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Targeting non-coding RNAs to overcome resistance and improving outcomes in glioblastoma

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ABSTRACT

Glioblastoma (GB) remains the most aggressive and treatment-resistant primary brain tumor, characterized by extensive heterogeneity, therapeutic resistance, and dismal prognosis. In this comprehensive review, we aimed to synthesize emerging insights into the roles of non-coding RNAs (ncRNAs)—including microRNAs, long non-coding RNAs, circular RNAs, and PIWI-interacting RNAs—in the regulation of glioblastoma progression, resistance mechanisms, and potential therapeutic strategies. We critically evaluated the molecular functions of ncRNAs in key oncogenic processes such as proliferation, angiogenesis, epithelial–mesenchymal transition (EMT), and immune evasion. Additionally, we reviewed current detection methods, delivery technologies, and clinical trials targeting these ncRNAs. A central goal of this review was to bridge a notable gap in the literature by highlighting underrepresented ncRNA classes such as circRNAs and piRNAs, which exhibit regulatory complexity and potential as biomarkers and therapeutic agents in GB. We further discussed delivery challenges posed by the blood–brain barrier and explored promising nanocarrier and exosome-based approaches to enhance therapeutic targeting. Through curated case studies, we showcased the translational potential of targeting specific ncRNAs to reverse multiple resistance types and improve immunotherapy response. This review provides a consolidated framework for understanding the dynamic role of ncRNAs in glioblastoma and proposes an expanded toolkit for precision oncology approaches. Our findings not only underscore the therapeutic promise of ncRNAs but also call for future investigations into the lesser-known subclasses that could redefine the landscape of GB management.

Introduction

Intro to glioblastoma: a therapeutic challenge

Glioblastoma (GB), classified as an isocitrate dehydrogenase (IDH)-wild-type adult-type diffuse glioma, represents the most aggressive and lethal form of primary brain tumor. It accounts for the majority of deaths among patients with gliomas due to its rapid progression, resistance to therapy, and poor prognosis. Despite advances in molecular diagnostics and treatment strategies,

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therapeutic outcomes for glioblastoma remain limited. Glioblastoma is a high-grade tumor characterized by high-grade histology, marked intratumoral heterogeneity and arises de novo with distinctive molecular signatures. The integration of molecular biomarkers, including DNA methylation profiles, into classification frameworks has enhanced diagnostic accuracy and facilitated the exploration of targeted therapies for this challenging malignancy [140].

Glioblastoma has an epidemiology that makes this the most common malignant central nervous system (CNS) tumor, accounting for 50.9 % of malignant brain tumors in the United States (U.S.), with a gender predilection for males. The incidence of CNS tumors based on the CBTRUS 2016–2020 data is 24.83 per 100,000 population; and mortality due to glioblastoma is quite high. Geographic incidence varies from highest to lowest in Europe and Asia, respectively. Ionizing radiation remains the only established environmental risk, while genetic predispositions such as neurofibromatosis type 1 (NF1), Li–Fraumeni syndrome, and specific germline mutations elevate glioma risk. Although genome-wide association studies (GWAS) identified susceptibility loci, clinical utility remains limited due to cost and psychosocial concerns [140].

Glioblastoma pathophysiology is driven by complex genetic and epigenetic alterations in IDH-wild-type tumors, primarily arising in patients over 50 years of age. These tumors commonly exhibit copy number gain of chromosome 7 and loss of chromosome 10 ($+7/-10$), mutations in the telomerase reverse transcriptase promoter (TERTp), tumor protein p53 (TP53), phosphatase and tensin homolog (PTEN), and neurofibromin 1 (NF1), along with homozygous deletions in cyclin-dependent kinase inhibitor 2 A/B (CDKN2A/CDKN2B). Amplification of genes such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor A (PDGFRA), and MET leads to activation of receptor tyrosine kinase pathways. Dysregulation of mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT), and nuclear factor-κB (NF-κB) pathways, coupled with tumor hypoxia and vascular endothelial growth factor (VEGF)-driven angiogenesis, further promotes tumor progression. Additionally, glioblastoma evades immune surveillance via transforming growth factor-β (TGF-β)-mediated immunosuppression, contributing to its aggressive phenotype and therapeutic resistance [140].

Glioblastoma presents formidable challenges due to its extensive intratumoral heterogeneity, aggressive invasiveness, and resistance to therapy. Glioblastoma stem cells (GSCs) are usually resistant to therapy and able to change, thereby driving tumor recurrence. Tumor progression and treatment efficacy are impeded by the tumor microenvironment (TME), consisting of immune cells, endothelial cells, extracellular matrix (ECM), and neurons. Blood-brain barrier (BBB) is partially intact, thus hindering drug delivery, and an immunosuppressive milieu generated by the tumor-associated macrophages (TAMs) and immune-regulating cytokines impedes immunotherapy. Moreover, glioblastoma evades antiangiogenic strategies through vessel co-option and vascular mimicry. These factors collectively contribute to preventing long-term therapeutic outcomes [12].

Isocitrate dehydrogenase 1 (IDH1)mutation, O6Methylguanine-DNA methyltransferase (MGMT) promoter methylation and EGFR amplification or EGFRvIII mutation are keymolecular biomarkers in glioblastoma. IDH1 mutations are associated with better prognosis and occur primarily in younger patients. MGMT promoter methylation predicts response to alkylating chemotherapy. EGFR alterations are linked to tumor aggressiveness and poor outcomes, making EGFR a therapeutic target. Despite their clinical utility, challenges persist due to intratumoral heterogeneity, inconsistent biomarker expression across tumor regions, and limited BBB permeability, which impedes effective drug delivery and reduces the success of targeted therapies in clinical settings [60].

Current therapies for GB include surgical resection, radiotherapy, and chemotherapy with temozolomide (TMZ). The Stupp protocol remains the standard of care, combining maximal safe resection, radiotherapy, and TMZ; however, survival outcomes remain modest. Tumor-treating fields (TTFields), a non-invasive modality applying alternating electric fields, have shown promise in extending survival when combined with TMZ. Despite advancements in intraoperative imaging techniques like 5-aminolevulinic acid (5-ALA) fluorescence and intraoperative magnetic resonance imaging (ioMRI), complete tumor removal remains challenging due to its invasive nature. Resistance mechanisms, such as DNA repair upregulation, GSCs, immune evasion, and poor drug delivery across BBB, severely limit treatment efficacy. Obstacles to the development of immunotherapies, targeted therapies, and nanotechnologies are: tumor heterogeneity, immune-suppressive TME, therapeutic resistance, and effective drug delivery [92].

Resistance mechanisms in glioblastoma

Intimate molecular mechanisms of resistance against conventional and targeted therapies hinder treatment against GB. Overexpression of MGMT, which repairs DNA damage induced by TMZ, and defects in mismatch repair proteins (MSH6, MLH1, PMS2) act to promote prolonged tumor proliferation despite treatment [94]. Disruption of HDAC6 also mediates downregulation of MSH6 and therefore exacerbates TMZ resistance [94]. Upregulated by MGMT independent long non-coding RNA (lncRNA) SNHG12 promotes resistance via sequestration of microRNA miR-129–5p, which leads to MAPK1 and E2F7-regulated cell survival pathways [94,112].

Radiotherapy resistance similarly arises from hyperactivated DNA damage response (DDR) mechanisms involving EZH2, NEK2, MELK, and claspin-stabilizing ubiquitin-specific protease 3 (USP3), modulated via hedgehog (Shh) signaling [94]. GB cells surviving radiotherapy often adopt resistant GSC phenotypes driven by transcription factors SOX2, OCT4, NANOG, and paracrine/autocrine signaling involving WISP1 and hepatocyte growth factor (HGF)/c-Met pathways [94].

Targeted therapy resistance arises from tumor heterogeneity, redundant signaling, BBB permeability issues, and unstable molecular targets. Despite frequent EGFR alterations and constitutively active EGFRvIII, therapies targeting EGFR (e.g., gefitinib, cetuximab) frequently fail due to dynamic EGFR expression and compensatory NF-κB and PI3K/AKT/mTOR signaling pathway activation [94,101]. Attempts to inhibit angiogenesis via bevacizumab encounter adaptive resistance mechanisms involving compensatory signaling by angiopoietin-2 (Ang-2) and integrins, limiting therapeutic success [112,141].

Clinical translation of immunotherapy remains limited by GB's immunosuppressive TME. Tumors upregulate immune checkpoints

like programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), along with increased myeloid-derived suppressor cells (MDSCs) and regulatory T-cells (Tregs) that hinder immune-mediated tumor clearance [94].

Preclinical evidence suggests combinatorial inhibition of HDAC6, EGFR, and angiogenic factors can re-sensitize resistant GB models [112]. Clinical efforts involve enhancing drug delivery across BBB, exploiting tumor metabolism (e.g., oxidative phosphorylation inhibitors), and targeting FGFR3-TACC3 (fibroblast growth factor receptor 3-transforming acidic coiled-coil-containing protein 3) fusions through precision medicine approaches [101]. Despite encouraging preclinical data, clinical outcomes remain modest, underscoring the urgent need for multifaceted therapeutic strategies and comprehensive molecular profiling to overcome GB resistance [101,112].

Role of non-coding RNAs in cancer

Epigenetic regulators are emerging biomarkers in various diseases [95–98]. One such category of these regulators is non-coding RNAs. Non-coding RNAs (ncRNAs) are RNA molecules transcribed from approximately 75 % of the human genome but not translated into proteins. Major classes of ncRNAs include microRNAs (miRNAs), lncRNAs, circular RNAs (circRNAs), and PIWI-interacting RNAs (piRNAs). miRNAs, approximately 22 nucleotides (nt) long, regulate gene expression post-transcriptionally by binding to complementary messenger RNA (mRNA) sequences, leading to their degradation via RNA-induced silencing complex (RISC) [143]. LncRNAs (> 200 nt) function through diverse mechanisms including epigenetic regulation, chromatin remodeling, acting as molecular scaffolds, or competing endogenous RNAs (ceRNAs), sponging miRNAs [143]. CircRNAs form closed-loop structures resistant to degradation, predominantly acting as miRNA sponges, protein interactors, or regulators of gene expression [5,143]. piRNAs (24–30 nt) bind PIWI proteins, crucially maintaining genome integrity by suppressing transposable elements primarily in germline cells but also in cancer cells [81,143].

ncRNAs critically influence cancer biology by modulating oncogenic or tumor-suppressive pathways. For example, miR-155 and miR-126 enhance tumorigenesis in breast, colorectal, and leukemic cancers by repressing tumor suppressors like p53 [143]. Conversely, let-7 and miR-34a suppress cancer progression by targeting oncogenic factors, including K-RAS, c-Myc, and stemness regulators [143]. LncRNAs such as HOTTIP and EPIC1 promote tumorigenesis via chromatin modifications and activation of oncogenic signaling pathways, whereas MALAT1 acts as a suppressor by disrupting metastatic transcriptional networks [143]. Similarly, circRNAs like circHIPK3 function oncogenically through miRNA sequestration, while circCDYL suppresses proliferation by stabilizing tumor suppressors [5,143].

Gastric and pancreatic cancers share pathophysiological similarities with gliomas, particularly GBs, as all exhibit aggressive tumor growth, invasive potential, therapeutic resistance mediated via genetic and epigenetic alterations, and involvement of similar oncogenic signaling pathways like PI3K/AKT and Wnt/β-catenin. In gastric cancer (GC), lncRNAs including HOTAIR, H19, and PVT1 enhance multidrug resistance (MDR) through the PI3K/AKT and Wnt/β-catenin pathways, influencing epithelial-mesenchymal transition (EMT) and TME interactions [5]. CircRNAs, notably circAKT3 and circPVT1, contribute to chemotherapy resistance by activating oncogenic pathways or maintaining cancer stem cell (CSC) populations [5]. In pancreatic cancer, ncRNAs similarly influence tumor growth, metastasis, and resistance. LncRNA EPIC1 is upregulated, promoting pancreatic tumor growth via direct interaction with oncogenic transcription factor MYC, enhancing expression of target genes involved in cell-cycle progression and proliferation [143]. Such ncRNAs hold promise as therapeutic targets given their prominent roles in tumor biology.

In astrocytomas, including GB, miRNAs such as miR-21, miR-196, miR-128, and miR-302–367 clusters significantly affect disease aggressiveness and therapeutic resistance. Upregulated miR-21 contributes to tumor progression by suppressing apoptosis and tumor-suppressive pathways involving p53, whereas miR-128 and miR-302–367 clusters have tumor-suppressive roles, targeting stemness and oncogenic regulators [109]. Given their detectability in biofluids, these miRNAs are potential non-invasive diagnostic and prognostic biomarkers, offering new avenues for targeted therapies and improved disease management in astrocytomas [109].

Non-coding RNAs in glioblastoma pathophysiology

NcRNAs play pivotal regulatory roles in neurological and neuropsychiatric disorders, influencing critical pathogenic mechanisms such as protein aggregation, neuroinflammation, and synaptic dysfunction [49]. MiRNAs, lncRNAs, circRNAs, and piRNAs have been implicated across diverse disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), epilepsy, stroke, multiple sclerosis (MS), autism spectrum disorder (ASD), schizophrenia, and depression [49]. For instance, miR-34a is elevated in AD brains, contributing to synaptic dysfunction and energy deficits, whereas MALAT1 provides neuroprotection against amyloid toxicity [49]. Similarly, dysregulated lncRNAs NEAT1 (Nuclear Enriched Abundant Transcript 1) and GAS5 are associated with inflammation, neurodegeneration, and disease severity in MS and stroke [49].

In GB, ncRNAs have emerged as key modulators of tumor biology, governing cell proliferation, angiogenesis, EMT, metastasis, and immune evasion [103]. MiRNAs such as miR-21 and miR-210 support GB growth and angiogenesis by targeting tumor suppressors, while tumor-suppressive miRNAs like miR-124 are often downregulated [103]. Additionally, circRNAs (e.g., circHIPK3) and lncRNAs (e.g., MALAT1, H19, HOTAIR) modulate critical pathways influencing the tumor microenvironment, angiogenesis, and chemoresistance, highlighting their potential as therapeutic targets [103].

Angiogenesis is central to GB progression, and specific ncRNAs critically regulate this process. LncRNA MALAT1 enhances angiogenesis by upregulating VEGF, angiopoietin-1 (ANG-1), and promoting endothelial proliferation [118]. CircRNAs like circDENND4C facilitate angiogenesis by enhancing VEGF expression, whereas miRNAs such as miR-125b inhibit vascular formation by directly targeting VEGF signaling pathways [118]. These interactions suggest therapeutic potential in targeting ncRNAs to disrupt GB

angiogenesis.

NcRNAs also significantly influence GB metastasis. MiR-376a-3p and miR-623 suppress glioma invasion by targeting transcription factors (KLF15 [Kruppel-like factor 15]) and EMT-promoting proteins (TRIM44 [Tripartite Motif Containing 44]), respectively [89]. LncRNAs FOXD2-AS1 and MALAT1 facilitate metastatic progression through modulation of EMT markers, miRNA sponging, and activation of signaling pathways like PI3K/AKT [89]. CircRNAs, notably circFBXW7 and circHIPK3, regulate metastatic properties and chemoresistance in glioma by sponging miRNAs such as miR-23a-3p and miR-524–5p, respectively [89].

Non-coding RNAs as therapeutic targets

NcRNAs have emerged as crucial regulators in GB, influencing tumor growth, angiogenesis, metastasis, and therapeutic resistance [30,149]. Their dysregulation significantly impacts disease progression, prognosis, and therapy responsiveness, highlighting their potential as diagnostic biomarkers and therapeutic targets [30,149].

The lncRNA LOXL1-AS1 is notably upregulated in glioma tissues and cells. Mechanistically, LOXL1-AS1 promotes glioblastoma progression by functioning as a molecular sponge for miR-374–5p, thus enhancing matrix metalloproteinase 14 (MMP14) expression. This interaction facilitates glioma cell proliferation, migration, invasion, and vasculogenic mimicry (VM), an alternative angiogenesis pathway associated with tumor malignancy. LOXL1-AS1 also directly influences the NF-κB signaling pathway by regulating RELB, further supporting tumor growth and inflammation [30].

Conversely, the lncRNA GAS5 (growth arrest-specific 5) exhibits tumor-suppressive properties and is commonly downregulated in glioblastoma. Reduced GAS5 expression correlates with aggressive tumor behavior and poor prognosis. Functionally, GAS5 suppresses glioblastoma cell migration and invasion through its role as a ceRNA, binding miR-135b-5p and upregulating adenomatous polyposis coli (APC), a known negative regulator of oncogenic pathways. Overexpression of GAS5 can inhibit the malignant phenotype of glioblastoma cells, underscoring its therapeutic potential as a target in glioblastoma management [149].

In metastatic brain tumors (MBTs), miRNAs exhibit distinct expression patterns compared to primary tumors, highlighting their diagnostic and prognostic utility. Specific miRNAs, such as miR-10b, miR-21, and miR-200, are markedly elevated in cerebrospinal fluid (CSF) of patients with brain metastases, reflecting their active involvement in metastatic processes. Additionally, miR-92b and miR-9/miR-9* can effectively distinguish primary from secondary brain tumors, with significant sensitivity and specificity, underscoring their potential as clinical biomarkers for accurate tumor classification and personalized treatment strategies [11].

Currently, RNA-based therapies approved by the U.S. Food and Drug Administration (FDA) primarily involve antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs). Although no RNA-based cancer therapies have yet been FDA-approved, several candidates are advancing through clinical trials, highlighting their promise in oncology [130]. Therapeutic strategies involving RNA face significant challenges, especially crossing the blood–brain barrier to deliver RNA-based therapeutics effectively. Emerging approaches to overcome these obstacles include the development of implantable devices for local RNA delivery, engineered nanoparticles, viral vector-based delivery systems, and lipid-based nanoparticles, which have already demonstrated safety in mRNA vaccine applications. Moreover, CRISPR/Cas-based epigenetic editing represents another promising frontier for precise RNA targeting in GB [130].

Delivery challenges and innovations

Effective detection and targeting of ncRNAs require advanced technologies. Some of the current detection methods are High-Throughput Sequencing (HTS), microarrays, Northern blotting, Reverse Transcription-Quantitative Polymerase Chain Reaction (RT-qPCR), and In Situ Hybridization (ISH). Next-Generation Sequencing (NGS), or called High Throughput Sequencing (HTS), enables the genome-wide identification of many ncRNAs without any prior sequence knowledge and is a revolutionized ncRNA profiling. While microarrays are still useful for the economical and rapid analysis of known ncRNAs, they are by no means reliable, and it is crucial to validate expression levels via RT-qPCR because this technique is the most sensitive. Visualization of ncRNA function within tissues is possible through northern blotting and ISH, which allow direct visualization of ncRNA size and localization, respectively [126].

Targeting ncRNAs therapeutically currently involves several strategies, including ASOs, locked nucleic acids (LNAs), peptide nucleic acids (PNAs), morpholino oligonucleotides (MOs), miRNA mimics, and antagomirs. By binding target ncRNAs, ASOs cause the affected ncRNAs, such as the oncogenic ncRNAs miR-10b and MALAT1, to be degraded by RNase H in preclinical glioma models. Because LNAs are stable against nuclease degradation, they are potentially able to effectively counteract miR-21 in glioblastoma cells and sensitize them to radiation and chemotherapy [104].

Promising outcomes are, nevertheless hindered by significant delivery challenges. Systemic delivery of ncRNA targeting therapeutics is complicated by rapid nuclease degradation, limited cell uptake, off-target effects, and activation of the immune system [8]. Because of the issues discussed above, advanced delivery technologies are needed to improve specificity, stability, and efficacy.

Nanoparticle-based platforms, exosomes, and advanced nanocarriers are emerging technologies that meet these challenges. Non-viral nanoparticles (NPs) are optimized for size, shape, and surface charge to cross the BBB. For example, spherical nucleic acids (SNAs) containing siRNAs to oncogenes such as Bcl2L12 penetrate the BBB and have shown GB clinical trials [42]. Functionalized nanoparticles, such as iron oxide nanoparticles conjugated with chlorotoxin delivering MGMT-siRNA, enhance tumor-specific targeting and magnetic resonance imaging (MRI) for treatment monitoring. Exosomes engineered to carry miRNAs (miR-124a) or miRNA sponges (miR-21) provide natural, biocompatible carriers with intrinsic BBB-crossing ability, offering robust therapeutic effects in preclinical models [42].

Clinical trials validate the therapeutic potential of these advanced delivery systems. MRX34, a liposome-based miR-34 mimic, although terminated due to immune-related adverse events, demonstrated proof-of-concept efficacy in advanced liver cancers. TargomiRs (miR-16 mimic in EDV™ nanocells) advanced through phase I clinical trials for malignant pleural mesothelioma, highlighting their clinical potential despite dose-related toxicity [8]. Additionally, siRNA-based spherical nucleic acid NU-0129 entered early-phase clinical trials for GB therapy, underscoring the promise of nanotechnology-enhanced RNA delivery systems in oncology [42].

Thus, continued innovation in detection and delivery technologies is pivotal for translating ncRNA-based therapies into clinical practice, offering significant promise for treating GB.

Clinical evidence and emerging therapies

Early clinical trials of ncRNA-based therapeutics illustrate significant potential for treating diverse cancers, including GB. Scientists demonstrated in a phase 0 trial that NU-0129, a SNA-based siRNA targeting B-cell lymphoma 2-like protein 12 (Bcl2L12), effectively penetrates GB tumors, reducing oncogene expression [38]. Likewise, MRX34 (miR-34a mimic) based miRNA therapies elicited antitumor effects in solid, refractory tumors and hepatocellular carcinoma, though with some immune-related adverse events [38]. A second promising trial again used DNA plasmid BC-819 (H19-DTA), which expresses diphtheria toxin selectively activated in tumors that overexpress lncRNA H19, and induced stable disease and improved survival in ovarian cancer [38].

Therapeutically, lncRNAs can be targeted by restoration of tumor suppressive lncRNAs or by targeting of oncogenic lncRNAs. The authors also restore MALAT1, which suppresses glioma invasion, demonstrating a reduction in tumor growth and migration in vitro, supporting its therapeutic potential [23]. On the other hand, targeting the oncogenic lncRNAs, HOXA11-AS and CRNDE, was found to be a possible strategy as lncRNA knockdown was able to block the GB cell proliferation and progression by targeting signaling axes in the form of miR-136–5p/Wnt2 [23].

Evidence of a promising preclinical safety profile of an ASO therapeutic targeting lncRNA TUG1 for rGB was revealed in the first-in-human phase 1 trial. It should be noted that formulated TUG1-ASO, composed of LNA gapmer and a polymeric drug delivery system, can well cross the blood–brain barrier. By targeting TUG1 to suppress oncogenic R-loop formation, it promises GB-specific toxicity without significant off-target effects [21]. The safety, maximum tolerated dose (MTD), and further trials targeting refractory cancers will be defined in this trial.

CircRNAs are stabilized, tumor-specific, and implicated in cancer progression, thus qualifying for therapeutic use. CircRNAs can be modulated using RNAi and ASOs, and CRISPR/Cas technology. For instance, although an attack against circRNA-specific back-spliced junctions would lead to selective depletion of those circRNAs that are oncogenic, it would not affect linear RNAs, making siRNAs against circRNA back spliced junctions exquisite therapeutics [34]. In addition, CRISPR-based Cas13 system for circRNA knockdown showed higher efficiency than conventional methods and with no off-target effects [34].

circZNF609 and circNFIX are examples of circRNAs that are potential therapeutic targets in GB. Expression of CircZNF609 was significantly higher in GB tissues, where it inversely correlated with the tumor–suppressive microRNA miR-145–5p and positively correlated with EGFR overexpression, and it promoted tumor proliferation via miR-145–5p/EGFR signaling [33]. Similarly, circNFIX exhibited oncogenic potential by sponging miRNAs, including miR-378e, contributing to GB progression and poor prognosis, highlighting circRNA–miRNA interactions as potential therapeutic targets [33].

Fig. 1 illustrates the workflow of ncRNA-based therapeutic development from identification to clinical translation in GB.

Authors' contribution, motivation and scope of review

We conceptualized this review with the goal of consolidating the rapidly expanding knowledge surrounding ncRNAs in GB, one of the most treatment-resistant and lethal brain malignancies. Over the past decade, the landscape of GB research has dramatically evolved, revealing ncRNAs as powerful regulators of tumor biology, drug resistance, and immune evasion [60,92]. While several recent studies have explored individual ncRNA molecules or mechanisms in general, we recognized a pressing need for a comprehensive synthesis that integrates their diverse roles and therapeutic implications to overcome resistance and improve outcomes [49,103,118].

Our contribution stems from a multi-layered effort to review the current literature on the regulatory functions, biomarker potential, and therapeutic utility of key ncRNA classes—namely microRNAs, long non-coding RNAs, circular RNAs, and PIWI-interacting RNAs. We examined how these ncRNAs influence GB hallmarks such as angiogenesis, apoptosis, stemness, and resistance to standard therapies including temozolomide and radiotherapy. We further assessed cutting-edge delivery technologies—ranging from viral vectors and exosomes to advanced nanoparticles—and how these platforms may help circumvent the blood–brain barrier, a longstanding obstacle in effective GB treatment.

This review not only compiles established findings but also addresses a key gap in current literature: the relative neglect of certain ncRNA subclasses, particularly circRNAs and piRNAs, in the context of GB pathophysiology and therapy [20,103]. Although miRNAs and lncRNAs have received the most attention, we identified that circRNAs—due to their stability and sponging capabilities—and piRNAs—through their epigenetic regulatory potential—warrant deeper exploration. By integrating their mechanistic insights alongside better-studied ncRNAs, we aim to expand the toolkit available for researchers and clinicians pursuing novel therapeutic strategies.

In essence, this review provides a broad yet detailed examination of the ncRNA-glioblastoma axis, offering a critical resource for both basic scientists and translational researchers. Our hope is that this comprehensive analysis not only informs ongoing research

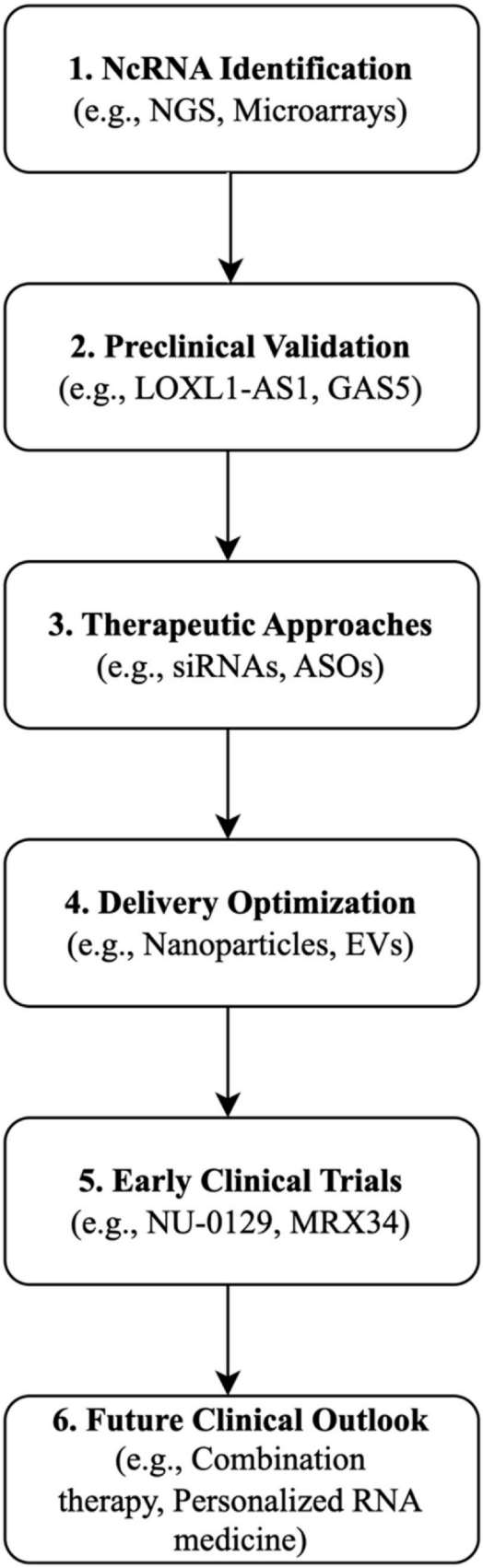

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Fig. 1. NcRNA therapeutics for glioblastoma.

but also catalyzes future investigations that push the boundaries of precision oncology in glioblastoma.

Search methodology and article selection

This comprehensive review evaluates the emerging landscape of ncRNAs in glioblastoma, with a focus on their roles in therapeutic resistance and improved treatment outcomes. To construct a robust evidence base, the authors employed a systematic literature review strategy. The primary search was conducted on the National Center for Biotechnology Information (NCBI)'s PubMed Advanced Search Builder using the term “non-coding RNAs AND glioblastoma,” yielding a substantial 3269 relevant articles. To enhance specificity, Boolean operators were used in combination with ncRNA subclasses, including "microRNAs", "long non-coding RNAs", "circular RNAs", and "PIWI-interacting RNAs", alongside terms such as “drug resistance”, “angiogenesis”, “apoptosis”, and “tumor microenvironment”. Additional searches were conducted across other platforms like Scopus, Google Scholar, and Web of Science to cross-reference data and ensure comprehensive coverage.

Inclusion criteria emphasized articles published from 2005 to 2025, written in English, and presenting primary data or robust reviews on ncRNAs in GB pathophysiology or therapy. Exclusion reasons included publication in duplicate, a conference abstract that lacks peer review, or a paper that is not relevant to glioblastoma or therapy. The authors prioritized studies offering molecular insights, experimental validations, and translational relevance.

This review integrates insights across several thematic domains:

- Overview of GB pathogenesis and resistance mechanisms.
- Classification, biogenesis, and evolutionary dynamics of ncRNAs.
- Role of miRNAs, lncRNAs, circRNAs, and piRNAs in GB progression and resistance.
- Therapeutic targeting of ncRNAs and advances in delivery systems.
- Emerging clinical evidence and future translational potential.

While most literature historically focused on miRNAs and lncRNAs, this review notably addresses a significant gap by highlighting underrepresented ncRNA classes—circRNAs and piRNAs—which possess unique regulatory mechanisms and therapeutic promise in GB. Their inclusion not only expands the scientific scope but also underscores the review’s novelty and comprehensiveness. By evaluating their mechanistic roles and biomarker potential, this work offers a forward-looking perspective on precision-targeted therapies and positions itself as a foundational reference for ongoing and future research in the ncRNA-glioblastoma axis.

Classification of non-coding RNAs

Evolution and biogenesis

NcRNAs represent a diverse and evolutionary complex class of molecules, including miRNAs and lncRNAs, which have distinct biogenesis mechanisms and evolutionary dynamics. miRNAs, short RNAs of about 20–28 nucleotides nt, belong to the small RNA family associated with Argonaute (Ago) proteins (V. N. [57]). They likely evolved from an ancestral siRNA pathway, initially emerging as a defense mechanism against viruses and transposons [6]. Animal miRNAs, such as the conserved mir-99/100 family present from cnidarians to humans, are primarily characterized by their seed regions crucial for targeting specific mRNAs [6]. Although nearly 1907 human miRNA genes are annotated in miRBase, recent high-confidence databases, such as miRGeneDB, reduced this to approximately 567 validated genes, reflecting stringent biogenesis and conservation criteria [29,58]. While some miRNAs exhibit deep evolutionary conservation, hundreds are rapidly evolving, often arising via duplication or de novo formation, with many quickly lost due to limited functional integration [87,88].

In contrast, lncRNAs demonstrate rapid evolutionary turnover, making their conservation challenging to characterize [128]. Unlike protein-coding genes, lncRNAs typically lack extensive nucleotide sequence similarity and instead may retain conserved genomic positioning, structural motifs, or transcriptional patterns [128]. For instance, approximately 20 % of human lncRNAs have detectable homologs in mice compared to 99 % for protein-coding genes [43,156]. Conservation of lncRNAs occurs through multiple dimensions—sequence, genomic position, processing, and structural features [128,129]. Examples include Air RNA, where transcription alone (not the RNA molecule) regulates nearby insulin-like growth factor 2 receptor (IGF2R) gene silencing [61]. Structural conservation also occurs; human HULC and mouse Pair lncRNAs interact similarly with phenylalanine hydroxylase (PAH) via conserved stem-loop structures (Y. Li et al. [71]).

miRNA biogenesis involves transcription of primary miRNA (pri-miRNA) by RNA polymerase II (RNAPII), processing by Drosha/DGCR8 (Microprocessor) into precursor miRNA (pre-miRNA), nuclear export via exportin 5 (Xpo5), cytoplasmic processing by Dicer, and loading onto Ago proteins to form the RISC (X. [15,62,63]) [13,79,146]. Alternative noncanonical pathways exist, bypassing Drosha or Dicer, as exemplified by mirtrons and miR-451 [4,6]. Posttranscriptional modifications, including target-directed miRNA decay (TDMD) mediated by highly complementary targets, also regulate miRNA stability, significantly influencing miRNA functional roles [17,113]. As a result, the evolutionary pathways of biogenesis of ncRNAs have dynamic and complex patterns, which are commensurate with their functional complexity and the extremely important role they have in cellular regulatory networks.

Classification

RNA molecules transcribed from DNA and that do not encode proteins are referred to as ncRNAs. NcRNAs, in general terms, are divided into housekeeping and regulatory ncRNAs, which are important for many cellular processes.

Housekeeping ncRNAs are constitutively expressed and are necessary for fundamental cellular activities. It includes small nuclear RNAs (snRNAs) that process the mRNA to splicing RNAs, transfer RNAs (tRNAs) that match three nucleotide codon sequence in mRNAs with specific amino acids on protein translation using ribosomes and ribosomal RNAs (rRNAs) that are a part of the structural and catalytic cores of ribosomes needed for protein translation. Furthermore, snoRNAs play an additional role in guiding chemical modification on other housekeeping RNAs that modulate their stability and function [44].

In contrast, regulatory ncRNAs are involved in dynamic modulation of gene expression and are implicated in developmental processes, cellular differentiation, homeostasis, and disease pathogenesis. Short and long non-coding RNAs can be further subdivision of regulatory ncRNAs.

Short regulatory ncRNAs comprise miRNAs, siRNAs, and piRNAs. miRNAs, about 21 nucleotides in length, typically repress target gene expression by binding partially complementary sites within the 3′ untranslated regions (3′-UTR) of target mRNAs. This interaction results in translational repression and mRNA degradation, significantly influencing numerous physiological and pathological processes, including cancer, cardiovascular diseases, and mental disorders [26,50,73,76,105]. miRNA biogenesis involves initial transcription by RNA polymerase II as pri-miRNAs, nuclear processing by the Drosha-DGCR8 complex (microprocessor) into pre-miRNAs, cytoplasmic processing by Dicer and co-factors TAR RNA binding protein (TRBP) or Protein activator of interferon-induced protein kinase (PACT), and incorporation of the mature miRNA into the RISC, guided by Argonaute and TNRC6 proteins [25,54,59,127]. Some clustered miRNAs, such as the miR-17–92 cluster, display intricate regulatory mechanisms involving intermediate forms like progenitor-miRNAs (pro-miRNAs), processed through additional factors including cleavage and polyadenylation specific factor 3 (CPSF3) and the splicing factor ISY1, adding layers of posttranscriptional control during embryonic development [24].

SiRNAs are typically processed from endogenous double-stranded RNAs (dsRNAs), originating either from long hairpin structures or bidirectional transcription of complementary genomic loci. Exogenous siRNAs (exo-siRNAs), conversely, derive from extracellular dsRNAs, particularly evident in antiviral responses observed in plants, nematodes, and insects [90,122]. Recent evidence indicates that in mammalian germ cells and pluripotent stem cells, endo-siRNAs contribute to genomic stability by repressing transposable elements, complementing piRNA function in germline defense mechanisms [123,139].

PiRNAs, predominantly expressed in germ cells, specifically associate with PIWI subfamily Argonaute proteins. They suppress

Fig. 2. Classification of ncRNAs.

expression of transposable elements, preserving genomic integrity. piRNAs originate from genomic clusters enriched with repetitive sequences, processed from long precursor transcripts into mature piRNAs through mechanisms distinct from miRNAs and siRNAs. Genetic deficiency of PIWI proteins in model organisms results in transposon activation and sterility, underscoring their crucial roles in genome defense [80,116].

Further studies reveal that processed fragments of classical housekeeping ncRNA had additional regulatory functions. The smaller fragments yielded by some snoRNAs could function similarly to miRNAs, or regulate cancer pathways like SNORD50A/B suppression of K-Ras signaling [32,36,41,108]. Furthermore, tRNA-derived fragments (tRFs) participate in canonical translational activities; however, they also modulate transcript stability and oncogenic pathways by interacting with RNA-binding proteins (RBP) like Y-box binding protein 1 (YBX1) to confer reduced metastatic potential [32,36,41,108].

Another category of such regulatory ncRNAs is LncRNAs (literally ncRNA) having an extent greater than 200 nucleotides and lacking protein-coding potential. The gene expression of nuclear lncRNAs occurs as transcriptional and epigenetic levels. This includes upstream DHFR locus transcripts modulating pre-initiation complex binding [84], as well as enhancer-associated RNAs, EVF2, PAUPAR, and LED, regulating transcription via enhancer–promoter interactions and epigenetic modifications [3,10,56,65,86,114,131].

Recent evidence increasingly highlights the evolving role of both short and long ncRNAs in brain cancers, particularly glioblastoma, suggesting their utility as potential biomarkers and therapeutic targets due to their involvement in tumor progression and chemoresistance. Collectively, this classification illustrates the extensive diversity, complexity, and functional versatility of ncRNAs within cellular regulation.

Fig. 2 illustrates the major categories of ncRNAs based on structure and function. These include housekeeping ncRNAs essential for core cellular processes, small regulatory ncRNAs involved in gene silencing and transposon suppression, lncRNAs that regulate transcription and chromatin dynamics, and emerging regulatory ncRNAs such as circRNAs and eRNAs with evolving roles in cancer biology, especially brain tumors.

Targeting non-coding RNAs to overcome resistance in glioblastoma

GB exhibits formidable treatment resistance due to its complex molecular and cellular heterogeneity, a highly immunosuppressive TME, and the protective nature of the blood–brain barrier. Intratumoral diversity, including genetically distinct subclones and GSCs, drives therapeutic evasion through differential activation of pathways such as Wnt, Shh, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and MAPK. The BBB and its tumor-altered variant, the blood–brain–tumor barrier, limit drug delivery and promote efflux of therapeutic agents. Resistance to chemotherapy and radiotherapy arises from enhanced DNA repair mechanisms, hypoxia, and GSC-mediated survival. Immune evasion is facilitated by TAMs, MDSCs, and Tregs, alongside low mutational burden and antigen presentation. These multifactorial mechanisms necessitate combinatorial, personalized strategies to overcome GB resistance and improve patient outcomes [94].

NcRNAs represent promising therapeutic targets for overcoming resistance in GB by regulating key oncogenic processes. NcRNAs modulate signaling pathways such as Wnt/β-catenin, Notch, and phosphatidylinositol-3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR), which control glioma cell proliferation, invasion, apoptosis, and EMT. By acting as miRNA sponges or epigenetic regulators, ncRNAs influence therapy resistance and tumor progression. Targeting dysregulated ncRNAs—such as SNHG1, SNHG18, circ-TTBK2, and PIWIL1-associated piRNAs—offers a novel strategy to sensitize glioma cells to chemoradiotherapy and inhibit tumor growth [89]. Below are the case studies which illustrate this.

[133] explored the role of lncRNA EPIC1 in glioma progression and TMZ resistance using in vitro cell lines and in vivo mouse models. The aim was to determine whether EPIC1 functions as an oncogenic driver in glioma. Using expression profiling and gene knockdown/overexpression assays, they found EPIC1 elevated Cdc20 levels, promoting proliferation, cell-cycle progression, and resistance to TMZ. Cdc20 knockdown reversed EPIC1-driven resistance, while EPIC1 depletion suppressed tumor growth. The study concluded that EPIC1 enhances glioma aggressiveness via Cdc20 and MYC activation.

[136] carried out in vitro and molecular assays using TMZ-resistant glioma cell lines to investigate the role of lncRNA KCNQ1OT1 in chemoresistance. Aimed at elucidating the KCNQ1OT1/miR-761/PIM1 axis, they profiled gene expression and validated downstream effects. They found that KCNQ1OT1 sponged tumor-suppressor miR-761, upregulating PIM1 and its targets MDR1, c-Myc, and Survivin, leading to enhanced TMZ resistance. Functional assays confirmed that targeting PIM1 reversed resistance. This study demonstrated KCNQ1OT1 as a key regulator of multidrug resistance and a promising lncRNA-based therapeutic target in GB, particularly via its control over pro-survival signaling cascades.

[75] evaluated GB cell lines and patient tissues to investigate the role of lncRNA SOX2OT in TMZ resistance. Aiming to understand SOX2OT's regulation of SOX2 expression, they used RNA-FISH, RNA pull-down, methylation assays, and expression profiling. Results showed SOX2OT promoted TMZ resistance by binding RNA demethylase ALKBH5, which upregulated SOX2, activating the Wnt5a/β-catenin pathway, enhancing proliferation, and suppressing apoptosis. SOX2OT levels correlated with worse prognosis and increased stemness markers. This study demonstrated SOX2OT as a potential target in GB by regulating SOX2-mediated chemoresistance and may guide future treatment strategies.

[72] found out that lncRNA SNHG15 was significantly upregulated in GB clinical and TMZ-R cells and aimed to assess its role in chemoresistance and tumorigenesis. Using patient tissues, cell lines, and PDX models, they observed elevated SNHG15 associated with poor prognosis, increased stemness, M2 glioma-associated microglia polarization, and expression of oncogenic markers like CDK6 and β-catenin. Palbociclib (CDK6 inhibitor) reduced SNHG15 and sensitized TMZ-R cells to TMZ. Mechanistically, palbociclib increased tumor suppressor miR-627–5p targeting CDK6. This study exemplified SNHG15, showing how its inhibition or CDK6 blockade can overcome TMZ resistance in GB.

[144] investigated the role of Linc00942 in TMZ resistance in GB. Using RACE, qRT-PCR, RNA-seq, ChIRP-MS, mutagenesis, and

Table 1
Key lncRNAs and miRNAs linked to therapy resistance in glioblastoma, with targets and therapeutic roles.

Sr.No	ncRNA Name	Mechanism	Therapeutic Effect	Delivery/Validation	References
1	HOTAIRM1	Sponges miR−17–5p to regulate TGM2	Reduces tumor growth and radioresistance	siRNA knockdown, in vitro/in vivo validation	Ahmadov et al., [1]
2	SBF2-AS1	Sponges miR−151a−3p to regulate XRCC4	Reverses TMZ resistance and promotes apoptosis	RIP, luciferase assay, xenograft validation	Z. [153]
3	PVT1	Sponges miR−365 to upregulate ELF4/SOX2	Suppresses stemness and increases TMZ sensitivity	Luciferase reporter, bioinformatics, knockdown	Gong et al., [35]
4	CRNDE	Regulates PI3K/Akt/mTOR pathway and autophagy	Improves TMZ sensitivity and blocks MDR/ autophagy	In vitro assays, PI3K inhibitor studies	Z. [155]
5	FOXD2-AS1	Sponges miR−98–5p to regulate CPEB4	Inhibits proliferation and drug resistance	Luciferase assay, gene silencing	Gu et al., [39]
6	TPTEP1	Sponges miR−106a−5p to upregulate MAPK14	Suppresses stemness and radioresistance	Rescue experiments, in vitro studies	Tang et al., [125]
7	miR−34a	Targets multiple resistance genes and pathways	Sensitizes cells to TMZ across subtypes	Nanocell delivery in vivo	Khan et al., [55]
8	miR−128–3p	Inhibits EMT and targets c-Met	Enhances TMZ efficacy and suppresses invasion	Luciferase assay, combination with TMZ	C. [154]
9	miR−144	Targets IDH1/2, TIGAR, PDK1	Reduces glycolysis and invasion	miR mimics, glycolytic assays	Cardoso et al., [16]
10	miR−451	Targets CAB39 to modulate AMPK loop	Blocks glucose adaptation and migration	AMPK knockdown, phosphorylation studies	Ogawa et al., [93]
11	miR−125b	Targets TAZ and enhances TRAIL-induced apoptosis	Promotes mitochondrial apoptosis with TRAIL	miR restoration and TAZ suppression	Ma et al., [82]
12	miR−22–3p	Targets IGF1R by sponging NCK1-AS1	Enhances cisplatin/radiation sensitivity	IGF1R knockdown and apoptosis analysis	B. Wang et al. [132]

in vivo orthotopic models, they aimed to elucidate Linc00942's mechanism. They found Linc00942 upregulated in TMZ-resistant cells, promoting phosphorylation and nuclear translocation of metabolic enzymes TPI1 and PKM2, activating STAT3/p300 and inhibiting HDAC3. This led to SOX9-driven stemness and resistance. Mutants lacking TPI1/PKM2-binding sites failed to maintain resistance. The results revealed that Linc00942 modulated TMZ resistance through non-metabolic functions. This study exemplified Linc00942 as a promising therapeutic lncRNA target to counter GB resistance via disrupting lncRNA-protein interactions.

[85] pointed out the clinical relevance of lncRNA TP73-AS1 in GB by analyzing three patient cohorts and employing glioblastoma stem-like cell (gCSC) models with CRISPR interference. They aimed to determine TP73-AS1's role in TMZ resistance. Datasets included RNA-seq, expression profiling, and functional assays. TP73-AS1 knockdown significantly enhanced TMZ sensitivity and downregulated ALDH1A1, a known cancer stem cell and drug resistance marker. Results suggested TP73-AS1 promotes metabolic pathways and stemness. The study concluded that TP73-AS1 confers TMZ resistance via ALDH1A1 regulation. It highlighted TP73-AS1 as a predictive biomarker and promising therapeutic target to overcome GB chemoresistance.

[18] mentioned the oncogenic role of miR-155–3p in GB and investigated its influence on TMZ resistance. They aimed to assess whether miR-155–3p contributes to GB progression by targeting the transcription factor Six1. Using GB cell lines and tumor xenografts, they showed that miR-155–3p overexpression promoted proliferation, apoptosis resistance, and TMZ resistance by suppressing Bax and p21 through Six1. Knockdown of miR-155–3p reduced tumor growth and improved mouse survival. These results unveiled miR-155–3p as a tumor promoter and uncovered the therapeutic potential of miR-155–3p. Consequently, glioma was found to be sensitive to TMZ by targeting the miR-155–3p, making miR-155–3p a potential therapeutic target in GB.

To understand how miR-4524 b-5p affects the radioresistance of glioblastoma, [147] examined GB cell lines and molecular assays. It has been investigated whether miR-4524b-5p targets ALDH1A3 to promote tumor progression and therapeutic response. To identify miRNAs that directly control glycolysis, they performed expression analyses and functional knockdowns and found that miR-4524b-5p directly reduced ALDH1A3 levels and consequently stopped glycolysis while deactivating the PI3K/AKT/mTOR pathway. As such, a proliferation of GB cells was inhibited, and radiosensitivity was increased. ALDH1A3 is found to be crucial for metabolic reprogramming and resistance. Finally, miR-4524b-5p–ALDH1A3 is shown to be a dtiRNA-target of overcoming radioresistance and improving radiotherapy outcome in GB.

[119] investigated the effects of gene silencing, overexpression, and of xenografts of lncRNA BC200 and miR-218–5p on GB TMZ resistance. In their search for resistance mechanisms, they saw that the GB tissues and cells have high BC200 and low miR-218–5p. Downregulation of BC200 downregulates MGMT, ABC transporters, and self-renewal markers, while upregulation exerts the opposite effect. miR-218–5p acts as a tumor suppressor that reverses BC200-mediated resistance. The combination of shBC200 and TMZ treatment also inhibited tumor growth in vivo. In this study, we also showed that miR-218–5p is a novel therapeutic target and biomarker of overcoming lncRNA-induced TMZ resistance in GB.

[2] proposed a study to investigate the part played by miR-221 in GB cell lines and patient datasets regarding resistance to TMZ and RT.They analyzed gene and protein expression patterns to clarify EGFR regulation post-treatment. MiR-221 was upregulated in resistant GB cells and inversely correlated with EGFR expression. High miR-221 levels enhanced cell survival and therapy resistance. Functional assays confirmed that miR-221 suppressed EGFR, reducing TMZ sensitivity. This study highlighted miR-221 as a therapeutic target for overcoming resistance in GB and proposed it as a biomarker for poor survival and recurrence.

[69] aimed to investigate the role of circular RNA hsa_circ_0110757 in TMZ resistance in GB. Using high-throughput sequencing of TMZ-resistant glioma tissues and cells, they identified overexpression of hsa_circ_0110757. Functional assays demonstrated that silencing this circRNA reduced cell viability and increased apoptosis. Mechanistically, hsa_circ_0110757 sponged miR-1298–5p, releasing suppression on ITGA1, thereby activating the PI3K/AKT signaling pathway. Overexpression of ITGA1 enhanced TMZ resistance, while miR-1298–5p mimics reversed this effect. This study exemplified how ncRNA targeting, specifically the hsa_circ_0110757/miR-1298–5p/ITGA1 axis, offers a promising therapeutic approach for overcoming chemoresistance in glioblastoma through modulation of apoptotic pathways.

[148] summarized the role of hypoxia-induced exosomal miR-301a in mediating radiation resistance in GB. Using hypoxic GB cell lines, they examined exo-miR-301a expression and its transfer to normoxic cells. They identified TCEAL7 as a direct miR-301a target and demonstrated that its downregulation activated the Wnt/β-catenin pathway. Knockdown of HIF-1α reduced exo-miR-301a, sensitizing cells to radiation. Their dataset included GB tissues and in vitro models under hypoxia. These findings highlighted that miR-301a represses tumor suppressor TCEAL7, enhancing radioresistance. This study established the exo-miR-301a/TCEAL7 axis as a potential therapeutic target to overcome hypoxia-induced resistance in GB treatment.

Table 1 highlights key ncRNAs associated with therapy resistance in glioblastoma and their therapeutic implications, while Fig. 3 outlines a strategic framework to target these ncRNAs for overcoming resistance.

Targeting non-coding RNAs to improve outcomes in glioblastoma

NcRNAs emerge as compelling therapeutic targets for GB due to their regulatory influence on tumor progression, therapy resistance, and metastasis. Regulatory ncRNAs—including miRNAs, lncRNAs, and circRNAs—modulate key pathways such as PI3K/AKT/mTOR, Wnt/β-catenin, and STAT3. By acting as molecular sponges, transcriptional repressors, or epigenetic modifiers, ncRNAs influence angiogenesis, apoptosis, proliferation, and treatment resistance. Dysregulated ncRNAs are associated with poor prognosis and GB recurrence. Therapeutically, ASOs, LNAs, MOs, PNAs, miRNA mimics, antagomirs, and CRISPR-Cas9 technologies are used to inhibit or modulate ncRNA expression. Small-molecule inhibitors targeting RNA structures are also under development. These targeted approaches allow for the precision modulation of GB pathogenesis and provide important approaches to overcome therapeutic resistance while improving patient survival and treatment efficacy. These findings can be seen in the following studies.

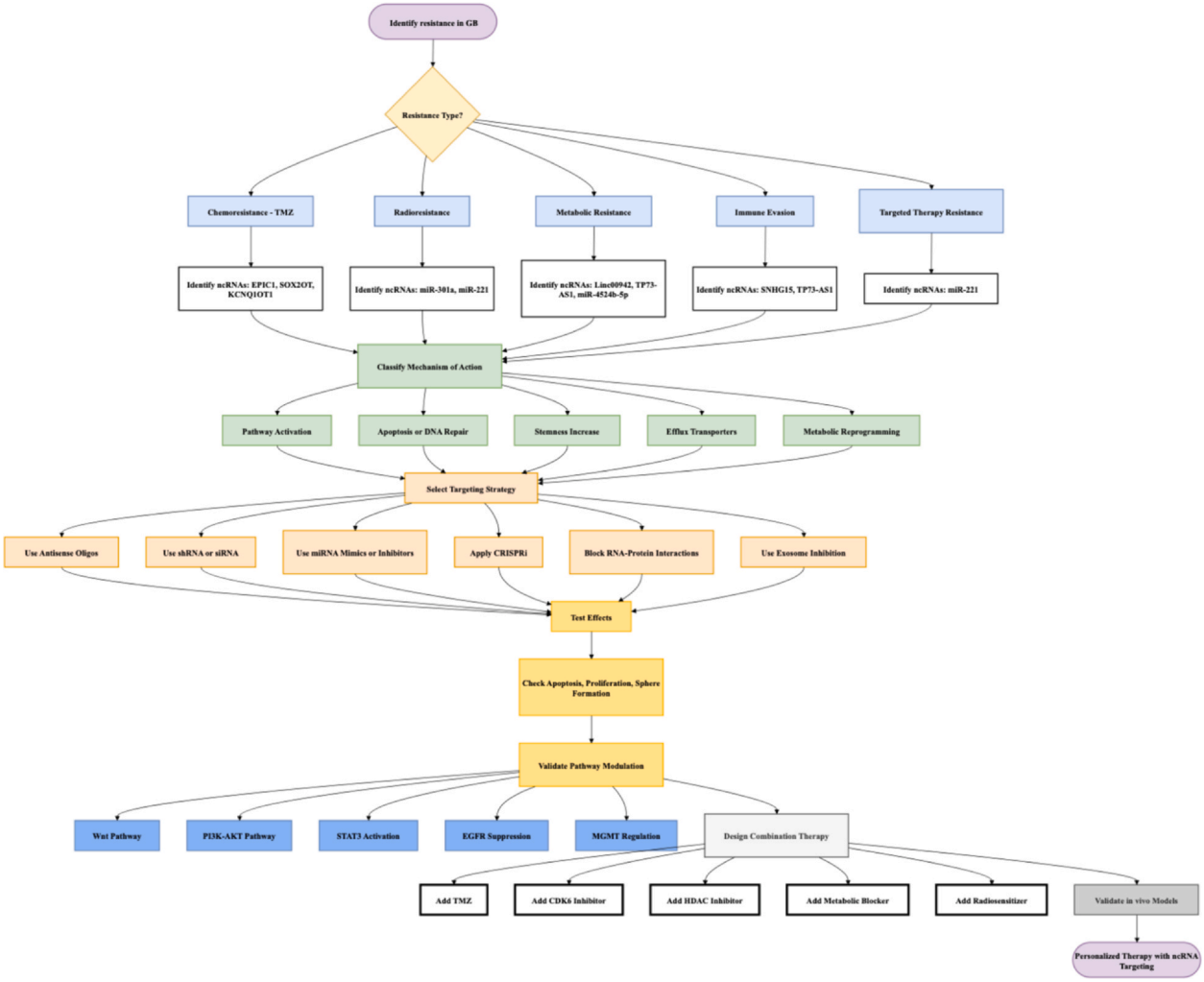

Fig. 3. Strategy map for targeting ncRNAs to overcome glioblastoma resistance and guide personalized therapy. Created using draw.io.

[31] measured lncRNAs' potential as GB immunophenotyping biomarkers using RNA-seq data on 149 TCGA GBsamples. In general, they aimed to discover immune subtype-related lncRNAs (im-lncRNAs) to differentiate between immune-high (IH) and immune-low (IL) tumor profiles. With the help of ssGSEA, consensus clustering, and machine learning, six im-lncRNAs, e.g., HCP5, PSMB8-AS1, were identified. Im-lncScore (AUC = 0.928) based on these lncRNAs is related to immune infiltration. It was enriched for IH patients who had better survival and for the mesenchymal subtype.

[78] discovered that immune-related lncRNA and radiomics features are predictive biomarkers for the GB prognosis. A multifactorial prognostic model was built by the analysis of a four-lncRNA signature and two FLAIR-based radiomics features using TCGA and TCIA datasets. Related to these signatures are immune cell infiltration and immune checkpoint blockade (ICB) genes, including PD-L1 and CTLA4. The clinical models were outperformed by the model in predicting overall survival. Furthermore, both negative correlations were found with NK cell activation and with immune GB pathways. Next, we showed that L1CAM correlated with lncRNAs that act as a biomarker, a biomarker-, and lncRNA and a target for L1CAM for stratification and the improvement of GB immunotherapy.

[66] revealed that WEE2-AS1, a recently identified m6A-modified lncRNA, facilitates GB progression. They employed in vitro, in vivo, and sequencing approaches to elucidate its role in tumor formation. We showed that stabilization of WEE2-AS1 by METTL3/IGF2BP3 is required for the elevation of RPN2 protein via preventing its CUL2-mediated ubiquitination. This stimulated the PI3K–Akt pathway, increasing GB growth. Knockdown of WEE2-AS1 sensitized GB cells to dasatinib, an FDA-approved CNS penetrant kinase inhibitor. However, this study first set up WEE2-AS1 as a prognostic marker and therapeutic target. Efforts to target this ncRNA further enhanced drug efficacy, indicating it to be useful in enhancing GB treatment through lncRNA-guided combination therapy.

To investigate lncRNA-driven immune regulation, [157] integrated TCGA and GTEx transcriptomic data to identify a ceRNA network in low-grade gliomas (LGGs). They aimed to build a lncRNA–miRNA–mRNA network to uncover therapeutic targets. Additionally, they identified lncRNA RP11–770J1.4 as an immune regulatory lncRNA that sponged hsa-miR-124–3p to regulate the

Table 2
Summary of molecular strategies involving non-coding RNAs to enhance therapeutic outcomes in glioblastoma.

Sr.No.	Therapeutic Focus	Biological Pathway or Mechanism Impacted	Specific ncRNA Example	Outcome in GB	References
1	Radiosensitivity Biomarker Discovery	PI3K-Akt, MAPK signaling, DNA damage response	Three-lncRNA signature	Stratifies patients by radiation response	W. [74]
2	m6A-Modification Risk Modeling	Immune checkpoint regulation, drug resistance	SOX21-AS1, AC005229.3	Predicts OS and therapy response	Xie et al., [142]
3	Novel Oncogenic Axis Identification	ceRNA network: PSMB8-AS1/miR−22–3p/DDIT4	PSMB8-AS1	Promotes proliferation via DDIT4	Hu et al., [46]
4	Transcriptional Regulation of Tumorigenesis	LINC01393/miR−128–3p/NUSAP1, NF-κB pathway	LINC01393	Drives GB via NF-κB activation	D. [67]
5	Immunotherapy Resistance Reversal	INCR1-driven PD-L1 and IDO1 upregulation	INCR1	Silencing improves IL−12 immunotherapy	Saini et al., [102]
6	Macrophage Metabolic Reprogramming	Lipid metabolism via hnRNPA1/CaM	HOXC-AS3	Enhances TAM malignancy and immunosuppression	Sheng et al., [111]
7	Tumor Suppressor miRNA Restoration	Wnt/β-catenin pathway, ZEB2 repression	miR−769–3p	Inhibits proliferation and invasion	K. [134]
8	Sensitization to Chemotherapy (CDDP)	E2F1 targeting	miR−485–5p	Enhances apoptosis with cisplatin	C. Huang et al. [47]
9	Targeting Migration and Apoptosis Pathways	RhoG regulation, PI3K pathway involvement	miR−124–3p	Suppresses migration and boosts apoptosis	S. [14]
10	Tetraspanin-Mediated Malignancy Suppression	Direct repression of TSPAN17	miR−378a−3p	Inhibits proliferation and migration	Guo et al., [40]
11	CRISPR-based miRNA Knockout Therapy	miR−21 knockout leading to Pten, Pdcd4 upregulation	miR−21a	Reduces tumor growth in vivo	Nieland et al., [91]
12	Liquid Biopsy miRNA Biomarker Profiling	miRNA cargo in plasma microvesicles (MVs)	miR−625–5p, miR−106b−5p	Indicates tumor state and prognosis	Simionescu et al., [115]

expression of CTXN1. In mouse models, knockdown of CTXN1 increased CD8 + T cell infiltration and improved survival. In addition, RP11–770J1.4 also influenced the cGAS-STING immune pathway, which represents its immunomodulatory role. They highlighted the lncRNA RP11–770J1.4–CTXN1 axis as possibly representing an immunotherapeutic target to change GB outcomes by modulating the microenvironment.

[135] showed that FAM131B-AS2 is a lncRNA promoting GB progression driven by copy number gain (CNG). Using differential expression and CNA analyses in GB samples, they attempted to identify lncRNA-facilitated replication stress resistance. Through USP7, FAM131B-AS2 stabilized RPA1 and activated ATR-CHK1 signaling and improved immune evasion. DNA repair, ATM activation, and tumor regression were impaired in GSC models with knockdown experiments. Further, immune modulation was underlain by suppression, which resulted in higher pro-inflammatory cytokines TNFα and IL-1β. Results showed FAM131B-AS2 to be of therapeutic relevance in replication stress and immunotherapy.

[70] demonstrated that LBX2-AS1 promoted GB progression via facilitating angiogenesis and metastasis. They wanted to explore the oncogenic role of LBX2 AS1 and its regulatory mechanisms using in vitro assays and expression profiling. Also, the study proved that LBX2AS1 elevated EMT markers and VEGFA, promoted endothelial tube formation, and enhanced the expression of IL4R via the recruitment of NFKB1. Suppression of IL4R expression suppressed GB malignancy and relieved the effect of LBX2-AS1. In this way, these findings pointed out a new LVBX2-AS1/NFKB1/IL4R axis that plays a critical role in GB vascularization and migration. This work has identified LBX2-AS1 as a putative therapeutic target to prevent tumor angiogenesis and metastasis in glioblastoma.

[145] reported that miR-138 is tumor suppressive in GB through tumor and functional assays. To assess miR-138's therapeutic relevance, they aimed to evaluate the expression and activity in the GB progression. They show that miR-138 was downregulated in primary GB patient samples and inversely associated with CD44 expression. Restoring miR-138 blocked proliferation, migration, and tumor growth in addition to promoting p27 nuclear translocation. In addition, PD-1/CTLA-4 expression was also repressed by miR-138, enhancing T-cell immunity. In contrast to glioma stem cells, the data of this study reinforced miR-138's therapeutic promise. This illustrated ncRNA's promise to target both tumor and immune cells as a potential new approach to improve GB outcome.

Using 3D microfluidic co-culture models, [45] validated the therapeutic impact of EV-mediated miR-124 delivery in GB. The miR-124 loaded EVs were designed to suppress tumor progression and microglial M2 polarization. In both GB cell lines and patient-derived cells, they showed that a reduction in proliferation, EMT, cytokine release, and increased chemosensitivity to temozolomide. MiR-124 EVs reduced STAT3 expression levels not only in GB but in microglia as well, thereby altering immune balance and increasing the natural killer cell infiltration. The results showed anti-tumoral and immunomodulatory effects of miR-124. On that basis, miR-124 was presented as a promising non-coding RNA therapeutic candidate to modulate tumor-immune dynamics and increase the effectiveness of glioblastoma therapy.

Through siRNA knockdown and dual-luciferase assays, [99] elucidated the oncogenic role of circRNA_0067934 in GB as well as its interaction with miR-7. Therefore, they attempted to explore the mechanism of circRNA_0067934 in GB progression. They used glioma tissues and cells to show that circRNA_0067934 was upregulated and sponged miR-7, decreasing its tumor suppressor function. Activation of the Wnt/β-catenin pathway resulted in the promotion of GB cell proliferation, invasion, and migration through this interaction. Validation by Western blot and immunofluorescence of pathway modulation was used. ncRNAs in this study were emphasized in circRNA_0067934 as a potential therapeutic target of GB and demonstrated that ncRNAs promote tumor progression through molecular signaling pathways.

[28] probed the tumor-suppressive role of miR-411 in GB using patient-derived tissues, cell lines, and dual-luciferase assays. They aimed to assess miR-411's clinical relevance and molecular mechanism in GB progression. miR-411 expression was downregulated in GB tissues and negatively correlated with KPS and IDH1 status. Overexpression of miR-411 suppressed GB cell proliferation, migration, and invasion. Mechanistically, miR-411 directly targeted STAT3, a known oncogenic factor in GB. These findings highlighted miR-411 as an independent prognostic indicator and regulator of GB aggressiveness.

[27], p. 2) examined the tumor-suppressive role of miR-744–5p in GB by analyzing patient tissues, cell lines, and gene interaction assays. They aimed to explore miR-744–5p's regulation of RFC2 and its effect on GB progression. Datasets revealed miR-744–5p was downregulated and RFC2 upregulated in GB. Overexpression of miR-744–5p inhibited GB cell proliferation, migration, and adhesion while promoting apoptosis by directly targeting RFC2. These outcomes highlighted miR-744–5p's therapeutic potential. Discussion proposed its involvement in TMZ sensitivity and future investigation into targets like XIAP and p53. This study underscored miR-744–5p as a promising ncRNA target for improving GB treatment outcomes.

[37] confirmed the oncogenic role of miR-92b in GB and explored its therapeutic targeting. Using patient datasets, in situ hybridization, qPCR, and bioinformatics, they aimed to validate FBXW7 as a direct miR-92b target. Results showed miR-92b was upregulated in GB and suppressed FBXW7, leading to increased proliferation, migration, and reduced apoptosis. Targeting miR-92b via a liposomal OMI formulation restored FBXW7 levels and reduced tumor growth in a GB mouse model. This outcome demonstrated FBXW7's tumor-suppressive role. Thus, the study highlighted miR-92b as an ncRNA therapeutic target to improve GB outcomes via FBXW7 modulation and liposomal delivery.

Table 2 illustrates specific therapeutic strategies leveraging non-coding RNAs (ncRNAs) to modulate glioblastoma progression and treatment response. Fig. 4 shows a stepwise workflow for targeting ncRNAs in glioblastoma, from discovery to therapeutic application.

Circular RNAs and PIWI-interacting RNAs in glioblastoma: The Emerging Players

CircRNAs and piRNAs, two distinct classes of ncRNAs, have recently emerged as critical regulatory molecules and potential biomarkers in GB, the most aggressive and lethal primary brain tumor. Their ability to regulate gene expression through diverse

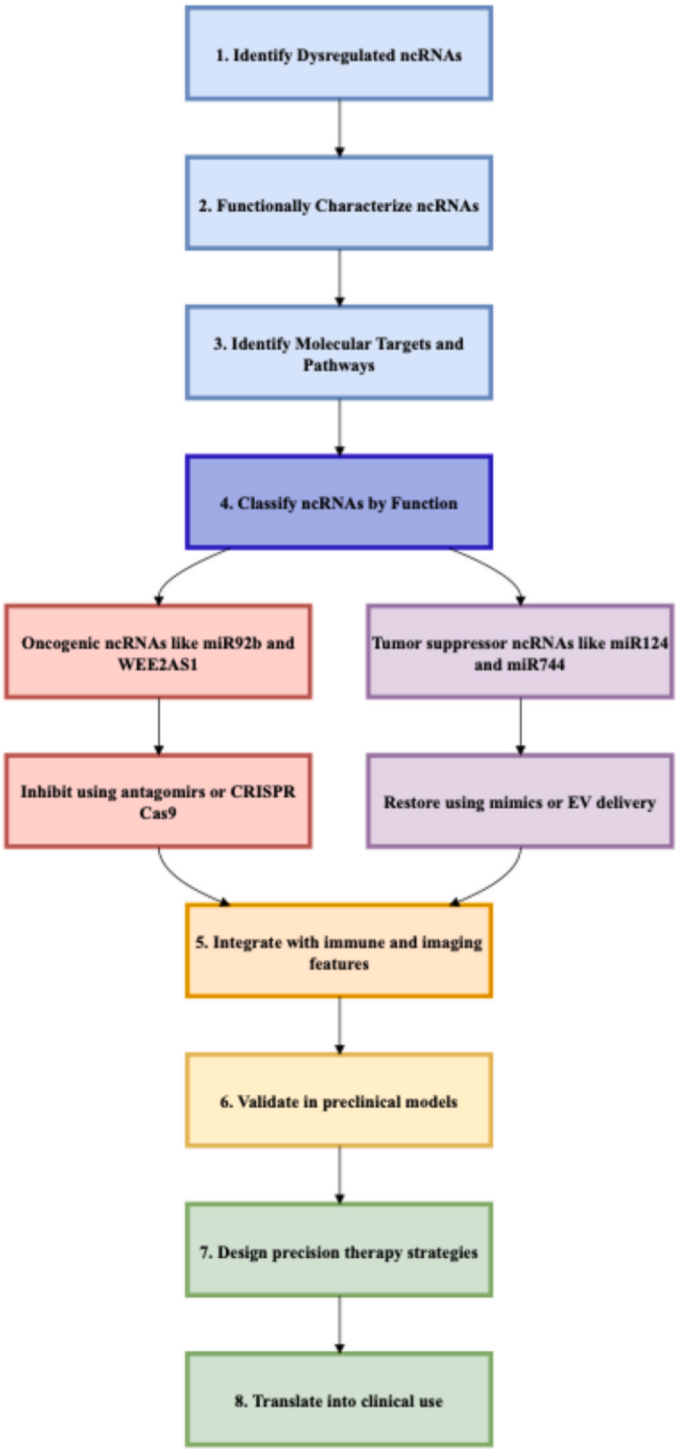

Fig. 4. Strategic workflow for targeting ncRNAs in glioblastoma, from identification to therapeutic modulation and clinical translation.

mechanisms makes them compelling candidates for diagnostic, prognostic, and therapeutic applications [124,138].

CircRNAs are covalently closed RNA molecules characterized by their high stability, abundance in extracellular fluids, and resistance to RNase-mediated degradation. In GB, circRNAs exert functional roles by acting as miRNA sponges, interacting with RNA-binding proteins (RBPs), regulating transcription, and encoding proteins through internal ribosome entry sites (IRES) or N6-methyladenosine (m6A)-mediated translation. For instance, hsa_circ_0021205 sponges microRNA (miR) 195–5p to control hormone sensitive lipase (HSL) and promoting proliferation and invasion. Circ_0027446 can also activate glycolysis and survival pathways by

miR-346/PGK1 (phosphoglycerate kinase 1) axis. On the contrary, the tumor suppressive circRNAs including circSMARCA5 and circCD44 suppress glioblastoma tumor growth by regulating splicing factors and sequestering oncogenic miRNAs. CircRNAs also influence hallmark cancer processes like EMT, angiogenesis, and metabolic reprogramming. For example, circ-E-Cad and hsa_circ_0067934 activate the PI3K/AKT signaling cascade, enhancing GB cell motility and therapy resistance. Additionally, some circRNAs modulate glioblastoma chemoresistance to TMZ and radiotherapy, offering promising targets for overcoming treatment failure [138].

Parallel to circRNAs, piRNAs—small ncRNAs ranging from 26 to 32 nucleotides—regulate gene expression predominantly through DNA methylation and transcriptional silencing, often in complex with PIWI proteins. Initially thought to be germline-specific, piRNAs and PIWI proteins are now recognized in somatic tissues, including the CNS, and are implicated in cancer biology. In glioblastoma, piR-8041 is significantly downregulated and suppresses tumor growth by promoting apoptosis and inhibiting cell survival pathways. Germline variant rs147061479 in piR-598 abolishes its tumor-suppressive function, promoting proliferation. PIWI family proteins such as PIWIL1 and PIWIL4 are also overexpressed in GB and correlate with poor prognosis and high tumor grade. The miR-384/PIWIL4/STAT3 axis, as well as the piR-DQ593109/PIWIL1/MEG3 regulatory loop, exemplify how these molecules modulate glioma pathogenesis and blood–tumor barrier (BTB) permeability [124].

Together, circRNAs and piRNAs represent powerful molecular regulators and promising biomarkers in glioblastoma. Their unique expression profiles, stability in body fluids, and regulatory complexity offer new avenues for early detection, prognosis, and precision-targeted therapies in this highly aggressive brain cancer as evident from the studies below.

[100] tested the role of circCOPA in GB using circRNA microarray screening of tumor and adjacent normal tissues. Aimed at exploring circRNA-mediated therapeutic resistance, they analyzed clinical samples and in vivo models. Lower circCOPA expression correlated with poor prognosis. They found circCOPA encodes COPA-99aa, which suppressed GB cell proliferation, migration, and invasion. COPA-99aa disrupted the NONO–SFPQ complex, impairing DNA repair and enhancing TMZ-induced damage. Functional rescue assays confirmed its suppressive effects. The study highlighted circCOPA as a prognostic biomarker, with COPA-99aa restoring TMZ sensitivity—demonstrating how circRNA-encoded peptides can improve GB treatment outcomes through targeted molecular regulation.

[151] systematized in vitro, in vivo, and molecular approaches to investigate exosomal circPRKD3's role in GB immunomodulation. Aimed at enhancing anti-tumor immunity, they used GSCs, macrophage assays, and lipid nanoparticle (LNP)-mediated delivery. circPRKD3 reprogrammed tumor-associated macrophages to secrete CXCL10, promoting CD8 + T cell infiltration. Mechanistically, it bound HNRNPC, downregulated IL6ST/STAT3 signaling, and disrupted glioma stem cell survival. Combining LNP-circPRKD3 with anti-PD-1 therapy extended survival in GB models. This study established exosomal circPRKD3 as a biomarker and therapeutic tool to remodel the tumor microenvironment and improve GB outcomes via immune activation and tumor cell suppression.

[150] concluded through molecular, localization, and functional assays that hsa_circ_0075323 promoted GB progression by modulating autophagy. They investigated its tumorigenic role by silencing hsa_circ_0075323 in GB cells and observed increased p62 levels and disrupted LC3B balance, impairing autophagosome formation. This outcome suggested inhibited autophagy, which is critical in therapy resistance. Dataset insights included cytoplasmic localization and inverse p62-LC3B expression patterns. The study highlighted hsa_circ_0075323 as a central regulator of autophagy homeostasis. Its role in radio- and chemo-resistant GB illustrated the potential of circRNAs as biomarkers and therapeutic targets for improving treatment outcomes in glioblastoma.

[121] indicated that circTOP2A was identified via microarray, co-expression profiling, and bioinformatics targeting miR-422a and RPN2. They aimed to reveal whether circTOP2A regulates glioma progression by sponging miR-422a to modulate RPN2. Functional assays and luciferase reporter analysis using glioma datasets confirmed circTOP2A as a competing endogenous RNA. CircTOP2A neutralized miR-422a and showed effects on RPN2 repression, thus inducing glioma cell proliferation and invasion, as shown by the results. The study showed that circTOP2A is related to WHO grade and prognosis. This example demonstrates that circTOP2A represents a glioblastoma biomarker for the noninvasive diagnosis and treatment of glioblastoma via the circTOP2A–miR422a–RPN2 axis.

To map the functional role of circNFIX in glioma progression, [22] utilized qRT-PCR, luciferase assays, and subcutaneous xenograft models. To unveil the mechanism of how circNFIX controls tumor behavior through the circNFIX/miR-378e/RPN2 axis, they sought to know. CircNFIX expression was elevated, and correlated with increased invasion, glycolysis, and reduction in apoptosis. Knockdown of it led to G0 G1 arrest, increased miR 378e, and reduced the oncogenic RPN2. Rescue assays supported that circNFIX functioned as a miRNA sponge. In vivo silencing inhibited tumor growth. We showed in these findings how targeting circRNAs resulted in modulation of tumor metabolism, apoptosis, and invasiveness, and described how circNFIX could serve as a promising glioblastoma biomarker.

[117] asserted that piRNAs, especially piR-823, could serve as promising serum biomarkers with diagnostic potential across cancers, including glioblastoma. They systematically reviewed 18 case-control studies and compared piRNA performance against standard markers like CEA and CA19–9. piR-823 demonstrated strong diagnostic accuracy with high sensitivity (83.3 %) and AUC (0.93). Notably, piR-823 has been linked to PIWI protein expression, which was previously associated with poor prognosis in glioblastoma. Its expression in blood and tumor tissues, along with functional interactions that regulate apoptosis and mitophagy, highlighted its translational relevance. The study concluded that piRNAs warrant further investigation as noninvasive biomarkers in glioma diagnostics.

[52] emphasized a post-GWAS and functional analysis strategy to evaluate piRNA variants in GB risk and progression. Using the GliomaScan cohort and U87 cell line, they identified five piRNA loci associated with glioma, notably rs147061479 in piR-598. Expression profiling and in vitro assays confirmed piR-598's role in apoptosis regulation via BAX and GOS2 and revealed that its wild-

Table 3
CircRNA and piRNAs as biomarkers in glioblastoma.

Sr. No	ncRNA Type	Biomarker	Mechanism	Functional Role in GB	Clinical Implication	References
1	piRNA	piR−8041	MAPK pathway suppression	Inhibits proliferation, induces apoptosis	Potential therapeutic molecule	Jacobs et al., [51]
2	circRNA	circ_0001583	miR−647/CKAP2L axis	Supports glycolysis, proliferation	Diagnostic/prognostic biomarker	Y. Zhang et al. [152]
3	circRNA	circMIB1	miR−1290/ceRNA network	Tumor suppressor, regulates circadian rhythm	Potential prognostic biomarker	S. [19]
4	circRNA	circLRFN5	PRRX2/GCH1 degradation	Induces ferroptosis in GSCs	Targets stemness via ferroptosis	Jiang et al., [53]
5	circRNA	circNDC80	miR−139–5p/ECE1	Maintains stemness, promotes invasion	GB progression target	Y. [137]
6	piRNA	piR−9491	Targets HRH1, ATXN3	Reduces colony formation	Potential liquid biopsy biomarker	Bartos et al., [7]
7	piRNA	piR−23231	Unknown	Associated with poor prognosis	Prognostic biomarker	Bartos et al., [7]
8	piRNA	piR−823	ERK/MAPK suppression	Induces apoptosis, restores RASSF1	Tumor suppressive therapy	Shen et al., [110]
9	piRNA	piR-DQ593109	MEG3/miR−330–5p/RUNX3	Modulates BTB permeability	Affects drug delivery, prognosis	Shen et al., [110]
10	PIWI protein	PIWIL1	Olig2/MCL1/CDKN1B regulation	Maintains GSC self-renewal	Cancer-testis antigen therapy	H. [48]

type suppressed GB growth, while its variant promoted colony formation. The findings indicated piR-598 as a promising prognostic biomarker. This demonstrated that piRNAs play a regulatory role in gliomagenesis and highlighted that they are potential therapeutic targets for improvement on GB outcomes.

[64] suggested that the piR DQ590027/MIR17HG/miR 153/miR 377/FOXR2 axis regulates glioma mediate BBB permeability. They examined the effect of piR-DQ590027 using qPCR and permeability assays in glioma endothelial cells (GECs). GECs were found to express less piR-DQ590027, miR-153, and miR-377 and more MIR17HG and FOXR2. Enhancement of BBB permeability was due to the reduction of ZO-1, claudin-5, and occludin, tight junction proteins, which was transcribedally reduced by FOXR2, which was transcriptionally reduced by increased miR-153/377 and reduced MIR17HG, which was reduced by piR-DQ590027 overexpression. Indeed, this revealed a new paracellular regulatory mechanism. Also, the study showed that piR-DQ590027 was a potential biomarker and therapeutic target for modulation of the BBB permeability in glioblastoma, which provided a new strategy to enhance drug delivery in GB treatment.

[77] reported that the PIWIL3/piR-30188/OIP5-AS1/miR-367–3p plays a regulatory role in glioma pathogenesis. They showed that PIWIL3, piR-30188, and miR-367–3p were downregulated, while OIP5-AS1, CEBPA, and TRAF4 were upregulated and correlated with poor prognosis using glioma tissues, VanOIP5-AS1, cell lines U87 and U251, attenuble xenografts, qPCR, luciferase, and RIP assays. PIWIL3 and piR-30188 were overexpressed, and OIP5-AS1 was silenced, which suppressed the growth of glioma by upregulating miR-367–3p that targeted CEBPA and downstream TRAF4. Tumor sizes and survival were smallest and longest, respectively, in vivo after combined modulation. This novel pathway identified piR-30188 as a promising biomarker and therapeutic target to improve glioblastoma outcomes.

[124] summarized current knowledge and mechanistic insights on the emerging role of piRNAs and PIWI proteins in glioma. They reviewed studies using glioma tissues, cell lines, and genome-wide datasets to assess expression patterns, clinical associations, and functional consequences of piRNAs like piR-598, piR-8041, and piR-30188. Key results showed that piR-8041 suppressed tumor growth, and piR-598 variant rs147061479 increased glioma risk. The review highlighted piRNA involvement in blood-brain barrier regulation, tumor suppressive pathways, and potential therapeutic targeting. This study exemplified how piRNAs such as piR-8041 and piR-598 may serve as biomarkers and therapeutic agents in improving glioblastoma outcomes.

Table 3 summarizes key circRNAs, piRNAs, and PIWI proteins in glioblastoma, detailing their mechanisms, functional roles, and clinical relevance as biomarkers or therapeutic targets. Fig. 5 visually categorizes these ncRNAs by function (oncogenic vs. tumor-suppressive) and highlights their potential as precision tools in GB diagnosis and therapy.

Challenges and future scope

Despite the rapidly growing body of evidence supporting the role of ncRNAs in GB progression, therapy resistance, and tumor microenvironment modulation, several critical challenges impede the clinical translation of ncRNA-based therapies. Future strategies must be rooted in a multidisciplinary understanding of RNA biology, delivery mechanisms, and tumor heterogeneity to overcome these barriers and improve patient outcomes.

One of the foremost challenges lies in the efficient delivery of RNAi-based molecules across the BBB and into glioma cells [9]. The BBB presents a highly selective barrier that precludes over 98 % of small molecules and virtually all large therapeutic agents from reaching the CNS [107]. While nanoparticle (NP)-based delivery systems—including liposomes, polymeric NPs, and dendrimer-entrapped nanoparticles—have shown promise in crossing the BBB and enhancing RNAi stability, many such platforms remain entrapped in the endolysosomal compartments, leading to cargo degradation [107]. A possible solution involves the surface modification of nanoparticles with ligands that facilitate receptor-mediated transcytosis and endosomal escape, such as polyethyleneimine (PEI) and transferrin [107]. Additionally, incorporating targeting ligands like angiopep-2 and ApoE peptides may improve specificity and biodistribution within GB tissues [107].

Another major obstacle is the immunogenicity and toxicity of certain RNAi delivery systems. Depending on the type of metal, the NPs containing iron, gold, or selenium can accumulate in peripheral organs, causing systemic toxicity [107]. Furthermore, NPs positively charged for cellular uptake are rapidly eliminated by the mononuclear phagocyte system and lead to unwanted immune responses [107]. Biodegradable carriers, for instance, chitosan, PLGA, or PBAEs, are safer alternatives and deliver their cargo with proven efficacy in preclinical GB models, either by intranasal or convection-enhanced delivery [107].

A major limitation to developing ncRNA-based therapies has been the absence of established delivery vehicles that can specifically target GSCs, which are responsible for recurrence and therapy resistance. Due to their high migratory capacity, GSCs present within their hidden hypoxic niches and are endowed with stemness properties, they escape conventional detection and remain difficult to target [107].The co-delivery of siRNAs targeting transcription factors, such as SOX2 and POU3F2 that are critical for GSC maintenance, has been possible with the help of lipopolymer NPs and PBAEs [107]. This resistant subpopulation can be eradicated by the development of GSC-specific surface markers and tailored nanocarriers.

Another major problem is the incorporation of ncRNAs as prognostic and predictive biomarkers into clinical practice. Numerous studies have shown the utility of including specific miRNAs, lncRNAs, and circRNAs for predicting therapy resistance or survival for patients, however, the heterogeneity between GB subtypes presents an obstacle to the standardization of biomarkers [120]. For example, ALDH and PLK2 show differences in expression correlated with chemoresistance and activation of Notch signalization across the patient samples [120]. To tackle this, single-cell sequencing and large-scale bioinformatics large scale analyses can be done to identify the patient-specific ncRNA expression patterns and thereby form personalized biomarker panels [120].

The therapeutic targeting, already complicated by sponging interactions, epigenetic modifications, and signaling crosstalk, is further complicated by the complexity of the ncRNA regulatory network. Contextual miRNAs, lncRNAs, and circRNAs frequently play

Fig. 5. Flowchart showing circRNAs and piRNAs as glioblastoma biomarkers and therapeutic tools.

either opposing or some contradictory roles (oncogenic and tumor suppressive), depending on the cellular environment [83]. However, future approaches should use systems biology modeling to map and simulate these regulatory networks, to select nsRNA targets with little or no off-target effects [83]. In addition, it is possible to identify novel interventional points in understanding the dynamics of GB cells to tumor microenvironment extracellular vesicle (EV) mediated ncRNA exchange [83].

While many therapeutic tools for directly modifying ncRNA function have been developed, they remain plagued by translational barriers. ASOs, LNAs, MOs, and CRISPR/Cas9 systems, all can target oncogenic ncRNAs with preclinical efficacy in GB models [106]. This, however, is seriously limited in its clinical application by off-target effects, poor BBB permeability, and poor delivery. To achieve these goals, chemical modifications that improve oligonucleotide stability, binding affinity as well as conjugation to ligands that target GalNAc or lipid nanoparticles, enhance CNS-specific delivery and reduce toxicity [106]. Additionally, utilizing chemoinformatics tools such as Inforna suggests it may be possible to identify small molecules that bind selectively to structured ncRNA motifs, as a non-oligonucleotide approach to therapeutics [106].

Clinical translation of these ncRNAs, therefore, remains in early phases with only a limited number of ongoing clinical trials targeting ncRNAs in GB. The majority of the existing trials are conducted for other cancer types or systemic diseases, miR-122 inhibitors in hepatitis C or miR-34a mimics in hepatocellular carcinoma, and therefore will not be covered in this review [106]. Studies like these draw lessons for GB-focused trials, which should focus on patient stratification based on ncRNA expression profile, careful monitoring of immune-related adverse events, as well as a novel combinatorial strategy combining ncRNA therapeutics with chemotherapy or immunotherapy.

Role of epitranscriptomic modifications (i.e., N6-methyladenosine (m6A) on ncRNA functions in GB is an emerging area of

exploration. Modifications of these can lead to changes in miRNA maturation, lncRNA protein interactions and circRNA translation, and hence influence angiogenesis and therapy resistance (D. Li et al. [68]). Nevertheless, there has been little understanding of the specific contributions of m6A-modified ncRNAs in GB. The future research should include mapping m6A landscapes in ncRNAs at a high-throughput scale and developing tools to selectively edit RNA modifications [68]. Furthermore, ncRNA fate and ncRNA function modulating RBPs may work as indirect but valuable targets of intervention ([68]).

New frontier in GB research is the ncRNA classes being unexplored, such as piRNAs, YRNAs and tsRNAs. However, although their functions on genome stability and tumor proliferation are confirmed in other cancers, the involvement of GB in their angiogenesis and drug resistance is unknown [68]. The expansion of the transcriptomic databases to include these more poorly studied RNA species and functional studies in orthotopic GB models will disclose new mechanisms and therapeutic targets.

Finally, the standardization of EV-based ncRNA delivery systems poses both a technical and regulatory hurdle. Although EVs exhibit superior biocompatibility and can cross the BBB, consistent methods for EV isolation, characterization, and cargo loading are lacking [68,83]. Developing scalable manufacturing pipelines and quality control metrics for EV therapeutics is essential for clinical adoption. Engineered EVs expressing BBB-permeable surface proteins or glioma-specific ligands could serve as next-generation delivery vehicles for RNA-based drugs [68,83].

In summary, while ncRNA-targeted strategies hold immense potential for combating GB resistance and improving clinical outcomes, a concerted effort involving molecular biologists, bioengineers, clinicians, and computational scientists is required to translate these findings into effective therapies. Future research must focus on refining delivery systems, validating clinical biomarkers, and unraveling the multifaceted roles of ncRNAs in GB biology to realize the promise of RNA-based precision medicine.

Conclusion

In this comprehensive review, we explored the pivotal roles of ncRNAs in GB, particularly in modulating therapy resistance and enhancing treatment outcomes. We synthesized emerging evidence on how diverse ncRNA classes—microRNAs, long non-coding RNAs, circular RNAs, and PIWI-interacting RNAs—collectively influence key hallmarks of GB, including angiogenesis, apoptosis, immune evasion, and stemness. Through this integration of molecular mechanisms, case studies, and therapeutic advances, we demonstrated that targeting ncRNAs holds substantial promise in addressing the multifactorial resistance mechanisms that plague conventional and targeted GB therapies.

Our findings underscore the dual nature of ncRNAs: while some function as oncogenes promoting tumor aggressiveness and therapy evasion, others act as tumor suppressors, restoring treatment sensitivity and hindering tumor progression. By focusing not only on well-characterized ncRNAs such as miRNAs and lncRNAs but also on emerging players like circRNAs and piRNAs, we addressed an important knowledge gap in current literature. CircRNAs, with their inherent stability and function as miRNA sponges, and piRNAs, with their epigenetic regulatory potential, remain underexplored in GB but show significant therapeutic relevance based on recent experimental data.

We also discussed cutting-edge RNA-targeting strategies—including antisense oligonucleotides, RNA interference, and CRISPR-Cas systems—and how novel delivery technologies such as lipid nanoparticles and exosome-mediated platforms are overcoming blood–brain barrier limitations to bring ncRNA therapeutics closer to clinical reality. Furthermore, we highlighted ongoing clinical trials and preclinical validations that emphasize the translational potential of these approaches.

Ultimately, our review highlights the centrality of ncRNAs in glioblastoma biology and the promise they hold in reshaping current therapeutic paradigms. Accordingly, we hope that this synthesis will provide a foundational reference for researchers and clinicians alike in their mechanistic understanding, identification of underutilized ncRNA targets, and the development of future RNA-based therapeutics for GB. Further elucidation of ncRNA functions and advancement of delivery will be critical in the development of ncRNA-based therapy to fundamentally change the treatment landscape for glioblastoma.

Authors contribution

All the authors make substantial contribution to this manuscript. DP, and MS participated in drafting the manuscript. DP wrote the main manuscript, and all the authors discussed the results and implications on the manuscript at all stages.

Ethics approval and consent to participate

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Data availability

All relevant data and material are presented in the main paper.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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