NO | LncRNA | mRNA | FUNCTION | GENE TARGET of miR | REFERENCES |
|---|---|---|---|---|---|
| 6. a | Maternally expressed gene 3 (MEG-3) – Tumor Suppressor | miR-96-5p | MEG3 inhibited the EMT of glioma cells. miRNA-96-5p (miR-96-5p) was a promising target of MEG3 | - | Zhang et al. 2019 |
| 6. b | | miR-93 | MEG3 restrained the activation of the PI3K/AKT pathway | Ki67, PCNA | Zhang et al. 2017a, b |
| 7.a | X-inactive specific transcript (XIST) – Tumor Suppressor | miR-133a | Small hairpin RNA XIST (sh-XIST) and mimics/inhibitors of miR-133a inhibit GBM cancer progression | - | Luo et al. 2020 |
| 7.b | | miR-152 | Knockdown of XIST exerted tumor-suppressive functions by reducing cell proliferation, migration, and invasion | - | Yao et al. 2015 |
| 7.c | | miR-137 | lncRNA XIST was increased in endothelial cells | FOXC1, ZO-2 | Yu et al. 2018 |
| 7.d | | miR-29c | DNA repair protein MGMT plays a crucial role in TMZ resistance | SP1 | Du et al. 2017 |
| 8 | Temozolomide associated LncRNA (TALC) | miR-20b-3p | lncRNA TALC increased MGMT expression by regulating the acetylation at H3K9, H3K27, and H3K36 on the MGMT promoter | C-met, Stat 3, p300 | Wu et al. 2019 |
| 9 | Plasmacytoma variant translocation 1 (PVT 1) – Tumor suppressor | miR-488-3p | PVT1 binds to miR-190a-5p and miR-488-3p, leading to the inhibition of the tumor | | Xue et al. 2018 |
| 10. a | Opa-interacting protein 5 antisense transcript 1 (OIP 5 AS1) | miR-129-5p | OIP5-AS1 sponged miR-129-5p and miR-129-5p targeted IGF2BP2 | IGF2BP2 | Wang et al. 2021a, b |
| 10.b | | miR-367 | RNA immunoprecipitation confirmed OIP5-AS1 and miR-367-3p interactions | CEBP—A | Liu et al. 2018 |
| 10. c | | miR-410 | Silencing OIP5-AS1 specifically blocks the Wnt-7b/β-catenin pathway via targeted upregulating miR-410 | Wnt-7b/β—catenin | Sun et al. 2019 |
| 11a | HOXD antisense growth-associated lncRNA (HOXD- AS1)—Oncogenic | miR-130a | HOXD antisense growth-associated lncRNA HOXD-AS1, an essential lncRNA | E2F8 | Chen et al. 2018 |
| 11. b | | miR-326 | HOXD-AS1 is directly bound with miR-326, thereby regulating its solute carrier family 27 member 4 (SLC27A4) | SLC27A4 | Ji et al. 2020 |
| 11. c | | miR-204 | HOXD-AS1 sponges miR-204 and reversed the effect of HOXD-AS1 | | Zhou et al. 2019 |
| 11.d | | miR-582-5p | MiR-582-5p target NNT-AS1 and EZH2 genes in GBM | EZH2 | Pan and Xue 2021 |

**Table 2** (continued)

| S.NO | LncRNA | mRNA | FUNCTION | GENE TARGET of miR | REFERENCES |
|---|---|---|---|---|---|
| 12. a | Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT 1)—Oncogene | miR-203 | LncRNA MALAT1 inhibition cause TMZ- sensitivity cells by upregulating miR-203. This led to the downregulation of T.S | Thymidylate synthase (T.S.) | Chen et al. 2017 |
| 12. b | | miR-101 | MALAT1 was an endogenous sponge to miR-101. The miR-101 targets genes such as STMN1, RAB5A, and ATG4D | STMN1, RAB5A, ATG4D | Fu et al. 2017 |
| 12.c | | miR-140 | Antagonist relationship between MALAT1 and miR-140. Knockdown of MALAT1 resulted in BTB permeability in GBM patients | - | Ma et al. 2016 |
| 12.d | | miR-199a | The *MALAT1*/miR-199a/ZHX1 axis promotes GBM cell proliferation and progression | ZHX1 | Liao et al. 2019 |
| 12. e | | miR-124 | MALAT1 overexpression or miR-124 inhibitor led to enhanced expression of ZEB2. In parallel, the knockdown of MALAT1 decreased tumor volume | ZEB2 | Cheng et al. 2021 |
| 12. f | | miR-101 | MALAT1 promoted the Rap1B expression by sponging miR-101 | Rap 1B | Li et al. 2017a, b |
| 12. g | | miR-155 | MALAT1 suppresses GBM cell viability by down-regulating the miR-155. FBXW7 mRNA was found to be a direct target of miR-155 in glioma | FBXW7 | Cao et al. 2016 |
| 12 h | | miR-384 | MiR-384 was a target of MALAT1. Inhibition of miR-384 eliminated the function of GOLM1 in GBM | Golgi membrane protein 1 (GOLM1) | Ma et al. 2020 |

**Table 3** Key RNA modifications in GBM cancer

| S.NO | BASES | FUNCTIONAL CONSEQUENCE | REFERENCE |
|---|---|---|---|
| 1 | $N^6$ Methyl adenosine ($m^6A$) | RNA modifications, such as $m^6A$, occur by, methyltransferases like 3 (METTL3), and α-ketoglutarate-dependent dioxygenase alkB homolog 5 (ALKBH5), regulate epigenetic mechanisms aggressiveness, of GBM, and of GSCs. The $m^6A$ modification of mRNA occurs in nuclear speckles. Emerging studies have identified the role of RNA modifications regulate RNA stability, and processing, of ncRNAs | Dong and Cui 2020; Lee et al. (2014) Meyer and Jaffrey 2017; Yu et al. 2018; Geula et al. 2015; Meyer et al. 2012; Xiao et al. 2016; Wang et al. 2014, 2015a, b; Patil et al. 2016 |
| 2 | 5-Methylcytosine ($m^5C$) | $m^5C$ is the modification of the fifth position of cytosine. $m^5C$ was found in various RNAs, including tRNAs, rRNAs, mRNAs, and sRNAs. $m^5C$ methylation regulates the structural and metabolic stability of tRNAs which plays an important role in the translation of tRNAs. Interestingly, $m^5C$ can regulate cell division and protein synthesis | David et al. 2017; Huang et al. 2016; Cui et al. 2017; Shanmugam et al. 2015; Yang et al. 2017a, b; Goll et al. 2006; Moon and Redman 2014; Xing et al. 2015; Tuorto et al. 2012 |
| 3 | Pseudo uridine (Ψ) | The writer of Ψ RNA modification is Dyskerin Pseudouridine Synthase 1 (DKC1), which was significantly upregulated in Glioma, and DKC 1 is involved in cell growth by stimulating cell cycle progression via upregulating N-cadherin, hypoxia-inducible factor 1 (HIF 1α), and MMP-2 | Miao et al. 2019 |
| 4 | $Hm^5C$ | The ten-eleven translocation (TET) family (TET1/2/3), forming 5-hydroxymethyl cytidine (hm5C) and 5-formyl-cytidine (5-fC), and are considered mediating substances during the demethylation pathway | Fu et al. 2014; Takai et al. 2014; García et al.2018; Carella et al. 2020 |
| 5 | $m^7G$ | $N^7$-methylguanosine ($m^7G$) is a modification of the N at the $7^{th}$ position RNA guanine with a methyl group | Furuichi et al. 1977 Shimotohno et al. 1977; Lin et al. 2018; Pandolfini et al. 2019; Guy and Phizicky 2014; Sloan et al. 2017 |
| 6 | 2-O-Methylation | 2-O-Methylation occurs in the methylation of RNA2′-OH, and this modification is widely found in tRNAs, rRNAs, and mRNAs in mammalian cells | Boccaletto et al. 2018; Ge et al. 2010; Ji and Chen 2012 |

therapeutic strategies. A further role of lncRNAs in gliomas may lead to the discovery of novel molecular mechanisms behind glioma biological features. It also enables the development of new solutions to overcome the most significant obstacles in treating glioma patients. Epigenetic alterations can cause the mis-regulation of ncRNAs. Primarily, lncRNAs will act as a scaffold for various epigenetic proteins, such as EZH2 and LSD1, and influence the epigenetic chromatin state at various genomic loci in cancer cells. Both miRNAs and lncRNAs can interact with numerous epigenetic modifiers and transcription factors to influence gene expression. Studies found that most abnormally expressed ncRNAs impact cellular proliferation and apoptotic pathways, and such changes are cancer-dependent. Further, the nature of miRNA binding to multiple mRNAs and the precise molecular and biological mechanisms targeting a miRNA should be carefully studied. These studies should be conducted not only in the tumor cells but also in the tumor microenvironment. LncRNAs hold great promise in the treatment of cancer. Up to 102,000 lncRNAs were known to regulate various processes by various interactions with DNA, mRNA, and protein in cancer cells. Recent studies have revealed urine, and blood-based lncRNAs as key diagnostic markers. For example, PCA3 was approved for the detection of prostate cancer. Similarly, lncRNAs such as CASC2, and CRNDE were found to be effective biomarkers against GBM. HOTAIR, and MALAT1 in case of breast and gastric cancers, etc. Several miRNAs and lncRNAs act as oncogenes as well as tumor suppressors. The important miRNAs include miR-10b in GBM and breast cancers, miR-21 in the case of B-chronic lymphocytic leukemia, miR-155 in the case of lymphoma, and miR-221 in liver cancer. Similarly, the key lncRNAs include GAS5 in the case of GBM, MEG3 in lung cancer, MALAT1 in lung cancer, and breast cancer, etc. Targeting some miRNAs and lncRNAs with RNA-interfering molecules in GBM cell lines and GBM mouse models has resulted in beneficial effects. However, delivering RNAi molecules to the brain is challenging as BBB precludes most substances' passage into the brain. Developing a complete network of all ncRNAs involved in glioma formation, and progression could supplement other therapeutic approaches such as immunotherapy and gene therapy.

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## Declarations

**Competing interests** Authors don't have any financial or non-financial interests directly or indirectly related to the work submitted for publication.

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