Molecular Therapy
Oncology
Review

Noncoding RNA landscape and their emerging roles as biomarkers and therapeutic targets in meningioma

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Meningiomas are among the most prevalent primary CNS tumors in adults, accounting for nearly 38% of all brain neoplasms. The World Health Organization (WHO) grade assigned to meningiomas guides medical care in patients and is primarily based on tumor histology and malignancy potential. Although often considered benign, meningiomas with complicated histology, limited accessibility for surgical resection, and/or higher malignancy potential (WHO grade 2 and WHO grade 3) are harder to combat, resulting in significant morbidity. With limited treatment options and no systemic therapies, it is imperative to understand meningioma tumorigenesis at the molecular level and identify novel therapeutic targets. The last decade witnessed considerable progress in understanding the noncoding RNA landscape of meningioma, with microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) emerging as molecular entities of interest. This review aims to highlight the commonly dysregulated miRNAs and lncRNAs in meningioma and their correlation with meningioma progression, malignancy, recurrence, and radioresistance. The role of "key" miRNAs as biomarkers and their therapeutic potential has also been reviewed in detail. Furthermore, current and emerging therapeutic modalities for meningioma have been discussed, with emphasis on the need to identify and subsequently employ clinically relevant miRNAs and lncRNAs as novel therapeutic targets and biomarkers.

INTRODUCTION

The term "meningioma" was suggested by Harvey Cushing in 1922.[1] Meningiomas are among the most prevalent primary CNS tumors in adults, accounting for nearly 38% of all primary CNS tumors diagnosed between 2013 and 2017 in the United States.[2] Annually ~1.8 to 13.0 per 100,000 individuals across the globe are diagnosed with meningioma.[3] In India, meningiomas comprise nearly 11.6%–21.0% of all brain neoplasms.[4] Derived from the arachnoidal cap cells of the leptomeninges, these tumors are primarily intracranial (~81.2%), while localization in the spinal meninges (~4.2%) has also been reported. Meningiomas are common in individuals older than 65 years of age, preferentially affect women (female to male ratio 3.5:1.0), and are rare in children. Although, there has been a rise in their incidence in younger individuals (15–39 years of age) as ~16% of all intracranial tumors in this age group are meningiomas.[2]

WHO grading and survival statistics in meningioma

The 2021 WHO Classification of Tumors of the Central Nervous System identifies meningioma as a single tumor type with 15 histological variants (subtypes) that are assigned to three malignancy grades based primarily on their histopathological features (number of mitotic figures, specific morphology, anaplastic features, invasive growth pattern), but also genetic characteristics such as telomerase reverse transcriptase (*TERT*) promoter mutations or homozygous deletions of cyclin dependent kinase inhibitor 2A/2B (*CDKN2A/2B*).[5] Most meningiomas (~80%) fall into the benign (WHO grade 1) category while ~15%–20% of cases are of advanced grade (WHO grade 2), and only 1%–2% of all cases are malignant (WHO grade 3), with a 5-year recurrence rate of up to 41%.[6] Grade 2 and grade 3 meningiomas are often detected at the convexity of the brain or with parasagittal location, while grade 1 meningiomas are commonly localized at the skull base.[7] The immense diversity in histological features, anatomical location, and biological behavior complicates the diagnosis and prediction of disease outcome in meningioma. Generally, meningioma tumors are slow-growing, with a linear growth rate of 2–4 mm/year, and develop over time. Even so, approximately 25% of all meningiomas show exponential growth with an aggressive phenotype. The estimated 10-year survival (overall 67.5%) for meningiomas is age dependent; for patients aged 20–44 years, the 10-year relative survival is approximately 77.3%, while for those 75 years and older, it is only 39.7%.[2]

Simpson grading and recurrence statistics in meningioma

Surgery and radiation therapy are the mainstays of treatment for meningiomas. Benign tumors can be treated with gross total resection (GTR) and radiotherapy; however, this may be of limited use depending on the tumor size and location. Higher-grade meningiomas (WHO grade 2 and 3) are often more challenging to treat and manage, have a poor prognosis, and are often associated with an enhanced probability of recurrence.[8] The postoperative Simpson

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grading system, based on the neurosurgeon's estimate of the extent of tumor resection, comprises five grades and is often a reliable parameter of recurrence in meningioma. Simpson grades I–III indicate GTR, while grades IV–V signify subtotal resection (STR).[9] After Simpson grade I GTR, the 5-year recurrence rates in WHO grades 1, 2, and 3 tumors are observed to be approximately 7%–23%, 50%–55%, and 72%–78%, respectively.[10] The majority of patients who undergo STR relapse within 15 years.[11] Tumor recurrence can thus lead to meningioma-specific mortality, with 10-year overall survival rates of 53% for grade 2 patients and 0% for grade 3 patients.[10] Currently, no systemic therapies have been clinically approved for meningioma treatment. The existing chemotherapeutic options are limited and used as salvage treatment for refractory meningioma cases.[12]

Current molecular landscape of meningioma

In the past decade, there have been significant advances in the molecular characterization of meningiomas, with identification of common genetic alterations and their association with disease outcome. The most common cytogenetic alteration in meningioma is the loss of chromosome 22, affecting the tumor suppressor gene *NF2*, which encodes the Merlin protein. The familial syndrome neurofibromatosis 2 is associated with abnormalities in *NF2* and is characterized by the development of primary CNS tumors, including meningiomas. Losses of chromosomes 1p, 6q, 9p, 10, 14q, 18q, and 19 are also associated with meningioma. Nearly 50% of all sporadic meningiomas harbor *NF2* mutations leading to NF2 inactivation and are often associated with increased chromosomal instability. Other recurrent "driver mutations" in meningioma, identified by many individual whole-genome, whole-exome, or targeted sequencing studies, include mutations in epigenetic modifiers such as *SMARCB1* (located in close proximity to NF2 on chr 22) in NF2-mutated meningiomas, while most *NF2*-nonmutated meningiomas often harbor mutations in *AKT1* and *mTOR* (members of the PI3K-AKT-mTOR pathway), *SMO* (encoding smoothened homolog, a member of the Hedgehog signaling pathway), *TRAF7* (E3 ubiquitin ligase, affecting numerous signaling pathways including MAPK signaling), *KLF4* (belonging to the Kruppel-like factor gene family that is involved in somatic cell reprogramming into pluripotent stem cells), *PIK3CA* (affecting the PI3K signaling pathway), or *POLR2A* (encoding the DNA-directed RNA polymerase II subunit RPB1) genes. Interestingly, most of these genetic alterations have been shown to affect WHO grade 1 meningiomas. Higher-grade meningiomas (WHO grade 2 and 3) harbor mutations in *TP53* and loss of *CDKN2A/CDKN2B* genes. *TERT* promoter mutations are common in secondary atypical WHO grade 3 meningiomas that have progressed from grade 1. Interestingly, recurrent mutations are often associated with tumor localization in meningioma; *NF2* and *SMARCB1* alterations are common in convexity meningiomas; skull-base meningiomas are associated with *AKT1, SMO, KLF4, TRAF7,* and *POLR2A* mutations; and *SMARCE1* mutations are generally exclusive to spinal meningiomas.[13] Transitional or fibroblastic meningioma subtypes are common in convexity meningiomas; however, meningothelial, secretory, and microcystic histological subtypes are common at the skull base and are characterized by *AKT1*, *KLF4*, *TRAF7*, *SMO*, *PIK3CA*, and *POLR2A* genetic mutations. Interestingly, *SMO* mutations are especially frequent in the anterior skull base while *POLR2A* mutations frequent near the tuberculum sellae region. *KLF4* mutations are exclusive to secretory meningiomas. Meningiomas with *PIK3CA* gene mutations can be of either meningothelial or transitional morphology. Interestingly, spinal cord meningiomas have a distinct molecular profile and frequently harbor *SMARCE1* mutations, often attributed to a clear cell meningioma subtype. *BAP1* mutation is a common genetic alteration in the rhabdoid subtype, such that its expression may separate rhabdoid meningiomas into more and less aggressive forms.[14] Interestingly, *NF2* mutations have been associated with tumor features such as vasogenic edema on preoperative imaging, large tumor volumes, and higher mitotic indices.[15] In their attempt to associate genetic abnormalities with embryological origins of the meninges, Okano et al. revealed driver genetic mutations *AKT1, KLF4, SMO*, and *POLR2A*, to be significantly associated with paraxial mesodermal origin of meninges. Significant association was observed between *NF2*-associated mutations and neural crest origin while *POLR2A* mutation was identified as a risk factor for recurrence.[16] A meningioma classification based on mutational status has been proposed with three tumor types: Type A comprising malignancies with minute chances of recurrence that correlate with presence of *TRAF7*, *AKT1*, or *KLF4* mutations but are devoid of chromosomal deletions; Type B meningiomas comprise those lacking the chromatin-modifying enzyme PRC2 with simultaneous deficiency in NF2/Merlin protein; and Type C tumors display heightened chromosomal instability along with NF2 deficiency and with greater susceptibility to recur.[17] Targetable mutations have been identified in meningioma and targeted therapies are being considered for patients who do not benefit from traditional clinical course of action in meningioma. For instance, a phase 2 study that assigned patients with meningioma to targeted treatments based on molecular features (*NF2*, *SMO*, *AKT1*) recently reported good tolerability of GSK2256098 (a focal adhesion inhibitor) and improved progression-free survival at 6 months in patients with recurrent or progressive *NF2*-mutated meningiomas compared with controls (ClinicalTrials.gov identifier NCT02523014).[18] Additionally, *CDKN2A/B* homozygous deletion is a possible therapeutic target for CDK4/6 inhibitors in advanced meningioma grades.[19]

In contrast to the significant progress made in understanding the mutational landscape in meningioma, the development in the identification of noncoding RNA (ncRNA) signatures in meningioma has been limited. MicroRNAs (miRNAs) and long noncoding RNAs (lncRNAs), two prominent classes of ncRNAs, play vital roles in the regulation of gene expression through direct or indirect interactions with their targets. The dysregulation of miRNAs and lncRNAs has been associated with the development of a plethora of diseases, including cancer.[20] With the advent of next-generation sequencing (NGS) technology, noncoding RNA profiling of different cancers is on the rise to uncover the role of these molecular entities in carcinogenesis. In meningioma, Saydam et al. were among the first to study miRNA profiles of sporadic benign meningioma tumors with respect to normal arachnoidal tissue controls (Table 1).[21] Thus, the earliest

miRNA signature of sporadic meningiomas came to light. Thereafter, the number of miRNAs and lncRNAs identified for their roles in meningioma pathogenesis has witnessed a sharp rise, and efforts have been made to correlate their expression patterns with demographic variables, clinicopathological features, and disease outcomes.

With this review, we aim to accentuate the noncoding RNA landscape of meningioma (focused on miRNAs and lncRNAs) and highlight key ncRNA players in meningioma pathogenesis with insights into their potential for use as biomarkers and/or therapeutic targets. We also elaborate on the recent progress in meningioma therapeutics and explore the scope of ncRNA-based therapy for meningioma.

MicroRNAs: SMALL MOLECULES WITH BIG IMPLICATIONS

MicroRNAs (miRNAs) are a dominant class of small ncRNAs with an approximate length of 19–25 nucleotides. These molecular entities hybridize with their target messenger RNA(s) (mRNAs), thereby affecting their translation or stability, thus aiding posttranscriptional control of gene expression. In the 1990s, two miRNAs, lin-4 and let-7, were discovered in *Caenorhabditis elegans,* with evidence for their important roles in the temporal regulation of the development of *C. elegans* larvae.[29] The latest release of miRBase (v22) enlists a set of 1,917 registered human miRNAs.[30] However, in a recent study undertaken to unveil a quantitative map of primary miRNA processing sites by Kim et al. using 1,886 miRNA entries in miRbase (v21) revealed that only 758 among these constituted confidently processed transcripts while a majority were noncanonical or false entries.[31] The MirGeneDB database includes 567 human miRNA genes that have been validated and annotated.[32] miRNAs are endogenously expressed and primarily rely on gene-silencing pathways to regulate a variety of biological processes, including cellular proliferation, apoptosis, differentiation, immune responses, fat metabolism, and oncogenesis.[33] However, endogenous miRNA:target pool ratios deeply influence their role as posttranscriptional regulators,[34] and are discussed further in subsequent sections.

miRNA biogenesis can occur through both canonical and noncanonical pathways. Canonical miRNA biogenesis involves miRNA transcription by RNA polymerase II to generate long primary transcripts (pri-miRNAs) comprising a local hairpin structure with embedded miRNA sequences. RNA-binding protein DGCR8 (DiGeorge Syndrome Critical Region 8) and type III RNase Drosha together constitute the "microprocessor complex" involved in cleaving the pri-miRNA to yield the precursor-miRNA (pre-miRNA). Upon export to the cytoplasm in an Exportin5/RanGTP-dependent manner, pre-miRNAs are processed by DICER (RNase III endonuclease), forming the mature miRNA duplex. Either the 5p or 3p strands of the mature miRNA duplex, originating from the 5′ end or 3′ end of the pre-miRNA hairpin loop, respectively, are loaded into the Argonaute (AGO) family of proteins (AGO1-4 in humans) in an ATP-dependent manner. The AGO-loaded miRNA strand is the "guide" strand, while the unloaded strand is called the "passenger" strand and is degraded by cellular machinery. miRNA loading forms the miRNA-induced silencing complex (miRISC) complex that impedes target mRNA translation, boosts sequestration of mRNA in cytoplasmic P-bodies and/or GW-bodies, and promotes mRNA degradation, thus directing transcriptional gene silencing of the target gene loci (RNA interference).[35] Mature miRNAs bound to AGO proteins are more stable (∼4 times) compared with mRNAs and may accumulate up to half-a-million copies per cell.[36] A single miRNA may regulate hundreds of functional targets, thus significantly impacting cellular fate.[37] Consequently, miRNA biogenesis is under tight control at various regulatory levels, including miRNA transcription, processing, transportation, binding, and decay.[38]

miRNAs act as guides through base-pairing with target mRNAs, while AGO proteins act as effectors through recruitment of factors that facilitate translational repression, deadenylation, and decay of target mRNAs.[39] The most common mechanism of miRNA-mediated gene expression control involves the interaction of the miRNA molecule with the 3′ untranslated region (3′ UTR) of target mRNAs, culminating in mRNA degradation and translation repression. However, there is growing evidence of diverse miRNA interactions with other regions, including the 5′ UTR, coding sequence, and gene promoters.[40] The "seed" region, spanning nucleotide positions 2 to 7 from the 5′ end of miRNAs, is crucial for recognition of target mRNAs and to direct these for suppression. miRNA binding sites are primarily located in the 3′ UTR of mRNAs. Since these extremely short seed sequences direct target recognition, one miRNA affects a plethora of genes, and singular genes can be regulated by multiple miRNAs. The two distinct mechanisms of gene silencing by miRNAs are defined as slicer-dependent and slicer-independent, where slicer activity is defined by the endonuclease cleavage of target mRNA by Ago2. The target specificity of miRISC depends on the extent of complementarity between the seed region of miRNA and miRNA response elements (MREs) on target mRNAs. Slicer-dependent silencing requires extensive base-pairing and destabilizes the association between AGO and the 3′ end of miRNA, promoting its degradation. Slicer-independent silencing mechanisms operate on limited miRNA:MRE base-pairing. Both mechanisms have either of two downstream effects, mRNA degradation or translation inhibition, both ultimately leading to downregulation of gene expression. Notably, mRNA decay is an irreversible process, while translation inhibition can be reversed by elimination of translational repressors.[41] Commonly known to facilitate posttranscriptional downregulation of gene expression, under specific conditions, miRNAs along with their associated protein complexes (microribonucleoproteins or miRNPs) may stimulate gene expression. microRNAs can compete with decay pathways such as AU-rich element (ARE)-mediated decay and other transcriptional repressors. They prevent the binding of ARE-binding proteins at their sites within 3′UTRs of target mRNAs, thus preventing decay and increasing mRNA stability. Additionally, miRNAs may bind to the target sites of repressive proteins and thus aid transcriptional upregulation.[42]

miRNAs are involved in the regulation of a plethora of biological processes, such as the cell cycle, differentiation, development, and

Table 1. Key miRNA profiling studies and miRNA signatures identified in meningioma

Sr No.	Study design: Patient cohort and clinical features	Method	Upregulated miRNAs	Downregulated miRNAs	Reference
			Sporadic WHO Grade 1 meningioma vs. healthy controls		
1	**Total tumor samples:** Sporadic benign meningioma tissue- WHO Grade 1 (N = 14) **Total controls:** Arachnoidal tissue samples (N = 3)	miRNA array using radioactive probes; RT-qPCR validation	let7b, let7d, let7g, miR-19b, miR-23b, miR-26a, miR-29a, miR-98, miR-100, **miR-335,** miR-103, miR-106a/b, miR-181a, miR-125a/b, miR-370	**miR-200a,** miR-373*, miR-575	Saydam et al.[21]
			Meningioma vs. healthy controls		
2	**Total tumor samples (N= 110):** All 3 WHO meningioma grades **Total controls (N = 35):** NAT samples **Training set (50 tumor samples vs. 15 NATs):** WHO Grade 1 (n = 34), WHO grade 2 (n = 9), and WHO Grade 3 (n = 7). Of these, 13 were recurrent. **Validation set (60 tumor samples vs. 20 NATs):** WHO Grade 1 (n = 30), WHO grade 2 (n = 18), and WHO Grade 3 (n = 12). Of these, 23 were recurrent.	RT-qPCR assay	miR-17-5p, miR-22-3p, miR-24-3p, miR-26b-5p, miR-7a/b-3p, miR-96-5p, miR-146a-5p, miR-155-5p, miR-186-5p, miR-190a, miR-199a	miR-29c-3p, miR-219-5p	Zhi et al.[22]
			Recurrent vs. non-recurrent meningiomas		
			miR-96-5p, miR-190a	miR-29c-3p, miR-219-5p	
			Meningioma vs. dura controls from meningioma patients and healthy patients		
3	**Total tumor samples (N= 15)** – WHO grade 1 (n = 12) and WHO grade 2 (n = 3) **Total controls:** 3 different controls (N = 14)- Dura controls from patients with tumor (n = 6); dura controls from patients without tumor (n = 3); and arachnoid controls from cadavers (n = 5).	SOLiD deep sequencing; RT-qPCR validation	let-miR-7g, miR-26b, **miR-34a,** miR-99a, miR-130a, miR-148b, miR-152, miR-218, miR-342-3p, miR-376c, miR-424	miR-17, **miR-21,** miR-143, miR-193b, miR-199a-5p, miR-451, miR-574-3p	El-Gewely et al.[23]
			WHO Grade 1 vs. WHO Grade 2		
			hsa-miR-34a*, hsa-miR-136, hsa-miR-376c, hsa-miR-497	–	
			WHO Grade 1 vs. WHO Grade 3		
			hsa-miR-34a*, hsa-miR-136, hsa-miR-376c, hsa-miR-497, **hsa-miR-195**, hsa-miR-218, hsa-miR-101	–	
			WHO Grade 2 vs. WHO Grade 3		
			hsa-miR-34a*, hsa-miR-218	–	
			Meningothelial WHO Grade 1 vs. WHO Grade 2		
			hsa-miR-34a*, hsa-miR-136, hsa-miR-376c	hsa-miR-222	
			Meningothelial WHO Grade 1 vs. WHO Grade 3		
			hsa-miR-34a*, hsa-miR-136, hsa-miR-376c, **hsa-miR-195,** hsa-miR-218	hsa-miR-222	
			Transitional WHO Grade 1 vs. WHO Grade 2		
			hsa-miR-34a*, hsa-miR-136, hsa-miR-376c, hsa-miR-497	–	
			Transitional WHO Grade 1 vs. WHO Grade 3		
4	**Total tumor samples (N= 150):** All 3 WHO grades including WHO Grade 1 subtypes- Transitional (T), Meningothelial (M), Fibrous (F), Microcystic (Mi), Psammomatous (P), and Angiomatous (A) **Total controls:** None **Array set (55 tumor samples):** WHO Grade 1 (n = 33), WHO grade 2 (n = 10), and WHO Grade 3 (n = 12). **Validation set (95 tumor samples):** WHO Grade 1 (n = 60), WHO grade 2 (n = 28), and WHO Grade 3 (n = 7).	Agilent human miRNA microarray; RT-qPCR validation			Ludwig et al.[24]

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Table 1. ***Continued***

Sr No.	Study design: Patient cohort and clinical features	Method	Upregulated miRNAs	Downregulated miRNAs	Reference
			hsa-miR-34a*, hsa-miR-136, hsa-miR-376c, **hsa-miR-195,** hsa-miR-497, hsa-miR-218, hsa-miR-101	–	
			Fibrous WHO Grade 1 vs. WHO Grade 2		
			hsa-miR-34a*, hsa-miR-136, hsa-miR-376c, **hsa-miR-195,** hsa-miR-497, hsa-miR-199a-3p, hsa-miR-377	–	
			Fibrous WHO Grade 1 vs. WHO Grade 3		
			hsa-miR-222, **hsa-miR-34a*,** hsa-miR-136, hsa-miR-376c, **hsa-miR-195,** hsa-miR-497, hsa-miR-199a-3p, hsa-miR-101	–	
			Meningothelial WHO Grade 1 vs. Fibrous WHO Grade 1		
			–	hsa-miR-222, **hsa-miR-34a*,** hsa-miR-136, hsa-miR-376c, **hsa-miR-195,** hsa-miR-497, hsa-miR-199a-3p, hsa-miR-377	
			Meningothelial WHO Grade 1 vs. Transitional WHO Grade 1		
			–	hsa-miR-222, **hsa-miR-34a*,** hsa-miR-376c**,** **hsa-miR-195,** hsa-miR-497, hsa-miR-101, hsa-miR-377	
5	**Total meningioma CSF samples (N= 175):** Brain tumor (BT) patient CSF samples including GBMs, LGGs, meningiomas and brain metastases. **Total control CSF samples (N = 40):** nontumor patients with hydrocephalus. **Discovery cohort:** BT patients (N = 70, 11 with meningioma) and controls (N = 19). **Validation cohort:** BT patients (N = 105, 44 with meningioma) and controls (N = 21).	Illumina small RNA sequencing of CSF samples; RT-qPCR validation	**Meningioma (CSF) vs. control (CSF)**		Kopkova et al.[25]
			let-7b/7c-5p, miR-10a/b-5p, **miR-21-3p,** miR-140-5p, miR-196a/b-5p	miR-30e-5p	
6	**Total meningioma serum samples (N = 230):** comprised of all 3 meningioma grades. Preoperative (N = 230), paired-Postoperative (N = 80) **Total control serum samples (N = 230):** healthy controls. (Both obtained from patient cohorts of 2 hospitals affiliated with Soochow University based in Changzhou and Soochow, China.)	TLDA assay; RT-qPCR validation	**Preoperative meningioma vs. healthy controls**		Zhi et al.[26]
			miR-106a-5p, miR-219-5p, miR-375, miR-409-3p	miR-197-3p, **miR-224-5p**	
			Preoperative meningioma vs. postoperative meningioma		
			miR-106a-5p, miR-219-5p, miR-375, miR-409-3p	miR-197, **miR-224**	
			Recurrent vs. non-recurrent meningioma		
			miR-409-3p	**miR-224**	
7	**Total meningioma serum samples (N = 74):** preoperative meningioma samples- WHO grade 1(n = 25),	RT-qPCR based miRNA quantification	**Preoperative meningioma vs. controls**		Abdelrahman et al.[27]
			miR-219	miR-497	

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Table 1. *Continued*

Sr No.	Study design: Patient cohort and clinical features	Method	Upregulated miRNAs	Downregulated miRNAs	Reference
	WHO grade 2 (n = 25), and WHO grade 3 (n = 24) **Total control serum samples (N = 53):** healthy controls				
8	**Total meningioma tumor samples (N = 55):** All WHO Grade 2 Atypical Meningioma (AM) cases having undergone GTR and ART. 2 groups-**Radiosensitive** (N = 43, no recurrence); **Radioresistant** (N = 12, recurrence within 3 years post GTR + ART)	miRNA microarray (Affymetrix)	**Radioresistant vs. radiosensitive meningioma** miR-4286, miR-4695-5p, miR-6732-5p, miR-6855-5p, miR-7977, miR-6765-3p, miR-6787-5p	miR-1275, miR-30c-1-3p, miR-4449, miR-4539, miR-4684-3p, miR-6129, miR-6891-5p	Zhang et al.[28]

Table comprises upregulated and downregulated miRNAs identified through different array/sequencing platforms, followed by RT-qPCR validation.
The miRNAs in bold represent those identified and validated by more than two individual studies.

metabolism, and chronic human diseases, such as diabetes, immune or neurodegenerative disorders, and cancer.[43] Dysregulation of miRNA expression in cancer is the cumulative effect of different mechanisms, such as amplification, deletion, mutation, and epigenetic silencing, or altered miRNA biogenesis machinery.[43] This results in a significant difference in miRNA expression profiles of tissues/cells/bodily fluids of diseased individuals when compared with those sourced from healthy counterparts. A host of studies have derived the miRNA signatures of different cancer types, subtypes, and other disease conditions. In addition to being tumor specific, miRNA signatures aid in the distinction of different subgroups of tumors and even help predict clinical outcome or response to therapy.[44]

KEY STUDIES ON DIFFERENTIAL miRNA EXPRESSION IN MENINGIOMA

A multitude of genome-wide miRNA profiling studies in different cancers have revealed that miRNA signatures are often associated with diagnosis, classification, progression, disease prognosis, and/or response to clinical therapies.[45] A decent number of studies have been conducted to reveal miRNA signatures in meningioma. We performed an extensive literature survey via PubMed (https://pubmed.ncbi.nlm.nih.gov/) using keywords "meningioma" and "microRNA"/"miR"/"miRNA," and tabulated the differentially expressed miRNAs in meningiomas identified through various studies (Table S1). Table 1 summarizes dysregulated miRNAs identified and validated by RT-qPCR via individual studies.

In a comprehensive study by Ludwig et al., the expression of 1,205 miRNAs in patient-derived tumor samples (inclusive of all three WHO grades and common histological subtypes) was determined via miRNA microarray. A subset of these miRNAs was validated using quantitative reverse-transcription PCR (RT-qPCR) (Table 1).[24] The miRNA microarray identified 13 dysregulated miRNAs among different histological subtypes of WHO grade 1 meningiomas. Interestingly, several of the dysregulated miRNAs within the meningothelial and fibroblastic subtypes (miR-195, miR-497, miR-181a/b) are known to play roles in epithelial-to-mesenchymal transition (EMT). A total of 51 miRNAs showed differential expression between anaplastic WHO grade 3 meningiomas and WHO grade 1 meningiomas (individual subtypes and combined). These miRNAs showed enrichment among different chromosomes, including those commonly harboring aberrations associated with meningioma. Of note, two clusters of miRNAs on chromosome 14 were identified in this study: 14q32.2 (DLK1-DIO3 cluster, associated with embryonal development and tumorigenesis) and 14q32.31 (linked to a variety of tumors, including glioblastoma). These clusters harbor genes of 11 miRNAs that are significantly downregulated in WHO grade 3 meningioma with respect to WHO grade 1 meningioma (predominantly transitional subtype). Interestingly, the loss of chromosome 14q has often been well associated with grade-dependent aggressiveness in meningioma. miR-34a*, miR-195, miR-136, and miR-376c emerged as key downregulated miRNAs in higher-grade meningiomas with successful validation by RT-qPCR. The putative and known targets of these miRNAs have been reported to be overexpressed in higher-grade

or aggressive meningiomas and linked to commonly dysregulated signaling pathways in meningioma, including the Wnt/β-catenin, transforming growth factor beta (TGF-β), MAPK/PI3K, and vascular endothelial growth factor (VEGF) pathways. Notably, a 4-miRNA signature (miR-222, miR-34a* [* denotes miRNA arising from passenger strand of miRNA duplex, denoted by miR-34a-3p in the latest nomenclature], miR-136, and miR-497) was proposed in this study as a potent biomarker panel for WHO grade 2 meningiomas (with respect to grade 1). It demonstrated an area under the curve (AUC) value of 0.75 and specificity of 0.91 but had a low sensitivity of 0.60.[24] While this study provides substantial information about dysregulated miRNAs within grade 1 subtypes and among all three malignancy grades, its prominent loophole is the lack of inclusion of controls (non-meningioma patient samples) in the set.

SOLiD deep sequencing by El-Gewely et al. identified 18 dysregulated miRNAs between meningiomas (grade 1 and grade 2) and controls, some of which were validated by RT-qPCR. A six-miRNA signature (Table 1) (upregulated-miR-218, miR-34a; downregulated-miR-143, miR-21, miR-193 b, and miR-451) in meningioma was proposed to distinguish tumors (WHO grade 1 or grade 2) from healthy controls based on RT-qPCR validation of four of these miRNAs. Interestingly, contrasting trends in the expression of two miRNAs (miR-21 and miR-218) were observed in this study when compared to their general expression pattern in most cancers. Commonly upregulated in most cancers, including WHO grade 3 meningiomas, miR-21 showed a 4-fold downregulation in grade 1 and grade 2 tumor samples relative to normal dura controls. A high abundance of the tumor suppressor miR-218 was observed in the studied meningiomas and may be attributed to its probable role in delaying the malignant transformation of low-grade meningiomas. The differential expression of miR-218, miR-34a, and miR-451 was also previously reported by Ludwig et al.[23]

More recently, small RNA sequencing of fresh-frozen meningioma tumor samples (N = 21); WHO grade 1 [n = 8], WHO grade 2 [n = 10], and WHO grade 3 [n = 3]) led to the identification of 26 differentially expressed miRNAs between these meningioma grades, including several 3p/5p counterparts derived from the same pre-miRNAs (miR-204-3/5p, miR-135b-3p/5p, miR-10a-3p/5p, miR-675-3p/5p, miR-124-3p/5p, miR-105-3p/5p, miR-9-3p/5p, miR-582-3p/5p, and miR-483-3p/5p). Notably, a grade-dependent increase in the levels of miR-483-5p in meningioma samples was observed in this study. "Active"' chromatin marks H3K27Ac, H3K4Me3, and H3K9Ac in the H19-IGF2 locus identified in samples underlie the epigenetic activation of the *IGF2* locus. Interestingly, grade-dependent upregulation of miR-483-5p was highly correlated with the expression of *IGF2*, which serves as its host gene. Inhibition of the miR-483/IGF-2 pathway drastically affected tumor cell viability.[46]

miRNAs impact numerous cellular pathways due to their ability to target multiple mRNAs. We performed pathway enrichment analysis for all dysregulated miRNAs in meningioma, tabulated in Table 1 using the miRPathDB 2.0 database (https://mpd.bioinf.uni-sb.de/). A customized heatmap was obtained for the dysregulated miRNAs that provided an overview of molecular functions and signaling pathways potentially regulated by them (Figure S1). Insulin signaling pathway, ErbB signaling pathway, apoptosis, Nod-like signaling pathway, focal adhesion, FoxO signaling pathway, and p53 signaling pathway were among the key enriched pathways. Most of these pathways have been implicated in meningioma pathogenesis and have been reviewed in detail elsewhere.[47]

KEY miRNA PLAYERS IN MENINGIOMA PATHOGENESIS

In this section, we elaborate on the role of "key miRNAs" (miRNAs altered in meningioma confirmed by two or more individual studies) in different aspects of meningioma pathogenesis, including cancer hallmarks, recurrence, and radiosensitivity or radioresistance (Figure 1).

These include **miR-26b, miR-146a-5p, miR-181a, and miR-335 that were found to be consistently upregulated in meningioma** in different individual studies; while **miR-34a, miR-497, miR-200a, and miR-195 were consistently downregulated in meningioma** with **miR-145 showing decreased expression in aggressive/advanced grade meningiomas** (all validated by RT-qPCR) (Tables S2 and S3). These miRNAs may thus be probed further to assess their "reproducibility" in the context of meningioma. Furthermore, in this section, the impact of dysregulation of some of these key miRNAs on their downstream targets, key signaling pathways, and cancer hallmarks is discussed (Figure 2).

miR-200a

miR-200a is a commonly dysregulated miRNA in virtually all cancer types and is generally downregulated. Saydam et al. identified miR-200a to be significantly downregulated (∼25-fold) in meningioma with respect to controls. The low levels of miR-200a in benign meningioma cells were correlated with increased β catenin and cyclin D1 levels, resulting in the activation of the Wnt signaling cascade, favoring tumorigenesis.[21] Moreover, miR-200a has been shown to target the non-muscle heavy chain IIb *(NMHCIIb)* gene in meningioma to influence cell growth and migration.[48] Most recently, miR-200a has been shown to be significantly downregulated in recurrent meningioma tumor samples compared with newly diagnosed samples, thus it may be further probed for its usage as a biomarker for recurrence in meningioma. Interestingly, the blood samples of male meningioma patients compared with healthy controls revealed considerably high levels of miR-200a.[49]

miR-224

Significant overexpression of miR-224 was observed in advanced pathological grades (WHO grade 2 and grade 3) of meningioma.[24,50] Patients with lower levels of miR-224 demonstrated significantly prolonged and recurrence-free survival than those with high levels of miR-224. Functional studies on IOMM-Lee cells (WHO grade 3 meningioma cell line) revealed cell growth suppression and enhanced apoptosis upon miR-224 downregulation, demonstrating its oncogenic role in meningioma. Enhanced apoptosis upon miR-224

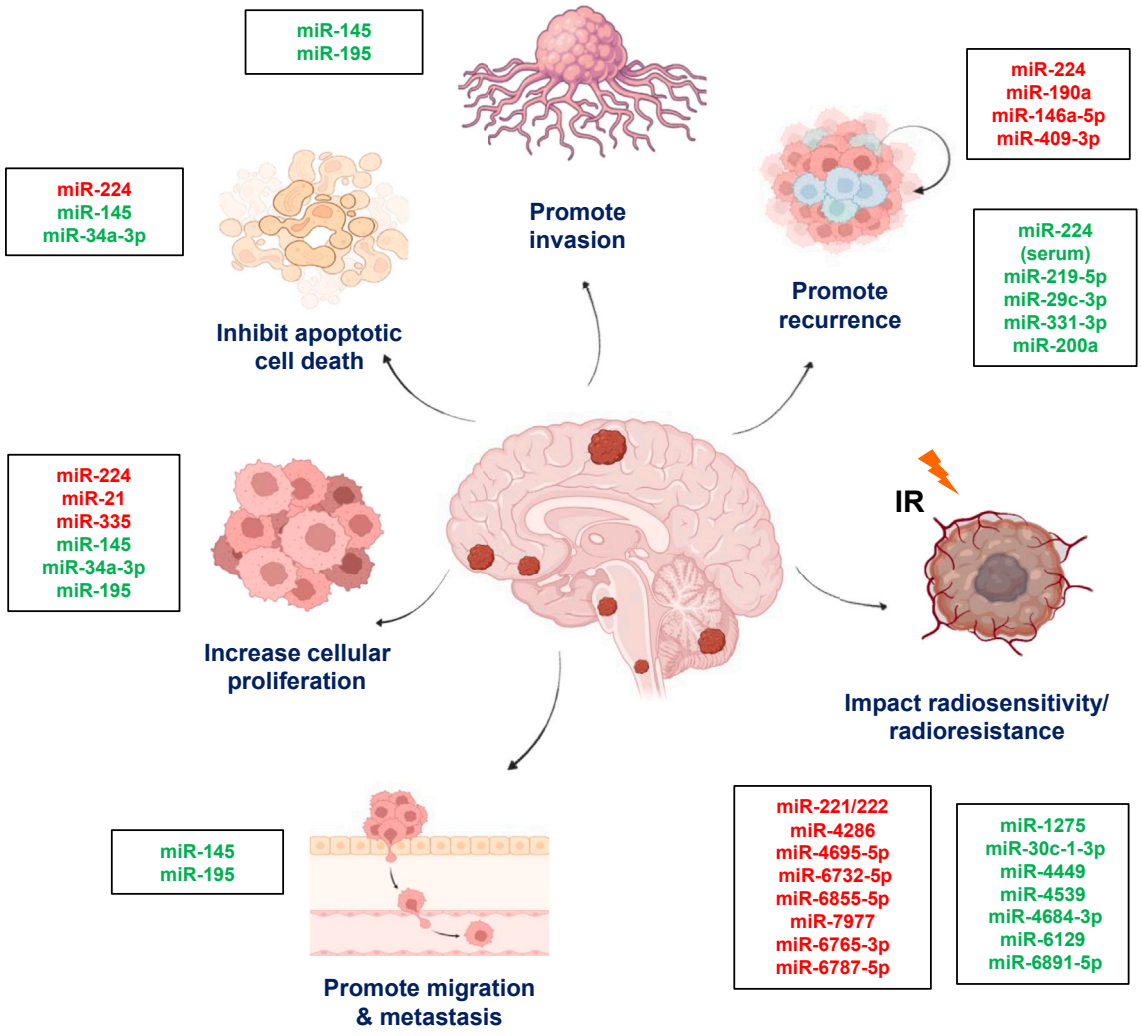

Figure 1. Dysregulated miRNAs in meningioma and their impact on cancer hallmarks, recurrence, and radiosensitivity or radioresistance
Created with BioRender.com. Red: Upregulated miRNAs in meningioma; Green: Downregulated miRNAs in meningioma.

downregulation was attributed to a consequential rise in the expression of its target genes *ERG2* and *BAK*, which are known to activate the ERG2-BAK-induced intrinsic apoptotic pathway.[50] After surgical resection of the tumor, meningioma patients with a significant rise in serum miR-224 levels were reported to have greater chances of recurrence. Thus, miR-224 may serve as a noninvasive biomarker for recurrence in meningioma. Interestingly, females demonstrated higher miR-224 levels, which may be attributed to the mapping of its sequence to chromosome X.[26]

miR-145

miR-145 is consistently downregulated and acts as a tumor suppressor in most cancers, including primary brain neoplasms. Correspondingly, miR-145 was significantly downregulated in grade 2 atypical and grade 3 anaplastic meningeal tumors compared with benign subtypes.[51] Overexpression of miR-145 in IOMM-Lee cells reduced proliferative capacity, increased susceptibility to apoptosis, reduced anchorage-independent growth, and reduced orthotopic tumor growth *in vivo* compared with controls. Moreover, meningioma cells with high miR-145 levels demonstrated diminished migratory potential and invasion *in vitro* and *in vivo,* thus suggesting the tumor-suppressive role of miR-145 in meningioma. The downregulation of miR-145 has been correlated with the upregulation of its target gene collagen type V alpha *(COL5A1)* in both grade 2 atypical and grade 3 anaplastic meningiomas. COL5A1 plays an indispensable role in collagen fibrillogenesis.[51] An independent study also established the role of the MALAT1/miR-145/COL5A1 ceRNA axis in meningioma invasiveness. In particular, the presence of the rs619586 A>G single nucleotide polymorphism (SNP) in MALAT1 reduced both MALAT1 and *COL5A1* expression and elevated miR-145 levels in patient-derived tumor/serum samples, leading to reduced invasiveness of meningioma.[52] Interestingly, downregulation of miR-145-5p

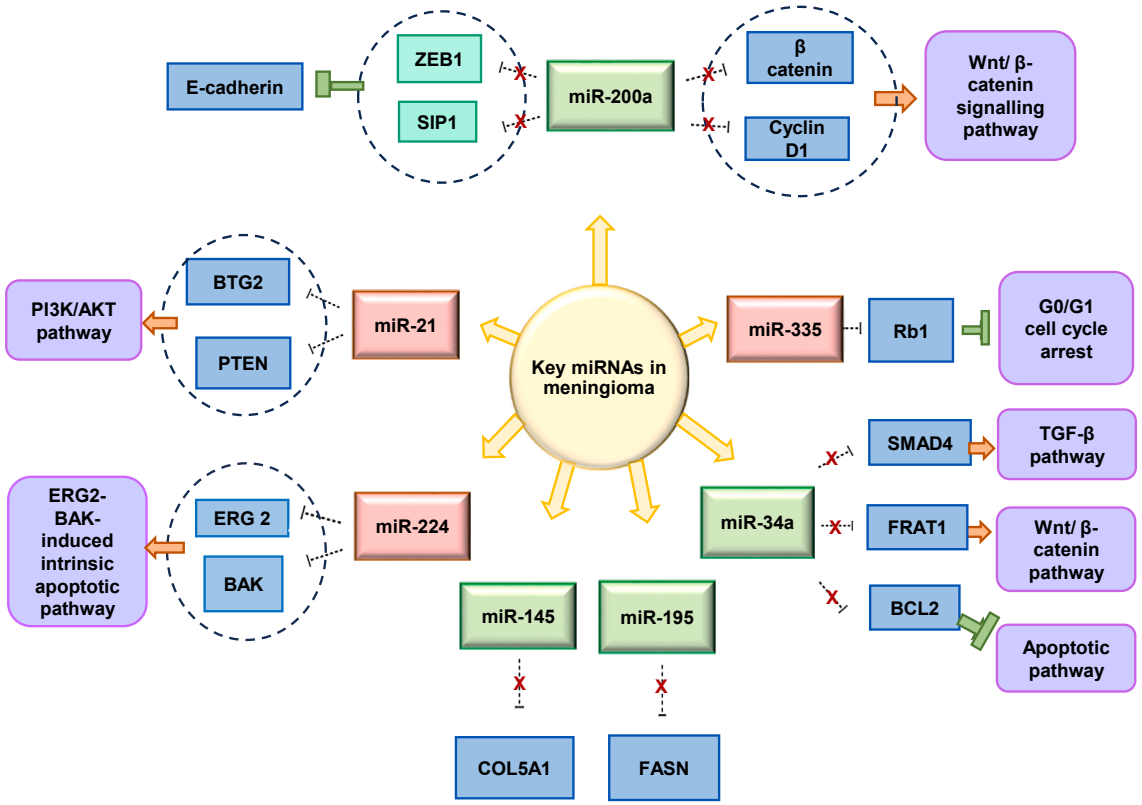

Figure 2. Downstream effects of key dysregulated miRNAs on target genes and associated signaling pathways

Created with BioRender.com. Red rectangle: Upregulated miRNAs; Green rectangle: downregulated miRNAs; Blue/sea-green rectangles: gene/transcription factor targets of miRNAs, respectively; dashed perpendicular line: inhibition by miRNA; red cross: loss of inhibition by miRNA; orange solid arrows: pathway upregulation; green solid perpendiculars: pathway downregulation; dashed circles: simultaneous regulation of distinct encircled genes by miRNA to impact a single pathway.

has also been associated with resting mast cells involved in meningioma development.[53]

miR-21

The dysregulation of miR-21 in meningioma has been reported in numerous independent miRNA expression studies, where it was mostly upregulated and associated with oncogenesis.[24,54,55] miR-21 expression shows a significant difference between benign and advanced meningioma grades. miR-21 levels were reported to rise with advancing histopathological grade in meningioma.[24] Overexpressed miR-21 in meningioma tumor samples and cell lines (with respect to Schwann primary cells) sustained tumor growth in meningioma and vestibular schwannoma through the repression of target genes such as *BTG2* and *PTEN*, which act as inhibitors of the PI3K/AKT signaling pathway.[56] In contrast, a study reported low levels of miR-21 and high levels of its target tumor suppressor gene *PTEN* in grade 2 and grade 1 meningioma compared with normal dura controls.[23]

miR-34a

miR-34a-3p is significantly downregulated in WHO grade 2 and grade 3 meningiomas.[57] SMAD family member 4 (*SMAD4*), frequently rearranged in advanced T cell lymphomas 1 (*FRAT1*), and B-cell CLL/lymphoma 2 (*BCL2*) have been identified as direct targets of miR-34a-3p in meningioma. Downregulation of miR-34a-3p interfered with the translational repression of *SMAD4, FRAT1,* and *BCL2* and resulted in their upregulation. These targets are components of the TGF-β, Wnt/β-catenin, and apoptotic signaling pathways, which are pathways that are commonly dysregulated in meningioma genesis and progression.[57] Consequently, sustained TGF-β and Wnt/β-catenin signaling and altered apoptotic pathways aided cellular proliferation and apoptosis inhibition in meningioma cells *in vitro*.[57] miR-34a* (retired nomenclature for functional miRNA that originates from the passenger strand of the miRNA duplex [denoted by *], now denoted as miR-34a-3p) was also shown to be significantly downregulated in anaplastic grade 3 meningiomas when compared with both atypical grade 2 and benign grade 1 subtypes.[24] Interestingly, resveratrol, a natural phytoalexin product, induced apoptosis in meningioma cells via miR-34a-3p upregulation and consequent *BCL2* suppression in a dose-dependent manner.[58]

miR-195

Significant downregulation of miR-195 has been reported in grade 3 malignant meningiomas with respect to benign grade 1 meningiomas

and their subtypes (transitional, fibroblastic, and meningothelial).[24,59] The grade-dependent overexpression of fatty acid synthase (*FASN*), a validated miR-195 target in meningiomas (with the highest levels in malignant grade 3 meningioma), correlated with miR-195 downregulation. Functional studies in the grade 3 meningioma cell line IOMM-Lee revealed inhibition of proliferation, migration, and invasion in these cells upon miR-195 upregulation and the consequent repression of *FASN*. Numerous studies have reported that FASN and its role in *de novo* lipogenesis are critical for the survival and proliferation of tumor cells.[59] *VEGF*, known to play a role in angiogenesis, is also frequently overexpressed, especially in higher-grade meningiomas, and is a validated target of miR-195.[60] Thus, miR-195 may play an indirect role in the regulation of metabolism, invasion, and metastasis in meningioma through its downstream targets.

miR-335

Saydam et al. identified a significant overexpression of miR-335 in sporadic WHO grade 1 meningiomas with respect to controls.[21] An individual study later revealed the overexpression of miR-335 in meningioma tumors and its positive correlation with advancing tumor grade (i.e., highest miR-335 levels reported in grade 3 meningiomas) when compared with normal brain arachnoid tissues.[61] The oncogenic potential of miR-335 in meningiomas was highlighted by its direct targeting of retinoblastoma 1 (Rb1) protein, a potent tumor suppressor previously implicated in tumorigenesis. In coherence, *Rb1* levels negatively correlated with miR-335 levels in meningiomas through advancing tumor grades. Elevated levels of miR-335 in primary meningioma cell lines enhanced cell growth and impeded cell-cycle arrest in the G0/G1 phase *in vitro*, thus aiding cellular proliferation. Meanwhile, the repression of miR-335 in meningioma cells, as predicted, inhibited cell proliferation and facilitated G0/G1 arrest in the cell cycle.[61]

miRNAs ASSOCIATED WITH RECURRENCE IN MENINGIOMA

Simpson grading has been widely used to categorize the extent of resection of intracranial meningiomas and its correlation with meningioma recurrence, but it has major limitations.[62,63] Based on "naked eye" observation of resection, this grading system is subjective and inaccurate. A majority of surgical studies that employed this system were performed before routine postoperative magnetic resonance imaging (MRI) surveillance and thus inconsistently assessed the extent of resection and the definition of recurrence.[64] At present, the WHO histopathological classification system is also inefficient in consistently predicting whether a tumor will recur after complete resection.[65]

MiRNAs may serve as promising factors to predict recurrence in meningioma. Zhi et al. proposed an miRNA signature to predict meningioma recurrence (Table 1). Elevated levels of miR-190a and significant dips in miR-29c-3p and miR-219-5p levels were found to correlate with advanced clinical stages and higher recurrence rates.[22] miR-190a mostly plays an oncogenic role,[66] while miR-219-5p and miR-29c-3p act as tumor suppressors in different cancers through downstream targeting of antiapoptotic molecules and proliferation factors.[67,68] High expression of miR-409-3p and low expression of miR-224 has also been significantly correlated with higher recurrence rates.[26] In a recent study, multivariate Cox regression models revealed miRNAs and clinicopathological features most predictive for recurrence in meningioma. miR-331-3p downregulation with partial tumor resection was the most predictive model for recurrence, while elevated levels of miR-146a-5p with respect to normal tissue, its grade-dependent decrease in meningioma, and extent of resection model stood second.[69] Recently, a unique study compared the expression patterns of select miRNAs (miR-21-3p, miR-34a-3p, miR-200a-3p, and miR-409-3p) in tumor and blood samples of meningioma patients (N = 51) with blood samples of healthy individuals (N = 20) and correlated these to the presence of aberrations of chromosomes 1, 14, 18, and 22 in native tumor tissue.[49] Loss of chromosome 1p has been previously identified as the most significant marker of recurrence in meningiomas, independent of histological grade.[70] In this study, miR-200a was proposed as a histologically independent marker for meningioma recurrence due to its significantly diminished expression in recurrent meningiomas and positive correlation with the presence of chromosomal aberration 1p.[49]

BIOMARKER POTENTIAL OF miRNAs IN MENINGIOMA

miRNAs are often introduced into circulating body fluids through apoptotic or necrotic cell death. Cell-free lipid carriers such as microvesicles, exosomes, and apoptotic bodies often comprise miRNAs as cargo.[71] Upon secretion and internalization by recipient cells, miRNAs bind target mRNA(s) and regulate gene expression, thus serving as mediators of intercellular communication. The tissue specificity and unique expression pattern of extracellular miRNAs in different cancer types render them suitable for use as biomarkers. miRNAs may reflect diverse tumor-specific attributes in real time due to detectable changes in their expression levels upon tissue injury or diseased state.[72]

Through the analysis of miRNA expression profiles of paired pre- and postoperative serum samples of meningioma patients, Zhi et al. revealed a panel of six differentially expressed serum miRNAs (Table 1) that may serve as biomarkers for meningioma diagnosis and tumor removal or prognosis. The levels of miR-106a-5p, miR-219-5p, miR-375, and miR-409-3p were significantly elevated, while those of miR-197 and miR-224 were markedly decreased. The combination of these six miRNAs could differentiate meningioma patients from healthy controls with high accuracy (AUC = 0.778). Post tumor removal, the serum expression levels of the respective upregulated and downregulated miRNAs were reversed. Elevated levels of miR-409-3p and diminished miR-224 levels were significantly correlated with higher recurrence rates.[26]

Negroni et al. reported downregulation of the miR-497∼195 cluster in meningioma with increasing malignancy grade. They proposed the use of this miRNA cluster as a biomarker for malignant meningiomas due to consistent diminished expression of this cluster in tissue and serum-derived exosomes of high-grade meningioma patients

with respect to benign samples. *Cyclin D1* is commonly overexpressed in meningioma and has been correlated with abnormalities in apoptosis, invasion, and cell-cycle progression.[73] In this study, the elevated levels of *Cyclin D1* negatively correlated with miR-497∼195 cluster levels in meningioma. Functional analysis revealed the modulation of the expression of the miR-497∼195 cluster by GATA binding protein 4 (GATA-4), a commonly upregulated transcription factor in malignant meningioma, thus culminating in increased levels of *Cyclin D1*.[74] Carneiro et al. proposed miR-181d as a noninvasive biomarker for disease progression in meningioma. A rise in miR-181d levels in both tumor tissue and plasma of meningioma patients significantly correlated with increasing pathological grade, with a more pronounced miR-181d upsurge seen in the latter sample type.[75]

Furthermore, another study[27] evaluated the serum and exosomal levels of miR-497 in meningioma samples (inclusive of the three WHO grades) against healthy controls from two biobanks (Graz biobank and Royal Preston Hospital biobank) by qRT-PCR (Table 1). A substantial decrease in the serum and exosomal levels of miR-497 in meningioma samples with respect to healthy controls, showed promise in distinguishing meningioma patients from healthy individuals (with serum miR-497 AUC = 0.9374 and exosomal miR-497 AUC = 0.8789). A statistically significant drop in both exosomal and serum miR-497 levels and an upsurge in miR-219 serum levels were observed with advancing tumor grade. The study proposed the combined signature of miR-497 and miR-219 as a robust predictor of meningioma grade (AUC = 0.9311). Interestingly, this was also among the early studies to correlate methylation status in meningioma with circulating miRNA levels. High levels of serum miR-497 and low serum levels of miR-219 correlated with a benign methylation class in meningioma.[27]

A study by Kopkova et al. performed high-throughput miRNA profiling of cerebrospinal fluid (CSF) samples from a discovery cohort of 70 brain tumor patients, including 11 meningioma patients and nontumor controls. The microarray data revealed 12 differentially expressed microRNAs in the CSF of meningioma patients with respect to controls ($p < 0.001$) (Table 1). Further validation by RT−qPCR revealed that let-7b, miR-10a, and miR-21-3p were able to stratify meningioma from other tumor types with 73% sensitivity and 72% specificity. Thus, these miRNAs may serve as diagnostic biomarkers for meningiomas in inconclusive cases or uncertain imaging, avoiding most invasive procedures such as stereotactic biopsy or biopsy.[25]

Despite promising attributes of miRNAs that render them suitable for use as biomarkers, some key concerns need to be addressed to facilitate their clinical use. There is considerable cross-reactivity of miRNAs with different pathologies or disease states and normal physiological states, and stages of a particular disease. Therefore, a panel of miRNAs together may serve as more reliable biomarkers for a disease, with enhanced discriminatory potential. Additionally, there is a lack of consistency between many miRNA signatures for the same diseased conditions reported by various groups. This may be attributed to high heterogeneity of methodologies including source sample type, sample preparation, handling, miRNA extraction and quantification, normalization technique, and choice of reference gene, among others.[76] Thus, there is a need to implement standardized protocols to minimize experimental variability.

miRNAs IMPACTING RADIOSENSITIVITY/RADIORESISTANCE IN MENINGIOMA

miR-221 and miR-222 are two highly homologous and conserved miRNAs with identical seed sequences and frequently act as a gene cluster (miR-221/222).[77] Downregulation of miR-221/222 was shown to reverse radiation-induced cell invasiveness in malignant meningiomas that were irradiated with doses less than 6 Gy, brought about by a possible EMT reversal mediated by the overexpression of the miR-221/222 target gene PTEN. Diminished levels of miR-221/222 also enhanced the pro-apoptotic and anti-proliferative effects of radiation, thus promoting radiosensitivity.[78]

Recently, a study revealed the differential miRNA signature in radioresistant and radiosensitive meningiomas through microarray analysis of tumor samples from patients with atypical meningioma (WHO grade 3) treated with GTR and adjuvant radiotherapy (ATR) (Table 1). Patients displaying signs of recurrence within 3 years of treatment were included in the radioresistant group, while others were included in the radiosensitive group. Interestingly, a number of miRNAs dysregulated in this study are associated with fatty acid biosynthesis and metabolism as well as the TGF-β signaling pathway.[78] This finding is of particular interest, as changes in fatty acid synthesis and metabolism have been identified in different cancers and have been shown to influence radiosensitivity in prostate cancer and nasopharyngeal carcinoma,[79,80] Furthermore, enough evidence exists for the role of the TGF-β signaling pathway in cell proliferation, development and progression of advanced grade meningiomas.[81]

LncRNAs: THE UNDERREPRESENTED PLAYERS IN MENINGIOMA

Long noncoding RNAs (lncRNAs) are a class of ncRNAs generally greater than 200 nucleotides in length and lacking the potential to be translated into proteins. lncRNAs arise from both intergenic and intronic regions of protein-coding genes. Their transcription and regulation are often independent of neighboring protein-coding genes.[82,83]

lncRNAs have intricate roles in virtually all stages of genetic regulation including epigenetic, transcriptional, posttranscriptional, translational, and posttranslational levels. Through modulation of histone or DNA modifications, primarily methylation and acetylation, lncRNAs facilitate epigenetic regulation. At the transcriptional level, they may directly bind DNA sequences and inhibit gene transcription; or interact with proteins (primarily transcription factors) to inhibit or activate the expression of downstream genes.[84] Splicing, nuclear export, mRNA localization and stability,

and protein translation are some of the posttranscriptional processes that lncRNAs often regulate.[85] Additionally, the direct interaction of lncRNAs with miRNAs can regulate miRNA functioning. The competing endogenous RNA (ceRNA) theory is among the most popular hypotheses to derive generalized mechanisms of lncRNA function. Briefly, lncRNAs may act as miRNA sponges or "ceRNAs" and can prevent recognition and binding of miRNAs to their target mRNA(s) through competing with target mRNAs for MREs.[86] Pseudogene-derived transcripts and circular RNAs (circRNAs) are among the lncRNA classes increasingly reported to act as functional ceRNAs. At the translational level, lncRNAs have been shown to impact efficiency through interactions with translational machinery. Finally, lncRNAs are also involved in various posttranslational modifications of proteins, mainly phosphorylation, ubiquitination, and acetylation, thereby regulating protein degradation or formation, and influencing protein expression.[84] To facilitate genetic regulation at these multiple levels, lncRNAs may function as decoys, signal, guide or scaffold RNAs.[87] As decoys, they directly interfere with transcription by titrating transcriptional molecules and proteins from the vicinity of their targets or binding to miRNAs to block their downstream activity. lncRNAs serve as signal molecules that respond to various stimuli to mediate transcription. Guide lncRNAs bind specific proteins and relocate them to specific target areas. Finally, scaffold lncRNAs enhance protein-protein, protein-RNA, and protein-DNA interactions via base complementarity or secondary structures. They also recruit different proteins and aid their assembly into multiprotein complexes.[88] Evidently, subcellular localization of lncRNAs significantly influences these diverse functions and interactions.[89]

lncRNAs can exert spatiotemporal control over gene expression during development, and dysregulation of their expression is related to several diseases, including cancer. There is mounting evidence for the involvement of lncRNAs with different cancer hallmarks, such as resistance to cell death, invasion, sustained proliferation, dysregulation of gene expression, genomic instability, and evasion of growth suppressors.[90] Recently, a study by Ahmad et al. highlighted that lncRNAs are associated not only with EMT but also with remodeling of the cancer cell cytoskeleton and crosstalk with the extracellular matrix, a major component of the tumor microenvironment.[91]

Over the past, multiple studies have highlighted the role of lncRNAs in the regulation of cell proliferation, migration, apoptosis, invasion, etc., and thus play critical roles in the process of tumorigenesis or tumor progression.[92] Recently, our group also reviewed the important role of lncRNAs in glioblastoma metastasis, highlighting their potential as diagnostic/prognostic biomarkers as well as therapeutic targets.[93] However, the current research in the case of meningioma places very little emphasis on lncRNAs and the associated lncRNA/miRNA/mRNA regulatory axes underlying key molecular mechanisms. Technical challenges related to lncRNA profiling, such as the low abundance of lncRNAs with respect to protein coding genes, requirement of large sample sizes and greater sequencing depth for their accurate differential analysis, incomplete annotation of lncRNAs, and a lack of universal guidelines for the same[94] can further impact the pace of lncRNA studies in meningioma. Here, we summarize the lncRNAs known to play a role in meningioma pathogenesis to date (Figure 3), with the aim of drawing attention to these underrepresented players in meningioma research.

IMAT1

It is postulated that invasiveness is associated with metastasis, malignant transformation, and meningioma recurrence.[95] However, the mechanism for meningioma invasion is currently not very well known and needs to be studied further. A recent study[96] reported that lncRNA-invasive meningioma-associated transcript 1 (**IMAT1**) is highly expressed in invasive meningiomas compared with noninvasive meningiomas. IMAT1 binds to and regulates the expression of hsa-miR22-3p. Sponging of hsa-miR22-3p by IMAT1 renders it incapable of recognizing and negatively regulating its target Snai1. Snai1 is an essential transcription factor regulating EMT in various tumors. Thus, IMAT1 overexpression in invasive meningiomas deregulates the negative correlation between hsa-miR22-3p and its target protein Snai1. In their previous study,[97] the authors showed that the expression of KLF4, a nuclear transcription factor, correlated with meningioma progression. KLF4 can positively regulate hsa-miR22-3p transcription by binding to its promoter. IMAT1 can regulate the normal functioning of the KLF4/hsa-miR22-3p/Snai1 inhibitory pathway in meningioma. Functional analysis showed that knocking out and overexpressing IMAT1 can inhibit or enhance meningioma cell proliferation and invasion, respectively, in KLF4-expressing cells. Thus, in meningiomas with low IMAT1 expression and high KLF4 expression, malignant transformation is inhibited by the KLF4/hsa-miR22-3p/Snai1 pathway. This suggests that IMAT1 knockdown can be a strategy to achieve inhibitory effects in patients with high IMAT1 expression. It has also been reported that IMAT1, showing higher expression in aggressive meningiomas, can promote meningioma progression, and can be a potential diagnostic, therapeutic, and prognostic molecule.[96]

SNHG1

A study by Zhang et al., 2020, demonstrated that lncRNA, small nucleolar RNA host gene 1 (**SNHG1**), was upregulated in meningioma cell lines compared with normal meningothelial cells.[98] SNHG1 was shown to play an oncogenic role by promoting cell proliferation and suppressing apoptosis. The binding of SNHG1 with miR-556-5p was then computationally predicted and experimentally validated, thus showing the inverse modulation of miR-556-5p by SNHG1. miR-556-5p can target and negatively regulate the expression of transcription factor 12 (TCF12), which is overexpressed in meningioma. Thus, miRNA sponging by SNHG1 leads to increased expression of *TCF12*, establishing the SNHG1/miR-556-5p/TCF12 axis. Furthermore, TCF12 was shown to increase SNHG1 expression by binding to its promoter, thus establishing a positive feedback loop. The authors validated that the SNHG1/miR-556-5p/TCF12 loop

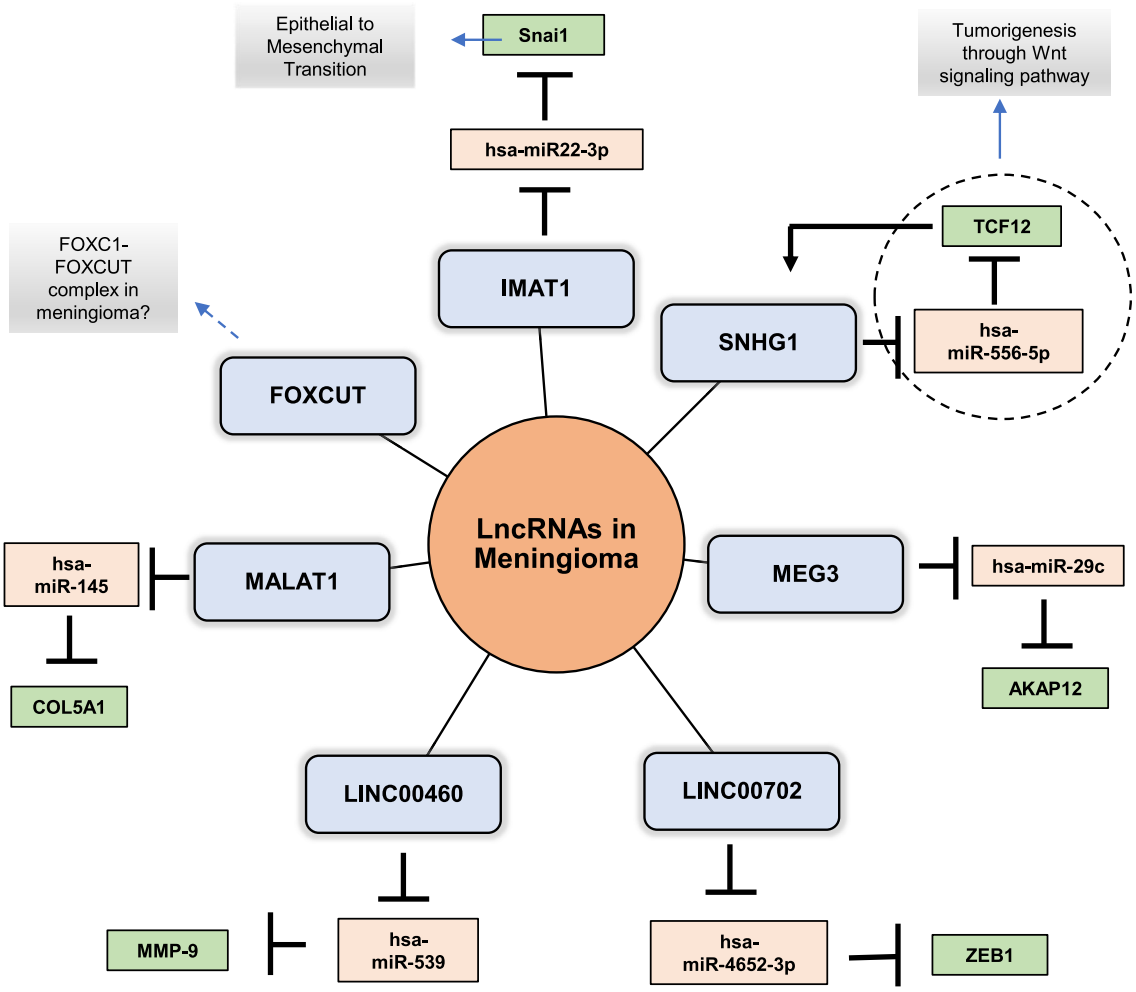

Figure 3. Dysregulated lncRNAs in meningioma

The figure highlights the lncRNAs known to be dysregulated in meningioma and the corresponding downstream miRNAs/mRNAs they regulate. Blue rectangles: Dysregulated lncRNAs in meningioma; cream rectangles: miRNA targets of lncRNAs; green rectangles: mRNA targets of miRNAs; Dashed oval: regulation loop; Solid perpendiculars: inhibition.

promotes meningioma tumorigenesis through the Wnt signaling pathway.[98]

LINC00702

A study by Li et al., 2019, demonstrated that the lncRNA long intergenic nonprotein coding RNA 702 (LINC00702) has an oncogenic function and promotes the malignant progression of meningioma. They experimentally demonstrated that LINC00702 downregulation leads to reduced cell proliferation, migration, and invasion and induces apoptosis in malignant meningioma. Using bioinformatic analysis and luciferase reporter assay, it was shown that LINC00702 acts as a sponge for miR-4652-3p. miR-4652-3p is downregulated in meningioma and is negatively correlated with LINC00702 expression. The study further revealed that zinc finger E-box-binding homeobox 1 (ZEB1), a transcription factor regulating EMT, is a target of miR-4652-3p and is significantly upregulated in malignant meningiomas. Rescue experiments reinforced the synergistic effect of LINC00702 and the miR-4652-3p/ZEB1 axis, as miR-4652-3p downregulation or *ZEB1* overexpression rescued the suppression of cell proliferation and migration caused by LINC00702 knockdown. LINC00702 can also augment the Wnt/β-catenin signaling pathway through the miR-4652-3p/ZEB1 axis, further regulating cell growth, differentiation, and apoptosis. The study thus suggests the role of LINC00702 as a potential prognostic biomarker as well as a therapeutic target in malignant meningioma patients.[99]

LINC00460

Similarly, a study by Xing et al.[100] revealed that the lncRNA long intergenic nonprotein coding RNA 460 **LINC00460** is highly expressed in meningioma tissues and cells, especially in malignant meningioma cell lines (IOMM-Lee, CH157-MN), compared with benign (Ben-Men-1). Functionally, knockdown of LINC00460 suppressed meningioma cell

proliferation and increased apoptosis. LINC00460 also plays a role in invasion, as LINC00460 knockdown significantly lessens the invasive ability of meningioma cells. It also leads to a decrease in the expression of the invasion-related proteins MMP-2, MMP-9, and ZEB1. Interestingly, the authors revealed that LINC00460 can target miR-539, which further targets MMP-9. Thus, by functioning as an hsa-miR-539 sponge, LINC00460 promotes MMP-9 expression and contributes to meningioma proliferation, metastasis, and malignant transformation. In the case of other cancers, LINC00460 has been implicated in playing an oncogenic role. For instance, it is associated with poor prognosis in non-small cell lung cancer (NSCLC) and promotes cell migration and invasion through EMT in lung cancer.[101] In the case of esophageal squamous cell carcinoma (ESCC), it has also been shown to be correlated with lymph node metastasis, ESCC TNM stage, and prognosis.[102] Similarly, miR-539 also acts as a tumor suppressor in other cancers, such as breast cancer[103] and hepatocellular carcinoma.[104] The study provides new insight into meningioma pathogenesis and highlights potential new therapeutic and diagnostic targets.

MEG3

Meningioma pathogenesis is often associated with abnormalities of chromosome 14q. The loss of chromosome 14q is commonly attributed to higher grade and recurrent meningiomas and thus is often associated with tumor progression and recurrence.[105,106] On careful analysis, it was observed that 14q32 is also the genetic site for a lncRNA, maternally expressed gene 3 (**MEG3**). Subsequently, it was found that MEG3 is highly expressed in normal arachnoid cells, while it shows very low expression in the human meningioma and meningioma cell lines IOMM-Lee and CH157-MN. It was found that the loss of MEG3 expression along with its gene copy number was more pronounced in higher-grade meningiomas, thus suggesting its role in meningioma progression.[107] It was also revealed that MEG3 plays a tumor-suppressive role in meningioma pathogenesis by inhibiting cell proliferation potential. Interestingly, an increase in CpG methylation within the promoter region of MEG3 in higher meningioma grades was also reported.[107] It has been widely reported to be involved in various cancers, such as prostate cancer,[108] hepatocellular cancer, and pituitary tumors.[109]

A study by Ding et al., 2020, showed that MEG3 acts as a sponge for miR-29c. It was shown that miR-29c was highly expressed in meningioma and inversely correlated with MEG3 expression. The direct interaction between MEG3 and miR-29c was confirmed through dual-luciferase reporter and RNA immunoprecipitation (RIP) assays. The authors also elucidated the role of MEG3 in regulating migration, invasion, cell proliferation, and cell-cycle arrest using meningioma cell lines IOMM-Lee and CH157-MN via interaction with miR-29c. The oncogenic impact of MEG3 was eliminated through co-transfection with miR-29c.[110] A-kinase anchor protein 12 (AKAP12), which is implicated in various cancers, also plays a key role in cell proliferation and metastasis in high-grade meningiomas.[111] The study validated the negative regulation of *AKAP12* by miR-29c. Thus, MEG3 regulates *AKAP12* expression by sponging miR-29c. The MEG3/miR-29c/AKAP12 axis plays an important role in meningioma pathogenesis. The study also suggests the use of MEG3 and miR-29c as potential biomarkers for meningioma diagnosis.[110] It has been reported that MEG3 is downregulated while miR-19a is overexpressed in malignant glioma tissues and cell lines. MEG3 is known to act as a sponge for miR-19a in glioma cells and can thus act as a tumor suppressor. miR-19a can regulate the expression of phosphatase and tensin homolog (PTEN) and thus promote cell migration, proliferation, and invasion. The MEG3/miR-19a/PTEN axis has been reported to be an important target for glioma pathogenesis.[112]

MALAT1

A recent study reported that the lncRNA metastasis-associated lung adenocarcinoma transcript 1 (**MALAT1**) is associated with tumor invasiveness in meningioma.[52] The effect of the rs619586 polymorphism on MALAT1 expression in meningioma was evaluated. It was observed that meningioma samples with the rs619586 polymorphism genotyped as GG showed the lowest MALAT1 expression, while the AA genotype showed the highest MALAT1 expression and was associated with a higher risk of invasive meningioma. The heterozygote genotype (AG) was correlated with a decreased risk of invasive meningioma. MALAT1 expression levels were shown to be inversely correlated with miR-145 expression, and the direct interaction between miR-145 and MALAT1 was experimentally validated. The study suggests that MALAT1 can also repress miR-145 expression by directly binding to it. It was also shown that miR-145 can directly target and negatively regulate the expression of COL5A1 (collagen alpha-1(V) chain). Downregulation of miR-145 and upregulation of COL5A1 have been reported in the case of high-grade meningiomas and are associated with higher invasiveness. Thus, the study suggests that the rs619586A>G SNP lowers the risk of meningioma invasion through the MALAT1/miR-145/COL5A1 ceRNA axis.[52] MALAT1 has previously been reported to play a role in biological processes such as cell proliferation, migration, and apoptosis in different cancers.[113]

FOXCUT

Recently, an interesting study on methylation patterns in meningioma samples compared with normal dura reported hypomethylation in the FOXC1 promoter as well as its upstream lncRNA transcript **FOXCUT**.[114] Consequently, a significant increase in FOXC1 mRNA and protein expression was observed in the tumors compared with controls. FOXC1 is a transcription factor involved in craniofacial patterning, and FOXC1 mutations in humans are associated with severe craniofacial abnormalities.[115] It has been observed in other studies that FOXC1 and FOXCUT form an mRNA-lncRNA complex that results in upregulation of the FOXC1/PI3K/AKT pathway and is involved in various cancers.[116] This study thus recommends further investigation to decipher the role of FOXC1/FOXCUT in meningioma pathogenesis.

Lnc-GOLGA6A-1

A recent study by Slavik et al., 2022, identified lnc-GOLGA6A-1 as a prognostic biomarker for meningioma recurrence.[117] The group performed differential analysis of mRNA and lncRNA transcripts

across different meningioma subgroups, followed by validation using RT-qPCR. The study, however, lacks functional characterization of the lncRNA beyond gene expression analysis.

Subcellular localization of lncRNAs is the primary determinant of their molecular functions, and it is a dynamic process that may undergo changes in different physiological and pathological conditions.[89] We used LncATLAS database (https://lncatlas.crg.eu.) to determine the subcellular localization of the lncRNAs described above. The lncRNAs described above differ in their subcellular localization. Strong evidence was available for primarily nuclear localization of SNHG1, MALAT1, and MEG3 while LINC00702 and LINC00460 were shown to be localized in the cytoplasm. However, information for the localization of FOXCUT, IMAT1, and Lnc-GOLGA6A-1 was not available (Figures S2A–S2E).

The tissue specificity of lncRNA expression surpasses that of protein coding transcripts.[118] Thus, they may serve as more reliable indicators of specific physiological and pathological states in a tissue-specific manner. To identify the bulk tissue-specific expression of the lncRNAs described above in the human brain, we used the GTEx portal (https://gtexportal.org/). Interestingly, MALAT1, SNHG1, and MEG3 were among the lncRNAs showing high overall expression in brain tissues, while FOXCUT, LINC00460, and LINC00702 were lowly expressed in overall brain tissues. Some of these lncRNAs were individually enriched in the cerebellum and cerebellar hemisphere (MALAT1, SNHG1, MEG3). LINC00460 was enriched in the caudate (basal ganglia) and nucleus accumbens (basal ganglia); LINC00702 in the spinal cord (cervical c-1); and FOXCUT was enriched in the frontal cortex (Figures S3A–S3H).

It is evident that the functional characterization of almost all lncRNAs described above in meningioma and their downstream effects have stemmed from the bioinformatic prediction and subsequent experimental validation of ceRNA axes. However, some key considerations should be kept in mind before drawing any definitive inferences. Many studies have relied on the exogenous overexpression of lncRNAs to study their ceRNA interactions, *in vitro*. However, models assessing transcriptome-wide target abundance have shown that individual transcripts (except under exceptional circumstances), do not reach the threshold abundance physiologically, to elicit competition.[119] This holds greatest relevance for lncRNAs as these noncoding RNA entities are generally lowly expressed. It has also been demonstrated that miRNAs expressed at low levels physiologically are more susceptible to ceRNA-mediated inhibition when compared with highly expressed miRNAs. Additionally, for ceRNAs to de-repress miRNA targets, the ceRNA abundance (in either physiological or pathological conditions) must approach the target abundance of the miRNA.[120] Mathematical modeling predicts that ceRNA inhibition is most optimal when equimolar concentration of both miRNA and targets is achieved, which is very uncommon in physiological conditions. However, compartmentalization or subcellular localization of ceRNA transcripts may aid in increasing the RNA concentration at the site of activity, thereby enhancing ceRNA activity, and an increase in ceRNA stability may also yield similar effects.[121] The close association between lncRNA subcellular localization and their function as well as their evolutionarily conserved secondary structures (conferring stability and facilitating interactions) may support this claim. Furthermore, minor transcriptomic changes in ceRNA expression may elicit larger downstream responses through positive feedback loops or pathway divergence through transcription factor regulation as 88% of lncRNAs share miRNA binding sites with transcription factor mRNAs that are also downregulated upon lncRNA knockdown.[122]

MENINGIOMA THERAPEUTICS: CURRENT OPTIONS

Asymptomatic meningiomas are often left untreated and observed for growth and aggressiveness with annual MRIs. For fast-growing and symptomatic meningiomas, maximal safe surgical resection is the gold standard for the clinical management of meningiomas. Meningiomas that undergo STR are followed up with radiation therapy as the adjuvant therapeutic option. Often, meningiomas that recur after surgery are followed up with radiotherapy. Several systemic therapies have been tested for meningiomas that become refractory to these therapeutic modalities. However, to date, there is no clinically approved systemic therapeutic option for meningiomas. Such patients with refractory meningiomas can only be enrolled in clinical trials for chemotherapeutic agents (Figure 4) as salvage treatment options.[123]

Several chemotherapeutic drugs, such as temozolomide,[124] irinotecan,[123] and hydroxyurea,[125,126] have been evaluated for meningioma treatment but have shown limited clinical efficacy. Similarly, combination therapies such as vincristine, Adriamycin, and cyclophosphamide (VAC)[127] have also not proven to be of significant clinical use. Trabectedin, a DNA-intercalating agent commonly used in cases of soft tissue sarcoma or ovarian cancer, was associated with high toxicity and showed no improvement in the overall survival (OS) and progression-free survival (PFS) of meningioma patients in a randomized phase 2 trial (EORTC 1320).[128]

Somatostatin receptor 2A is often overexpressed in meningiomas[129]; thus, the effect of somatostatin analogs such as pasireotide and octreotide[130,131] and radionucleotide therapy[132] have been evaluated in multiple studies, reporting variable efficacy. Recently, octreotide has been studied in combination with an mTOR inhibitor, everolimus, in a phase II CEVOREM trial. The study reported that the combination is effective in reducing the growth rate of all grades of meningiomas.[133] Similarly, progesterone receptors are overexpressed in the case of meningiomas; thus, anti-progesterone agents such as mifepristone have been tested, although no clinical efficacy has been reported.[134] Anti-estrogen agents such as tamoxifen have also not yielded any significant clinical results.[135,136]

Systemic therapies often involve antibodies or small molecule inhibitors that target growth factor receptors, which are often overexpressed in cancers. In the case of meningioma, the efficacy of such

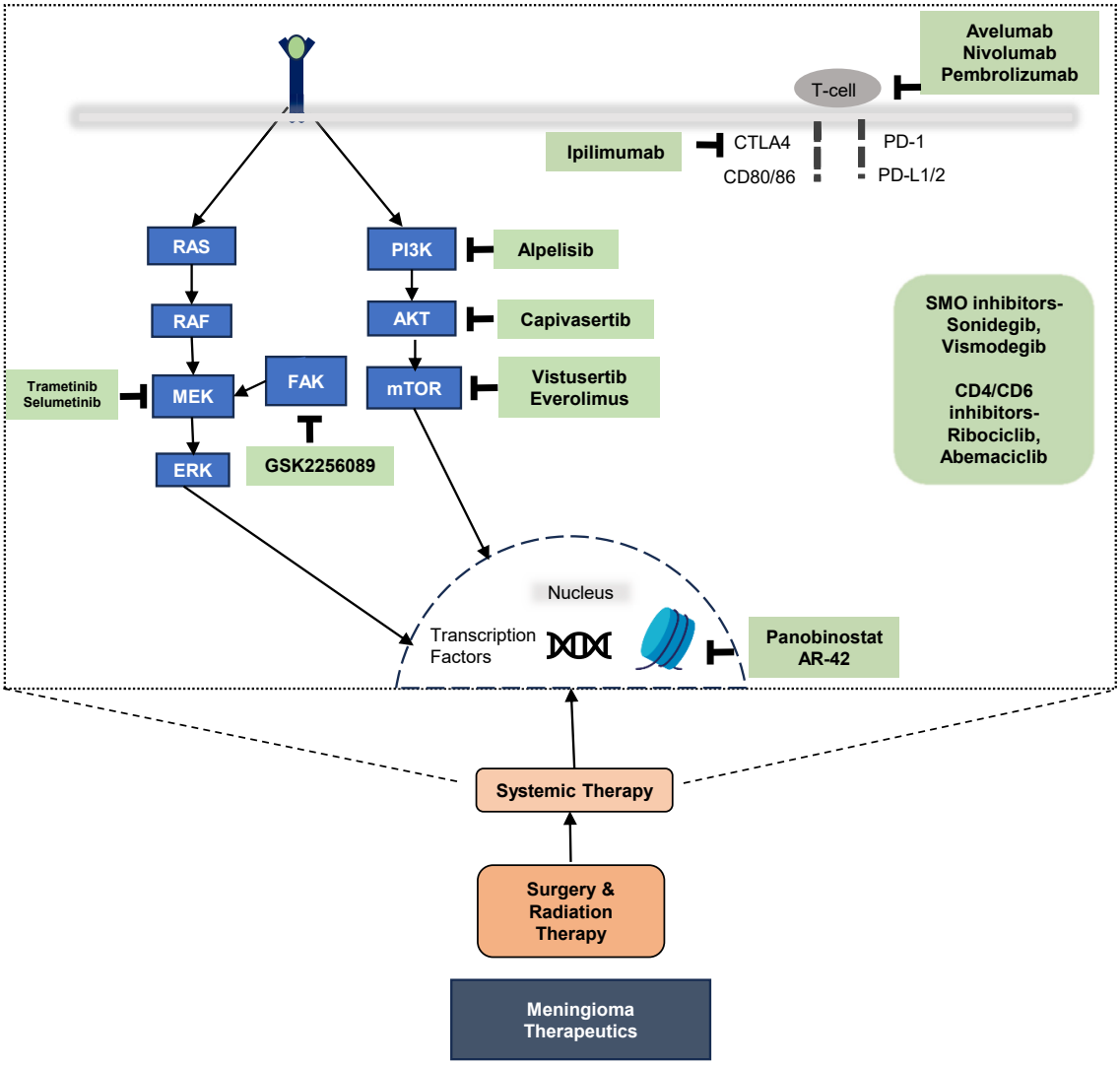

Figure 4. Current treatment modalities for meningioma

The figure shows the current options for meningioma therapeutics, highlighting the molecular targets of the new candidates being investigated in ongoing clinical trials. Created with BioRender.com.

inhibitors and antibodies is also being tested in ongoing clinical trials, including MEK (mitogen-activated protein kinase kinase) inhibitors (trametinib,[137] selumetinib[138]), FAK (focal adhesion kinase) inhibitors (GSK2256098[139]), mTOR (mammalian target of rapamycin) inhibitors (vistusertib,[140] everolimus), SMO (smoothened, frizzle class receptor) inhibitors (vismodegib), AKT (AKT serine/threonine kinase) inhibitors (capivasertib[141]), and CDK4/6 (cyclin-dependent kinase) inhibitors (abemaciclib, ribociclib[142]). Combinatorial therapies, such as the combination of the PI3K (phosphoinositide-3-kinase) inhibitor alpelisib along with trametinib, are also in clinical trials with promising initial results.[137]

Reportedly, some encouraging results have been obtained upon targeting angiogenic pathways, especially the VEGF signaling pathway. Bevacizumab, a monoclonal anti-VEGF receptor antibody, showed promise in a phase II clinical trial for recurrent and refractory meningiomas, leading to longer PFS of meningioma patients.[143] As observed through longitudinal imaging analyses, bevacizumab has been associated with meningioma growth inhibition and reduced peritumoral edema.[144] A phase II trial of bevacizumab in combination with the mTOR inhibitor everolimus showed mild improvement in the PFS of meningioma patients.[145] With the results of this combination being similar to the studies of bevacizumab alone, the study has been terminated.[146] Additionally, antibodies targeting other immune checkpoints that have shown efficacy in other cancers, such as nivolumab, avelumab, pembrolizumab, and ipilimumab, are also in early clinical trials for meningioma.[12]

The kinase inhibitor sunitinib can target both VEGF and platelet-derived growth factor (PDGF) receptors. In a phase II trial, including 36 patients with higher-grade meningiomas, sunitinib treatment led to a PFS of 42% at 6 months, a significant improvement from the naturally occurring PFS of 5%–30% at 6 months. However, toxicity was reported in most of the patients, making use of sunitinib a cause of concern and warranting further investigation of the drug.[147] Similarly, another small molecule targeting the two receptors, vatalanib, has also been tested in a phase II trial, showing limited clinical efficacy.[148] Small molecule inhibitors of the epidermal growth factor (EGF) receptors gefitinib and erlotinib have also been tested in previous studies for recurrent meningiomas, with no improvement in the OS or PFS of the patients.[149] Likewise, imatinib, a kinase inhibitor of PDGF receptor, reported no contribution to the betterment of the PFS in a phase II trial.[150,151]

Cytokine interferon alpha (IFN-α) plays a therapeutic role in meningioma in some case reports and small clinical trials.[152,153] It has been proposed to play immune-modulatory, anti-proliferative, and antiangiogenic functions in cancer.[154] However, some studies also report that IFN-α does not show significant clinical efficacy in higher grades of meningioma.[155]

There has been a discussion for determining an appropriate endpoint to evaluate the treatment efficacy of various systemic therapies. Some studies suggest the use of a 6-month PFS,[156] while others recommend using a combination of 6-month PFS and radiographic response.[157] As per current regulations, IFN-α, somatostatin analogs, and VEGF receptor inhibitors are the only Food and Drug Administration-approved salvage treatment options that have shown minimal benefit in the case of meningiomas.

Methylation analysis for meningioma classification and its association with prognosis and tumor location, among others, has been suggested by recent studies.[158,159] Mutations in genes encoding histone demethylases (KDM6A, KDM5C) or those involved in transcription-related chromatin remodeling (SMARCE1, SMARCB1) have been identified through genomic analysis in meningioma.[160] As per a report, vorinostat, a histone deacetylase (HDAC) inhibitor, showed antitumoral activity in *ex vivo* models of specific molecular patterns based on RNA sequencing, DNA methylation analysis, copy number alterations, and whole-exome sequencing.[161] The clinical efficacy of the HDAC inhibitor AR-42 in the case of NF2-associated meningiomas was evaluated in a phase I pilot trial[162] and showed uncertain results, requiring further analysis. The phase I clinical trial of panobinostat, an HDAC inhibitor, along with stereotactic radiation therapy for patients with high-grade meningiomas was terminated due to poor accrual.[163] However, a recent study by Tatman et al. (2021), involving high-throughput screening of epigenetic compounds, reported panobinostat as the most effective epigenetic compound among all tested compounds for meningioma treatment. Thus, the study highlights the importance of targeting HDACs in meningiomas and the need for further research in this direction.[164]

SCOPE OF ncRNA-BASED THERAPIES IN MENINGIOMA

Different miRNA signatures and some deregulated lncRNAs in meningioma have been thoroughly discussed in the previous sections of this review. Some of these ncRNA entities may be further probed for use as therapeutic targets in meningioma.

miRNAs appear to be attractive therapeutic entities primarily due to their simultaneous targeting of numerous mRNAs often involved in different signaling pathways by a single miRNA entity (exceptional therapeutic bandwidth). This multi-target approach of miRNAs is particularly beneficial to targeting cancer, as modulation of multiple pathways is a prerequisite to its effective treatment.[165] For instance, miR-34a-3p directly targets *SMAD4, FRAT1,* and *BCL2* in meningioma. Targeting miR-34a thus might help in simultaneous regulation of TGF-β, Wnt/β-catenin, and apoptotic signaling pathways.[57]

lncRNAs also hold promise as therapeutic targets and biomarkers due to ease of their detection in biological samples (saliva, serum, plasma, urine, and tumor tissues), remarkable stability in bodily fluids (due to extensive secondary structures, stabilizing posttranslational modifications, and protective exosomal transport), "druggable" secondary structures, tissue-specific and spatiotemporally controlled expression patterns, and noninvasive detection via common molecular techniques such as *in situ* hybridization, RT-qPCR, or transcriptomic profiling.[166]

Various RNA-based cancer therapies have been developed with different underlying mechanisms of action. These can be extended to meningioma and further evaluated for their efficacy. lncRNAs may be targeted using antisense oligonucleotides (ASOs) that are complementary to them, consequently forming DNA/RNA heteroduplexes, and are ultimately degraded in an RnaseH1-dependent manner. AntagoNATs, which are antagonists of natural antisense transcripts (NATs), may be used to inhibit *cis*- and *trans*-regulation via NATs through inhibition of sense-antisense interactions. Small interfering RNAs (siRNAs) and short hairpin RNAs (shRNAs) are based on RNA interference and may be used for targeting both miRNAs and lncRNAs. Oligonucleotide-based miRNA inhibitors such as anti-miRs may be used to functionally repress oncogenic miRNAs, while miRNA mimics (unnatural double-stranded RNA fragments that mimic endogenous miRNA function and are engineered to cause translational repression of a target gene of interest) may be used to enhance the function of heavily downregulated tumor-suppressive miRNAs (miRNA replacement therapy). miRNA sponges (natural circRNAs or artificial RNA constructs with multiple miRNA binding sites) may be used to exert their function via sequestration of multiple endogenous miRNA targets. Last, CRISPR-Cas9-based gene editing could be employed to modulate the genomic loci of target lncRNAs.[167]

However, several limitations precede the translational use of ncRNA-based therapeutics in clinics. Suboptimal pharmacokinetic

and pharmacodynamic properties are displayed by oligonucleotides due to their high molecular size, negatively charged phosphodiester backbones, and hydrophilic nature. It is also difficult to ensure the efficient delivery of RNA molecules with retained function and structural integrity.[167] miRNAs are prone to degradation by nucleases upon addition into biological systems, have cell membrane permeability issues, are often entrapped in endosomes, and display poor binding affinity for complementary sequences. The packaging of circulating miRNAs in exosomes (∼10%) or in complexes with proteins (∼90%), such as argonaute 2 (Ago2), prevents their digestion by RNases that commonly populate bodily fluids and confer miRNA stability.[71]

Particularly, delivery of ncRNAs to target tissues can be challenging and may result in off-target effects and undesirable toxicities and/or activation of innate immune responses.[168] ncRNAs may be encapsulated in various delivery systems that are commonly lipid- and polymer-based vectors and ligand-oligonucleotide conjugates to overcome challenges associated with their delivery. Lipid-based nanoparticles (LNPs) containing nucleic acids as cargo are the most tested delivery vehicles in both pre-clinical and clinical studies. LNPs have cationic or ionizable lipids for RNA complexation, neutral lipids for NP stabilization, helper phospholipids that aid formation and intracellular release, and PEGylated lipids or polyethylene imine (PEI)-based lipids that reduce nonspecific interaction. Synthetic or natural polymers are characterized over lipid carriers due to their versatile size, structure, and molecular composition. Different polymers are actively being investigated *in vitro* and *in vivo* for miRNA mimic or antimiR delivery alone or in combination with chemotherapeutic agents, and include PEI and polylactic-co-glycolic acid (PLGA) among others. Virus-based delivery systems like bacteriophage minicell delivery vehicles, target cell-specific ligand-oligonucleotide conjugates, and use of engineered exosomes with loaded ncRNA(s) are some of the other available methods to overcome the aforementioned hurdles to the clinical utility of ncRNAs in therapy.[167]

Specificity issues arise from cellular uptake in untargeted cells (undesired on-target effects), sequence similarities, or overdosing beyond physiological levels (off-target effects). Loading of the passenger instead of the guide strand into the RISC may also contribute to off-target effects. Incorporation of locked nucleic acids (LNAs) at the 5′-end of the passenger strand, is an example of improvement in RISC loading via third-generation chemical modifications. Other solutions include (1) cell-specific miRNA modulations (through cloning of RNA therapeutic under a suitable promoter, overexpressed in desired cells, in a suitable vector) and (2) targeting precursor miRNAs (via peptide nucleic acid [PNA] oligomers with high precision binding affinity to their RNA targets).[167] A common strategy to facilitate precise delivery is to link the targeting RNA to a ligand often overexpressed in cells of interest. This primarily increases uptake at the cellular level, and is particularly suited to target overexpression receptors overexpressed in cancerous cells.[169]

Dosing poses a clear challenge to the potency of miRNA-based therapeutics. For instance, at pathological levels, the oncogenic miR-17-92 cluster shows a 2- to 36-fold upregulation (in lymphoma cell lines or tissue samples). However, transient transduction of mimics of the miR-17-92 cluster at experimental concentrations led to an elevated expression of up to 400-fold.[167] This resulted in nonspecific changes in gene expression and accumulated mutated and tailed variants of the mimics. Lower concentrations, however, were incapable of demonstrating a specific gene knockdown. However, till date, clinical studies have rarely thrown light upon the determination of the appropriate dose of an RNA therapeutic with successful delivery to the desired cell type.

Presence of membrane barriers (the endothelial and blood brain barrier, the renal clearance system, and the reticuloendothelial system) is also often associated with inefficiency of nucleic acid-based drugs. Cationic lipids and polymers have shown promise in destabilizing the endolysosomal barrier or in changing the intra-endosomal pH, thus altering endosome stability and trafficking.[169]

Diverse extracellular and intracellular PAMP receptors in the immune system aid in the recognition of both single-stranded (ss) and double-stranded (ds) RNA molecules. Different toll-like receptors (TLRs) in endosomes mediate extracellular recognition while intracellular recognition is aided by cytoplasmic receptors such as RIG1 and NOD1/2, among others. The TLR signaling pathway is prominent in the recognition of RNA therapeutics and immunogenicity of different ncRNAs may be reduced via different second- and third-generation chemical modifications.[167] In the context of meningiomas, it would be of interest to test whether exogenous RNA entities elicit an innate immune response upon delivery in the brain due to recognition by tumor-associated microglia. However, the blood brain barrier may have minute effects on the delivery of exogenous RNA molecules to meningiomas, as these tumors grow outside the blood brain barrier.[170]

Conclusions

There is an immense scope of expansion of the ncRNA landscape of meningioma. While many studies have emerged in the past 2 decades that focus on identifying the miRNA signatures in meningioma (primarily via small RNA profiling) and functionally characterizing these small molecular entities, similar studies for lncRNAs and circRNAs are scarce. In fact, to date, only one published study[117] identified the dysregulation of a novel lncRNA transcript, Lnc-GOLGA6A-1, in meningioma through transcriptomic profiling of patient FFPE tumor samples. All other lncRNAs identified to play a role in meningioma pathogenesis discussed in this review, such as MEG-3, MALAT-1, and IMAT-1, are well-known players in cancer development and thus were probed for their involvement in meningioma carcinogenesis, sans the need for sequencing. Despite some therapeutic molecules reaching clinical trials, to date, no therapeutic alternatives have been approved for use in meningioma treatment. Thus, it may be useful to explore ncRNAs such as miRNAs and lncRNAs as novel therapeutic alternatives for meningioma.

Assessment of their efficacy as therapeutic molecules would require further probing *in vivo* through genetically engineered mouse models (GEMMs) and *in vitro* on patient-derived xenografts (PDXs). ncRNAs are molecular entities with booming potential for use as diagnostic and prognostic biomarkers, as well as potent therapeutic targets for cancer. It is thus necessary to address the described challenges associated with their clinical utility and streamline their use in meningioma research.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.omton.2024.200782.

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AUTHOR CONTRIBUTIONS

R.K. conceived the idea behind the review article. R.J. and A.S. equally contributed toward writing the manuscript. R.J. prepared Figures 1 and 2 and A.S. prepared Figures 3 and 4. R.K. reviewed the manuscript. All authors have read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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