Review

Discovery Medicine 2026; 38(214): 3430–3456
https://doi.org/10.24976/Discov.Med.202638214.264

Emerging Role of MicroRNAs in Early Diagnosis, Prognosis, and Therapeutic Resistance in Brain Tumors: A Molecularly Stratified Narrative Review Across Five Tumor Subtypes

Ibrahim Abdullah Almazni[1,2,*]

[1]Department of Clinical Laboratory Sciences, Faculty of Applied Medical Sciences, Najran University, 61441 Najran, Saudi Arabia
[2]Health Research Center, Najran University, 61441 Najran, Saudi Arabia
*Correspondence: eaalmazni@nu.edu.sa (Ibrahim Abdullah Almazni)
Submitted: 4 July 2026 Revised: 7 August 2026 Accepted: 18 August 2026 Published: 25 November 2026

Brain tumors, including glioblastoma, isocitrate dehydrogenase (IDH)-wildtype (GBM), astrocytomas, medulloblastomas, high-grade meningiomas, and aggressive pituitary adenomas, are difficult to treat. GBM is particularly aggressive, with a median overall survival of only 14–16 months, even after maximal surgical resection and temozolomide (TMZ) chemoradiotherapy. MicroRNAs (miRNAs), endogenous noncoding RNAs of 18–22 nucleotides, serve as key posttranscriptional regulators of oncogenesis, therapeutic resistance, and tumor microenvironment remodeling across primary brain tumor subtypes. This structured narrative review employed a semi-systematic search of PubMed, Scopus, and Web of Science, which yielded 140 cited references, of which 123 empirical studies met the prespecified eligibility criteria and were included in the qualitative synthesis. The findings were synthesized using a purpose-built three-axis Molecular-Stratified miRNA Classification (MSMC) framework that places each finding within its molecular covariable stratum, functional role, and clinical–translational domain. Using this framework, the review covered five brain tumor subtypes across four thematic domains: (i) dysregulation of miRNA biogenesis and the oncomiR/tumor suppressor axis; (ii) the diagnostic and prognostic value of circulating miRNA biomarkers in plasma, serum, and cerebrospinal fluid (CSF), with reported areas under the curve of up to 0.97 for multi-miRNA panels and 0.885 for individual markers such as miR-214; (iii) miRNA-mediated resistance to TMZ, cisplatin, vincristine, radiation, and dopamine agonists, including specific miRNA–drug–target triads such as miR-21/PTEN/TMZ, miR-584-5p/HDAC1/vincristine, and miR-145-5p/TPT1/bromocriptine; and (iv) extracellular vesicle–encapsulated miRNA transfer as a route for horizontal multidrug resistance propagation in GBM. A cross-subtype comparative synthesis showed a steep evidence-maturity gradient, from an emerging biomarker evidence base in GBM and astrocytoma to mechanistic-only evidence in medulloblastoma and pituitary adenoma. A nascent single-cohort biomarker signal emerged for high-grade meningioma (exosomal miR-497/195; see "High-Grade Meningioma: WHO Grade-Stratified miRNA Profiles"). The lack of standardized preanalytical protocols (serum vs. plasma vs. CSF variability), the absence of validated endogenous normalizers for liquid biopsy miRNA quantification, small single-center cohorts, and the blood–brain barrier (BBB) were identified as the principal barriers to clinical translation. IDH mutation and O6-methylguanine-DNA methyltransferase (MGMT) methylation status were treated throughout as Axis I molecular covariables, resolving several apparently contradictory findings in the literature, including the context-dependent, tumor-lineage-specific behavior of the miR-221/222 cluster. Multi-miRNA diagnostic panels generally outperform single biomarkers, but this advantage is best established in GBM and remains largely unvalidated in the other four subtypes. No miRNA therapeutic has yet been approved for brain tumors. However, magnetic resonance–guided focused ultrasound–enabled BBB-opening trials (NCT03626896) may provide critical delivery infrastructure for future brain-targeted miRNA therapeutics. Furthermore, multitarget miRNA combination strategies are a promising, though still preclinical, avenue for eventual clinical translation. The MSMC framework introduced here provides a reusable structure for organizing future IDH/MGMT- and subgroup-stratified biomarker validation studies and for AI-driven multi-omics integration in precision neuro-oncology.

Keywords: microRNA; glioblastoma; astrocytoma; medulloblastoma; liquid biopsy; therapeutic resistance; IDH mutation; MGMT methylation

Copyright: © 2026 The Author(s). Published by Discovery Medicine. This is an open access article under the CC BY 4.0 license.
Note: *Discovery Medicine* stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Introduction

Brain tumors remain difficult to treat and encompass a biologically diverse set of neoplasms arising within the central nervous system (CNS). In the United States, primary brain and other CNS tumors are the fifth most prevalent cancer overall, with an estimated prevalence of >1.3 million cases (approximately 14% malignant). Glioblastoma alone causes >15,000 deaths each year, and the 5-year survival rate has remained <6% despite multimodal treatment—essentially unchanged for the past two decades [1]. Gliomas constitute the largest histological group of primary CNS neoplasms, including astrocytomas, glioblastomas, isocitrate dehydrogenase (IDH)-wildtype (GBMs, WHO Grade 4), oligodendrogliomas, and ependymomas [2]. Despite decades of progress in neurosurgical techniques, radiotherapy protocols, and chemotherapy, outcomes for patients with malignant brain tumors have changed little. After maximal surgical resection, adjuvant radiotherapy, and temozolomide (TMZ), the median survival for patients with GBM is only 14–16 months [3,4].

The discovery of microRNAs (miRNAs) was a major milestone in late-twentieth-century molecular biology, later recognized by the 2024 Nobel Prize in Physiology or Medicine. Lee et al. [5] identified lin-4, the first miRNA, in *Caenorhabditis elegans* in 1993, describing a small non-protein-coding RNA that controlled larval timing via antisense complementarity to lin-14 mRNA and introducing a new mode of posttranscriptional gene regulation. A second miRNA, let-7, was identified in 2000 by Pasquinelli et al. [6] and found to be conserved across animal species, reframing miRNAs as a broad regulatory class rather than a species-specific curiosity. The link between miRNAs and human cancer was established in 2002, when Calin et al. [7] showed that miR-15a and miR-16-1 are located on chromosome 13q14, a locus deleted in more than half of patients with chronic lymphocytic leukemia, and that both miRNAs target the antiapoptotic oncogene BCL2 [8]. This finding helped establish cancer miRNomics as a distinct field. In neuro-oncology, early microarray-based miRNA profiling of brain tumors in the mid-2000s revealed distinct, reproducible signatures that distinguished tumor from normal brain tissue, laying the groundwork for the field that followed [9].

A major barrier to success in brain tumor therapy is that tumor cells can be intrinsically resistant to treatment or develop resistance over time. This resistance involves activation of prosurvival signaling cascades such as the PI3K/AKT and MAPK/ERK pathways, epigenetic silencing of drug targets, enhanced DNA damage repair capacity [10], alterations in drug efflux transporters (*Multidrug resistance gene 1* (MDR1)/P-glycoprotein), and evasion of apoptotic cell death [11]. The tumor microenvironment, characterized by profound immunosuppression, hypoxia, and aberrant vascularity—particularly the hypoxic niche where glioma stem cells (GSCs) reside—further exacerbates therapeutic failure and sustains tumor-initiating cell populations refractory to cytotoxic treatment [12]. Two 2024 reviews of glioma stem cell biology highlight the significance of this population. One systematically maps the molecular pathways (Notch, Wnt/β-catenin, Hedgehog, and PI3K/AKT) that GSCs exploit for self-renewal and treatment evasion [13]. The other emphasizes that GSCs are not a static population but a dynamically maintained state—sustained in part by microRNA-regulated signaling—and frames miRNA-targeted GSC elimination as a therapeutic strategy distinct from bulk-tumor cytoreduction [14].

MicroRNAs are short, endogenous, noncoding RNAs, typically 18–22 nucleotides long, that function posttranscriptionally by binding complementary sequences in the 3′-untranslated regions of target mRNAs, thereby repressing translation or triggering mRNA degradation [15,16,17]. According to certain estimates, miRNAs regulate >60% of human protein-coding genes [18], shaping nearly every major biological process—cell cycle progression, differentiation, apoptosis, angiogenesis, immune modulation, and stem cell maintenance [19]. In cancer, a given miRNA can act either as an oncomiR, driving tumor progression when overexpressed, or as a tumor suppressor, restraining oncogenic signaling at normal expression levels (as discussed further in "OncomiRs and Tumor Suppressor miRNAs"). miRNAs in biological fluids remain remarkably stable, protected either by encapsulation in extracellular vesicles (EVs) or by association with Ago2 protein complexes—a property that makes them attractive candidates for non-invasive liquid biopsy (as explored further in "Circulating miRNA Biomarkers in Brain Tumors"). This review synthesizes current evidence on the role of miRNAs in brain tumor biology across five tumor subtypes, covering biogenesis, diagnostic and prognostic utility, mechanisms of therapeutic resistance, extracellular vesicle biology, detection methods, clinical translation, and the field's key limitations. The Materials and Methods section outlines the literature search and synthesis methodology used throughout this review. The section titled "A Proposed Conceptual Framework: Molecular-Stratified miRNA Classification for Precision Neuro-Oncology" introduces the three-axis Molecular-Stratified miRNA Classification (MSMC) framework, which is applied in the relevant sections and used to structure the cross-subtype comparative synthesis presented in "Discussion: Critical Synthesis, Contradictions, and Research Priorities".

Materials and Methods

Literature Search Strategy

This article is a structured narrative review using a semi-systematic search approach. Given the mechanistic and clinical breadth across five histologically and molecularly distinct brain tumor subtypes, a single systematic

review question was not feasible. A semi-systematic approach, combining a structured, reproducible search-and-screening protocol with thematic, hypothesis-generating synthesis, consistent with published guidance for the conduct and quality assessment of narrative reviews, was therefore adopted [20]. PubMed/MEDLINE, Scopus, and Web of Science were searched from database inception through February 2026 using combinations of controlled and free-text terms "microRNA" OR "miRNA" AND ("glioblastoma" OR "astrocytoma" OR "glioma" OR "medulloblastoma" OR "meningioma" OR "pituitary adenoma" OR "somatotropinoma" OR "prolactinoma"), cross-referenced against ("biomarker" OR "liquid biopsy" OR "diagnosis" OR "prognosis" OR "chemoresistance" OR "radioresistance" OR "temozolomide" OR "extracellular vesicle" OR "exosome" OR "IDH mutation" OR "MGMT methylation"). Reference lists of retrieved reviews and meta-analyses were hand-searched to identify additional primary studies not captured by the electronic search.

Eligibility Criteria and Study Selection

Eligible sources included peer-reviewed original research articles, systematic reviews, meta-analyses, and authoritative mechanistic reviews published in English. These sources reported quantitative diagnostic or prognostic performance metrics, such as sensitivity, specificity, or area under the curve (AUC), for circulating or tissue miRNAs, or detailed, validated mechanistic roles of specific miRNAs in therapeutic resistance across at least one of the five tumor subtypes examined. Exclusions comprised conference abstracts without full-text articles, non-peer-reviewed preprints, case reports lacking mechanistic or biomarker data, and articles whose full texts did not match their abstracts. The author screened titles, abstracts, and full texts in two separate passes, spaced at least 1 week apart, to minimize temporal bias—although this is not a substitute for the reliability of independent double screening (see "Methodological Quality Across the Reviewed Evidence Base"). Ambiguous cases were reevaluated three times against the predefined criteria before final inclusion. Verified references were cross-checked in PubMed and CrossRef to confirm that the DOI led to the correct article rather than a retracted or unrelated paper; if verification failed, the reference was replaced with a supporting one, acknowledging potential citation bias (see "Methodological Quality Across the Reviewed Evidence Base"). This process yielded 140 verified references, including 123 empirical studies that met the eligibility criteria and formed the basis for the qualitative synthesis (Fig. 1); the remaining 17 references provide background and methodological context only. Noneligible citations mainly comprised reviews and methodological sources used for general context. To clarify, contextual and methodological citations that did not meet the eligibility criteria—such as the miRNA discovery history in the Introduction and journal-guidance references like [20]—were included only for background narration. These citations were not part of the 123 empirical studies that underwent the formal screening process, as summarized in Fig. 1.

Framework for Data Synthesis

To address the limitations of a purely descriptive, tumor-by-tumor catalog of miRNA findings, data were systematically mapped onto three orthogonal axes: (i) the molecular covariable in which the finding was generated (such as IDH/MGMT status for gliomas, WNT/SHH/Group 3/Group 4 for medulloblastoma (MB), WHO grade for meningioma, and AIP mutation for somatotropinoma); (ii) the functional role attributed to the miRNA (oncomiR, tumor suppressor, or dual-role regulator, depending on context); and (iii) the clinical–translational domain studied (diagnostic/prognostic biomarker, resistance mediator, or therapeutic target/delivery vehicle). This three-axis MSMC framework, introduced in "A Proposed Conceptual Framework: Molecular-Stratified miRNA Classification for Precision Neuro-Oncology", was used both prospectively to organize findings across the relevant sections and retrospectively for cross-subtype comparisons and contradiction analysis in "Discussion: Critical Synthesis, Contradictions, and Research Priorities". Fig. 1 illustrates the search and study-selection process described above.

A Proposed Conceptual Framework: Molecular-Stratified miRNA Classification for Precision Neuro-Oncology

Rationale and Novelty

Studies on miRNA biology in brain tumors frequently list individual miRNA–target–phenotype relationships for each tumor type without a clear framework to link these findings to the tumor's molecular subtypes, histological features, or treatment resistance [9]. This approach obscures a pattern that emerges when data from all five tumor subtypes are compared side by side: the same miRNA may appear to act differently across studies, not because its biology is inconsistent, but because the studies examine different points in a three-dimensional evidence space. This paper introduces the MSMC framework as a conceptual framework for organizing, comparing, and critically evaluating miRNA evidence across brain tumor subtypes. This framework is used throughout this review, especially in the synthesis and contradiction analysis in "Discussion: Critical Synthesis, Contradictions, and Research Priorities".

The Three Axes of the MSMC Framework

Axis I, the molecular covariable stratum, categorizes findings based on the tumor's molecular subtype: IDH-mutant/glioma CpG island methylator phenotype (G-CIMP) vs. IDH-wild-type and MGMT promoter methylation in diffuse gliomas (detailed in "IDH Mutation, MGMT Methylation, and miRNA Crosstalk: A Critical Molecu-

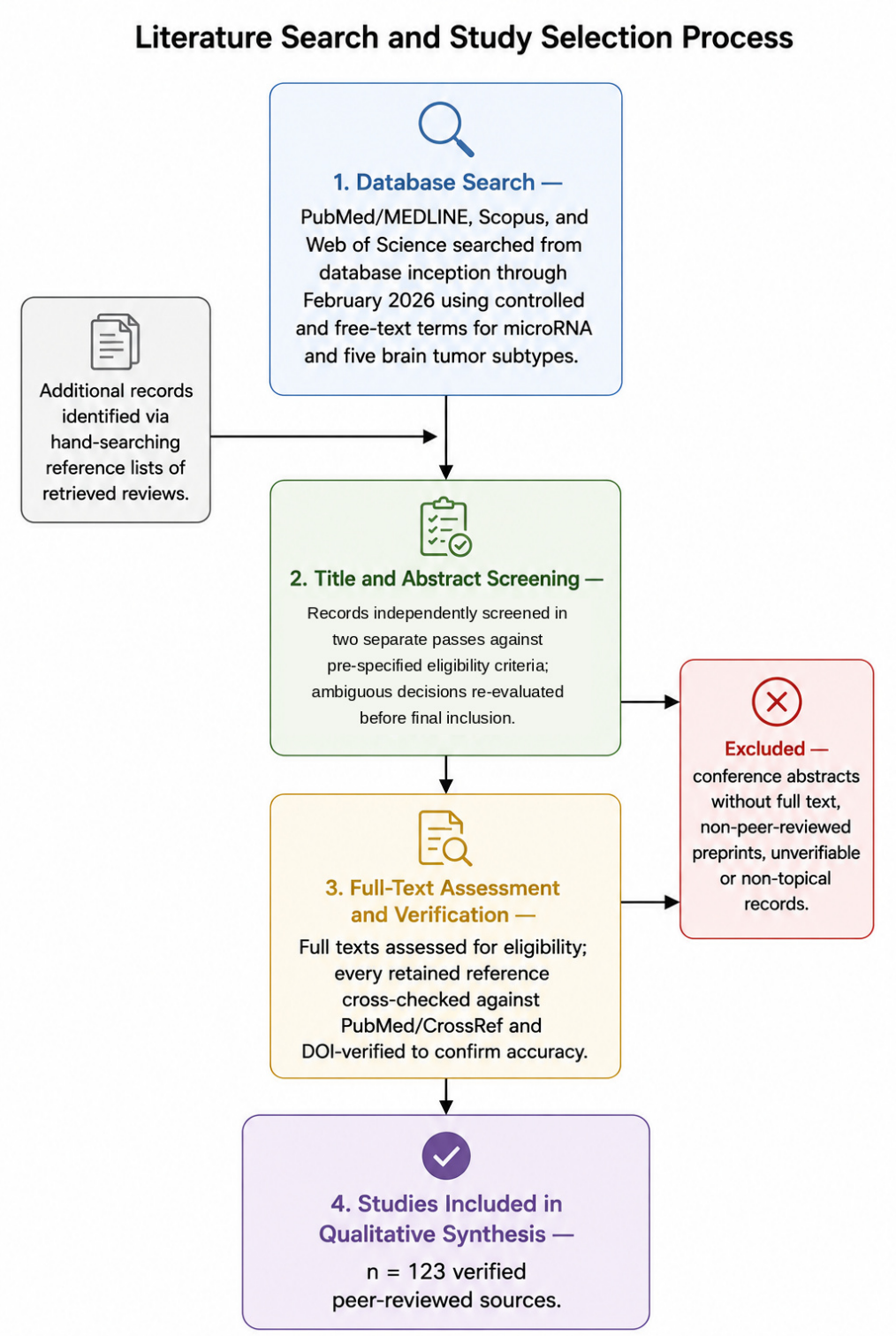

Fig. 1. Literature search and study selection process. Semi-systematic search of PubMed/MEDLINE, Scopus, and Web of Science, followed by two-pass title/abstract screening, full-text assessment, and DOI-level verification, yielding 123 peer-reviewed empirical studies included in the final qualitative synthesis. Figure created by the author using ChatGPT-5 (OpenAI, San Francisco, CA, USA). A further 17 references were cited for background and methodological context only (140 references in total).

lar Framework"); the WNT, SHH, Group 3, and Group 4 transcriptional groups in MB (see "MB: Subgroup-Specific miRNA Resistance Profiles"); WHO Grade 1–3 for meningioma (see "High-Grade Meningioma: WHO Grade-Stratified miRNA Profiles"); and AIP-mutation status in somatotropinoma (see "Pituitary Adenoma: Dopamine Ag-

Table 1. The molecular-stratified miRNA classification (MSMC) framework: representative worked examples across the three synthesis axes.

Representative miRNA	Axis I: Molecular stratum	Axis II: Functional role	Axis III: Translational domain	Section title
miR-21	IDH-wild-type GBM	OncomiR	Resistance mediator (PTEN/PDCD4 axis)	miR-21 as Master Regulator of Chemoresistance in GBM
miR-221/222	GBM (IDH-wild-type)	OncomiR (radioresistant)	Resistance mediator	Radiosensitizing and Radioresistant miRNAs
miR-221/222	High-grade meningioma (WHO Gr.2–3)	Context-dependent (radiosensitizing)	Resistance mediator	High-Grade Meningioma: WHO Grade-Stratified miRNA Profiles
let-7 family	IDH-mutant/G-CIMP glioma	Tumor suppressor	Prognostic co-variable	IDH Mutation, MGMT Methylation, and miRNA Crosstalk: A Critical Molecular Framework
miR-17-92 cluster	Group 3 medulloblastoma (MYC-amplified)	OncomiR	Resistance mediator	MB: Subgroup-Specific miRNA Resistance Profiles
miR-34a	AIP-mutant somatotropinoma	Context-dependent (paradoxical up-regulation)	Resistance mediator	Pituitary Adenoma: Dopamine Agonist and Somatostatin Analog Resistance
miR-181d	GBM, MGMT-regulatory	Tumor suppressor/ regulator	Diagnostic-prognostic biomarker	Specific miRNA Biomarkers in Glioma
miR-9 (exosomal)	GBM, TMZ-exposed	OncomiR (MDR1-linked)	Therapeutic target (anti-miR)	EV-miRNAs in GBM Multidrug Resistance

GBM, glioblastoma, IDH-wildtype; IDH, Isocitrate dehydrogenase; G-CIMP, Glioma CpG island methylator phenotype; MGMT, O6-methylguanine-DNA methyltransferase; MDR1, Multidrug resistance gene 1; TMZ, Temozolomide. Section title refers to sections of this review where the underlying primary evidence is presented in full.

onist and Somatostatin Analog Resistance"). Axis II, the functional role class, indicates whether an miRNA functions as an oncomiR, a tumor suppressor, or as a context-dependent dual-role regulator whose overall effect varies with tissue type or molecular background. Axis III, the clinical–translational domain, notes whether the evidence pertains to diagnostic or prognostic biomarkers, specific mechanisms of therapeutic resistance, or treatment targets or delivery methods. Table 1 illustrates this framework with examples from the evidence discussed later in this review, each precisely situated at its Axis I–II–III position.

How the Framework Resolves Apparent Contradictions

The clearest example of the framework's usefulness is the miR-221/222 cluster. In IDH-wild-type GBM, up-regulation of miR-221/222 promotes Akt-driven radioresistance (Axis I: GBM/IDH-wild-type; Axis II: oncomiR). Conversely, in high-grade meningioma, downregulation of the same cluster enhances radiosensitivity (Axis I: meningioma, WHO Grade 2–3; Axis II: context-dependent). Although these findings appear contradictory when viewed in isolation, within the MSMC framework they are two distinct yet consistent coordinates in the same evidence space, distinguished by tumor lineage on Axis I. This framework is used prospectively in the relevant sections and revisited in the Discussion (see "Context-Dependency and Apparent Contradictions in miRNA Function"), where similar Axis I/II tensions in the literature are analyzed in the same manner.

MicroRNA Biogenesis and Dysregulation in Brain Tumors

Canonical miRNA Biogenesis Pathway

miRNA biogenesis is a tightly regulated, multistep process that spans several cellular compartments (Fig. 2) [21]. The process begins in the nucleus, where RNA polymerase II transcribes miRNA genes into long primary transcripts called pri-miRNAs [22]. These transcripts fold into characteristic hairpin structures that the Drosha–DGCR8 microprocessor complex recognizes and cleaves into shorter (approximately 70-nucleotide) stem-loop precursors known as pre-miRNAs [23]. Exportin-5 then transports the pre-miRNAs from the nucleus to the cytoplasm in a GTP-dependent step [24]. In the cytoplasm, the endoribonuclease Dicer—working with TRBP—cleaves the pre-miRNA hairpin into an imperfect approximately 22-nucleotide duplex [25]. One strand of this duplex, the guide strand (the mature miRNA), is loaded onto Ago2 proteins to form the RNA-induced silencing complex [26]. The complex then guides complementary sequences on target mR-

Table 2. Key components of miRNA biogenesis machinery and their clinical significance in brain tumors.

Component	Location	Function	Clinical significance
Drosha	Nucleus	Cleaves pri-miRNA to pre-miRNA	Reduced in GBM; correlates with poor prognosis
DGCR8	Nucleus	Co-factor of Drosha microprocessor complex	Dysregulation alters global miRNA output
Exportin-5	Nuclear envelope	Transports pre-miRNA to cytoplasm	Mutations reduce mature miRNA levels in tumors
Dicer	Cytoplasm	Cleaves pre-miRNA to mature duplex	Lost expression found in GBM, neuroblastoma
TRBP	Cytoplasm	Dicer partner; stabilizes miRNA loading	Promotes tumor growth when dysregulated
Ago2	Cytoplasm	Core RISC component; mediates silencing	Somatic mutations in GBM; p53-Ago2 interaction alters let-7

GBM, glioblastoma, IDH-wildtype; RISC, RNA-induced silencing complex; Ago2, Argonaute 2.

NAs, leading to translational inhibition or transcript degradation [27,28]. Table 2 outlines the key components of this biogenesis machinery and their clinical relevance in brain tumors.

Mechanisms of miRNA Dysregulation in Brain Tumors

Multiple interconnected mechanisms contribute to miRNA dysregulation in brain tumors. Genomic alterations such as somatic mutations, chromosomal deletions, and amplifications at miRNA gene loci can directly influence the levels of specific miRNAs produced. Additionally, epigenetic silencing—particularly promoter hypermethylation—is a frequent pathway leading to the loss of tumor suppressor miRNAs in gliomas. A notable example is the miR-137 promoter, in which hypermethylation silences its expression, removing a regulatory check on the oncogene GLIPR-1. The biogenesis machinery itself can also be disrupted: reduced Drosha, Dicer, or TRBP expression, observed in GBM, pineoblastoma, and neuroblastoma, lowers overall mature miRNA output, is linked to worse survival, and loss of Dicer activity shapes the characteristics of glioma stem cells and the tumors they generate [29]. This aligns with a comprehensive 2025 overview of the miRNA life cycle, which highlights Argonaute loading fidelity and target-directed miRNA decay as other, less-explored points at which this machinery might be disrupted in cancer [30]. Oncoproteins also disrupt this machinery—mutant p53 binds RNA helicases away from the Drosha microprocessor complex to inhibit miRNA maturation [31], and hypoxia-activated EGFR phosphorylates Ago2 at Y393, reducing its binding with Dicer and broadly diminishing miRNA activity [32]. Overall, cellular stress conditions such as hypoxia, nutrient deprivation, and genotoxic stress alter miRNA biogenesis at various stages, from transcription to Argonaute loading. This provides tumor cells with an additional layer of adaptive posttranscriptional regulation under the challenging conditions typical of the brain tumor microenvironment [33].

OncomiRs and Tumor Suppressor miRNAs

miRNAs linked to brain tumors fall into two main groups: oncomiRs that promote tumor growth by inhibiting tumor suppressor genes, and tumor suppressor miRNAs that, when downregulated, lift the brakes on oncogenes [34]. miR-21 is among the most studied oncomiRs across cancers, showing significant upregulation in GBM cells compared with normal brain tissue, with reports of up to 100-fold overexpression. It exerts oncogenic effects by suppressing multiple tumor suppressor targets, including PTEN, PDCD4, HNRNPK, TOPORS, TGFBR2/3, TIMP3, RECK, and DAXX [35,36]. miR-221 functions as an oncomiR by promoting cell cycle deregulation and correlates with poor prognosis in glioma and other cancers [37]. The miR-106b family enhances invasiveness in pituitary adenomas via the PTEN–PI3K/AKT/MMP9 pathway. Conversely, tumor suppressor miRNAs such as miR-7, miR-128, miR-137, miR-145, miR-195, and members of the let-7 family inhibit the growth of gliomas and other brain tumors by targeting oncogenic receptors, transcription factors, and kinases [38].

IDH Mutation, MGMT Methylation, and miRNA Crosstalk: A Critical Molecular Framework

The 2021 WHO Classification of Tumors of the Central Nervous System redefined glioma taxonomy based on molecular features, primarily using IDH1/2 mutation status as a key diagnostic marker. Meanwhile, MGMT promoter methylation is considered a predictor of treatment response rather than a diagnostic marker [39]. Although this paradigm shift impacts miRNA biology, biomarker frameworks are yet to fully adapt. IDH1/2-mutant gliomas (Grade 2–3 astrocytomas and oligodendrogliomas) often show a hypermethylator phenotype (G-CIMP) with extensive CpG island methylation, including at miRNA gene promoters, which results in a distinctive miRNA expression profile compared with IDH-wild-type GBM (Grade 4). Specifically, IDH-mutant gliomas have higher levels of let-7 family and miR-181 species, which correlate with better prognosis and less aggressive growth. By contrast, IDH-wild-type GBM—marked by EGFR amplification, PTEN loss, and TERT promoter mutations—shows an miRNA

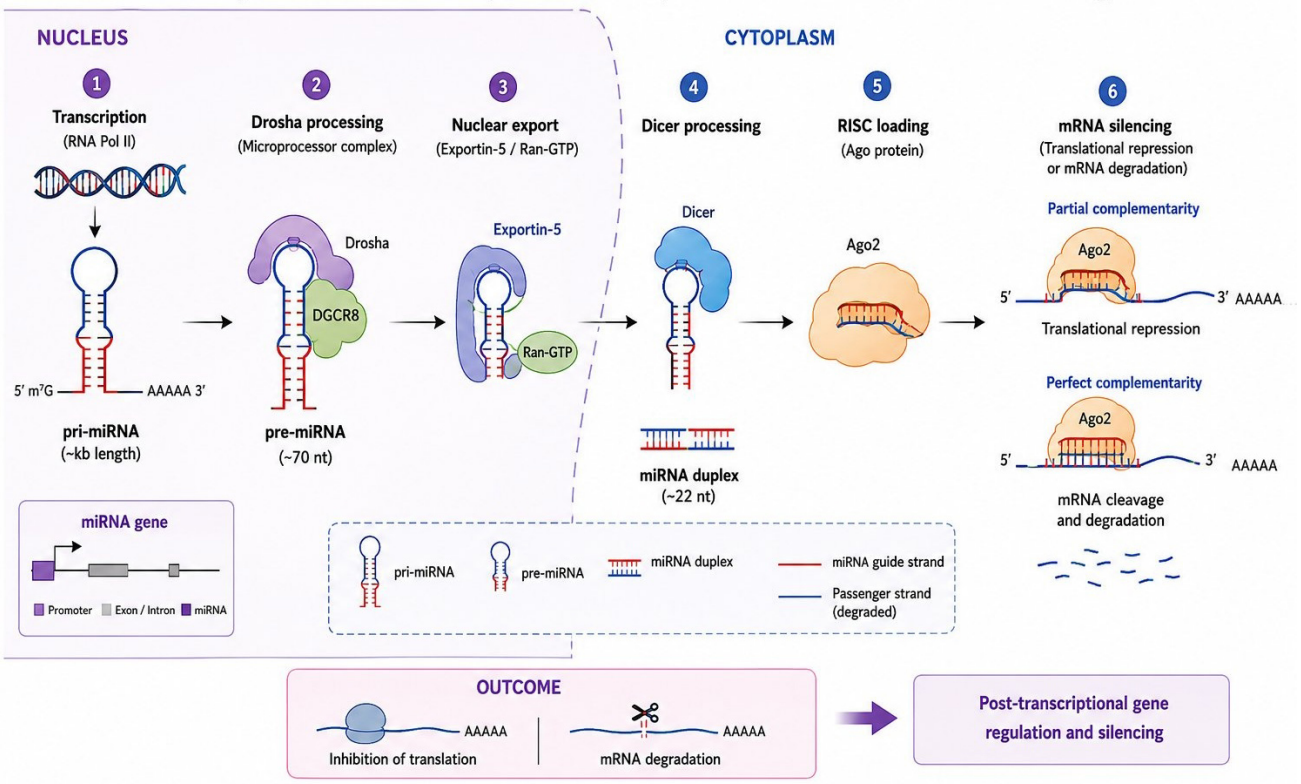

Fig. 2. Canonical miRNA biogenesis pathway. Sequential steps from pri-miRNA transcription by RNA Pol II, Drosha/DGCR8-mediated nuclear cleavage to pre-miRNA (~70 nt), Exportin-5/Ran-GTP nuclear export, Dicer cleavage to miRNA duplex (~22 nt), Ago2-RISC loading, and final mRNA silencing via translational repression or mRNA cleavage/degradation. Figure created by the author using ChatGPT-5 (OpenAI, San Francisco, CA, USA).

profile with increased oncomiRs (miR-21, miR-10b, miR-93, and miR-106b) and decreased tumor suppressor miRNAs (miR-128, miR-7, and miR-124). This molecular heterogeneity implies that miRNA biomarker studies combining both IDH-mutant and wild-type gliomas often produce composite signatures that reflect tumor diversity rather than specific biological mechanisms.

MGMT promoter methylation suppresses MGMT expression via epigenetic mechanisms, impairs repair of DNA alkylation damage, and is the most predictive biomarker of TMZ sensitivity in GBM [40]. Despite its importance, the interaction between miRNAs and MGMT regulation has not been well explored clinically. Several miRNAs, including miR-181d and miR-648, influence MGMT levels either directly or via epigenetic pathways; their expression correlates with MGMT protein levels and promoter methylation, suggesting a possible role in regulating TMZ response, although a direct causal link requires further evidence [41]. This leads to a testable clinical hypothesis: Patients with GBM who have unmethylated MGMT and express high levels of MGMT-suppressing miRNAs might respond to TMZ similarly to those with methylated MGMT, suggesting a subset for whom standard TMZ therapy could still be effective despite unmethylated status. Conversely, miR-181d is lower in GBMs with methylated MGMT promoters than in those with unmethylated MGMT promoters, indicating that high miR-181d and unmethylated MGMT define the most resistant molecular subtype [42]. Future research and clinical trials should stratify patients with GBM by IDH status and MGMT methylation status, rather than treating GBM as a uniform molecular entity. These molecular distinctions appear throughout the diagnostic and treatment evidence discussed later and are explicitly revisited within the MSMC framework's Axis I (see "The Three Axes of the MSMC Framework") and in the cross-subtype synthesis of the "Discussion: Critical Synthesis, Contradictions, and Research Priorities".

Circulating miRNA Biomarkers in Brain Tumors

The Case for Circulating miRNAs in Liquid Biopsy

Brain tumor diagnosis has conventionally relied on neuroimaging and, when necessary, stereotactic biopsy. Although neuroimaging effectively detects established tumors, it cannot offer molecular-level diagnostic discrimination or identify early, presymptomatic neoplasia. Liquid biopsy, which examines cancer biomarkers in blood, CSF, or urine, provides a practical, noninvasive alternative [43] (Fig. 3). Of the circulating biomarkers, miRNAs are par-

Table 3. Clinically significant circulating miRNA biomarkers for brain tumor diagnosis and prognosis: AUC values, cohort sizes, and key findings.

miRNA	Tumor type	Expression	Biofluid	AUC (95% CI)	Cohort (n)	Clinical significance/Key finding
miR-21	GBM, Meningioma Gr.II–III	↑ Up	Plasma/ CSF	0.71–0.83	n = 120–480	First cancer-linked miRNA; diagnosis, prognosis, TMZ/bevacizumab treatment response; PTEN/PDCD4 targets
miR-301a	GBM	↑ Up	Serum exosome	0.83	n = 55	Strong diagnostic/predictive exosomal biomarker; activates Wnt/β-catenin; promotes radioresistance via TCEAL7
miR-181d	GBM (IDH-wt)	↑ Up	Plasma/ CSF	0.79	n = 80	8 protein targets regulated; correlates in tumor vs. plasma; guides carmustine wafer use decision; MGMT-regulatory
miR-214	Glioma Gr.I–II	↑ Up	Serum	0.885	n = 100	Independent prognostic factor for OS; normalizes post-surgery; Gr.I shows higher elevation than Gr.II
miR-29b	High-grade glioma	↓ Down	Blood	NR	n = 240+240	Evaluated alongside VEGFA as a diagnostic candidate; high diagnostic value for Grade III–IV; targets BCL2; expression inversely correlates with VEGFA
miR-185	GBM	↑ Up	Plasma	0.84	n = 60	Significantly elevated vs. benign lesions; returns to normal post-surgery + chemotherapy; real-time progression biomarker
miR-221/222	Glioma	↑ Up	Plasma	0.84/0.92	n = 50+51	Cell cycle deregulation; poor OS; confers TMZ+radioresistance via Akt; radiosensitizer when inhibited
9-miRNA serum panel	Astrocytoma (all grades)	Mixed (↑)	Serum	0.97	n = 90+110	9-miRNA panel achieved sensitivity 0.933, specificity 0.945; 9 miRNAs decreased post-operatively; 3-miRNA subset (miR-19a-3p, miR-106a-5p, miR-181b-5p) independently predicted survival

GBM, glioblastoma, IDH-wildtype; CSF, Cerebrospinal fluid; AUC, Area under ROC curve; OS, Overall survival; IDH-wt, IDH-wild-type; Gr., Grade. Arrow (↑) = upregulated; (↓) = downregulated. AUC values represent pooled or single-study reported values from cited literature.

ticularly promising because they remain stable in biological fluids via EV encapsulation or Ago2 binding [44,45], are highly tissue-specific, and their levels fluctuate with tumor burden and treatment. They can also be measured with sensitive, standardized techniques [46]. CSF is often more specific than blood for CNS tumors due to its proximity to the disease site, but lumbar puncture limits frequent sampling [47]. Plasma collected in ethylenediaminetetraacetic acid tubes is increasingly favored over serum for circulating miRNA analysis, as coagulation can release platelet-derived miRNAs such as miR-21, miR-223, and miR-451, which can skew results [48]. Table 3 lists clinically relevant miRNA biomarkers in brain tumors with validated AUC values and cohort sizes.

Specific miRNA Biomarkers in Glioma

Of the various circulating miRNAs linked to glioma, miR-21 is among the earliest associated with malignancy and remains the most studied. A meta-analysis of multiple microarray datasets identified 27 candidate miRNAs involved in glioma initiation, progression, and prognosis. Notably, miR-15a, miR-16, miR-21, miR-23a, and miR-9 were consistently upregulated, whereas miR-124 was downregulated relative to normal brain tissue, providing a broader context for evaluating individual biomarkers [49,50,51]. MiR-301a, highly expressed in blood exosomes from GBM (AUC 83; n = 55), shows potential as a diagnostic and predictive biomarker because it activates Wnt/β-catenin signaling by suppressing TCEAL7 and contributes to radioresistance [52,53]. In a single-center cohort, miR-214 demonstrated notable diagnostic performance, with an AUC of 0.885 among 100 preoperative patients with glioma, and its expression independently correlated with overall survival in a multivariate analysis [54]. miR-29b levels in blood decreased as glioma advanced and were evaluated alongside VEGFA, a key driver of glioma-related angiogenesis and a target of antiangiogenic therapies [55,56], for high-grade glioma diagnosis in a cohort of 240 patients and matched controls [57]. Significantly, plasma miR-185 levels were elevated in patients with GBM relative to those with benign lesions and normalized after surgery and chemotherapy, supporting its role as a real-time biomarker for treatment response and recurrence [58]. A serum miRNA profiling study of 106 patients with GBM identified a prognostic panel (miR-222-3p, miR-182, miR-20a-5p, miR-106a-5p, and miR-145-5p), in which higher

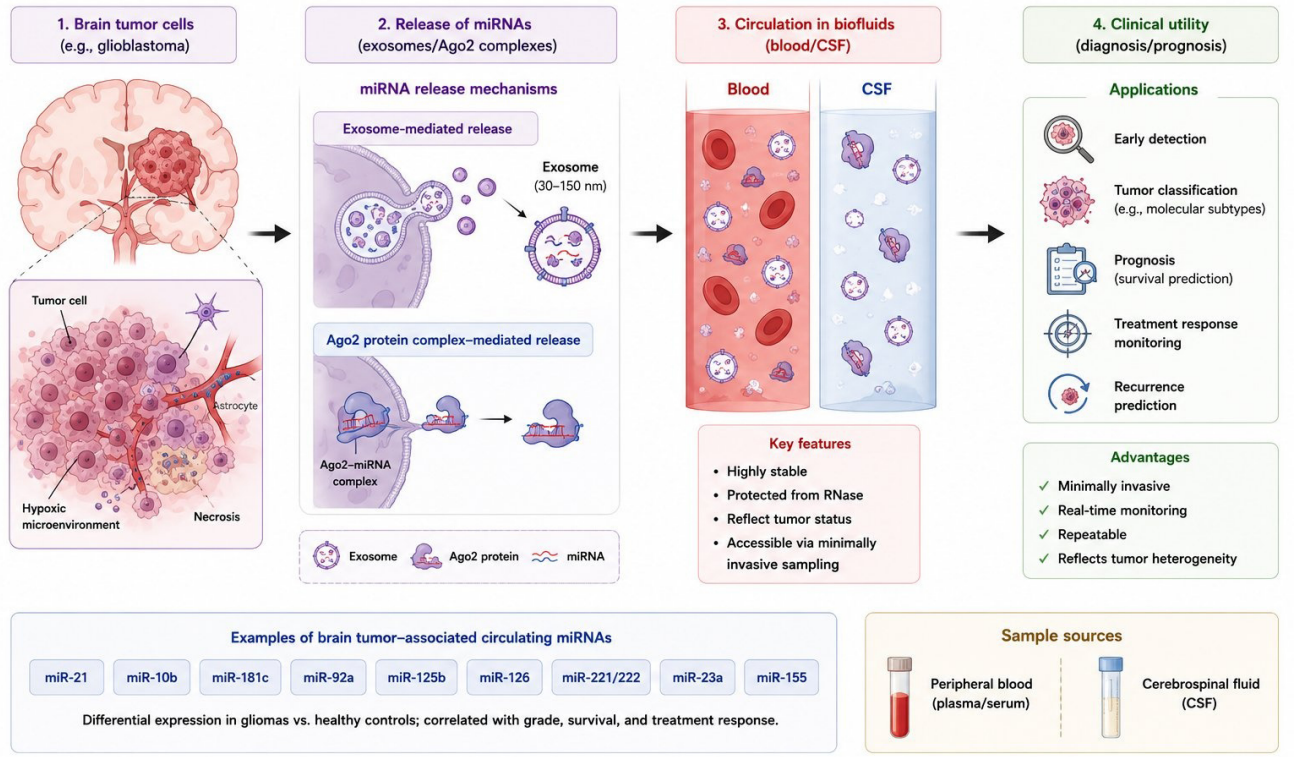

Fig. 3. Circulating miRNA biomarkers in brain tumor liquid biopsy. miRNA release from glioblastoma cells via exosome-mediated and Ago2 protein complex-mediated pathways into blood and CSF. Key circulating miRNAs (miR-21, miR-10b, miR-181c, miR-221/222, miR-125b) enable early detection, tumor classification, prognosis, treatment response monitoring, and recurrence prediction as minimally invasive liquid biopsy biomarkers. Figure created by the author using ChatGPT-5 (OpenAI, San Francisco, CA, USA).

risk scores were associated with poorer overall and disease-free survival, highlighting the prognostic value of multi-miRNA signatures beyond diagnosis [59]. Another plasma signature, including downregulated miR-181a/b and miR-410 and upregulated miR-155, achieved an AUC of at least 0.75 for distinguishing high- from low-grade gliomas before and after surgery. Each miRNA independently predicted overall survival, strengthening the role of circulating miRNA panels as both diagnostic and prognostic tools in high-grade glioma [60]. A 2025 study also supported this approach, showing that circulating miRNA panels tracked treatment response and prognosis throughout therapy in patients with GBM, emphasizing the importance of longitudinal monitoring over one-time assessments [61].

Multi-miRNA Panels and Diagnostic Performance

Since single miRNA biomarkers often lack sufficient sensitivity or specificity because of tumor heterogeneity, researchers have increasingly focused on multi-miRNA panels. Zhou et al.'s [62] systematic review and meta-analysis found that circulating miRNAs generally have strong diagnostic accuracy for glioma, with pooled sensitivity of 0.85, specificity of 0.90, and an AUC of 0.93. They also noted that miRNA panels tend to perform better than individual miRNAs [62]. A more recent meta-analysis that included both diagnostic and prognostic data reported similar pooled estimates (sensitivity 0.82, specificity 0.83, and AUC 0.89), confirming the reproducibility of miRNAs as biomarkers across studies [63]. These results underscore the importance of population-specific validation studies before clinical use. The nine-serum miRNA panel identified by Zhi et al. [64] and the 7-miRNA LASSO recurrence classifier developed by Chen et al. [65] demonstrate that data-driven multianalyte signatures—when validated in independent cohorts—can achieve diagnostic and prognostic accuracy adequate to complement MRI-based assessment in clinical neuro-oncology.

MicroRNAs in Resistance to Chemotherapy and Pharmacological Treatment

Molecular Mechanisms of Therapeutic Resistance

Resistance to chemotherapy in brain tumors involves both intrinsic resistance, present before treatment, and acquired resistance, which develops under selective therapeutic pressure [66,67]. The molecular mechanisms include activation of prosurvival pathways, such as PI3K/AKT and MAPK/ERK [68], and suppression of apoptotic pathways, including Bcl-2 overexpression, p53 mutations, and reduced CD95 expression [69]. Additionally, enhanced

Table 4. MicroRNAs involved in chemotherapy and pharmacological drug resistance in malignant brain tumors.

miRNA	Tumor	Drug	Gene target	Mechanism	Effect
miR-21	GBM	TMZ, Taxol	PTEN, PDCD4, Bcl-2	Suppresses apoptosis; activates PI3K/AKT	Chemoresistance
miR-128-3p	GBM	TMZ	c-Met/EMT pathway	Reduces proliferation, invasion, migration	Sensitizes to TMZ
miR-224-3p	GBM	TMZ	HIF-1α / VEGF	Suppresses HIF-1α; reduces autophagy	Increases chemosensitivity
miR-186	GBM	Cisplatin	YY1	Inhibits GIC phenotype formation	Reverses resistance
miR-let-7f-1	Medulloblastoma	Cisplatin	HMGB1	Inhibits autophagy	Sensitizes tumor cells
miR-29c-3p	Medulloblastoma	Cisplatin	Bcl-2/Wnt2	Increases apoptosis	Overcomes resistance
miR-584-5p	Medulloblastoma	Vincristine	HDAC1/eIF4E3	Cell cycle arrest; DNA damage	Sensitizes to vincristine
miR-34a	Somatotropinoma	Octreotide	cAMP pathway	Antiproliferative effect via SSA	Pharmacological resistance
miR-145-5p	Prolactinoma	Bromocriptine	TPT1	Restores DA sensitivity	Overcomes DA resistance

GBM, glioblastoma, IDH-wildtype; TMZ, Temozolomide; HIF-1α, Hypoxia-inducible factor 1-alpha; VEGF, Vascular endothelial growth factor; SSA, Somatostatin analogs; DA, Dopamine agonist; MDR1, Multidrug resistance gene 1.

DNA repair, upregulation of drug efflux transporters such as MDR1/P-glycoprotein, induction of autophagy as a protective response, and preservation of cancer stem cell populations capable of repopulating tumors after cytotoxic treatments contribute to resistance. MicroRNAs regulate nearly all of these resistance mechanisms. Table 4 details the miRNAs involved in chemotherapy and drug resistance across different brain tumor subtypes.

miR-21 as Master Regulator of Chemoresistance in GBM

miR-21 is a key miRNA involved in GBM chemoresistance, attracting extensive research and serving as a major regulatory factor (Fig. 4) [70]. It targets multiple resistance pathways: suppressing PTEN to activate PI3K/AKT signaling and promote cell survival, inhibiting PDCD4 to block proapoptotic pathways, reducing Bax levels to favor antiapoptosis, and activating LRRFIP1/NF-κB signaling to enhance radioresistance. Clinical data from various GBM cohorts support these findings, showing that high miR-21 expression correlates with shorter progression-free and overall survival in patients treated with TMZ [71]. The HIF-1α/miR-224-3p/ATG5 axis illustrates how hypoxia—a hallmark of the GBM environment—intersects with miRNA-induced autophagy to drive therapeutic resistance. Under low oxygen conditions, HIF-1α levels rise while miR-224-3p decreases over time, creating a feedback loop that boosts HIF-1α activity, leading to BNIP3-dependent protective autophagy and bevacizumab resistance. Restoration of miR-224-3p levels suppresses HIF-1α, reduces GBM cell motility, lowers VEGF expression, and improves TMZ sensitivity *in vitro* [72]. Furthermore, other miRNAs influence TMZ and cisplatin sensitivity via unique mechanisms: miR-128-3p enhances TMZ response by inhibiting c-Met and reversing the epithelial–mesenchymal transition phenotype [73], while miR-186 reverses cisplatin resistance and reduces the GBM-initiating cell phenotype by targeting Yin Yang 1 [74].

MB: Subgroup-Specific miRNA Resistance Profiles

MB (WHO Grade 4) is classified into four molecular subgroups—WNT, SHH, Group 3, and Group 4—that exhibit markedly different biological behaviors, prognoses, and responses to therapy [75,76,77]. This molecular diversity is evident in distinct miRNA expression profiles, so miRNA-based resistance mechanisms or biomarkers should be evaluated within specific MB subgroups rather than applied universally. The WNT subgroup MB, with the best prognosis (>90% 5-year survival), overexpresses miR-193a, miR-224/452, and the miR-182/96/183 cluster, which inhibit WNT pathway inhibitors and cause nuclear β-catenin accumulation. The SHH subgroup MB, driven by mutations in PTCH1, SMO, or SUFU, uniquely upregulates miR-9 and miR-125b, thereby modulating the Hedgehog pathway and contributing to vismodegib resistance by sustaining GLI transcriptional activity. Group 3 MB, with the poorest prognosis and the highest metastasis rate, features MYC amplification and elevated levels of miR-17-92 cluster members—including miR-17-5p, miR-18a, and miR-19a—that suppress p21, PTEN, and BIM, promoting aggressive growth and resistance. miRNA-mediated resistance mechanisms specific to Group 4 MB remain poorly characterized. In terms of drug resistance, miR-34a targets MAGE-A family members (MAGE-A2, A3, A6, and A12), releasing p53 from MAGE-A repression and enhancing sensitivity to cisplatin and etoposide [78]. miR-let-7f-1 increases cisplatin sensitivity by targeting HMGB1 and blocking protective autophagy, while miR-584-5p, which

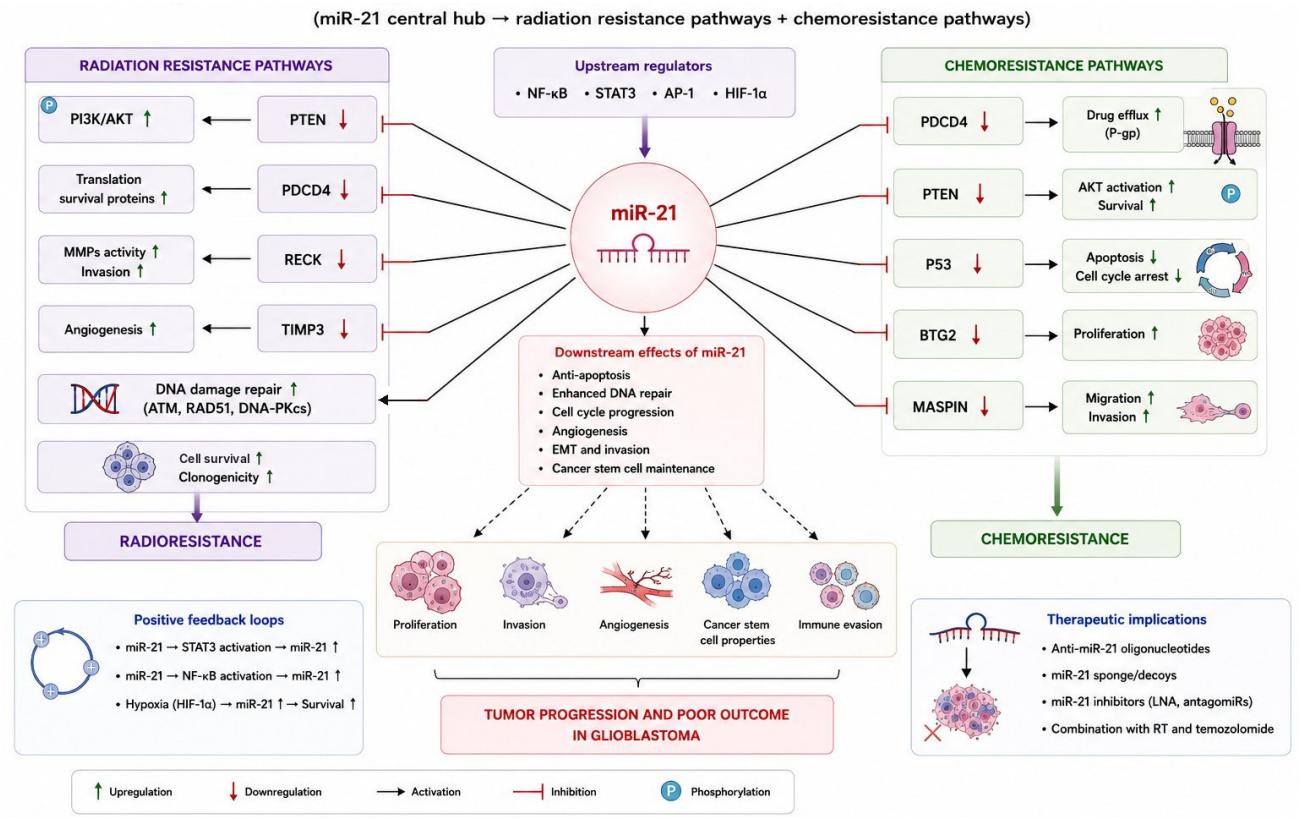

Fig. 4. miRNA regulatory network in chemo- and radioresistance in glioblastoma. miR-21 functions as the central oncomiR hub, suppressing tumor suppressors (PTEN, PDCD4, RECK, TIMP3, p53, BTG2, MASPIN) to activate PI3K/AKT survival signaling, enhance DNA damage repair, promote EMT and invasion, and maintain cancer stem cells. Positive feedback loops via STAT3, NF-κB, and HIF-1α amplify miR-21 expression, collectively driving radioresistance and chemoresistance to TMZ in GBM. Figure created by the author using ChatGPT-5 (OpenAI, San Francisco, CA, USA).

targets HDAC1/eIF4E3, causes spindle defects, DNA damage, and cell cycle arrest, thereby boosting vincristine efficacy in high-risk MB [79]. The long noncoding RNA CRNDE binds miR-29c-3p in MB cells; reducing CRNDE or increasing miR-29c-3p restores cisplatin sensitivity, inhibits proliferation, and promotes apoptosis, suggesting that this RNA interaction influences platinum resistance [80]. A 2024 review highlights that resistance mechanisms are either shared across MB subgroups or specific to certain subgroups, emphasizing the importance of subgroup-specific models rather than a universal approach to understanding resistance [81].

High-Grade Meningioma: WHO Grade-Stratified miRNA Profiles

Meningiomas are the most common primary CNS tumors in adults. Most are benign WHO Grade 1, but approximately 15%–20% are atypical (Grade 2) or anaplastic (Grade 3). These high-grade types tend to recur often, grow invasively, and are resistant to radiotherapy. miRNA expression patterns vary markedly across WHO grades of meningioma and should be analyzed separately for each grade. In Grade 1 meningioma, elevated levels of tumor suppressor miRNAs, such as miR-200a, miR-145, and miR-195, are characteristic of slow-growing tumors. Moving to Grade 2 (atypical meningioma), there is a progressive decrease in miR-145 (which targets COL5A1), miR-195 (which targets FASN), and the miR-497–195 cluster (which targets GATA-4), along with an increase in miR-224 (which targets ERG2). In Grade 3 (anaplastic meningioma), further loss of tumor suppressor miRNAs and a sharp increase in proliferative oncomiRs promote invasive growth and resistance to treatment. A microarray study of 55 patients with atypical meningioma comparing radiosensitive and radioresistant groups identified 14 miRNAs significantly dysregulated: seven were upregulated in the radioresistant group, including miR-4286, miR-4695-5p, and miR-6732-5p, and seven were downregulated, including miR-1275, miR-30c-1-3p, and miR-4449. These changes suggest involvement of transforming growth factor-β signaling and fatty acid biosynthesis pathways in resistance [82]. Serum exosomal miR-497 and miR-195 are reduced in Grade 2–3 compared with Grade 1 disease, with exosomal miR-497 showing better discrimination (AUC 0.89) than miR-195 (AUC 0.78). Mechanistically, they act by upregulating GATA-4 and Cyclin D1, which contribute to resistance to chemother-

apy and radiotherapy [83]. Interestingly, while the miR-221/222 cluster promotes resistance in GBM, its downregulation in meningioma enhances radiosensitivity and reduces radiation-induced invasiveness at higher doses. This finding indicates that inhibiting miR-221/222, combined with optimized radiotherapy, might improve treatment outcomes for high-grade meningioma [84]. Supporting this view, a 2024 review confirmed miR-497, miR-224, and the miR-221/222 cluster as key biomarkers and therapeutic targets across various studies [85]. Moreover, a four-miRNA plasma panel, including miR-200a, was validated as a histology-independent predictor of meningioma recurrence, advancing the potential for clinical biomarker use [86]. In addition, a 2025 multicohort genomic and functional analysis identified CKS2 as a prognostic driver of tumor recurrence. It is upregulated due to the downregulation of tumor suppressor miRNAs miR-26a-5p and miR-101-3p. This led to the identification of the CKS2/miR-26a/miR-101 axis as a promising diagnostic and prognostic marker, expanding the meningioma biomarker landscape [87].

Pituitary Adenoma: Dopamine Agonist and Somatostatin Analog Resistance

Among pituitary adenomas, two pharmacological resistance phenotypes carry the greatest clinical significance: dopamine agonist (DA) resistance in prolactinomas, affecting approximately 10–15% of patients; and somatostatin analog (SSA) resistance in somatotropinomas, affecting 30–40% of acromegaly patients. In bromocriptine-resistant prolactinomas, miR-145-5p is markedly downregulated, and restoring miR-145-5p expression through mimic transfection sensitizes tumor cells to bromocriptine by suppressing TPT1 (translationally controlled tumor protein 1), which normally inhibits apoptotic signaling [88]. miR-93-5p participates in bromocriptine resistance through TGF-β1/Smad3 signaling activation and consequent fibrosis induction—the fibrotic stroma physically impeding drug penetration to tumor cells [89]. In AIP-mutated somatotropinomas—a genetically defined subset associated with young-onset acromegaly and particularly poor SSA response—miR-34a is paradoxically upregulated relative to sporadic somatotropinomas, and this elevation promotes octreotide resistance by suppressing cAMP signaling downstream of somatostatin receptor 2 (SSTR2) [90]. This mechanistic insight suggests that targeting miR-34a in AIP-mutated tumors, counterintuitively, might restore SSA sensitivity—a hypothesis warranting prospective validation. Table 5 consolidates these molecular subgroup- and grade-stratified miRNA signatures across medulloblastoma, meningioma, and pituitary adenoma, complementing the GBM-centered chemoresistance and radiosensitivity data presented in Table 4.

A 2024 scoping review of miRNA networks in prolactinoma corroborates this oncomiR/tumor-suppressor architecture at a larger scale, systematically cataloguing six recurrent oncogenic miRNAs (including miR-93 and miR-1299) and nineteen tumor-suppressive miRNAs (including miR-145-5p) across the prolactinoma literature, and proposes ceRNA-network normalization as a route to more consistent biomarker performance in this tumor type [91].

MicroRNAs in Radiotherapy Resistance

Mechanisms of Radiation Resistance and miRNA Modulation

Radiotherapy remains a cornerstone of brain tumor treatment, but radioresistance—mediated through enhanced DNA double-strand break repair, activation of pro-survival signaling, hypoxia-driven HIF pathway activation, and maintenance of radioresistant cancer stem cells—significantly limits its efficacy, and a 2024 pan-cancer synthesis of radioresistance-related miRNAs (“radio-miRs”) confirms that these same DNA-repair, survival-signaling, and stemness axes recur as the dominant miRNA-regulated resistance mechanisms across tumor types, not just in brain tumors [92]. Microarray profiling comparing radiotherapy-sensitive and radiotherapy-resistant GBM patients has identified distinct miRNA expression signatures distinguishing the two groups, supporting the use of miRNA profiles as predictive biomarkers of radiotherapy response [93]. miRNAs modulate radiosensitivity through regulation of these interconnected mechanisms. Table 6 summarizes the key miRNAs governing brain tumor radiosensitivity.

Radiosensitizing and Radioresistant miRNAs

In GBM, miR-221/222 confer radioresistance by activating Akt-mediated DNA damage repair independently of PTEN status, and their knockdown significantly increases the radiosensitivity of glioblastoma cells [94]. miR-181d, acting through MALT1-dependent NF-κB suppression, attenuates mesenchymal-phenotype acquisition—a process closely tied to epithelial-to-mesenchymal transition (EMT) programs that drive therapy resistance across solid tumors [95]—a critical driver of GBM radioresistance—and reduces anchor-independent growth, migration, invasion, and tube formation [96]. miR-124-3p simultaneously targets mTOR, MAPK, TGF-β, and PI3K-Akt pathways, providing broad suppression of prosurvival signaling and substantially enhancing GBM radiosensitivity *in vivo*. Conversely, in atypical teratoid/rhabdoid tumor, loss of miR-142-3p in $CD133^{+}$ stem-like cells de-represses its direct targets Sox2 and ADCY9, promoting cancer stem-like and radioresistant properties, whereas its restoration increases radiosensitivity [97]. Pharmacological modulation of miRNA-linked radioresistance pathways has also been explored: the stilbenoid compound pterostilbene suppresses irradiation-resistant CD133-positive glioma stem cells by downregulating GRP78, an effect accompanied by elevated miR-205 expression, and increases the sensitivity of these stem-like cells to irradiation [98]. Fig. 5 summarizes these conver-

Table 5. Molecular subgroup- and grade-stratified miRNA signatures in medulloblastoma, meningioma, and pituitary adenoma.

Tumor subtype	Molecular subgroup/ Grade	Key miRNAs	Target/Pathway	Functional consequence
Medulloblastoma	WNT (best prognosis, >90% 5-yr survival)	miR-193a, miR-224/452, miR-182/96/183 cluster	WNT pathway inhibitors	Nuclear beta-catenin accumulation
Medulloblastoma	SHH	miR-9, miR-125b	GLI transcription factors (downstream of SMO)	Vismodegib resistance
Medulloblastoma	Group 3 (worst prognosis, MYC-amplified)	miR-17-92 cluster (17-5p, 18a, 19a)	p21, PTEN, BIM	Aggressive proliferation, therapy resistance
Meningioma	WHO Grade 1 (benign)	miR-200a, miR-145, miR-195 (high)	Tumor-suppressor network	Indolent phenotype
Meningioma	WHO Grade 2 (atypical)	miR-145, miR-195, miR-497~195 (down); miR-224 (up)	COL5A1, FASN, GATA-4, ERG2	Progression marker; radioresistance
Meningioma	WHO Grade 3 (anaplastic)	Further tumor-suppressor miRNA loss; oncomiR gain	Multiple	Invasive growth, treatment resistance
Pituitary adenoma	Prolactinoma (DA-resistant)	miR-145-5p (down), miR-93-5p	TPT1; TGF-beta1/Smad3	Bromocriptine resistance
Pituitary adenoma	Somatotropinoma (AIP-mutant)	miR-34a (up)	cAMP/SSTR2	Octreotide resistance

DA, Dopamine agonist; SMO, Smoothened; GLI, Glioma-associated oncogene homolog; AIP, Aryl hydrocarbon receptor-interacting protein. Table 5 complements Table 4, which focuses predominantly on GBM.

Table 6. MicroRNAs regulating radiosensitivity in malignant primary brain tumors.

miRNA	Tumor	Target	Expression	Mechanism	Response
miR-221/222	GBM	Akt/PTEN	Down	Inhibit tumor growth, promote apoptosis	Radiosensitive
miR-181d	GBM	NF-κB	Up	Suppresses proliferation and invasion	Radiosensitive
miR-124-3p	GBM	mTOR, MAPK, PI3K-Akt	Up	Inhibits tumor growth; promotes apoptosis	Radiosensitive
miR-205	GBM	GRP78, c-Myc, β-catenin	Up	Decreases sphere-forming; inhibits migration	Radiosensitive
miR-203	GBM	HIF-1α	Up	Suppresses HIF-1α; targets hypoxia pathway	Radiosensitive
miR-142-3p	ATRT	Sox2/ADCY9	Down	Loss de-represses Sox2/ADCY9; maintains CSC stemness	Radioresistant
miR-221/222	Meningioma	PTEN	Down	Inhibit invasive growth; promote apoptosis	Radiosensitive

GBM, glioblastoma, IDH-wildtype; CSC, Cancer stem cell; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; mTOR, Mammalian target of rapamycin.

gent and divergent miRNA-mediated radiosensitization and radioresistance pathways.

Extracellular Vesicle miRNAs in Therapeutic Resistance

Biology of EV-Mediated miRNA Transfer

Extracellular vesicles, including exosomes (30–100 nm, of endosomal origin) and microvesicles (100–1000 nm, shed from the plasma membrane)—are now understood to be critical mediators of intercellular communication within the tumor microenvironment [99] (Fig. 6). Tumor cells are particularly prolific EV producers, secreting vesicles enriched in bioactive cargo including miRNAs, mRNAs, lncRNAs, proteins, and lipids. EVs from tumor cells can be transferred to neighboring cells or, via systemic circulation, to distant anatomical sites, delivering functional regulatory molecules able to reprogram recipient cell behavior. Across cancer types, exosome-mediated transfer of resistance-conferring miRNAs is a recurring theme—for example, cancer-associated fibroblast-derived exosomal miR-196a confers cisplatin resistance in head and neck cancer—illustrating that the mechanisms described here for brain tumors reflect a broader principle of exosome-mediated therapy resistance across solid tumors [100,101]. The selective packaging of specific miRNAs into EVs—governed by EXOmotif sequences, sumoylated heterogeneous nuclear ribonucleoproteins (hnRNPs), and ceramide-dependent sort-

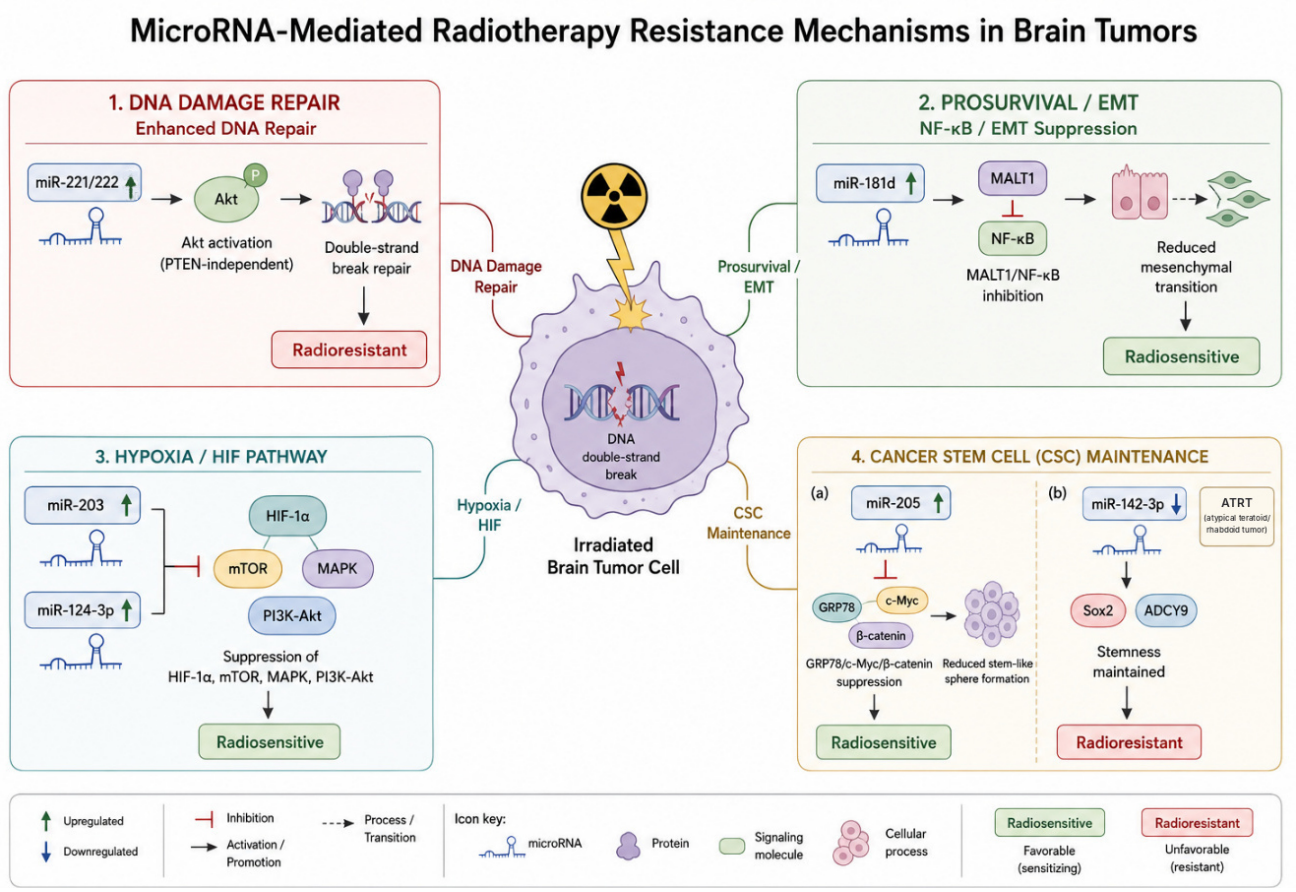

Fig. 5. MicroRNA-mediated radiotherapy resistance mechanisms in brain tumors. Radiation-induced DNA damage triggers divergent miRNA-regulated responses: miR-221/222 upregulation enhances Akt-mediated DNA repair independent of PTEN status (radioresistant); miR-181d upregulation suppresses MALT1/NF-κB signaling and reduces mesenchymal transition (radiosensitive); miR-203 and miR-124-3p upregulation inhibit HIF-1α, mTOR, MAPK, and PI3K-Akt pathways (radiosensitive); miR-205 upregulation suppresses GRP78/c-Myc/β-catenin-driven stemness (radiosensitive), while miR-142-3p downregulation de-represses its direct targets Sox2 and ADCY9, maintaining cancer stem-cell characteristics in atypical teratoid/rhabdoid tumor (radioresistant). Figure created by the author using ChatGPT-5 (OpenAI, San Francisco, CA, USA).

ing mechanisms—ensures non-random cargo composition reflecting the functional state of the donor cell. Notably, this packaging process is itself pharmacologically modulable: in U87 GBM cells, metformin treatment increases both exosome biogenesis and secretion, raising the possibility that commonly used metabolic drugs could inadvertently or therapeutically alter the EV-mediated signaling described throughout this section [102]. Table 7 catalogues exosomal/EV-associated miRNAs implicated in GBM therapeutic resistance.

EV-miRNAs in GBM Multidrug Resistance

In GBM, EV-mediated miRNA transfer has been directly implicated in the horizontal propagation of TMZ resistance. A landmark study demonstrated that miR-9, upregulated in TMZ-resistant GBM cells, is transferable via exosomes derived from mesenchymal stem cells (MSCs), where anti-miR-9 delivery reverses MDR1 upregulation—and restoring TMZ sensitivity and enhancing apoptotic cell death [103]. Loss of miR-151a in TMZ-resistant GBM cells drives acquired resistance by de-repressing XRCC4-dependent non-homologous end joining (NHEJ) DNA repair, whereas restoring exosomal miR-151a suppresses XRCC4 and resensitizes resistant cells to TMZ [104]. miR-603 released by irradiated GBM cells in EVs upregulates IGF1/IGF1R signaling and MGMT expression in recipient GSCs, promoting CSC state maintenance and acquired radiation resistance [105]. This radiation-induced bystander effect—where non-irradiated tumor cells acquire radioresistance through EV uptake from irradiated neighbors—is a distinct mechanism of treatment failure with significant clinical implications. Tumor-associated macrophage-derived EVs enriched in miR-27a-3p, miR-22-3p, and miR-221-3p also promote proneural-to-mesenchymal transition (PMT) in glioma stem cells, linking the immune microenvironment to miRNA-mediated therapeutic resistance [106]. Additional exosomal cargo contributes to TMZ resistance through distinct mechanisms: exosomal miR-1238, en-

Table 7. Extracellular vesicle (EV)-associated miRNAs involved in glioblastoma therapeutic resistance.

miRNA	Drug/Radiation	Vehicle	Target	Mechanism	Effect
miR-151a	Temozolomide	Exosome	XRCC4	Loss drives resistance via de-repressed XRCC4-mediated DNA repair	Restoration promotes chemosensitivity (loss promotes resistance)
miR-9	Temozolomide	Exosome (MSC)	MDR1	Anti-miR-9 reduces MDR1; restores TMZ sensitivity	Overcomes MDR
miR-301a	Ionizing radiation	Exosome	Wnt/β-catenin/TCEAL7	Depresses radiation sensitivity in GBM	Radioresistance
miR-124	Temozolomide	Exosome	CDK6	Exogenous delivery suppresses CDK6; restores TMZ sensitivity	Promotes chemosensitivity
miR-603	Ionizing radiation	EV	IGF1, IGF1R, MGMT	Promotes CSC state; upregulates DNA repair	Radioresistance
miR-93/miR-193	Temozolomide	Exosome	Cyclin D1	Decreases cell cycling quiescence	TMZ resistance
miR-21-5p	TMZ + Pacritinib	Exosome	STAT3/PDCD4	Inhibits drug resistance when suppressed	Reverses resistance
miR-27a-3p	Ionizing radiation	EV (macrophage)	CHD7	Promotes proneural-mesenchymal transition in GSCs	Radioresistance

TMZ, Temozolomide; MDR, Multidrug resistance; MGMT, O6-Methylguanine-DNA methyltransferase; GSC, Glioma stem cell; EV, Extracellular vesicle; PMT, Proneural-to-mesenchymal transition.

riched in TMZ-resistant GBM cells and their secreted vesicles, is taken up by sensitive cells and disseminates resistance by suppressing caveolin-1 and activating EGFR-PI3K-Akt-mTOR signaling [107], while miR-93 and miR-193, identified within exosomes from TMZ-resistant GBM cells, decrease Cyclin D1 expression and reduce cell cycling quiescence, promoting a resistant phenotype [108]. The EV-delivery paradigm can also be exploited therapeutically in the reverse direction: Wharton's jelly-derived mesenchymal stem cells can deliver exogenous miR-124 to GBM cells, where it suppresses CDK6, reduces proliferation and migration, and restores TMZ chemosensitivity—illustrating the potential of engineered EVs as miRNA replacement vehicles [109].

This hypoxia-driven EV signaling has been mechanistically extended by work showing that hypoxic glioma stem-like cells preferentially package miR-30b-3p into extracellular vesicles via hnRNPA2B1-mediated sorting, and that this hypoxic EV cargo confers substantially greater temozolomide resistance on recipient GBM cells than EVs from normoxic cells, directly linking the hypoxic niche to horizontal chemoresistance transfer [110]. Beyond direct chemoresistance transfer, a 2026 small-RNA sequencing study of circulating EVs in GBM patients found that specific EV-associated miRNAs (miR-142-3p, miR-19b-3p, miR-98-5p) correlate with distinct gene-expression signatures in peripheral blood mononuclear cells, suggesting that GBM-derived EV miRNA cargo may also systemically prime peripheral immune cells, extending the functional reach of EV-mediated miRNA signaling beyond the local tumor microenvironment [111].

Competing Endogenous RNA Networks and miRNA Sponging in Brain Tumors

A useful concept for understanding of miRNA regulation in brain tumors is the competing endogenous RNA (ceRNA) hypothesis, first formally proposed by Salmena et al. [112] in 2011, which posits that all RNA transcripts bearing miRNA response elements (MREs) can compete for the same pool of miRNA molecules, effectively functioning as molecular sponges that titrate miRNA availability and regulate the expression of all other transcripts sharing the same MREs. In glioblastoma and other brain tumors, three classes of ceRNAs have been identified as critical regulators of the miRNA landscape: long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and pseudogene transcripts.

Long non-coding RNAs constitute the most extensively characterized ceRNA class in brain tumors. HOTAIR (HOX antisense intergenic RNA), a 2.2 kb lncRNA originally identified as an epigenetic regulator, is markedly overexpressed in GBM and functions as a ceRNA by sponging miR-34a and miR-326—and de-repressing their shared targets including CDK6 and BCL2, promoting cell cycle progression, anti-apoptosis, and TMZ resistance. Serum-derived EVs from GBM patients are enriched in HOTAIR, and EV-HOTAIR transfer to recipient GBM cells has been mechanistically demonstrated to confer TMZ resistance,

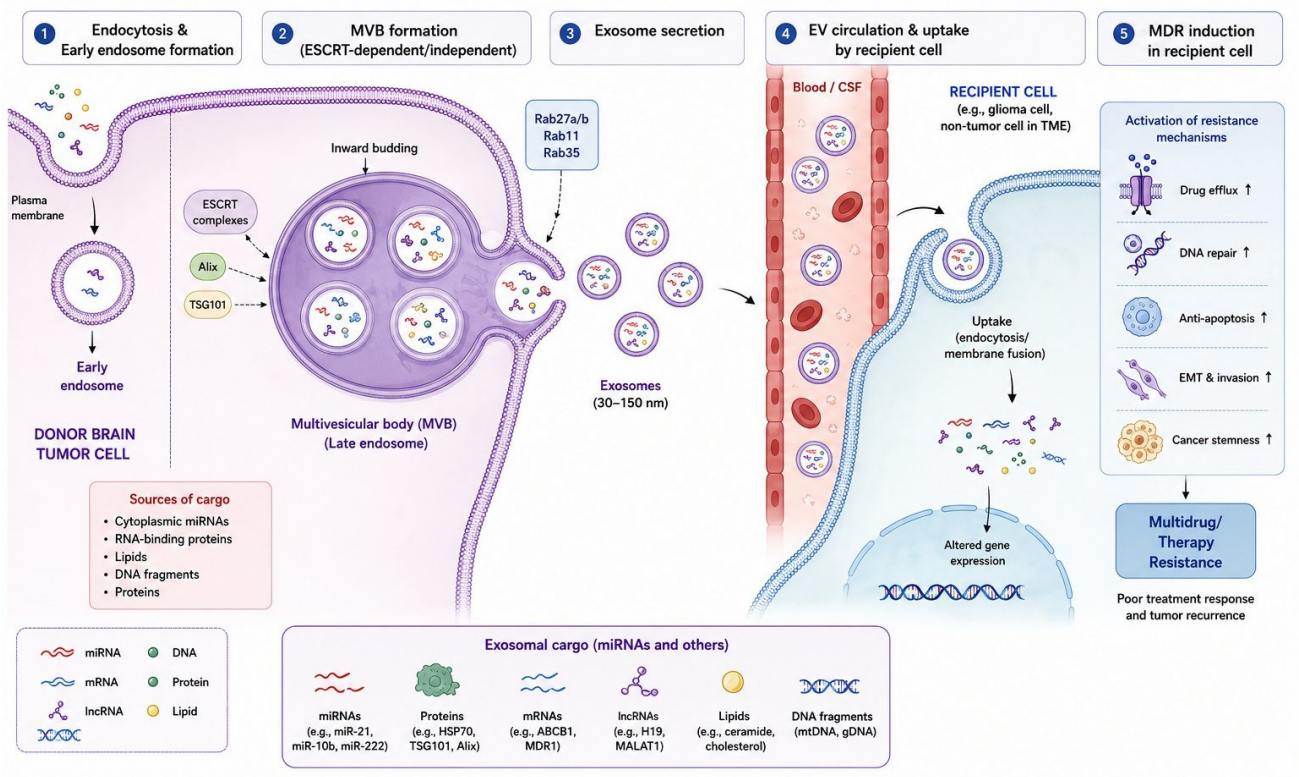

Fig. 6. Biogenesis of exosomes and EV-mediated miRNA transfer in brain tumor resistance. Sequential steps of exosome biogenesis in donor GBM cells: plasma membrane endocytosis → early endosome → ESCRT/Alix/TSG101-dependent MVB formation → Rab27a/b, Rab11, Rab35-regulated exosome secretion → EV circulation in blood/CSF → recipient cell uptake via endocytosis or membrane fusion → miRNA-mediated altered gene expression → activation of drug efflux, DNA repair, anti-apoptosis, EMT, and cancer stemness pathways, culminating in multidrug/therapy resistance. Figure created by the author using ChatGPT (OpenAI, San Francisco, CA, USA). Upward arrows indicate increased activity or enhancement of the corresponding resistance mechanisms.

in part by sequestering tumor suppressor miRNAs away from their downstream regulatory targets [113]. MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is another lncRNA highly expressed in GBM that sponges the tumor suppressor miR-101, derepressing its target Rap1B and promoting glioma cell proliferation while suppressing apoptosis [114]. The lncRNA H19, an imprinted growth-promoting RNA, has similarly been proposed to function as a ceRNA for miRNAs that target cell-cycle oncoproteins such as CDK6 and E2F1, contributing to GBM proliferation in a miRNA-dependent manner.

Circular RNAs (circRNAs), covalently closed single-stranded RNA molecules resistant to exonuclease degradation, function as particularly potent ceRNA regulators in brain tumors because of their exceptional stability. ciRS-7 (also known as CDR1as), one of the most abundant circRNAs in mammalian brain tissue, contains over 60 conserved miR-7 binding sites and has been proposed to function as an endogenous sponge that suppresses miR-7 activity, although a spatial expression study indicates that ciRS-7/CDR1as is largely confined to stromal rather than tumor cells in several cancers, complicating its interpretation as a tumor-intrinsic ceRNA [115]. Exosomal circZNF800, secreted by glioma stem-like cells and detectable in patient-derived exosomes, has been shown to sponge miR-139-5p and activate the PIEZO1/Akt signaling axis, promoting GBM cell proliferation and migration while inhibiting apoptosis [116]. The clinical significance of ceRNA networks extends beyond mechanistic biology: disrupting specific lncRNA-miRNA or circRNA-miRNA axes may offer a targetable vulnerability unique to the GBM molecular landscape. Therapeutic strategies targeting HOTAIR expression, or delivering competitor oligonucleotides that displace tumor suppressor miRNAs from their ceRNA captors, are being explored preclinically and may offer approaches to simultaneously modulate multiple miRNA-regulated pathways.

Detection Methods for miRNA in Clinical Practice

Conventional Detection Approaches

Accurate miRNA quantification is a prerequisite for using them as biomarkers or treatment-monitoring tools [117]. Conventional methods include reverse transcription quantitative PCR (RT-qPCR), DNA microarray hybridiza-

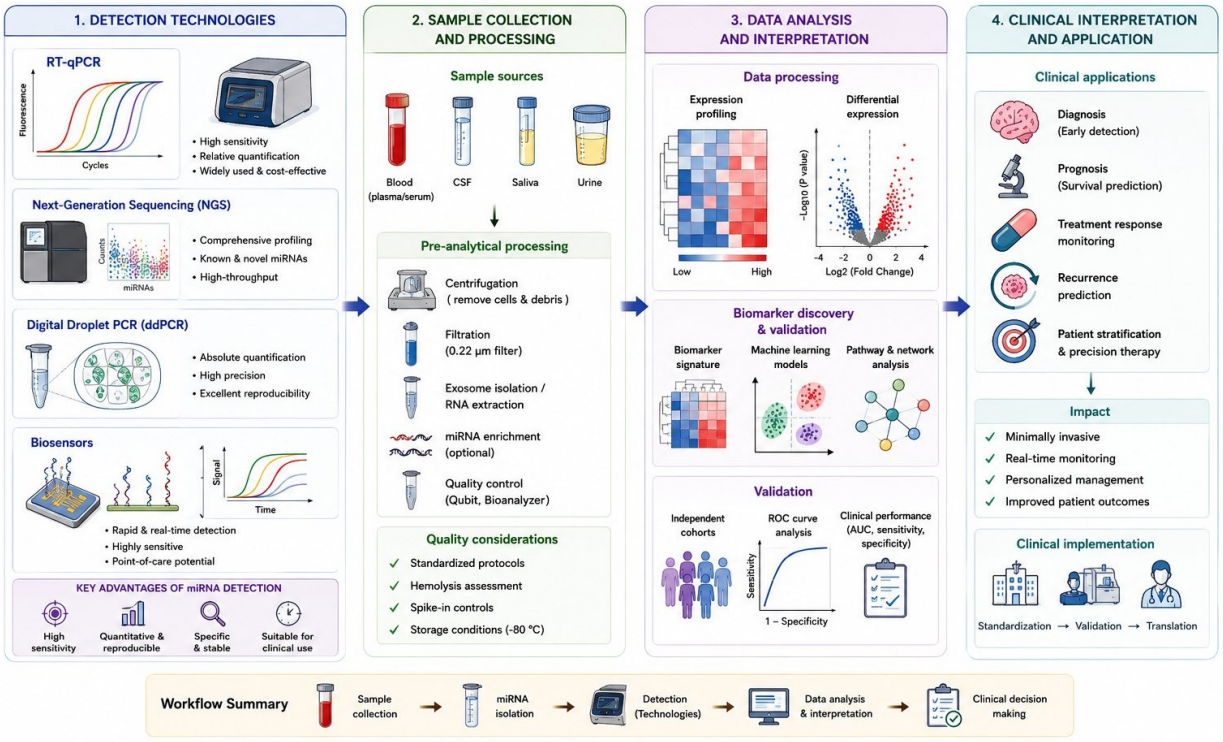

Fig. 7. MicroRNA detection technologies and clinical liquid biopsy workflow. Integrated workflow encompassing (1) detection technologies — RT-qPCR, NGS, ddPCR, and electrochemical biosensors; (2) sample collection and pre-analytical processing from blood, CSF, saliva, and urine; (3) data analysis including expression profiling, differential expression, machine learning biomarker validation, and ROC curve analysis; and (4) clinical interpretation for diagnosis, prognosis, treatment response monitoring, recurrence prediction, and precision patient stratification. Figure created by the author using ChatGPT (OpenAI, San Francisco, CA, USA).

tion, next-generation sequencing (NGS), and Northern blot analysis. RT-qPCR, particularly in stem-loop and poly(A)-tailing configurations, currently serves as the gold standard for miRNA quantification owing to its high sensitivity, specificity, and relative ease of implementation. Droplet digital PCR (ddPCR) offers absolute quantification without external calibration curves and demonstrates particular advantage for detecting low-abundance miRNAs, with a study reporting up to sevenfold greater day-to-day reproducibility compared with RT-qPCR [118].

Electrochemical Biosensors and Emerging Technologies

Electrochemical biosensors are becoming an interesting option for miRNA detection because they are sensitive, relatively inexpensive, and can potentially be used at the bedside or in outpatient settings [119]. Researchers have improved these systems by adding nanomaterials such as gold structures, carbon nanotubes (SWCNTs), graphene, magnetic nanoparticles, and dendritic nanoarchitectures, which can push detection limits into the femtomolar range [120]. Another important step forward is the use of CRISPR-Cas13 with electrochemical platforms. In some setups, this allows miRNAs to be detected directly from minimally processed body fluids, without amplification, and still gives very low limits of detection [121] (Fig. 7).

Recent biosensor-focused reviews reinforce this translational trajectory: a 2024 review of microRNA biosensors for glioblastoma detection catalogues electrochemical platforms achieving femtomolar sensitivity without PCR amplification, while a complementary 2023 review of label-free optical, electrochemical, and electronic biosensors specific to glioma biomarkers highlights multiplexing capability as the key remaining engineering barrier to clinical point-of-care deployment [122,123].

Brain Tumor-Specific Barriers: Blood-Brain Barrier, Heterogeneity, and Therapeutic Strategies

The Blood-Brain Barrier as a Fundamental Obstacle

One of the biggest problems in bringing miRNA-based diagnostics and therapies into neuro-oncology is the blood-brain barrier. As of 2024, no miRNA-targeting therapy has been approved by the FDA or EMA for brain tumors. Even so, the field is moving forward through preclinical work and early clinical studies. On the diagnostic side, circulating miRNAs are being tested more often as non-invasive biomarkers in GBM, which reflects the broader

move toward liquid biopsy in brain tumor care [124]. Sippl et al. [125] showed that plasma miR-181d levels track with tumor tissue expression and survival in GBM, which makes it a possible preoperative marker. Plasma miR-21 has also been studied as a pharmacodynamic marker in patients with recurrent GBM treated with bevacizumab. ClinicalTrials.gov now includes several studies looking at circulating miRNAs in glioma, medulloblastoma, and meningioma. In the therapeutic space, miR-34a remains one of the most studied candidates because of its links to p53 signaling and its activity in GBM, somatotropinomas, and medulloblastoma. It was also the first miRNA to enter systemic clinical trials in solid tumors through MRX34 (NCT01829971), although that trial was stopped early after serious immune-related adverse events, including patient deaths [126]. That experience is an important reminder that systemic delivery is probably not the best route for CNS applications. For this reason, MRgFUS-mediated BBB opening trials in GBM (NCT03626896, NCT04063514) are especially relevant because they are helping define the safety and pharmacokinetics needed for future brain-targeted miRNA delivery [127,128].

Intratumoral Heterogeneity and the Hypoxic Niche

Glioblastoma is not a single uniform disease. It contains multiple molecularly distinct subclones within the same tumor mass, a pattern known as intratumoral heterogeneity (ITH). A genomic study has shown that one GBM tumor can contain cells from several transcriptional subtypes at the same time, including Proneural, Classical, and Mesenchymal, and these groups often differ in miRNA expression, signaling behavior, and treatment response [129]. This matters because a miRNA that acts as a tumor suppressor in one subclone may behave differently in another. Treatment also changes the composition of the tumor by removing sensitive cells and leaving behind resistant ones. Liquid biopsy adds another layer of difficulty, because it gives an overall signal and may miss the small resistant population that drives relapse. The hypoxic niche is another major factor in GBM. In low-oxygen regions, HIF-1α changes the expression of many miRNAs. For example, miR-224-3p is downregulated under hypoxia, and its restoration suppresses cell mobility and chemoresistance via the HIF-1α/ATG5 axis [72] and by inhibiting hypoxia-induced protective autophagy [130], while miR-210 downregulates the mitochondrial enzyme ALDH5A1 to drive a glycolytic shift [131]. Tumor cells in these hypoxic, perivascular niches use these changes to maintain stemness, escape apoptosis, and resist both chemotherapy and radiation. Medulloblastoma adds a different challenge, since it is divided into four molecular subgroups, each with its own miRNA profile [132]. Any clinically useful miRNA marker or therapy therefore needs to be tested separately across these subgroups rather than treated as universally applicable.

MicroRNA-Based Therapeutic Strategies and Clinical Translation

Two broad strategies are being explored for miRNA-based therapy in brain tumors. The first is miRNA replacement therapy, which uses synthetic double-stranded RNA mimics to restore tumor suppressor miRNAs such as miR-34a, miR-128, miR-7, and miR-145. The second is miRNA inhibition therapy, which uses antagomirs, LNA anti-miRNAs, or miRNA sponges to block oncomiRs such as miR-21, miR-221/222, and miR-93. Even when the target is correct, delivery is still a major challenge, and several classes of miRNA delivery vehicles for neuro-oncology applications have been systematically catalogued elsewhere [133]. Therapeutic molecules have to deal with rapid clearance, immune activation, endosomal trapping, and off-target toxicity. Lipid nanoparticles are one of the more promising platforms, especially when combined with targeting ligands such as angiopep-2 or transferrin. MSC-derived exosomes are also attractive because they naturally home to the CNS and can carry miRNA cargo. Locoregional delivery approaches such as convection-enhanced delivery, already explored for other glioblastoma therapeutics, offer a further route to bypass the BBB entirely for intratumoral miRNA administration [134]. In preclinical work, nanocell systems carrying miR-34a and targeting EGFR have improved TMZ sensitivity in GBM models [135]. For now, the most realistic near-term strategy is combination therapy, where miRNA-based treatment is paired with standard TMZ and radiation rather than used alone.

The standardization, regulatory, and delivery-risk barriers that limit translation of these therapeutic strategies are examined in full in “Barriers to Analytical Standardization, Regulatory Translation, and Therapeutic Delivery Risk”.

Barriers to Analytical Standardization, Regulatory Translation, and Therapeutic Delivery Risk

Pre-Analytical and Analytical Standardization Gaps

The single largest obstacle to clinical deployment of miRNA biomarkers in brain tumors is the absence of standardization across the entire analytical workflow, from sample collection through final quantitative result [136]. At the pre-analytical level, the choice of biofluid introduces systematic bias: serum preparation activates the coagulation cascade, releasing platelet-derived miRNAs such as miR-21, miR-223, and miR-451 and artifactually elevating their apparent concentration relative to plasma. Plasma collected in EDTA tubes is increasingly treated as the reference standard, but many archived cohorts are available only as serum, complicating cross-study comparison. Anticoagulant choice, time-to-centrifugation, hemolysis, freeze-thaw cycles, and storage temperature each independently shift the detected miRNA profile [136]. CSF is more brain-

proximal and specific than blood but requires lumbar puncture, limiting serial sampling, and its very low miRNA concentration demands ultrasensitive detection and introduces its own amplification-related noise. At the analytical level, normalization of detected signal against technical variation in RNA input remains unresolved: endogenous normalizers validated for tissue miRNA studies (U6 snRNA, RNU44, RNU48) are absent or highly variable in biofluids, making them poor reference genes for liquid biopsy assays. Exogenous spike-in controls such as cel-miR-39 are now standard practice but do not correct for differences in extraction efficiency across sample types [117]. Taken together, these unresolved pre-analytical and analytical variables mean that the AUC values summarized in Table 3 should be read as proof-of-concept estimates from single-center cohorts rather than as assay performance figures ready for direct clinical adoption, a point revisited critically in "Methodological Quality Across the Reviewed Evidence Base".

Regulatory Landscape and Therapeutic Delivery Risk

While circulating miRNAs in biological fluids exhibit remarkable stability due to EV encapsulation and Ago2 protein association, synthetic miRNA mimics and antagomirs used therapeutically face a starkly different stability landscape. Unmodified oligonucleotides are rapidly degraded by serum ribonucleases with half-lives of minutes to hours, necessitating chemical modifications (phosphorothioate backbone, 2′-O-methyl, LNA, cholesterol conjugation) that substantially improve stability but also alter pharmacokinetics and biodistribution in ways that are difficult to predict, as has been extensively documented across the broader field of RNA-targeted therapeutics [137]. The functional pleiotropy of individual miRNAs—their capacity to regulate hundreds of distinct mRNA targets simultaneously across diverse cell types and tissues—creates the risk of profound off-target effects when a therapeutically administered miRNA reaches non-target tissues. miR-34a, the most clinically advanced miRNA therapeutic candidate and a well-characterized tumor suppressor across multiple cancer types [138], demonstrated unexpected immune-mediated toxicity in the MRX34 clinical trial, which was closed early following severe immune-related adverse events including patient deaths [126], a pattern consistent with sequence-specific innate immune activation—a concern that applies to any miRNA mimic. For brain tumor applications, immune-mediated CNS toxicity would carry additional safety implications beyond peripheral organ toxicity. The computational prediction of off-target miRNA-mRNA interactions remains imprecise; seed sequence matching algorithms identify thousands of potential targets, but functional target validation requires extensive *in vitro* and *in vivo* experimentation that is rarely performed comprehensively before clinical evaluation.

These translational risks sit within a formal regulatory context. The FDA Biomarker Qualification Program offers a defined pathway for advancing candidate miRNA biomarkers from exploratory to qualified status for a specific context of use, but qualification submissions for circulating miRNA panels in oncology have historically been slow to progress, reflecting both the standardization gaps described in "Pre-Analytical and Analytical Standardization Gaps" and the modest scale of most validation cohorts [139]. No miRNA-targeted diagnostic or therapeutic has yet achieved FDA or EMA approval for any brain tumor indication.

Discussion: Critical Synthesis, Contradictions, and Research Priorities

Cross-Subtype Comparative Synthesis

Placing the five tumor subtypes side by side, rather than treating each in isolation as prior sections necessarily do, exposes a steep and clinically consequential gradient in evidence maturity that a purely descriptive review would leave implicit. Table 8 summarizes this gradient using four criteria: the scale of the best-validated biomarker cohort, the dominant resistance axis implicated, the relevance of Axis I molecular co-variables, and an estimated clinical-readiness tier. Because the underlying evidence within and across subtypes spans heterogeneous study types — correlational biomarker cohorts (AUC-based), *in vitro* mechanistic assays, animal models, and small clinical series — each Clinical-Readiness Tier was assigned only after an explicit quality assessment of the supporting evidence: tiers were downgraded one level whenever the best-available evidence for that subtype was limited to single-center cohorts, retrospective design, or findings without independent replication, and the specific quality constraint responsible for each downgrade is stated in the Principal Evidence Gap column; no tier was assigned from AUC, cell-based, animal, or clinical-cohort data pooled together without this design-quality check.

The gradient in Table 8 is not incidental. GBM's evidence base is deeper by roughly an order of magnitude than that of medulloblastoma, meningioma, or pituitary adenoma, largely because GBM alone has benefited from large, molecularly annotated cohorts such as The Cancer Genome Atlas, which support IDH/MGMT-stratified reanalysis of archived samples. For medulloblastoma, meningioma, and pituitary adenoma, the reviewed evidence remains confined to mechanistic case series with cohorts under 100 patients and no independent replication; treating these findings with the same clinical-readiness expectations applied to GBM would overstate their translational maturity.

Table 8. Comparative evidence strength and clinical readiness of miRNA applications across five primary brain tumor subtypes.

Tumor subtype	Best-validated biomarker evidence	Dominant resistance axis	Axis I relevance	Clinical-readiness tier	Principal evidence gap
GBM/diffuse glioma	Multi-miRNA panels, pooled AUC 0.89–0.97 (see "Circulating miRNA Biomarkers in Brain Tumors")	PI3K/AKT, HIF-1a, EV-mediated MDR	High (IDH/ MGMT-defined)	Emerging	IDH/ MGMT-unstratified pooled cohorts
Astrocytoma (non-GBM)	9-miRNA serum panel, n = 90–110 (see "Multi-miRNA Panels and Diagnostic Performance")	Overlaps with glioma-wide mechanisms	High	Emerging	Grade-specific validation cohorts scarce
Medulloblastoma	Subgroup-specific mechanistic series (see "MB: Subgroup-Specific miRNA Resistance Profiles")	MYC/miR-17-92; MAGE-A/p53	High (WNT/SHH/Gr3/Gr4)	Low	No prospective biomarker cohort
High-grade meningioma	Exosomal miR-497/195, n = 55 (see "High-Grade Meningioma: WHO Grade-Stratified miRNA Profiles")	TGF-beta, fatty-acid biosynthesis	Moderate (WHO grade)	Low	Single-center, unreplicated
Pituitary adenoma	Mechanistic case series only (see "Pituitary Adenoma: Dopamine Agonist and Somatostatin Analog Resistance")	cAMP/SSTR2; TGF-β1/Smad3	Emerging (AIP status)	Very low	No biomarker validation study identified

GBM, glioblastoma, IDH-wildtype; AUC, Area under the ROC curve; MDR, Multidrug resistance; SSTR2, Somatostatin receptor 2. Clinical-readiness tiers reflect the authors' qualitative synthesis of cohort scale, replication, and prospective validation status described in the relevant sections, not a formal certification standard.

Context-Dependency and Apparent Contradictions in miRNA Function

Applying the MSMC framework introduced in "A Proposed Conceptual Framework: Molecular-Stratified miRNA Classification for Precision Neuro-Oncology" to the evidence assembled here resolves several findings that would otherwise read as contradictory. The miR-221/222 cluster, radioresistance-promoting in GBM (see "Radiosensitizing and Radioresistant miRNAs") but radiosensitizing in high-grade meningioma (see "High-Grade Meningioma: WHO Grade-Stratified miRNA Profiles"), is the clearest case: the same seed sequence produces opposite phenotypic output depending on the Axis I tumor lineage it operates within, most plausibly because its target repertoire (Akt-pathway components versus PTEN-independent invasion regulators) differs between glial and meningothelial cell backgrounds. miR-34a shows a comparable pattern: it functions as a canonical, p53-linked tumor suppressor in sporadic somatotropinoma and multiple other cancer types [138], yet is paradoxically up-regulated in AIP-mutant somatotropinoma, where it instead promotes somatostatin-analog resistance by suppressing cAMP signaling (see "Pituitary Adenoma: Dopamine Agonist and Somatostatin Analog Resistance"). Neither pattern reflects inconsistent biology; both reflect incomplete stratification in how the underlying studies were designed and reported. A practical implication follows directly: biomarker or therapeutic candidate selection for any given miRNA should be conditioned explicitly on Axis I molecular stratum rather than generalized across tumor lineages.

Methodological Quality Across the Reviewed Evidence Base

A critical reading of the evidence synthesized in the relevant sections, rather than a simple restatement of reported effect sizes, surfaces recurring methodological limitations that qualify essentially every diagnostic and prognostic claim in this field. Median cohort sizes for the AUC estimates summarized in Table 3 are small (commonly un-

der 150 patients per arm), and the great majority of studies are single-center, retrospective, and lack an independent external validation cohort. Several of the higher-performing multi-miRNA panels were derived and validated in overlapping or related cohorts from the same research groups, raising the possibility of optimistic bias from incomplete separation between discovery and validation sets. Older biomarker studies that pooled IDH-mutant and IDH-wild-type gliomas without stratification, noted already in "IDH Mutation, MGMT Methylation, and miRNA Crosstalk: A Critical Molecular Framework", generate composite signatures that likely reflect tumor heterogeneity rather than a single reproducible biological mechanism, and should be re-interpreted cautiously in light of the 2021 WHO molecular classification. Publication bias toward positive AUC findings is difficult to exclude given the near-absence of published null results for candidate miRNA panels. None of this invalidates the mechanistic biology reviewed in the relevant sections, which rests on more directly manipulable experimental systems (knockdown, mimic rescue, xenograft), but it does mean that biomarker-performance claims in "Circulating miRNA Biomarkers in Brain Tumors" and "MicroRNAs in Resistance to Chemotherapy and Pharmacological Treatment" warrant materially more caution than mechanistic-resistance claims when judging near-term clinical utility. This review's own methodology carries analogous limitations: title/abstract and full-text screening were conducted by a single author in two temporally separated passes rather than by independent co-reviewers, which cannot fully replicate the inter-rater reliability of formal double screening; and a small number of references that could not be verified against their indexed abstract were substituted with an alternative source supporting the same claim, a practice that, despite being applied conservatively, introduces a degree of citation-selection discretion that readers should weigh when appraising the synthesis presented here.

Positioning This Review Relative to Existing Literature

Recent single-tumor-type treatments of this topic, including a 2025 review focused specifically on GBM pathogenesis and treatment resistance [9], provide valuable depth within glioblastoma but do not attempt a cross-subtype synthesis or an explicit molecular-stratification framework. The contribution of the present review is threefold: it spans five histologically distinct primary brain tumor subtypes within a single comparative structure rather than treating GBM as a proxy for brain tumors generally; it elevates IDH mutation and MGMT methylation status, together with subgroup and grade stratification for the non-glioma subtypes, from background context to an explicit organizing axis (see "A Proposed Conceptual Framework: Molecular-Stratified miRNA Classification for Precision Neuro-Oncology" and "IDH Mutation, MGMT Methylation, and miRNA Crosstalk: A Critical Molecular Framework"); and it grades cross-subtype clinical readiness explicitly (Table 8) rather than leaving evidence maturity implicit in narrative tone. We regard this integrative structure, rather than any single mechanistic finding, as the review's principal original contribution.

Future Research Priorities

Five concrete priorities follow from the synthesis above, in descending order of near-term feasibility. First, prospective, multi-center validation cohorts that stratify enrollment by IDH and MGMT status (gliomas) or by molecular subgroup/grade (medulloblastoma, meningioma) are needed before any circulating miRNA panel can be considered for the FDA Biomarker Qualification pathway discussed in "Regulatory Landscape and Therapeutic Delivery Risk". Second, consensus pre-analytical and normalization standards, building on existing ISEV extracellular-vesicle guidelines and MIQE quantitative-PCR reporting standards, would directly address the standardization gaps described in "Pre-Analytical and Analytical Standardization Gaps".

Third, artificial-intelligence and multi-omics integration is a genuinely near-term opportunity: convolutional neural networks trained on combined imaging-genomic data already classify IDH1 mutation, 1p/19q co-deletion, and MGMT methylation status in gliomas with high accuracy [140], and extending comparable multitask frameworks to incorporate miRNA expression alongside genomic and epigenomic features is a natural, technically tractable next step. Fourth, MRgFUS-mediated blood-brain-barrier opening trials in GBM [127,128] remain the most realistic near-term route to brain-targeted miRNA delivery, given the systemic-toxicity signal observed with MRX34 (see "Regulatory Landscape and Therapeutic Delivery Risk"). Fifth, and most structurally important, subtype-inclusive biomarker registries that extend prospective data collection beyond GBM to medulloblastoma, meningioma, and pituitary adenoma are required simply to bring the weakest rows of Table 8 up to a level where cross-subtype comparison becomes statistically meaningful rather than illustrative.

Conclusion

MicroRNAs play a central and varied role in the molecular biology of brain tumors, from glioblastoma and astrocytoma to medulloblastoma, meningioma, and aggressive pituitary adenomas. Organizing this evidence within the three-axis Molecular-Stratified miRNA Classification framework introduced in "A Proposed Conceptual Framework: Molecular-Stratified miRNA Classification for Precision Neuro-Oncology", rather than presenting it tumor type by tumor type in isolation, shows that miRNAs function simultaneously as drivers of oncogenesis, mediators of resistance to temozolomide, radiation, and pharmacological

agents, and accessible non-invasive biomarkers in plasma, serum, and cerebrospinal fluid, and that apparently contradictory findings, such as the opposite roles of the miR-221/222 cluster in GBM and meningioma, resolve once tumor lineage and molecular stratum are specified jointly.

The cross-subtype comparative synthesis in "Discussion: Critical Synthesis, Contradictions, and Research Priorities" makes clear that this evidence base is not uniformly mature: GBM and astrocytoma have an emerging, if still single-center and largely unvalidated, biomarker literature, while medulloblastoma and pituitary adenoma remain confined to mechanistic case series, with high-grade meningioma showing only a single-cohort exosomal biomarker signal (miR-497/195) not yet independently replicated. Important barriers persist across all five subtypes: the blood-brain barrier restricts therapeutic delivery, intratumoral and inter-tumoral heterogeneity make targets unstable, and the absence of standardized pre-analytical protocols, validated normalization strategies, and prospective multi-center validation cohorts limits immediate clinical use. The path forward will require IDH/MGMT- and subgroup-stratified prospective trials, consensus analytical standardization, AI-driven multiomics integration, and BBB-penetrant delivery systems, applied with the same rigor used for other biomarker and drug classes. If these barriers are addressed systematically, and if future studies adopt an explicit molecular-stratification structure of the kind proposed here, miRNA-centered precision neuro-oncology could meaningfully improve the diagnosis, monitoring, and treatment of brain tumors and, in turn, patient survival and quality of life.

Availability of Data and Materials

Not applicable.

Author Contributions

IAA is the sole contributor to this manuscript. The author confirms sole responsibility for the following: conceptualization, literature search, writing the original draft, reviewing, editing, approval of the final version of the manuscript, and accountability for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The author is thankful to the Deanship of Graduate Studies and Scientific Research at Najran University for funding this work.

Funding

This work was funded by the Deanship of Graduate Studies and Scientific Research at Najran University, Growth Funding Program (grant number: NU/GP/MRC/14/2830-1).

Conflict of Interest

The author declares no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

The original conception, literature research, and drafting of this manuscript were performed independently by the author. During preparation of the manuscript, the author used Claude (Anthropic, San Francisco, CA, USA) solely for language polishing and editorial refinement of the author's original draft text. Claude was not used to generate original scientific content, conceptual framing, literature interpretation, or reference selection. All figures in this manuscript were generated by the author using ChatGPT-5 (OpenAI, San Francisco, CA, USA); these figures are original illustrative schematics created for this manuscript and are not reproduced or adapted from copyrighted third-party sources. The author has reviewed, verified, and revised all AI-assisted content and takes full responsibility for the accuracy, integrity, and originality of the published work.

References

[1] Price M, Ballard CAP, Benedetti JR, Kruchko C, Barnholtz-Sloan JS, Ostrom QT. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2018-2022. Neuro-oncology. 2025; 27: iv1–iv66. https://doi.org/10.1093/neuonc/noaf194

[2] Gritsch S, Batchelor TT, Gonzalez Castro LN. Diagnostic, therapeutic, and prognostic implications of the 2021 World Health Organization classification of tumors of the central nervous system. Cancer. 2022; 128: 47–58. https://doi.org/10.1002/cncr.33918

[3] Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. The New England Journal of Medicine. 2005; 352: 987–996. https://doi.org/10.1056/NEJMoa043330

[4] Schaff LR, Mellinghoff IK. Glioblastoma and Other Primary Brain Malignancies in Adults: A Review. JAMA. 2023; 329: 574–587. https://doi.org/10.1001/jama.2023.0023

[5] Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993; 75: 843–854. https://doi.org/10.1016/0092-8674(93)90529-y

[6] Pasquinelli AE, Reinhart BJ, Slack F, Martindale MQ, Kuroda MI, Maller B, et al. Conservation of the sequence and temporal expression of let-7 heterochronic regulatory RNA. Nature. 2000; 408: 86–89. https://doi.org/10.1038/35040556

[7] Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, et al. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proceedings of the National Academy of Sciences of the United

States of America. 2002; 99: 15524–15529. https://doi.org/10.1073/pnas.242606799

[8] Cimmino A, Calin GA, Fabbri M, Iorio MV, Ferracin M, Shimizu M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102: 13944–13949. https://doi.org/10.1073/pnas.0506654102

[9] Shah S, Patnala SL, Kalawatia M, Lucke-Wold B. Recent advances in molecular mechanisms of microRNAs in pathogenesis and resistance of treatment in glioblastoma. Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2025; 27: 4329–4341. https://doi.org/10.1007/s12094-025-03969-z

[10] Li H, Wu Y, Chen Y, Lv J, Qu C, Mei T, et al. Overcoming temozolomide resistance in glioma: recent advances and mechanistic insights. Acta Neuropathologica Communications. 2025; 13: 126. https://doi.org/10.1186/s40478-025-02046-4

[11] Eckerdt F, Platanias LC. Emerging Role of Glioma Stem Cells in Mechanisms of Therapy Resistance. Cancers. 2023; 15: 3458. https://doi.org/10.3390/cancers15133458

[12] Srivastava R, Dodda M, Zou H, Li X, Hu B. Tumor Niches: Perspectives for Targeted Therapies in Glioblastoma. Antioxidants & Redox Signaling. 2023; 39: 904–922. https://doi.org/10.1089/ars.2022.0187

[13] Sahoo OS, Mitra R, Nagaiah NKH. The hidden architects of glioblastoma multiforme: glioma stem cells. MedComm – Oncology. 2024; 3: e66. https://doi.org/10.1002/mog2.66

[14] Agosti E, Antonietti S, Ius T, Fontanella MM, Zeppieri M, Panciani PP. Glioma Stem Cells as Promoter of Glioma Progression: A Systematic Review of Molecular Pathways and Targeted Therapies. International Journal of Molecular Sciences. 2024; 25: 7979. https://doi.org/10.3390/ijms25147979

[15] Dexheimer PJ, Cochella L. MicroRNAs: From Mechanism to Organism. Frontiers in Cell and Developmental Biology. 2020; 8: 409. https://doi.org/10.3389/fcell.2020.00409

[16] Shang R, Lee S, Senavirathne G, Lai EC. microRNAs in action: biogenesis, function and regulation. Nature Reviews. Genetics. 2023; 24: 816–833. https://doi.org/10.1038/s41576-023-00611-y

[17] Saliminejad K, Khorram Khorshid HR, Soleymani Fard S, Ghaffari SH. An overview of microRNAs: Biology, functions, therapeutics, and analysis methods. Journal of Cellular Physiology. 2019; 234: 5451–5465. https://doi.org/10.1002/jcp.27486

[18] Friedman RC, Farh KKH, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. Genome Research. 2009; 19: 92–105. https://doi.org/10.1101/gr.082701.108

[19] Bofill-De Ros X, Vang Ørom UA. Recent progress in miRNA biogenesis and decay. RNA Biology. 2024; 21: 36–43. https://doi.org/10.1080/15476286.2023.2288741

[20] Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. Research Integrity and Peer Review. 2019; 4: 5. https://doi.org/10.1186/s41073-019-0064-8

[21] Lin S, Gregory RI. MicroRNA biogenesis pathways in cancer. Nature Reviews. Cancer. 2015; 15: 321–333. https://doi.org/10.1038/nrc3932

[22] Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, et al. MicroRNA genes are transcribed by RNA polymerase II. The EMBO Journal. 2004; 23: 4051–4060. https://doi.org/10.1038/sj.emboj.7600385

[23] Denli AM, Tops BBJ, Plasterk RHA, Ketting RF, Hannon GJ. Processing of primary microRNAs by the Microprocessor complex. Nature. 2004; 432: 231–235. https://doi.org/10.1038/nature03049

[24] Yi R, Qin Y, Macara IG, Cullen BR. Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. Genes & Development. 2003; 17: 3011–3016. https://doi.org/10.1101/gad.1158803

[25] Hutvágner G, McLachlan J, Pasquinelli AE, Bálint E, Tuschl T, Zamore PD. A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. Science (New York, N.Y.). 2001; 293: 834–838. https://doi.org/10.1126/science.1062961

[26] Khvorova A, Reynolds A, Jayasena SD. Functional siRNAs and miRNAs exhibit strand bias. Cell. 2003; 115: 209–216. https://doi.org/10.1016/s0092-8674(03)00801-8

[27] Bartel DP. Metazoan MicroRNAs. Cell. 2018; 173: 20–51. https://doi.org/10.1016/j.cell.2018.03.006

[28] Ha M, Kim VN. Regulation of microRNA biogenesis. Nature Reviews. Molecular Cell Biology. 2014; 15: 509–524. https://doi.org/10.1038/nrm3838

[29] Mansouri S, Singh S, Alamsahebpour A, Burrell K, Li M, Karabork M, et al. DICER governs characteristics of glioma stem cells and the resulting tumors in xenograft mouse models of glioblastoma. Oncotarget. 2016; 7: 56431–56446. https://doi.org/10.18632/oncotarget.10570

[30] Ding S, Wang P. The Life of MicroRNAs: Biogenesis, Function and Decay in Cancer. Biomolecules. 2025; 15: 1393. https://doi.org/10.3390/biom15101393

[31] Tornesello ML. TP53 mutations in cancer: Molecular features and therapeutic opportunities (Review). International Journal of Molecular Medicine. 2025; 55: 7. https://doi.org/10.3892/ijmm.2024.5448

[32] Shen J, Xia W, Khotskaya YB, Huo L, Nakanishi K, Lim SO, et al. EGFR modulates microRNA maturation in response to hypoxia through phosphorylation of AGO2. Nature. 2013; 497: 383–387. https://doi.org/10.1038/nature12080

[33] Olejniczak M, Kotowska-Zimmer A, Krzyzosiak W. Stress-induced changes in miRNA biogenesis and functioning. Cellular and Molecular Life Sciences: CMLS. 2018; 75: 177–191. https://doi.org/10.1007/s00018-017-2591-0

[34] Ju J. Challenges and opportunities in microRNA-based cancer therapeutics. Cell Reports. Medicine. 2025; 6: 102057. https://doi.org/10.1016/j.xcrm.2025.102057

[35] Masoudi MS, Mehrabian E, Mirzaei H. MiR-21: A key player in glioblastoma pathogenesis. Journal of Cellular Biochemistry. 2018; 119: 1285–1290. https://doi.org/10.1002/jcb.26300

[36] Tluli O, Al-Maadhadi M, Al-Khulaifi AA, Akomolafe AF, Al-Kuwari SY, Al-Khayarin R, et al. Exploring the Role of microRNAs in Glioma Progression, Prognosis, and Therapeutic Strategies. Cancers. 2023; 15: 4213. https://doi.org/10.3390/cancers15174213

[37] Areeb Z, Stuart SF, West AJ, Gomez J, Nguyen HPT, Paradiso L, et al. Reduced EGFR and increased miR-221 is associated with increased resistance to temozolomide and radiotherapy in glioblastoma. Scientific Reports. 2020; 10: 17768. https://doi.org/10.1038/s41598-020-74746-x

[38] Knowles T, Huang T, Qi J, An S, Burket N, Cooper S, et al. LIN28B and Let-7 in Diffuse Midline Glioma: A Review. Cancers. 2023; 15: 3241. https://doi.org/10.3390/cancers15123241

[39] Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-oncology. 2021; 23: 1231–1251. https://doi.org/10.1093/neuonc/noab106

[40] Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. The New England Journal of Medicine. 2005; 352: 997–1003. https://doi.org/10.1056/NEJMoa043331

[41] Cardia A, Epistolio S, Zaed I, Sahnane N, Cerutti R, Cipriani

D, et al. Identification of MGMT Downregulation Induced by miRNA in Glioblastoma and Possible Effect on Temozolomide Sensitivity. Journal of Clinical Medicine. 2023; 12: 2061. https://doi.org/10.3390/jcm12052061

[42] Jesionek-Kupnicka D, Braun M, Trąbska-Kluch B, Czech J, Szybka M, Szymańska B, et al. MiR-21, miR-34a, miR-125b, miR-181d and miR-648 levels inversely correlate with MGMT and TP53 expression in primary glioblastoma patients. Archives of Medical Science: AMS. 2019; 15: 504–512. https://doi.org/10.5114/aoms.2017.69374

[43] Jelski W, Mroczko B. MicroRNAs as Biomarkers of Brain Tumor. Cancer Management and Research. 2024; 16: 1353–1361. https://doi.org/10.2147/CMAR.S484158

[44] Wang Z, Wang Q, Qin F, Chen J. Exosomes: a promising avenue for cancer diagnosis beyond treatment. Frontiers in Cell and Developmental Biology. 2024; 12: 1344705. https://doi.org/10.3389/fcell.2024.1344705

[45] Ma Y, Zhang X, Liu C, Zhao Y. Extracellular vesicles in cancers: mechanisms, biomarkers, and therapeutic strategies. MedComm. 2024; 5: e70009. https://doi.org/10.1002/mco2.70009

[46] Metcalf GAD. MicroRNAs: circulating biomarkers for the early detection of imperceptible cancers via biosensor and machine-learning advances. Oncogene. 2024; 43: 2135–2142. https://doi.org/10.1038/s41388-024-03076-3

[47] Bunda S, Zuccato JA, Voisin MR, Wang JZ, Nassiri F, Patil V, et al. Liquid Biomarkers for Improved Diagnosis and Classification of CNS Tumors. International Journal of Molecular Sciences. 2021; 22: 4548. https://doi.org/10.3390/ijms22094548

[48] Zendjabil M. Preanalytical, analytical and postanalytical considerations in circulating microRNAs measurement. Biochemia Medica. 2024; 34: 020501. https://doi.org/10.11613/BM.2024.020501

[49] Valle-Garcia D, Pérez de la Cruz V, Flores I, Salazar A, Pineda B, Meza-Sosa KF. Use of microRNAs as Diagnostic, Prognostic, and Therapeutic Tools for Glioblastoma. International Journal of Molecular Sciences. 2024; 25: 2464. https://doi.org/10.3390/ijms25052464

[50] Sufianov A, Begliarzade S, Ilyasova T, Liang Y, Beylerli O. MicroRNAs as prognostic markers and therapeutic targets in gliomas. Non-coding RNA Research. 2022; 7: 171–177. https://doi.org/10.1016/j.ncrna.2022.07.001

[51] Sufianov A, Begliarzade S, Ilyasova T, Xu X, Beylerli O. MicroRNAs as potential diagnostic markers of glial brain tumors. Non-coding RNA Research. 2022; 7: 242–247. https://doi.org/10.1016/j.ncrna.2022.09.008

[52] Lan F, Qing Q, Pan Q, Hu M, Yu H, Yue X. Serum exosomal miR-301a as a potential diagnostic and prognostic biomarker for human glioma. Cellular Oncology (Dordrecht, Netherlands). 2018; 41: 25–33. https://doi.org/10.1007/s13402-017-0355-3

[53] Yue X, Lan F, Xia T. Hypoxic Glioma Cell-Secreted Exosomal miR-301a Activates Wnt/β-catenin Signaling and Promotes Radiation Resistance by Targeting TCEAL7. Molecular Therapy: the Journal of the American Society of Gene Therapy. 2019; 27: 1939–1949. https://doi.org/10.1016/j.ymthe.2019.07.011

[54] Wang J, Che F, Zhang J, Zhang M, Xiao S, Liu Y, et al. Diagnostic and Prognostic Potential of Serum Cell-Free microRNA-214 in Glioma. World Neurosurgery. 2019; 125: e1217–e1225. https://doi.org/10.1016/j.wneu.2019.02.009

[55] Zhang AB, Mozaffari K, Aguirre B, Li V, Kubba R, Desai NC, et al. Exploring the Past, Present, and Future of Anti-Angiogenic Therapy in Glioblastoma. Cancers. 2023; 15: 830. https://doi.org/10.3390/cancers15030830

[56] Ahir BK, Engelhard HH, Lakka SS. Tumor Development and Angiogenesis in Adult Brain Tumor: Glioblastoma. Molecular Neurobiology. 2020; 57: 2461–2478. https://doi.org/10.1007/s12035-020-01892-8

[57] Liu Q, Liao F, Wu H, Cai T, Yang L, Fang J. Different expression of miR-29b and VEGFA in glioma. Artificial Cells, Nanomedicine, and Biotechnology. 2016; 44: 1927–1932. https://doi.org/10.3109/21691401.2015.1111237

[58] Tang H, Liu Q, Liu X, Ye F, Xie X, Xie X, et al. Plasma miR-185 as a predictive biomarker for prognosis of malignant glioma. Journal of Cancer Research and Therapeutics. 2015; 11: 630–634. https://doi.org/10.4103/0973-1482.146121

[59] Zhao H, Shen J, Hodges TR, Song R, Fuller GN, Heimberger AB. Serum microRNA profiling in patients with glioblastoma: a survival analysis. Molecular Cancer. 2017; 16: 59. https://doi.org/10.1186/s12943-017-0628-5

[60] Wu J, Al-Zahrani A, Beylerli O, Sufianov R, Talybov R, Meshcheryakova S, et al. Circulating miRNAs as Diagnostic and Prognostic Biomarkers in High-Grade Gliomas. Frontiers in Oncology. 2022; 12: 898537. https://doi.org/10.3389/fonc.2022.898537

[61] Ali E, Ahmed MA, Shawki MA, El Arab LRE, Khalifa MK, Swellam M. Expression of some circulating microRNAs as predictive biomarkers for prognosis and treatment response in glioblastoma. Scientific Reports. 2025; 15: 1933. https://doi.org/10.1038/s41598-024-83800-x

[62] Zhou Q, Liu J, Quan J, Liu W, Tan H, Li W. MicroRNAs as potential biomarkers for the diagnosis of glioma: A systematic review and meta-analysis. Cancer Science. 2018; 109: 2651–2659. https://doi.org/10.1111/cas.13714

[63] Hasani F, Masrour M, Jazi K, Ahmadi P, Hosseini SS, Lu VM, et al. MicroRNA as a potential diagnostic and prognostic biomarker in brain gliomas: a systematic review and meta-analysis. Frontiers in Neurology. 2024; 15: 1357321. https://doi.org/10.3389/fneur.2024.1357321

[64] Zhi F, Shao N, Wang R, Deng D, Xue L, Wang Q, et al. Identification of 9 serum microRNAs as potential noninvasive biomarkers of human astrocytoma. Neuro-oncology. 2015; 17: 383–391. https://doi.org/10.1093/neuonc/nou169

[65] Chen W, Yu Q, Chen B, Lu X, Li Q. The prognostic value of a seven-microRNA classifier as a novel biomarker for the prediction and detection of recurrence in glioma patients. Oncotarget. 2016; 7: 53392–53413. https://doi.org/10.18632/oncotarget.10534

[66] Shen Y, Thng DKH, Wong ALA, Toh TB. Mechanistic insights and the clinical prospects of targeted therapies for glioblastoma: a comprehensive review. Experimental Hematology & Oncology. 2024; 13: 40. https://doi.org/10.1186/s40164-024-00512-8

[67] Khan SU, Fatima K, Aisha S, Malik F. Unveiling the mechanisms and challenges of cancer drug resistance. Cell Communication and Signaling: CCS. 2024; 22: 109. https://doi.org/10.1186/s12964-023-01302-1

[68] Afrashteh Nour M, Rahmati-Yamchi M, Shimia M, Yousefi B, Majidinia M. Emerging Insights into the PI3K/AKT/mTOR Signaling Pathway and Non-Coding RNA-mediated Drug Resistance in Glioblastoma. Current Molecular Medicine. 2025; 25: 710–722. https://doi.org/10.2174/0115665240309647240516042716

[69] Vogler M, Braun Y, Smith VM, Westhoff MA, Pereira RS, Pieper NM, et al. The BCL2 family: from apoptosis mechanisms to new advances in targeted therapy. Signal Transduction and Targeted Therapy. 2025; 10: 91. https://doi.org/10.1038/s41392-025-02176-0

[70] Gareev I, Beylerli O, Liang Y, Xiang H, Liu C, Xu X, et al. The Role of MicroRNAs in Therapeutic Resistance of Malignant Primary Brain Tumors. Frontiers in Cell and Developmental Biology. 2021; 9: 740303. https://doi.org/10.3389/fcell.2021.740303

[71] Hermansen SK, Dahlrot RH, Nielsen BS, Hansen S, Kristensen BW. MiR-21 expression in the tumor cell compart-

ment holds unfavorable prognostic value in gliomas. Journal of Neuro-oncology. 2013; 111: 71–81. https://doi.org/10.1007/s11060-012-0992-3

[72] Huang S, Qi P, Zhang T, Li F, He X. The HIF-1α/miR-224-3p/ATG5 axis affects cell mobility and chemosensitivity by regulating hypoxia-induced protective autophagy in glioblastoma and astrocytoma. Oncology Reports. 2019; 41: 1759–1768. https://doi.org/10.3892/or.2018.6929

[73] Zhao C, Guo R, Guan F, Ma S, Li M, Wu J, et al. MicroRNA-128-3p Enhances the Chemosensitivity of Temozolomide in Glioblastoma by Targeting c-Met and EMT. Scientific Reports. 2020; 10: 9471. https://doi.org/10.1038/s41598-020-65331-3

[74] Li J, Song J, Guo F. miR-186 reverses cisplatin resistance and inhibits the formation of the glioblastoma-initiating cell phenotype by degrading Yin Yang 1 in glioblastoma. International Journal of Molecular Medicine. 2019; 43: 517–524. https://doi.org/10.3892/ijmm.2018.3940

[75] Funakoshi Y, Sugihara Y, Uneda A, Nakashima T, Suzuki H. Recent advances in the molecular understanding of medulloblastoma. Cancer Science. 2023; 114: 741–749. https://doi.org/10.1111/cas.15691

[76] Joshi P, Katsushima K, Zhou R, Meoded A, Stapleton S, Jallo G, et al. The therapeutic and diagnostic potential of regulatory non-coding RNAs in medulloblastoma. Neuro-oncology Advances. 2019; 1: vdz023. https://doi.org/10.1093/noajnl/vdz023

[77] Coluccia D, Figuereido C, Isik S, Smith C, Rutka JT. Medulloblastoma: Tumor Biology and Relevance to Treatment and Prognosis Paradigm. Current Neurology and Neuroscience Reports. 2016; 16: 43. https://doi.org/10.1007/s11910-016-0644-7

[78] Weeraratne SD, Amani V, Neiss A, Teider N, Scott DK, Pomeroy SL, et al. miR-34a confers chemosensitivity through modulation of MAGE-A and p53 in medulloblastoma. Neuro-oncology. 2011; 13: 165–175. https://doi.org/10.1093/neuonc/noq179

[79] Abdelfattah N, Rajamanickam S, Panneerdoss S, Timilsina S, Yadav P, Onyeagucha BC, et al. MiR-584-5p potentiates vincristine and radiation response by inducing spindle defects and DNA damage in medulloblastoma. Nature Communications. 2018; 9: 4541. https://doi.org/10.1038/s41467-018-06808-8

[80] Sun XH, Fan WJ, An ZJ, Sun Y. Inhibition of Long Noncoding RNA CRNDE Increases Chemosensitivity of Medulloblastoma Cells by Targeting miR-29c-3p. Oncology Research. 2020; 28: 95–102. https://doi.org/10.3727/096504019X15742472027401

[81] Slika H, Shahani A, Wahi R, Miller J, Groves M, Tyler B. Overcoming Treatment Resistance in Medulloblastoma: Underlying Mechanisms and Potential Strategies. Cancers. 2024; 16: 2249. https://doi.org/10.3390/cancers16122249

[82] Zhang X, Zhang G, Huang H, Li H, Lin S, Wang Y. Differentially Expressed MicroRNAs in Radioresistant and Radiosensitive Atypical Meningioma: A Clinical Study in Chinese Patients. Frontiers in Oncology. 2020; 10: 501. https://doi.org/10.3389/fonc.2020.00501

[83] Negroni C, Hilton DA, Ercolano E, Adams CL, Kurian KM, Baiz D, et al. GATA-4, a potential novel therapeutic target for high-grade meningioma, regulates miR-497, a potential novel circulating biomarker for high-grade meningioma. EBioMedicine. 2020; 59: 102941. https://doi.org/10.1016/j.ebiom.2020.102941

[84] Zhang Q, Song LR, Huo XL, Wang L, Zhang GB, Hao SY, et al. MicroRNA-221/222 Inhibits the Radiation-Induced Invasiveness and Promotes the Radiosensitivity of Malignant Meningioma Cells. Frontiers in Oncology. 2020; 10: 1441. https://doi.org/10.3389/fonc.2020.01441

[85] Beylerli O, Ilyasova T, Shi H, Sufianov A. MicroRNAs in meningiomas: Potential biomarkers and therapeutic targets. Non-coding RNA Research. 2024; 9: 641–648. https://doi.org/10.1016/j.ncrna.2024.02.011

[86] Urbschat S, Landau B, Bewersdorf NC, Schuster C, Wagenpfeil G, Schulz-Schaeffer WJ, et al. MicroRNA 200a as a histologically independent marker for meningioma recurrence: Results of a four microRNA panel analysis in meningiomas. Cancer Medicine. 2023; 12: 8433–8444. https://doi.org/10.1002/cam4.5566

[87] Sharma A, Joshi R, Shahdeo D, Singh J, Suri V, Kulshreshtha R. CKS2 is overexpressed in high-grade and recurrent meningiomas and functions as an oncogene via the CKS2/miR-26a/miR-101 axis. Computers in Biology and Medicine. 2025; 198: 111142. https://doi.org/10.1016/j.compbiomed.2025.111142

[88] Jian M, Du Q, Zhu D, Mao Z, Wang X, Feng Y, et al. Tumor suppressor miR-145-5p sensitizes prolactinoma to bromocriptine by downregulating TPT1. Journal of Endocrinological Investigation. 2019; 42: 639–652. https://doi.org/10.1007/s40618-018-0963-4

[89] Hu B, Mao Z, Du Q, Jiang X, Wang Z, Xiao Z, et al. miR-93-5p targets Smad7 to regulate the transforming growth factor-β1/Smad3 pathway and mediate fibrosis in drug-resistant prolactinoma. Brain Research Bulletin. 2019; 149: 21–31. https://doi.org/10.1016/j.brainresbull.2019.03.013

[90] Bogner EM, Daly AF, Gulde S, Karhu A, Irmler M, Beckers J, et al. miR-34a is upregulated in AIP-mutated somatotropinomas and promotes octreotide resistance. International Journal of Cancer. 2020; 147: 3523–3538. https://doi.org/10.1002/ijc.33268

[91] Rad SG, Orang FN, Shadbad MA. MicroRNA networks in prolactinoma tumorigenesis: a scoping review. Cancer Cell International. 2024; 24: 418. https://doi.org/10.1186/s12935-024-03529-5

[92] Pedroza-Torres A, Romero-Córdoba SL, Montaño S, Peralta-Zaragoza O, Vélez-Uriza DE, Arriaga-Canon C, et al. RadiomiRs: a comprehensive view of radioresistance-related microRNAs. Genetics. 2024; 227: iyae097. https://doi.org/10.1093/genetics/iyae097

[93] Wu HM, Wang HD, Tang Y, Fan YW, Hu YB, Tohti M, et al. Differential expression of microRNAs in postoperative radiotherapy sensitive and resistant patients with glioblastoma multiforme. Tumour Biology: the Journal of the International Society for Oncodevelopmental Biology and Medicine. 2015; 36: 4723–4730. https://doi.org/10.1007/s13277-015-3121-z

[94] Li W, Guo F, Wang P, Hong S, Zhang C. miR-221/222 confers radioresistance in glioblastoma cells through activating Akt independent of PTEN status. Current Molecular Medicine. 2014; 14: 185–195. https://doi.org/10.2174/1566524013666131203103147

[95] Liaghat M, Ferdousmakan S, Mortazavi SH, Yahyazadeh S, Irani A, Banihashemi S, et al. The impact of epithelial-mesenchymal transition (EMT) induced by metabolic processes and intracellular signaling pathways on chemo-resistance, metastasis, and recurrence in solid tumors. Cell Communication and Signaling: CCS. 2024; 22: 575. https://doi.org/10.1186/s12964-024-01957-4

[96] Yang F, Liu X, Liu Y, Liu Y, Zhang C, Wang Z, et al. miR-181d/MALT1 regulatory axis attenuates mesenchymal phenotype through NF-κB pathways in glioblastoma. Cancer Letters. 2017; 396: 1–9. https://doi.org/10.1016/j.canlet.2017.03.002

[97] Lee YY, Yang YP, Huang MC, Wang ML, Yen SH, Huang PI, et al. MicroRNA142-3p promotes tumor-initiating and radioresistant properties in malignant pediatric brain tumors. Cell Transplantation. 2014; 23: 669–690. https://doi.org/10.3727/096368914X678364

[98] Huynh TT, Lin CM, Lee WH, Wu ATH, Lin YK, Lin YF, et al. Pterostilbene suppressed irradiation-resistant glioma stem cells by modulating GRP78/miR-205 axis. The Journal of Nutritional

Biochemistry. 2015; 26: 466–475. https://doi.org/10.1016/j.jnutbio.2014.11.015

[99] Zhang L, Yu D. Exosomes in cancer development, metastasis, and immunity. Biochimica et Biophysica Acta. Reviews on Cancer. 2019; 1871: 455–468. https://doi.org/10.1016/j.bbcan.2019.04.004

[100] Li I, Nabet BY. Exosomes in the tumor microenvironment as mediators of cancer therapy resistance. Molecular Cancer. 2019; 18: 32. https://doi.org/10.1186/s12943-019-0975-5

[101] Qin X, Guo H, Wang X, Zhu X, Yan M, Wang X, et al. Exosomal miR-196a derived from cancer-associated fibroblasts confers cisplatin resistance in head and neck cancer through targeting CDKN1B and ING5. Genome Biology. 2019; 20: 12. https://doi.org/10.1186/s13059-018-1604-0

[102] Soraya H, Sani NA, Jabbari N, Rezaie J. Metformin Increases Exosome Biogenesis and Secretion in U87 MG Human Glioblastoma Cells: A Possible Mechanism of Therapeutic Resistance. Archives of Medical Research. 2021; 52: 151–162. https://doi.org/10.1016/j.arcmed.2020.10.007

[103] Munoz JL, Bliss SA, Greco SJ, Ramkissoon SH, Ligon KL, Rameshwar P. Delivery of Functional Anti-miR-9 by Mesenchymal Stem Cell-derived Exosomes to Glioblastoma Multiforme Cells Conferred Chemosensitivity. Molecular Therapy. Nucleic Acids. 2013; 2: e126. https://doi.org/10.1038/mtna.2013.60

[104] Zeng A, Wei Z, Yan W, Yin J, Huang X, Zhou X, et al. Exosomal transfer of miR-151a enhances chemosensitivity to temozolomide in drug-resistant glioblastoma. Cancer Letters. 2018; 436: 10–21. https://doi.org/10.1016/j.canlet.2018.08.004

[105] Ramakrishnan V, Xu B, Akers J, Nguyen T, Ma J, Dhawan S, et al. Radiation-induced extracellular vesicle (EV) release of miR-603 promotes IGF1-mediated stem cell state in glioblastomas. EBioMedicine. 2020; 55: 102736. https://doi.org/10.1016/j.ebiom.2020.102736

[106] Zhang Z, Xu J, Chen Z, Wang H, Xue H, Yang C, et al. Transfer of MicroRNA via Macrophage-Derived Extracellular Vesicles Promotes Proneural-to-Mesenchymal Transition in Glioma Stem Cells. Cancer Immunology Research. 2020; 8: 966–981. https://doi.org/10.1158/2326-6066.CIR-19-0759

[107] Yin J, Zeng A, Zhang Z, Shi Z, Yan W, You Y. Exosomal transfer of miR-1238 contributes to temozolomide-resistance in glioblastoma. EBioMedicine. 2019; 42: 238–251. https://doi.org/10.1016/j.ebiom.2019.03.016

[108] Munoz JL, Walker ND, Mareedu S, Pamarthi SH, Sinha G, Greco SJ, et al. Cycling Quiescence in Temozolomide Resistant Glioblastoma Cells Is Partly Explained by microRNA-93 and -193-Mediated Decrease of Cyclin D. Frontiers in Pharmacology. 2019; 10: 134. https://doi.org/10.3389/fphar.2019.00134

[109] Sharif S, Ghahremani MH, Soleimani M. Delivery of Exogenous miR-124 to Glioblastoma Multiform Cells by Wharton's Jelly Mesenchymal Stem Cells Decreases Cell Proliferation and Migration, and Confers Chemosensitivity. Stem Cell Reviews and Reports. 2018; 14: 236–246. https://doi.org/10.1007/s12015-017-9788-3

[110] Yin J, Ge X, Shi Z, Yu C, Lu C, Wei Y, et al. Extracellular vesicles derived from hypoxic glioma stem-like cells confer temozolomide resistance on glioblastoma by delivering miR-30b-3p. Theranostics. 2021; 11: 1763–1779. https://doi.org/10.7150/thno.47057

[111] Popovic-Vukovic M, Kolic I, Stankovic A, Zivkovic M, Milicevic M, Bogdanovic I, et al. Circulating EV miRNA Cargo in Glioblastoma Patients Is Associated with Distinct Gene Expression Signatures in Peripheral Immune Cells, Suggesting an Early, Compartment-Specific Immune Priming State. Biomedicines. 2026; 14: 703. https://doi.org/10.3390/biomedicines14030703

[112] Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell. 2011; 146: 353–358. https://doi.org/10.1016/j.cell.2011.07.014

[113] Wang X, Yu X, Xu H, Wei K, Wang S, Wang Y, et al. Serum-derived extracellular vesicles facilitate temozolomide resistance in glioblastoma through a HOTAIR-dependent mechanism. Cell Death & Disease. 2022; 13: 344. https://doi.org/10.1038/s41419-022-04699-8

[114] Li Z, Xu C, Ding B, Gao M, Wei X, Ji N. Long non-coding RNA MALAT1 promotes proliferation and suppresses apoptosis of glioma cells through derepressing Rap1B by sponging miR-101. Journal of Neuro-oncology. 2017; 134: 19–28. https://doi.org/10.1007/s11060-017-2498-5

[115] Kristensen LS, Ebbesen KK, Sokol M, Jakobsen T, Korsgaard U, Eriksen AC, et al. Spatial expression analyses of the putative oncogene ciRS-7 in cancer reshape the microRNA sponge theory. Nature Communications. 2020; 11: 4551. https://doi.org/10.1038/s41467-020-18355-2

[116] Zhang N, Wu P, Mu M, Niu C, Hu S. Exosomal circZNF800 Derived from Glioma Stem-like Cells Regulates Glioblastoma Tumorigenicity via the PIEZO1/Akt Axis. Molecular Neurobiology. 2024; 61: 6556–6571. https://doi.org/10.1007/s12035-024-04002-0

[117] Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Proceedings of the National Academy of Sciences of the United States of America. 2008; 105: 10513–10518. https://doi.org/10.1073/pnas.0804549105

[118] Hindson CM, Chevillet JR, Briggs HA, Gallichotte EN, Ruf IK, Hindson BJ, et al. Absolute quantification by droplet digital PCR versus analog real-time PCR. Nature Methods. 2013; 10: 1003–1005. https://doi.org/10.1038/nmeth.2633

[119] Dastidar MG, Schumann U, Nisbet DR, Natoli R, Murugappan K, Tricoli A. Emerging electrochemical nanoscale architectures for point-of-care detection of miRNA biomarkers. Chemical Engineering Journal. 2025; 508: 160903. https://doi.org/10.1016/j.cej.2025.160903

[120] Sengupta J, Hussain CM. MXene-Based Electrochemical Biosensors: Advancing Detection Strategies for Biosensing (2020-2024). Biosensors. 2025; 15: 127. https://doi.org/10.3390/bios15030127

[121] Bruch R, Baaske J, Chatelle C, Meirich M, Madlener S, Weber W, et al. CRISPR/Cas13a-Powered Electrochemical Microfluidic Biosensor for Nucleic Acid Amplification-Free miRNA Diagnostics. Advanced Materials (Deerfield Beach, Fla.). 2019; 31: e1905311. https://doi.org/10.1002/adma.201905311

[122] Fattahi M, Maghsudlu M, Razipour M, Movahedpour A, Ghadami M, Alizadeh M, et al. MicroRNA biosensors for detection of glioblastoma. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2024; 556: 117829. https://doi.org/10.1016/j.cca.2024.117829

[123] Saha S, Sachdev M, Mitra SK. Recent advances in label-free optical, electrochemical, and electronic biosensors for glioma biomarkers. Biomicrofluidics. 2023; 17: 011502. https://doi.org/10.1063/5.0135525

[124] Beylerli O, Encarnacion Ramirez MDJ, Shumadalova A, Ilyasova T, Zemlyanskiy M, Beilerli A, et al. Cell-Free miRNAs as Non-Invasive Biomarkers in Brain Tumors. Diagnostics (Basel, Switzerland). 2023; 13: 2888. https://doi.org/10.3390/diagnostics13182888

[125] Sippl C, Quiring A, Teping F, Schulz-Schaeffer W, Urbschat S, Ketter R, et al. MiRNA-181d Expression Correlates in Tumor versus Plasma of Glioblastoma Patients-the Base of a Preoperative Stratification Tool for Local Carmustine Wafer Use. World Neurosurgery. 2022; 159: e324–e333. https://doi.org/10.1016/j.

wneu.2021.12.053

[126] Hong DS, Kang YK, Borad M, Sachdev J, Ejadi S, Lim HY, et al. Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours. British Journal of Cancer. 2020; 122: 1630–1637. https://doi.org/10.1038/s41416-020-0802-1

[127] Carpentier A, Canney M, Vignot A, Reina V, Beccaria K, Horodyckid C, et al. Clinical trial of blood-brain barrier disruption by pulsed ultrasound. Science Translational Medicine. 2016; 8: 343re2. https://doi.org/10.1126/scitranslmed.aaf6086

[128] Mainprize T, Lipsman N, Huang Y, Meng Y, Bethune A, Ironside S, et al. Blood-Brain Barrier Opening in Primary Brain Tumors with Non-invasive MR-Guided Focused Ultrasound: A Clinical Safety and Feasibility Study. Scientific Reports. 2019; 9: 321. https://doi.org/10.1038/s41598-018-36340-0

[129] Verhaak RGW, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell. 2010; 17: 98–110. https://doi.org/10.1016/j.ccr.2009.12.020

[130] Guo X, Xue H, Guo X, Gao X, Xu S, Yan S, et al. MiR224-3p inhibits hypoxia-induced autophagy by targeting autophagy-related genes in human glioblastoma cells. Oncotarget. 2015; 6: 41620–41637. https://doi.org/10.18632/oncotarget.5871

[131] Mondal I, Gupta N, Sharma V, Sarkar C, Mishra DP, Kulshreshtha R. ALDH5A1/miR-210 axis plays a key role in reprogramming cellular metabolism and has a significant correlation with glioblastoma patient survival. Cancer Cell International. 2024; 24: 259. https://doi.org/10.1186/s12935-024-03432-z

[132] Kool M, Korshunov A, Remke M, Jones DTW, Schlanstein M, Northcott PA, et al. Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. Acta Neuropathologica. 2012; 123: 473–484. https://doi.org/10.1007/s00401-012-0958-8

[133] Gareev I, Beylerli O, Tamrazov R, Ilyasova T, Shumadalova A, Du W, et al. Methods of miRNA delivery and possibilities of their application in neuro-oncology. Non-coding RNA Research. 2023; 8: 661–674. https://doi.org/10.1016/j.ncrna.2023.10.002

[134] D'Amico RS, Aghi MK, Vogelbaum MA, Bruce JN. Convection-enhanced drug delivery for glioblastoma: a review. Journal of Neuro-oncology. 2021; 151: 415–427. https://doi.org/10.1007/s11060-020-03408-9

[135] Khan MB, Ruggieri R, Jamil E, Tran NL, Gonzalez C, Mugridge N, et al. Nanocell-mediated delivery of miR-34a counteracts temozolomide resistance in glioblastoma. Molecular Medicine (Cambridge, Mass.). 2021; 27: 28. https://doi.org/10.1186/s10020-021-00293-4

[136] Binderup HG, Madsen JS, Heegaard NHH, Houlind K, Andersen RF, Brasen CL. Quantification of microRNA levels in plasma - Impact of preanalytical and analytical conditions. PloS One. 2018; 13: e0201069. https://doi.org/10.1371/journal.pone.0201069

[137] Liu M, Wang Y, Zhang Y, Hu D, Tang L, Zhou B, et al. Landscape of small nucleic acid therapeutics: moving from the bench to the clinic as next-generation medicines. Signal Transduction and Targeted Therapy. 2025; 10: 73. https://doi.org/10.1038/s41392-024-02112-8

[138] Zhang L, Liao Y, Tang L. MicroRNA-34 family: a potential tumor suppressor and therapeutic candidate in cancer. Journal of Experimental & Clinical Cancer Research: CR. 2019; 38: 53. https://doi.org/10.1186/s13046-019-1059-5

[139] Collins G, Allen JD, Andrews HS, Navarro-Serer B, Stewart MD. Hurry Up and Wait: Timelines and Takeaways from the Biomarker Qualification Program. Therapeutic Innovation & Regulatory Science. 2026; 60: 302–308. https://doi.org/10.1007/s43441-025-00889-6

[140] Chang P, Grinband J, Weinberg BD, Bardis M, Khy M, Cadena G, et al. Deep-Learning Convolutional Neural Networks Accurately Classify Genetic Mutations in Gliomas. AJNR. American Journal of Neuroradiology. 2018; 39: 1201–1207. https://doi.org/10.3174/ajnr.A5667