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Exploring the roles and clinical potential of exosome-derived non-coding RNAs in glioma

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ABSTRACT

Non-coding accounts for 98 %-99 % of the human genome and performs many essential regulatory functions in eukaryotes, involved in cancer development and development. Non-coding RNAs are abundantly enriched in exosomes, which play a biological role as vectors. Some biofunctional non-coding RNAs are specifically designed as exosomes for the treatment of cancers such as glioma. Glioma is one of the most common primary tumors within the skull and has varying degrees of malignancy and histologic subtypes of grades I-IV. Gliomas are characterized by high malignancy and an abundant blood supply due to rapid cell proliferation and vascularization, often with a poor prognosis. Exosomal non-coding RNAs can be involved in the tumorigenesis process of glioma from multiple directions, such as angiogenesis, tumor proliferation, metastatic invasion, immune evasion, apoptosis, and autophagy. Therefore, non-coding RNAs in exosomes are suitable as markers or therapeutic targets for early diagnosis of diseases and for predicting the prognosis of a variety of diseases. Regulating exosome production and the level of exosomal non-coding RNA expression may be a new approach to prevent or eliminate glioma. In this review, we review the origin and characteristics of exosomal non-coding RNAs, and introduce the functional studies of exosomal non-coding RNAs in glioma and their potential clinical applications, in order to broaden new ideas for the treatment of glioma.

1. Introduction

Glioma is considered one of the most common types of malignant tumors, which accounting for about 80 % of all malignant intracranial tumors (Asadi et al., 2023) and is distinguished by its complexity, multiplicity and its unfavourable prognosis. Gliomas occur in glial cells, which are cells that help neurons function normally and play a supportive role (Gusyatiner and Hegi, 2017), and include astrocytomas, ventricular meningiomas, and oligodendrogliomas, of which glioblastoma (GBM) is the most lethal glioma, accounting for 60–80 % of all diffuse glioma diagnoses, with a median overall survival rate of approximately 450 days (Molinaro et al., 2019). The 2021 edition of the WHO classification of central nervous system tumors classifies gliomas as grades I-IV, and WHO grade III-IV gliomas are classified as high-level malignant tumors (Mortensen et al., 2022). Current treatment is based on surgical re-excision of the tumor combined with radio- and chemotherapy as well as targeted drug treatment (Ostrom et al., 2014). GBM stem cells (GSCs) have a high level of malignancy and worse outcome due to multidrug resistance (MDR) to common chemotherapeutic agents and tumor recurrence (Anastasiadou et al., 2017; Mahinfar et al., n.d.), and it has also been suggested that glioma treatment failure is related to the anatomical location and blood-brain barrier (BBB) (Wang et al., 2021). The poor prognosis of GBM is mostly due to its rapid proliferation and extensive invasion of tissues, as well as the lack of understanding of its molecular pathogenesis. Diagnostic and therapeutic monitoring tools with high specificity and sensitivity for early diagnosis have not yet been sought (Mahinfar et al., n.d.; Reifenberger et al., 2016). Therefore, further exploration of reliable biomarkers is essential for the diagnosis and treatment of patients and for predicting their prognosis.

In recent years, researchers have explored the tumour microenvironment (TME), providing new insights into carcinogenesis, growth and treatment. The TME of cancer cells often includes fibrous cells, vessels, neurofibrils, immunocyte, and other stromal cells and the extracellular vacuoles that encase various genetic signals (Vitale et al., 2019). In the normal microenvironment there is a state of homeostasis that prevents the spread of malignant cells, nevertheless, as the cancer progresses and histological grade increases, it leads to changes in the surrounding tissue layers and communicates with immune cells, promoting immunity,

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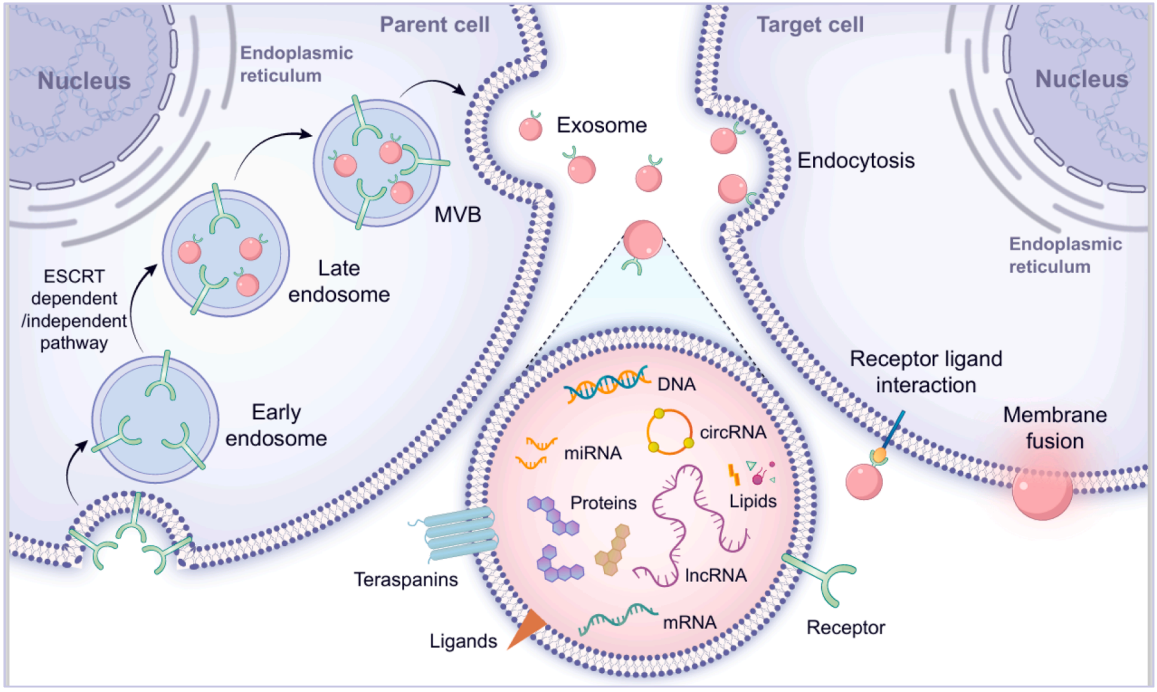

Fig. 1. Exosomes originate from an endosomal pathway within living cells and are subsequently released into the extracellular environment. During their formation, they encapsulate a variety of cellular components, including proteins, lipids, metabolites, small molecules, DNA, RNA, and cell membrane surface proteins. These exosomes can then interact with recipient cells through endocytosis or plasma membrane invagination, leading to fusion. Exosomes released by parent cells can be taken up by recipient cells via endocytosis or membrane fusion, and they can also elicit a biological response by binding to cell surface proteins or receptors.

simultaneous activation of angiogenesis, tumour nerves and epithelial-mesenchymal transition (EMT), creating a favourable tumour microenvironment for successful tumour growth(Chen et al., 2021; Mao et al., n.d.; Li et al., 2021). There is growing evidence that communication among tumour cells and peripheral constituents of the glioma the microenvironment can influence positively various features of glioma (Klemm et al., 2020; Godlewski et al., 2015) and promote glioma growth and invasion. In recent years, exosomes have emerged as a new mediator of intercellular communication that can contain many cellular components, such as DNA, RNA, lipids, metabolites, and cytoplasmic and cell surface proteins (Wei et al., 2020). As a result, exosomes are of great interest. Among these components, non-codingRNA (non-coding RNAs, ncRNAs) are abundant and stable in exosomes, and studies have shown that non-coding rna is inextricably linked to cancer development, progression and prognosis (Anastasiadou et al., 2017; Slack and Chinnaiyan, 2019). This paper reviews the origin and characteristics of exosomal ncRNA and describes the role of exosomal ncRNA in glioma and its potential clinical applications.

1.1. Origin and characterization of exosomes

Also known as intraluminal vesicles (ILVs), exosomes are 40–160 nm in diameter (mean ~100 nm) and are a subset of extracellular vesicles (EVs), the investigation of which has the potential to uncover unknown cellular and molecular mechanisms in cell-to-cell transmission, organ homeostasis and disease (Nojima and Proudfoot, 2022). The released exosomes can alter the microenvironment of the extracellular matrix, delivering signals and macromolecules, including proteins, DNA, lipids, messenger RNAs (mRNAs), microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), to facilitate cellular intercellular communication(Zhan et al., 2024). The released exosomes can alter the microenvironment of the extracellular matrix, delivering signals and molecules to recipient cells to trigger changes in their pathophysiological functions. Originally observed by John stone (Johnstone et al., 1987) in 1986 in sheep reticulocytes, exosomes were considered to be "waste" after membrane function was shed and their biological relevance was long overlooked due to the lack of certain structures and biological activities. In recent years, it has been discovered that almost all cell types are capable of secreting exosomes, such as plasma, serum, cerebrospinal fluid (CSF), lymph, urine, bile, saliva, mother's milk, amniotic fluid and semen (Hornick et al., 2015; Andreea et al., 2016; Goto et al., 2018; Kagota et al., 2019; Zlotogorski-Hurvitz et al., 2015; Dixon et al., 2018). These specific cellular signals probably therefore contains information that can be used for cancer diagnosis, treatment and disease prognosis.

Exosome biogenesis involves a series of sequential processes, the foremost of which is the endosomal sorting complex required for transport(ESCRT), which is instrumental in the generation of ILVs and MVEs and is the driving force behind membrane formation and cleavage (Wei et al., 2021; Niel et al., 2018). The ESCRT family composed of the ESCRT-0, ESCRT-I, ESCRT-II and ESCRT-III protein complexes, that together with the vesicular protein sorting gene 4 (VPS4) protein AAAATPase function in various pathways regarding MVB biosynthesis, cytokinesis, nuclear membrane resealing, self-phagocytosis and viral exosomes (Coomans et al., 2024; Henne et al., 2011).The exosome has been demonstrated to contain ESCRT and TSG101 has become a frequently used marker within the exosome. The proproteins of the ESCRT-0 and ESCRT-I complexes are present in the exosome and cause substantial aggregation of membrane bridge-associated and the cytoplasmic proteins to which they subsequently incorporate.Thus, ESCRT-0 and ESCRT-I proteins are in charge of anti-packaging ubiquitinated proteins and protein-containing precursor/serine precursor (PT/SAP) patterns into exosomes(Lee et al., 2023; Nabhan et al., 2012; Cheng et al., n.d.), Assembly of ESCR-III is then promoted by the ESCR-II complex; ESCR-III forms mature vesicles and promotes vesicle budding by switching on the deubiquitination mechanism(Hu et al., 2022). Ultimately, of these early endosomes are matured as MVBs, and lysosomes degrade these MVBs directly or fuse them with the plasma membrane to release secretion of their contents, including exosomes(Huber et al., 2020; Kalluri and Lebleu, 2024; Wang et al., 2021).Exosome uptake is a

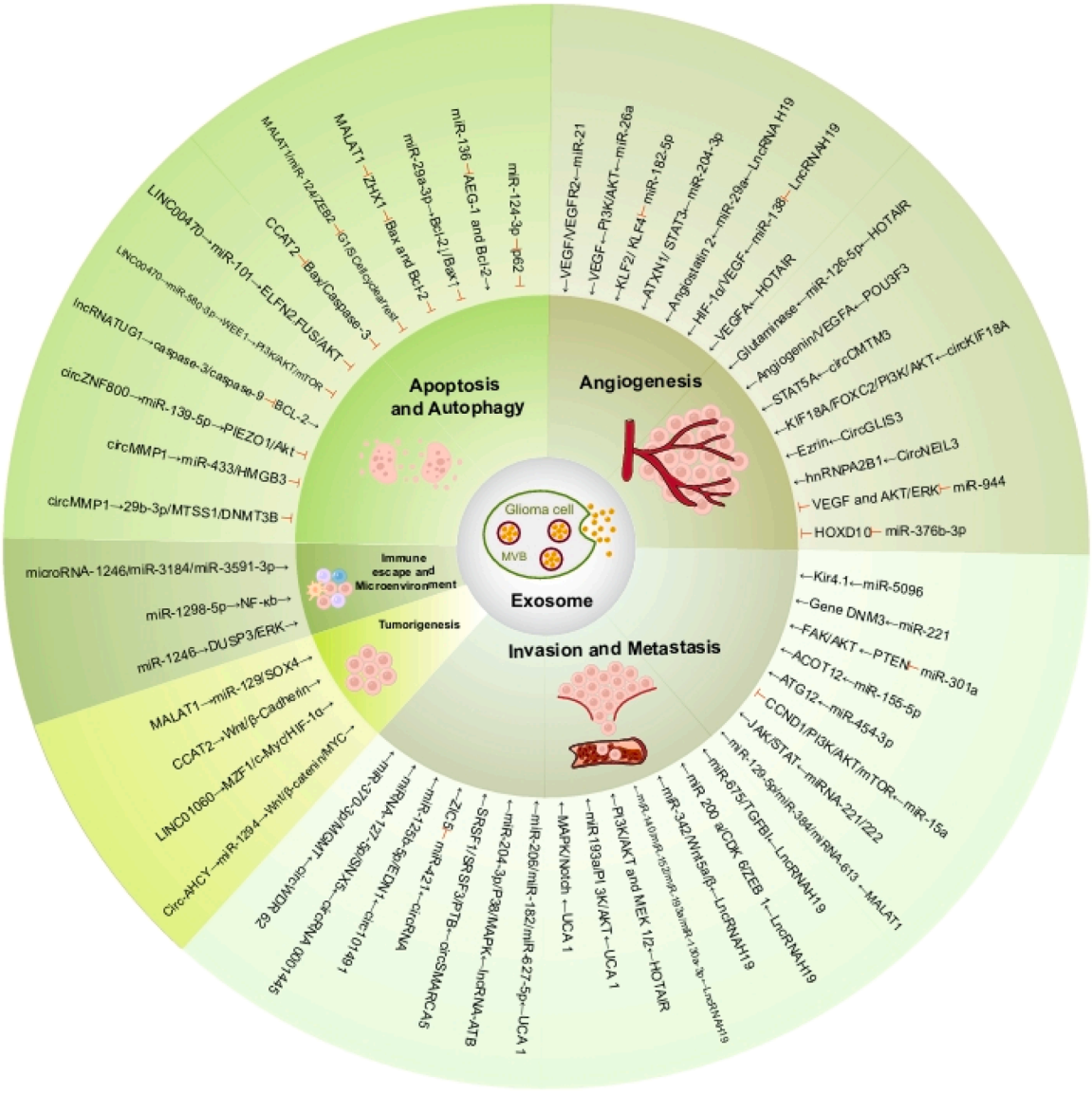

Fig. 2. The specific mechanisms by which exosomal-derived ncRNAs participate in the occurrence and development of gliomas.

multifaceted process that includes three key steps: receptor contact, membrane fusion, and endocytosis/phagocytosis(The assembly process of exosomes is shown in Fig. 1). After the secretion, exosomes are taken up by target cells.If exosomes have a definite characteristic, it is heterogeneity. Due to the limited carrying capacity only a limited amount of proteins can be carried. The composition within individual exosomes depends mainly on the material near the exosome of each nascent exosome, Ayuko Hoshino et al. (Hoshino et al., 2020),clarified the heterogeneity of extracellular nanoparticles and defined them as three different subpopulations, namely small exosomes (Exo-S), large exosomes (Exo-L) and exosomes (Yang et al., 2019), collectively referred to as extracellular vesicles and granules (EVP), and they analyzed the proteomic distribution of 426 human body fluid samples, and a total of 862 specific proteins of interest were identified in the study. Surprisingly, the lowest protein diversity was found in the plasma and serum of cancer patients, while the highest number of proteins was found in EVPs. It was confirmed that certain specific proteins (CD9, TSG101, CD81 and CD63) increased with cancer staging and were highly enriched in exosomes, with CD81 being the most abundant, and CD81 has become the most commonly used exosomal marker protein (Teng and Fussenegger, 2024). Additional drivers of exosome heterogeneity are associated with differential gene expression, while the environment also induces changes in gene exocytosis, such as diet and physical radiation(Neuwelt et al., 2020). In conclusion, tumour-derived exosomes significantly mediate the interplay among tumour cells and the microenvironment, and stimulate tumour growth and progression through specific signalling pathways related to metastasis, treatment resistance and immunosuppression. This has inspired us to detect exosome species and their levels in human body fluids and to establish effective biomarkers to monitor the prediction, progression and prognosis of gliomas.

1.2. *Non-coding RNA in exosomes*

An increasing number of studies have demonstrated that exosomes are rich in non-coding RNAs and that the membrane structure of exosomes protects ncRNAs from degradation by enzymes and other chemicals, thus significantly improving the stability of ncRNAs within exosomes. Functional regulatory molecules mediating cellular processes, including chromatin remodeling, transcription, post-transcriptional modifications and signal transduction, are key regulators of physiological programs in developmental and disease contexts (T et al., 2020; Rezaei et al., 2021). Non-coding RNAs are classified into

Table 1
Summary of exosomal miRNA in glioma.

Function	Biomarker	Target or Axis	References
Angiogenesis	miR−21	miR−21/VEGF/VEGFR2	(Sun et al., 2017)
	miR−26a	PI3K/AKT	(Yue et al., 2016)
	miR−204–3p	ATXN1/ STAT3	(Ren et al., 2024)
	miR−944	VEGFC and AKT/ERK	(Jiang et al., 2021)
	miR−376b−3p	HOXD10	(Jiang et al., 2020 Jun 2)
Proliferation and Invasion	miR−182–5p	KLF2 and KLF4	(Xiong et al., 2020)
	miR−5096	Kir4.1	(Thuringer et al., 2017)
	miR−221	DNM3	(Yang et al., 2017)
	miR−301a	PTEN,FAK and AKT	(Lan et al., 2018)
	miR−148a	CADM1	(Cai et al., 2018)
		ITGA9	(Yang, 2019)
	miR−155–5p	ACOT12	(Bao et al., 2022)
	miR−454–3p	ATG12	(Shao et al., 2018)
	miRNA−221/222	JAK/STAT	(Xu and Liu, 2019)
Regulate TME	miR−25–3p		(Li et al., 2022)
	miR−155–3p		(Xue et al., 2024)
	micro−1246		(Qian et al., 2020)
	miR−3184		(Xu et al., 2022)
	miR−3591–3p		(Li et al., 2022)
	miR−1298–5p	NF-κb	(Jia and Jia, 2022)
	miR−1246	DUSP3/ERK	(Qi et al., 2022)
	miR−29a and miR−92a	Hbp1 and Prkar1a	(Qiu et al., 2024)
	miR−10a and miR−21	Rora and Pten	(Guo et al., 2019)
	miR124	Volume-regulated anion channel	(Ghafouri-Fard et al., 2021)
	miR124	Glutamic acid	(Serpe et al., 2022)
	miR−15a	CCND1/PI3K/AKT/mTOR	(Ren et al., 2023)
Apoptosis and Autophagy	miR−124–3	p62	(Ghasemi and Mondanizadeh, 2024)
	miR−29a−3p	Bcl−2 and Bax	(Riahi Samani and Parker, 2023)
	miR−136	AEG−1 and Bcl−2	(Yang et al., 2024)

structural ncRNAs and regulatory ncRNAs according to their functions, and the main focus of current research is mostly on regulatory ncRNAs. Swati et al., classified regulatory ncRNAs into microRNA (miRNA), long ncRNA (lncRNA), circular RNA (circRNA), PIWI-interacting RNA (piRNA) and small interfering RNA(siRNA). As for non-coding RNA in glioma exosomes,On the one hand,The expression of lncRNAs is highly specific to various tissue types.As tumors progress,the ncRNA released in exosomes also dynamically changes,thereby promoting cancer progression.On the other hand,ncRNAs are bidirectional and specifically associated with cancer, being oncogenic drivers and tumor suppressors in certain cancer types, for example miR-200c inhibits the development of EMT and prevents the initiation of cancer metastasis, but it is overexpressed in advanced cancers and promotes their distant metastasis (Vescarelli et al., 2020). The same phenomenon was observed in gliomas (Beermann et al., 2016). They serve as key players in glioma progression, emitted by cancer cells to orchestrate interactions within the tumor microenvironment. Exosomes drive cell invasion, migration, proliferation, stemness, angiogenesis, immune evasion, and malignant transformation (Banerjee et al., n.d.).Therefore, ncRNAs enriched in exosomes can not only be used as biomarkers for the early diagnosis of glioma, but a deeper understanding of ncRNAs also provides a unique opportunity to design better therapeutic interventions as potential therapeutic targets.

Extracellular vesicle-enriched ncRNAs are closely related to glioma formation. Studies suggest that extracellular vesicle ncRNAs are involved in processes such as glioma tumor formation, angiogenesis, metastasis and invasion, immune escape, autophagy, and apoptosis. They can serve as highly potential biomarkers for glioma diagnosis(The specific mechanism is reflected in Fig. 2). Compared to traditional diagnostic methods for gliomas, imaging tests are not sensitive enough, and tumor tissue biopsies are invasive, cannot be performed repeatedly in large quantities, and more importantly, biopsy samples cannot encompass the entirety of the tumor's characteristics. Exosomes are stably present in various bodily fluids, and compared to traditional diagnostic methods, they offer advantages in terms of sample acquisition, high sensitivity, and low invasiveness(Skouras et al., 2023). The potential of exosomes for early tumor diagnosis has been widely studied and confirmed. Among the various contents of exosomes, ncRNAs have attracted increasing attention. Multiple types of exosome-associated miRNAs, lncRNAs, and circRNAs have been identified as diagnostic markers for gliomas. Furthermore, they can be used to predict tumor differentiation levels, survival rates, and recurrence and metastasis, directly indicating the prognosis.In the future, it is expected that meaningful ncRNAs will be integrated and screened, and exosome ncRNA kits for clinical applications will be developed to guide the diagnosis and prognosis of glioma.

1.3. MiRNA

MiRNAs are endogenous single-stranded ncRNAs consisting of approximately 18–25 nucleotides in length. miRNAs bind to the 3′ untranslated regions of target genes as a means to regulate cell cycle, apoptosis, cell development, differentiation, and metabolism. in 2002, Calin et al. (Calin et al., 2002), observed genomic changes in the miR-15a/16 cluster in leukemia, and this landmark study revealed evidence for the association of aberrant miRNA expression consequences with human cancers.Gradually,miRNAs becomes the most studied type of ncRNAs, which is related to their extensive role and can be involved in more tumor progression processes after crosstalk with lncRNAs and circRNAs (He et al., n.d.).A large number of studies have confirmed that miRNAs are involved in the disease progression of glioma in many aspects, such as angiogenesis, proliferation, invasion, TME transformation, and TMZ resistance, by regulating cell-to-cell communication and gene expression(Liegro, 2024) (Different miRNA targets and their functions are summarized in Table 1).

First, numerous teams explored which exosome-derived miRNAs could be used as reliable biomarkers for diagnosing glioma. In a landmark move, expert Lu's team found that up to 200 miRNAs had significant differences in expression levels between glioma patients and healthy individuals.The differential changes of miRNA are particularly prominent in the comparison with nucleic acids and proteins. Therefore, the great potential of miRNAs for the diagnosis of glioma is highlighted (Lu et al., 2005).Exosomes can be isolated from tumor tissue, cerebrospinal fluid, and numerous samples of blood from glioma patients. MirNA in exosomes was determined using a variety of methods such as flow cytometry, western blotting, PCR detection, high-throughput detection, and microarray analysis. Confirmed markers include miR-210(Tabibkhooei et al., 2020)、miR-29b(Fengying,Zhong,Ting, 2019)、miR-454–3p(Shao et al., 2018)、miR-124(Wang et al., 2019)、miR-205(Yue et al., 2016)、miR-222(Santangelo and Imbrucè, 2018)、miR-21(Shi et al., 2015)、miR-155–5p(Bao et al., 2022)、miR-182–5p (Xiong et al., 2020)、miR-766–5p(Nikoobakht et al., 2021).In addition, miR-491 has a significant decline in high-grade gliomas and can be used to distinguish brain metastases from gliomas. MiR-491 has reference significance for predicting the degree of differentiation and metastasis of glioma(Hao et al., 2024).

Secondly, miRNAs can participate in tumor formation from multiple direction such as angiogenesis, tumor proliferation, invasion and metastasis, apoptosis and autophagy. Malignant tumors often have the characteristics of unlimited replication, self-supply of nutrients, and disorders of cellular energy metabolism. Fast-growing glioma tissues are often accompanied by active angiogenesis, and exosomal miRNAs play a key role in this process(Yang et al., 2022).Exosomes carrying high levels of miR-21 are transferred from glioma cell line U-251 to endothelial

Table 2
Summary of exosomal lncRNA in glioma.

Biomarker	Target or Axis	Function	References
MALAT 1	miR−199 a/ZHX 1	Anti-apoptosis, inhibition of proliferation	(Liao et al., 2019)
	miR−124/ZEB2	Anti-apoptosis, inhibition of proliferation	(Cheng et al., 2021)
	miR−129/SOX4	Maintain stem cell properties	(Xiong et al., 2017)
	Crosstalk with miR−129–5p, miR−384, and miRNA−613	Growth, metastasis, and invasion	(Su et al., 2024; Ma et al., 2020; Yang et al., 2020)
	ZEB 1	promot EMT	(Hashemi et al., 2024)
	miR−140 and NFYA	Increase blood-brain barrier permeability	(Ma et al., 2016)
H19	miR−29a/ vasohibin2	Angiogenesis	(Jia et al., 2016)
	miR−138/HIF−1α/ VEGF		(Li et al., 2024)
	H19/miR−675/ TGFBI axis	Proliferation and invasion	(Yadav et al., 2021; Lu and Zhang, 2024; Chen et al., 2018; Chen et al., 2021; Zhou et al., 2022; Qi and Jianxing, 2018; Xin et al., 2019)
	H19/miR 200 a/ CDK 6/ZEB 1axis		
	H19/miR−342/ Wnt5a/β-Cadherin axis		
	sponge action with miR−140, miR−152, miR−193a, miR−130a−3p		
HOTAIR	VEGFA	Angiogenesis	(Sun et al., 2018)
	miR−126–5p, Glutaminase	Proliferation, invasion,	(Luan et al., 2017)
	PI3K/AKT和MEK 1/ 2	metastasis	(Ke et al., 2015)
	BET		(Pastori et al., 2015)
CCAT2	VEGFA and TGFβ, Bax and caspase−3	Promote angiogenesis, inhibit programmed death	(Lang and Guo-Wen, 2017)
	PI3K/AKT	Promote angiogenesis, inhibit programmed death	(Sun et al., 2020 May)
	Wnt/β-Cadherin signaling pathway	Reduce the malignant phenotype of glioma cells	(Guo et al., 2016)
	sponging with miR−424	Promote angiogenesis	(Ghafouri-Fard and Askari, 2024)
UCA1	mir193a-mediated PI3K/AKT, MAPK, and Notch pathways	Proliferation and migration	(Yadav et al., 2021; He et al., 2018; Huang et al., 2019; Fan et al., 2018; Zhao et al., 2017 Jun)
	UCA 1/miR−206/ CLOCKaxis		
	UCA1/ miR−182axis		
	UCA1-miR−627–5p axis		
POU3F3	Angiogenin,VEGFA	Angiogenesis	(Lang et al., 2017)
ATB	miR−204–3p	Astrocyte phenotype transformation	(Er-Bao et al., 2019)
LINC 01060	MZF1/c-Myc/ HIF−1α Signal axis	Proliferation	(Li et al., 2020; Marangon and Lecca, 2023)
LINC 00470	miR−101,ELFN 2	Inhibit autophagy	(Changhong et al., 2018)
	AKT,FUS		(Changhong et al., 2018)

cells, and the miR-21/VEGF/VEGFR2 axis mediates angiogenesis effects (Sun et al., 2017).The bioactive miR-26a uses exosomes as a medium to achieve transfer from glioma cells to endothelial cells. It further activates the PI3K/AKT axis and increases VEGF levels in endothelial cells, thereby improving glioma angiogenesis(Yue et al., 2016).Glioma exosome miR-204–3p can accelerate angiogenesis. This is due to activation of the ATXN1/STAT3 signaling pathway, which allows vascular endothelial cells to form tubular cells(Ren et al., 2024).Interestingly , miR-944 which secreted from glioma cell exosomes can effectively thwarts glioma proliferation and angiogenesis by repressing VEGFC expression and impeding the AKT/ERK axis.When the glioma grade is higher, the MiR-944 level is lower(Jiang et al., 2021).Similarly, miR-376b-3p targets HOXD10 to produce an angiogenesis inhibition effect, thereby exerting a protective effect against malignant glioma (Jiang et al., 2020 Jun 2).In glioblastoma exosomes, the level of miR-182–5p was notably increased, which promoted the process of tumor angiogenesis and proliferation by inhibiting the activity of Kruppel-like factor 2 (KLF2) and KLF4(Xiong et al., 2020).In glioma cell line U251, miR-5096 is released by exosomes and acts on potassium channel Kir4.1 to promote the invasion of glioblastoma cells (Thuringer et al., 2017).After co-incubation of SHG-44 cells with U87MG-derived exosomes, it was found that miR-221 acted on DNM3 gene to promote glioma invasion and migration(Yang et al., 2017).Exosomal miR-301a negatively regulates PTEN, stimulates FAK and AKT signal transduction, and ultimately enhances the proliferation and invasion capabilities of glioma-derived H4 cells(Lan et al., 2018).There are also a number of exosome-derived miRNAs and their targets that have been clearly confirmed to regulate the proliferation, migration, and invasion of glioma, including miR-148a targeting CADM1 and ITGA9 (Cai et al., 2018; Yang, 2019), miR-155–5p targeting ACOT12 (Bao et al., 2022), miR-454–3p targeting ATG12 (Shao et al., 2018), and miRNA-221/222 targeting JAK/STAT (Xu and Liu, 2019)·The downstream target genes of miR-136 are AEG-1 and Bcl-2, which inhibit the anti-apoptotic effect of these two genes, thereby accelerating the apoptosis process of glioma cells(Yang et al., 2024).MiR-29a-3p in exosomes from glioma also exerts significant anti-apoptotic effects due to the downregulation of the anti-apoptotic factor Bcl-2 and the increased expression of the pro-apoptotic factor Bax(Riahi Samani and Parker, 2023).Highly aggressive gliomas tend to correspond to low-level replication of miR-124 in exosomes. The decrease of miR-124–3p was accompanied by an increase in the level of autophagy regulator p62, which ultimately hindered the autophagy progression of glioma(Ghasemi and Mondanizadeh, 2024).

Moreover, the important role of exosomal miRNAs is also reflected in cell communication, where primary communication occurs between tumor cells, while high-level communication occurs between glioma cells and the surrounding tumor microenvironment(TME).Immune reversal occurs in the tumor microenvironment (TME) of gliocytoma. In the context of tumors, the immune cells that are originally responsible for suppressing tumors gradually transform, thereby assisting tumor escape(Russo et al., 2022; Luo et al., 2023).In the immune-related microenvironment, macrophage polarization and myeloid suppressor cell formation play a crucial part(Toledo et al., 2024; Shokati and Safari, 2023).Exosomes carrying the tumor modulators miR-25–3p, miR-155–3p,microRNA-1246,miR-3184 and miR-3591–3p detach from tumor cells, then polarize macrophages to an M2-like phenotype, ultimately inhibits adaptive immunity(Li et al., 2022; Xue et al., 2024; Qian et al., 2020; Xu et al., 2022; Li et al., 2022). The hypoxic environment of tumors accelerates the transcription and selective packaging of the aforementioned types of miRNA(Jia and Jia, 2022).MiR-1298–5p can be excreted from glioma cells through exosomes, which promotes the immunosuppression and malignant progression of MDSCs mediated by NF-κb(Qi et al., 2022).Exosomal miR-1246 from the body fluids of glioma patients can activate the DUSP3/ERK pathway, which plays a key role in the activation of myeloid-derived suppressor cells(Qiu et al., 2024).Exosomal miR-29a/Hbp1, miR-92a/Prkar1a, miR-10a/Rora, and

Table 2 (*continued*)

Biomarker	Target or Axis	Function	References
	LC3 II,PTEN		(Biyin and Wenwu, 2023)
	miR−580–3p/ WEE1/PI3K/AKT/ mTOR	Autophagy	(Khan and Umar, 2022)
TUG1	Sponginess miR−145, PRC2-TUG1-YY1Compound formation	Cell self-renewal	(Katsushima et al., 2016)
	caspase−3, caspas−9,BCL−2	Apoptosis	(Zhao et al)
	miR−299,VEGFA	Angiogenesis	(Simon et al., 2020)
lncRNA ROR1-AS1	miR−4686	Proliferation, migration, and invasion	(Fan and Zhou, 2024; Carelli et al., 2024; Sisakht and Malekan, 2023)
lncRNA ZEB1-AS1	miR−577	Proliferation, migration, and invasion	
lncRNA GAS5-AS1	miR−106b−5p	Proliferation, migration, and invasion	

miR-21/Pten can all participate in the communication between glioma cells and myeloid-derived suppressor cells (MDSCs), at the same time, activate the immunosuppressive function of MDSCs(Guo et al., 2019; Guo and Qiu, 2018).The complexity of this microenvironment lies in the fact that tumor cells are able to positively regulate TME, and the dynamic changes in TME also have an impact on tumor growth.MiR-15a is expressed at low levels in M2 macrophage-derived exosomes. Further exploration of its mechanism of action showed that miR-15a quickly activated the PI3K/AKT/mTOR signaling axis after binding to CCND1, which in turn hindered the migration and infiltration of glioma cells(Ren et al., 2023).Astrocytes and microglia are likewise important components of the microenvironment. Under the action of tumor cells, astrocyte NHAs were converted to TAA, and microglia underwent M2 polarization(Li and Zhu, 2024; Guo and Qiu, 2024).As is well known, MiR124 is an inhibitory gene that is enriched in brain tissue and is also involved in central nervous system diseases such as hypoxic-ischemic encephalopathy and ischemic stroke(Ghafouri-Fard et al., 2021).When miR124, a tumor suppressor concentrated in astrocyte-derived exosomes, acts on glioma GL261 cells in reverse effect, it can weaken the volume-regulated anion channel activity and hinder tumor migration and invasion(Serpe et al., 2022).Microglia-derived exosomes potently inhibit glioma development via modulation of tumor cell metabolism and augmentation of glutamate elimination,miR-124 is a key medium in this process(Serpe et al., 2021).

1.4. Lnc RNA

LncRNAs are RNA transcripts that are at least 200 nucleotides in length and lack significant protein encoding abilities or have limited capabilities(St. Laurent et al., 2015; Sideris et al., 2022). lncRNAs have structures similar to mRNAs (Sun et al., 2018; Bunch, 2017), such as: a methylation cap at the 5′ end,a polyadenylated tail at the 3′ end, both exogenous and intronic, and despite the low level of expression of lncRNAs, the However, it is more tissue-specific and dynamic than mRNA, i.e., it has different expression patterns and different biological roles depending on the stage of tissue development, pathophysiological state (Deveson et al., 2017). The folded secondary and tertiary structures enhance the stability of LncRNA (Long non-coding, 2016; Lv et al., 2020). This could be considered the most promising marker for the diagnosis of GBM and the presumption of disease progression.

In the last decade, great interest has been shown from the regulatory gene expression to the protein translation role of LncRNAs. LncRNAs can be further categorised into five groups based on their relevance to the genomic sites of adjacent proteincoding genes (Xu et al., 2022; Peng et al., 2018): sense lncRNAs (Herman et al., 2022), antisense lncRNAs (Ma et al., 2013), bidirectional lncRNAs (Stackhouse et al., 2020), intronic lncRNAs(Maurano et al., 2012) and intergenic (lincRNAs). They are able to interact with other nucleic acids (e.g. DNA and RNA) and proteins (Statello et al., 2024). LncRNAs mediate gene expression in cis-structures and bind directly to DNA for epigenetic modifications and recruitment of chromatin modifiers, leading to activation or repression of transcription (Stamidis and Żylicz, n.d.; Guh et al., 2020; Zhang et al., 2020) and DNA repair by binding proteins (Hu et al., 2020), while in the cytoplasm, lncRNAs also show functional diversity.Regulates the processing of RNA, thereby influencing the stabilisation of mRNA or directly regulating the behaviours of proteins.(Lin et al., 2016; Ouyang et al., 2022) lncRNAs can also be categorised as exosomes and contribute to an intercellular interface in the tumour microenvironment. The lncRNAs in exosomes can be involved in the development and progress of gliomas, and these may become attractive therapeutic targets. Targeting tumour-specific lncRNA abnormalities for treatment due to regulation of the lncRNA net meshes the counterproliferative effects of malignancies and invokes treatment outcomes.LncRNAs are involved in the regulation of glioma development and progression. The following highlights several lncRNAs that are currently the most studied(Summarize in Table 2):

LncRNA MALAT 1 was first identified as a tumor biomarker in non-small cell lung cancer. It has been gradually confirmed to be involved in the evolution of cancer at multiple sites(Eraky et al., 2022; Stackhouse et al., 2020; Xu et al., 2024).Exosomes encapsulate MALAT1 and transfer from GBM cells to microglia, which is beneficial to promote tumor invasion and immune evasion(Fattahi et al., 2024).Both in glioma tissue specimens and in experimental cell lines(U87 and U251),the researchers all detected Meaningful elevations of MALAT1 levels.In addition, elevated MALAT1 levels have been shown to be associated with the degree of glioma malignancy, and can also shorten the survival of patients(Jianping et al., 2016).Compared to primary gliomas , MALAT1 exhibits higher expression levels in recurrent tumor(Su et al., 2021).This reflects the close correlation between MALAT1 and the prognosis of glioma.A large number of experiments have proved that MALAT1, as an important miRNA sponge, can affect the interaction between miRNA and target genes, so it plays a biological role in the evolution of glioma.Liao's team found that tumor volume was shrinked after knockdown of MALAT 1 in an GBM mouse model.One of the specific mechanisms is that the MALAT 1/miR-199 a/ZHX 1 axis drives GBM cell proliferation.In addition, ZHX 1, as a downstream target of MALAT 1, can regulate Bax and Bcl-2, thereby exerting anti-apoptotic effects(Liao et al., 2019).Cheng's team also explored the mechanism of tumor shrinkage after MALAT 1 knockout. They found that the MALAT1/miR-124/ZEB2 pathway induces cell cycle arrest in the G1/S phase, which promotes apoptosis and inhibits proliferation of glioma cells(Cheng et al., 2021). Expert xiong used microarray analysis to screen MALAT1, one of the lncRNAs highly expressed in glioma stem cells, and further confirmed that the MALAT1/miR-129/SOX4 axis can maintain the viability of glioma stem cells and exert the role of pro-tumor genes(Xiong et al., 2017)·It has been confirmed by the research of multiple teams,crosstalk between MALAT1 and miR-129–5p, miR-384 and miRNA-613 promotes glioma growth, metastasis and invasion (Su et al., 2024; Ma et al., 2020; Yang et al., 2020).In glioma cell lines, MALAT 1 was clearly found to regulate the expression of ZEB 1 protein, which not only induces the loss of E-cadherin and promotes the Epithelial-mesenchymal transition (EMT) process, but also accompanies metastasis and invasion of tumor cells(Hashemi et al., 2024).Ma found that knockdown of MALAT 1 was able to upregulate miR-140 and target NFYA, ultimately leading to damage to the blood-brain barrier and increased permeability(Ma et al., 2016).

LncRNA H19 is the first member of the LncRNA family to be discovered , and also is known to play a regulatory role as an oncogenic factor in a variety of malignancies(Zhang et al., 2024). The statistical

analysis of lncRNA-related diseases using neighborhood analysis and collaborative filtering found that lncRNA H19 was significantly associated with the occurrence and development of glioma, guiding scientists to verify this important biological indicator (Suzuki et al., 2023). LncRNA H19 is encapsulated in exosomes released by glioblastoma multiforme and subsequently transported to endothelial cells (Fattahi et al., 2024).In an in-depth study of the biological behavior of glioma-related endothelial cells, Jia et al. found that LncRNA H19 can directly bind to miR-29a, and the complex regulates vasohibin2 levels, then mediates endothelial cell proliferation, migration, and tubular formation, ultimately promoting glioma angiogenesis (Jia et al., 2016). The mechanism by which H19 promotes angiogenesis in gliomas can also be achieved by lowering miR-138 and further upregulating HIF-1α/VEGF (Li et al., 2024).With regard to glioma proliferation and invasion, multiple signaling pathways play a important role , including the H19/miR-675/TGFBI axis, the H19/miR 200 a/CDK 6/ZEB 1 axis, and the H19/miR-342/Wnt5a/β-catenin axis. In addition, the sponge effect of H19 and miR-140、miR-152、miR-193a、miR-130 a-3 p also promotes the proliferation and invasion of glioma (Yadav et al., 2021; Lu and Zhang, 2024; Chen et al., 2018; Chen et al., 2021; Zhou et al., 2022; Qi and Jianxing, 2018; Xin et al., 2019).The cancer stem cell markers CD133, NANOG, Oct4 and Sox2 in a variety of GBM cell lines were found to be down-regulated after H19 deficiency, which confirmed that H19 played a positive role in maintaining the stem cell malignancy characteristics of GBM(Li, 2016).

The long non-coding RNA HOTAIR is abundantly expressed in exosomes secreted by Glioma tissues and cell lines. After HOTAIR is delivered to endothelial cells, it induces angiogenesis by upregulating the expression of VEGFA, a significant pro-angiogenic factor (Sun et al., 2018).In another study, HOTAIR was shown to promote angiogenesis in gliomas by targeting glutaminase through sponging endogenous miR-126–5p (Luan et al., 2017).In the glioma patient population, high HOTAIR expression tends to correspond to low survival (Xavier-Magalhães et al., 2018).Studies on the gene product expression, methylation status and copy number of glioma HOTAIR found that HOTAIR was positively correlated with glioma grade (Ahmad et al., 2024 Feb 16).However, after knocking out the HOTAIR gene, the proliferation, invasion, metastasis and other biological behaviors of glioma were inhibited.The rationale is the involvement of the PI3K/AKT and MEK 1/2 signaling pathways.This experiment highlights the importance and therapeutic potential of HOTAIR in glioma[148].In addition, HOTAIR is involved in glioma proliferation as a target gene downstream of the Bromodomain and extraterminal (BET) control protein. While BET inhibitors down-regulated HOTAIR levels, the glioma cell cycle was in a state of arrest (Pastori et al., 2015).

LncCCAT2 was first identified as a pro-tumor gene in colon cancer, and it was subsequently demonstrated to be associated with multiple types of human tumors (Pirlog et al., 2021).Studies have shown that CCAT2 accumulates in large numbers in glioma cells.There was a positive relationship between the expression level of CCAT2 and the stage advancement of tumor (Xin et al., 2016).Exosomes serve as carriers to deliver abundant CCAT2 from glioma cells to endothelial cells. Overexpressed CCAT2 can activate VEGFA and TGFβ, which in turn promote endothelial cell proliferation and vascularization.CCAT2 can also promote angiogenesis through the sponge miR-424.Furthermore , CCAT2 reduces programmed cell death in glioma by inhibiting the expression of Bax and caspase-3 152,153]. After the application of sh-CCAT 2 to knock down CCAT 2, the PI3K/AKT signaling pathway was inhibited, which in turn hindered the proliferation of glioma cells(Sun et al., 2020 May). Silencing the CCAT 2 gene can also reduce the malignant cell phenotype of glioma by inhibiting the activity of the Wnt/β-catenin signaling pathway (Guo et al., 2016).

LncRNA UCA1 is a world-recognized oncogene , the analysis of exosome components isolated from the cerebrospinal fluid of glioma patients revealed a high level of expression of UCA1, which is associated with tumor invasion and poor prognosis (Fattahi et al., 2024).In glioblastoma U-118 MG and A172, knockdown of UCA 1 attenuates tumor invasion and metastasis, which is attributed to miR 193a-mediated involvement of PI 3K/AKT, MAPK and Notch pathways (Yadav et al., 2021).Evidence suggests that both the the UCA 1/miR-206/-CLOCK axis, UCA1/miR-182 axis,UCA1-miR-627–5p axis are involved in glioma formation and invasion.Therefore, UCA1 can be used as a reliable biomarker to assess the prognosis of glioma (He et al., 2018; Huang et al., 2019; Fan et al., 2018; Zhao et al., 2017 Jun).

LINC-POU3F3, a highly conserved long non-coding RNA (lncRNA), was initially discovered in esophageal malignancies. Subsequent research on glioma revealed that POU3F3-abundant exosomes disseminated from tumor cells to endothelial cells. Both in vivo and in vitro experiments conclusively demonstrated that upon reaching endothelial cells, POU3F3 activates angiopoietin, VEGFA, and other essential factors, thereby fostering angiogenesis in glioma (Lang et al., 2017). Another study not only revealed the overexpression of POU3F3 in high-grade glioma tissues, but also further pointed out that POU3F3 plays an important role in promoting the survival and proliferation of tumor cells (Guo et al., 2015).

LncRNA-ATB was first recognized in hepatocellular carcinoma, and it is involved in hepatocellular carcinoma invasion as a competitive endogenous RNA for miR-200a. Bian's team confirmed that the same mechanism worked in glioma (Chun-Chun and Ma, 2016).Further studying the glioma microenvironment, they found that glioma cell-derived exosomes can transport lncRNA-ATB to astrocytes, and the arriving lncRNA-ATB can cause phenotypic transformation of astrocytes by regulating miR-204–3p, thus achieving glioma invasion (Er-Bao et al., 2019).Another study showed that lncRNA ATB could also boost glioma invasion by activating the P38/MAPK pathway (Tang et al., 2019).

In Li's invitro experiments, exosomes were isolated from glioma stem cells (under hypoxic conditions, under aerobic conditions) and glioblastoma. After further high-throughput sequencing of the lncRNA species in the exosome, it was clearly found that LINC01060 was one of the significantly upregulated molecules.For glioma patients, LINC01060 levels were high in exosomes from serum, cerebrospinal fluid, and tumor tissue samples, especially in high-grade glioma tissues. When the LINC01060 value was measured again after the patient underwent surgery, this index decreased sharply. Clearly, LINC01060 can be used as a promising biomarker for diagnosing glioma.Further experiments proved that LINC01060 promoted the proliferation of glioma cells through the activation of MZF1/c-Myc/HIF-1α signaling axis (Li et al., 2020; Marangon and Lecca, 2023).

Accumulating evidence suggests that exosome-derived LINC00470 are involved in glioma progression as autophagy inhibitors, and high expression LINC00470 often corresponds to low survival rates (Ma et al., 2021).LINC 00470 can upregulate ELFN 2 levels by crosstalk with miR-101, thereby limiting glioma autophagy (Changhong et al., 2018). LINC00470 acts directly on FUS as an AKT activator to inhibit glioma autophagy (Changhong et al., 2018). LC3 II and PTEN are used as downstream targets of LINC 00470 to induce its attenuating effect on autophagy(Biyin and Wenwu, 2023).LINC00470 binding to miR-580–3p regulates the expression of WEE1, which inhibits autophagy by activating the PI3K/AKT/mTOR pathway 171].

In addition to the above lncRNAs,it is worth noting that lncRNA TUG1 enrichment can be found in exosomes released in a variety of tumor environments such as retinoblastoma nasopharyngeal carcinoma, and breast cancer (Wang et al., 2019). A large number of studies have confirmed that TUG1 is involved in the occurrence and development of glioma.The role of lncRNA TUG1 in glioma is still controversial.Most studies have shown that TUG1 is involved in the development of glioma as a oncogenic lncRNA.But at the same time, it has been confirmed that TUG1 can also act as a tumor suppressor lncRNA.This is due to the fact that different biological processes leading to specific functions.This is due to different biological processes leading to specific functions.In the cytoplasm, TUG1 coordinates self-renewal by spongylating miR-145 and

Table 3
Summary of exosomal circRNA in glioma.

Biomarker	Target or Axis	Function	References
circCMTM3	STAT5A ,	Neovascularization	(Wang et al., 2024)
circKIF18A	KIF18A,FOXC2, PI3K/AKT		(Jiang et al., 2022)
circGLIS3	Ezrin Phosphorylation		(Li et al., 2021)
circSMARCA5	SRSF1/SRSF3/PTB Signal pathway	Proliferation, migration, invasion	(Davide et al., 2018)
circHIPK3	miR−421 sponge, inhibiting ZIC5		(Wei and Shi, 2022)
circ101491	miR−125b−5p sponging and EDN1		(Zhang et al., 2023)
circ0001445	miRNA−127–5p/ SNX5 axis		(Han et al., 2024)
circWDR62	circWDR 62/ miR−370–3p/ MGMT Signal pathway		(Geng et al., 2024)
circNEIL3	GF2BP3		(EWSR1-induced, 2022)
circBTG2	miR−25–3p/PTEN Signal pathway		(Shi et al., 2022)
circ-HIPK3	miR−124–3p sponge		(Wei and Shi, 2022)
circ-AHCY	Wnt/β-catenin /CTNNB1		(Li et al., 2023)
circZNF800	miR−139–5p/ PIEZO1/Akt		(Zhang and Wu, 2024)
circMMP1	miR−433/ HMGB3,29b−3p/ MTSS1/DNMT3B	Apoptosis	(Wu et al., 2023; Zhang and Guan, 2022)

recruiting polycomb. In the nucleus, TUG1 is involved in locus-specific methylation of H3K27 after the formation of the PRC2-TUG1-YY1 complex, inhibiting tumor self-renewal (Katsushima et al., 2016).The transwell invasion test and CCK-8 test showed that TUG1 affected the proliferation and invasion of glioma, resulting in cell cycle arrest in G 0/G1 phase (Zhao et al).Li's team found that lncRNA TUG1 promotes the activation of caspase-3 and caspase-9 in endogenous pathways, inhibits the BCL-2-regulated anti-apoptotic pathway, and is involved in the apoptosis of glioma cells (Simon et al., 2020).In glioblastoma tissues and cell lines, upregulated TUG 1 regulates VEGFA through sponging on miR-299. VEGFA is widely recognized to initiate endothelial cell proliferation, migration, and angiogenesis, turning on the switch for glioblastoma-induced angiogenesis (Cai et al., 2017).

The sponge interaction of exosomal lncRNA and miRNA plays an important role in the development of glioma. A number of studies have confirmed that the sponge interaction of exosomal lncRNA ROR1-AS1 and miR-4686, lncRNA ZEB1-AS1 and miR-577, and lncRNA GAS5-AS1 and miR-106b-5p is involved in the proliferation, migration and invasion of glioma cells (Fan and Zhou, 2024; Carelli et al., 2024; Sisakht and Malekan, 2023).

1.5. CircRNA

Circular RNA (circRNA) has recently emerged as a novel type of RNA, gaining widespread attention and research in recent years. CircRNAs are single-stranded RNAs characterized by their stable covalent closed-loop structures (Xu et al., 2020).This characteristic is due to the lack of a free 5′ or 3′ end, allowing circular RNAs to resist degradation by ribonucleases. Beilleri et al. also found that circRNAs are conserved and specific to tissues and developmental stages (Beilerli et al).Furthermore, based on their varying levels in different body fluids or exosomes, they provide new insights into the diagnosis and prognosis of cancer types. An increasing body of research indicates that circRNAs are abundantly present in neurons and are very stable in cells, exosomes, and body fluids, participating in the progression of neurological diseases. Another characteristic of circRNAs is their functional diversity, which can be generated in any region of the genome. Like lncRNAs, circRNAs serve as miRNA sponges in various human tumors, interacting with proteins, regulating gene splicing or transcription, translating proteins or peptides, and epigenetic regulation (Yuan et al., 2018; Hansen et al., 2013; Wang et al., 2023).Therefore, circular RNAs have become the subject of research for clinical diagnostic biomarkers, participants in disease progression, and prognostic assessment(Different types of cirRNA and their mechanisms of action are summarized in Table 3).

Expert Xia used microarray methods to screen three significantly elevated circRNAs in plasma exosomes of glioma patients: circ-0055202, circ-0074920, and circ-0043722. After inhibiting the expression of these three circRNAs in the U87 cell line, it was found that the proliferative activity of glioma was also impaired, and it is speculated that the above circRNAs could be used as feasible biomarkers for the detection of GBM (Lou and Yan, 2024).Stella and colleagues screened from the ExoRBase database and compared the differences in circ-RNA within exosomes between healthy individuals and glioma patients, discovering that the tumor suppressor gene circSMARCA5 and the oncogene circHIPK3 are statistically significant and can serve as diagnostic biomarkers for GBM (Stella et al., 2021).CircSMARCA5 can modulate the SRSF1/SRSF3/PTB signaling pathway to exert an inhibitory effect on the migration of glioma cells (Davide et al., 2018).Exosome-derived circ-HIPK3 has been identified as a key factor in glioma growth. This circRNA acts as a sponge for miR-421, which inhibits the availability of ZIC5, thereby driving tumor cells towards a more aggressive tumor phenotype (Han et al., 2020).In addition, the sponge effect of circRNA-HIPK3 with miR-124–3p can accelerate the proliferation,invasion,and epithelial-mesenchymal transition of gliomas (Wei and Shi, 2022).Circ-AHCY is a novel glioma exosomal RNA discovered by Li's team, which can isolate miR-1294 to activate the Wnt/β-catenin signaling pathway, positively regulate the transcription factor MYC of CTNNB1, and ultimately accelerate tumor cell proliferation (Li et al., 2023).Glioma cell-derived exosomes circCMTM3 can promote tumor neovascularization.The target is STAT5A, whose degradation is hindered, and its phosphorylation is enhanced (Wang et al., 2024).After polarization, M2 microglia from glioblastoma patients can release exosomal circKIF18A, which promotes angiogenesis in GBM by transporting KIF18A, binding to FOXC2, and activating the PI3K/AKT signaling pathway (Jiang et al., 2022).High levels of circ101491 can be detected in both the exosomes of tumor tissues and plasma samples from patients with gliomas. Through in vivo and in vitro experiments, Zhang demonstrated that upregulated circ101491 is not only associated with the TNM stage of the tumor,but also enhances the vitality and migration of glioma cells, accompanied by the sponging of miR-125b-5p and the upregulation of EDN1 (Zhang et al., 2023).Studies have shown that exosomal circRNA 0001445 can act as a sponge to adsorb miRNA-127–5p, thereby relieving the inhibitory effect of miRNA-127–5p on SNX5. When SNX5 is suppressed, the proliferation and invasion of glioma are enhanced. Therefore, exosomal circRNA 0001445 promotes the malignant progression of glioma by regulating the miRNA-127–5p/SNX5 axis (Han et al., 2024).Geng's team discovered that the expression of circWDR 62 is upregulated in exosomes derived from TMZ-resistant glioma cells, and elevated levels of circWDR 62 are correlated with a unpromising prognosis in glioma. The circWDR 62/miR-370–3p/MGMT signal pathwaypromotes tumor cell proliferation, migration, and infiltration (Geng et al., 2024).In Zhang's in vitro research assay, high levels of circZNF800 were detected in glioma stem cell-like cell exosomes. The sponge interaction of circZNF800 with miR-139–5p activates the PIEZO1/Akt axis, reduces GBM cell apoptosis, and increases GBM cell proliferation and metastasis. Further studies have found that silencing circZNF800 is able to rescue the survival rate of GBM transplant models (Zhang and Wu, 2024).The Warburg effect is a unique metabolic phenomenon in tumor cells that can promote the release of exosomal circ-0072083 from glioma cells. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) and protein blotting have confirmed that circ-0072083 is upregulated in

Table 4
Summary of exosomal siRNA applied to glioma.

Source	Target	Function	References
Mesenchymal stem cells	F3-T3	Inhibit tumor cell vitality	(Kerrigan et al., 2020)
Mesenchymal stem cells	MALAT1	Inhibit growth and invasion	(Fattahi et al., 2024)
Liver cells	EGFR/ TNC	Therapeutic effect	(Fu et al., 2021)

glioma tissues and cells. Knockdown of circ-0072083 can reduce glioma proliferation, invasion and increase apoptosis (Ding et al., 2020).In glioma exosomes, high levels of circ MMP1 are important anti-apoptotic mediators. The activation of the circMMP1/miR-433/HMGB3 signal axis is involved. The circ MMP1/29b-3p/MTSS1/DNMT3B signaling axis is also a well-known anti-apoptotic pathway (Wu et al., 2023; Zhang and Guan, 2022).CircGLIS3 is overexpressed in highly malignant glioma, and secreted into the microenvironment by tumor cells via exosomes.CircGLIS3 enhances angiogenic capacity and invasiveness by regulating the phosphorylation of Ezrin at T567, thereby promoting the progression of gliomas (Li et al., 2021).CircNEIL3 is packaged into exosomes of glioma cells through hnRNPA2B1 and is transferred to infiltrating macrophages. CircNEIL3 induces immune escape and expands glioma invasion by stabilizing IGF2BP3. Therefore, the measurement of circNEIL3 in exosomes is a highly potential biomarker for the diagnosis of glioma (EWSR1-induced, 2022).Conversely, in the glioma microenvironment, macrophage-derived exosomal circBTG2 acts as a tumor suppressor gene to hinder the progression of tumors. Specifically, exosomal circBTG2 inhibits the proliferation and invasion of glioma by targeting the miR-25–3p/PTEN signaling pathway (Shi et al., 2022).

2. PiRNA and SiRNA

Although the research on miRNA, lncRNA, and circRNA in glioma-derived exosomes has been relatively thorough, there is less research on piRNA. One reason is that piRNA sequences are extremely complex, with each biological species having a large number of unique piRNA sequences. Another reason is that piRNA detection methods face difficulties, not as mature and standardized as those for miRNA (Tamtaji and Behnam, 2020). Although a few studies have shown that piRNA is associated with the onset of gliomas, it is not yet clear whether exosomes play a role in this (Xiaobai et al., 2018; Leng et al., 2018; Shen et al., 2017).

SiRNA is often studied in the field of disease treatment because it can specifically degrade mRNA molecules that are complementary to it, thereby preventing the expression of specific genes (Ubanako et al., 2024).In actual research work in gliomas, scholars have found multiple reasons that lead to siRNA delivery obstacles, including short blood half-life, difficulty penetrating the blood-brain barrier, high intracellular degradation, and low uptake efficiency of naked siRNA (Teng et al., 2022). In vitro, mesenchymal stem cell-derived exosomes can successfully deliver siRNA to glioma cells, then targeting F3-T3 and suppress the vitality of tumor cells (Kerrigan et al., 2020).In similarly designed experiments with mesenchymal stem cell (MSC) exosomes, exosomes engineered to carry siRNAs against MALAT1 have demonstrated the ability to inhibit the growth and invasion of glioblastoma (GBM) cells (Fattahi et al., 2024).Fu's team reprogrammed mouse livers using plasmid DNA, inducing the synthesis of siRNA within the liver and its self-assembly into secretory exosomes. The assembled siRNA targeted brain tissue, silenced EGFR/TNC, and ultimately exerted a therapeutic effect on glioma (Fu et al., 2021)(The Summary of exosomal siRNA applied to Glioma shows in Table 4).Overall, exosomal siRNA therapy for glioma has not been extensively researched and applied. One reason is the low yield of exosomes isolated from cells. More inevitably, endogenous miRNAs have multiple target genes, while exogenous miRNAs may exhibit "off-target effects",so the side effects of siRNA therapy limit its application.

2.1. Exosomal ncRNAs and treatment resistance

The currently accepted treatment plan for glioma is still surgery supplemented by radiotherapy and chemotherapy, with the DNA alkylating agent temozolomide (TMZ) being the preferred chemotherapeutic drug (Zhang et al., 2024).Multidrug resistance (MDR) remains an irreplaceable cause of treatment failure in high-grade glioblastoma, with specific mechanisms including upregulation of MDR transporters, apoptosis, immune stress, DNA repair defects, enhanced repair of cancer stem cell damage, abnormal expression of oncogenes and tumor suppressor genes, and epithelial-mesenchymal transition. Exosomal ncRNA has a dual effect between sensitivity and resistance in glioma treatment (Luo et al., 2023).

Exosomes miRNA-93 and −193 downregulate Cyclin D1 expression and reduce cell cycle arrest and induce TMZ resistance (Munoz et al., 2019).After miR-9-carrying mesenchymal stem cells exosome reached glioma cells, miR-9 acted on the efflux transporter P-glycoprotein, and then the caspase activity and TMZ sensitivity increased (Munoz et al., 2013).Upon arrival of miR-1238-loaded exosomes in TMZ-sensitive cells, the CAV1/EGFR axis is activated, and TMZ sensitivity is lost (Jianxing and Yin, 2019).Highly metastatic tumours transport miR-1246 via EVs to induce drug resistance in endothelial cells, a phenomenon not only in gliomas but also in breast cancer and melanoma (Wang et al., 2021).MiR-151a enhances the susceptibility of glioblastoma (GBM) cells to TMZ by repressing the activity of XRCC4, a protein involved in DNA repair. By elevating the levels of exosomal miR-151a, the resistance of GBM cells to TMZ can be effectively reversed (Jiang et al., 2022).Exosomal miRNAs not only self-regulate TMZ resistance, but can also participate in the resistance effect of sponge circRNA and lncRNA. HOTAIR is a significantly increased lncRNA in exosomes from TMZ-resistant glioma cells, and the HOTAIR/miR-519a-3p/RRM1 axis and HOTAIR/miR-125/HK2 axis both mediate TMZ resistance (Zhang et al., 2023; Han et al., 2024).H19 knockdown significantly increases TMZ sensitivity (Geng et al., 2024; Ding et al., 2020).After TMZ treatment for glioma, a screening of the whole genome expression profile revealed that MALAT1 is one of the most significantly overexpressed genes. Further research found that MALAT1 promotes TMZ resistance through its crosstalk with miRNA-101 and miRNA-203. MALAT1 reduces the sensitivity of glioblastoma cells to TMZ by upregulating EMT-associated proteins.Moreover, downregulating MALAT1 can increase the sensitivity of glioma to radiotherapy (Li et al., 2021; EWSR1-induced, 2022; Shi et al., 2022; Tamtaji and Behnam, 2020; Xiaobai et al., 2018; Leng et al., 2018).Acid hydrolase acts as a mediator to assist the exosome circ-0042003 in shuttling between TMZ-resistant and sensitive glioma cells, constituting a mechanism for glioma resistance to TMZ chemotherapy (Shen et al., 2017).A variety of exosomal ncRNAs play a role in the sensitivity and resistance of temozolomide, and regulating the expression of exosomal ncRNAs to enhance drug sensitivity may become a new therapeutic approach.

Radiation resistance also leads to a poor prognosis. After irradiation therapy intervention in the co-culture system of glioblastoma cells and microglia, the expression of circ-0012381 derived from glioblastoma cells is upregulated. Subsequently,this circRNA enters microglia,act on the miR-340–5p/ARG1 axis and induce M2 polarization. The phenotypically altered microglia then feedback on glioblastoma cells via the CCL2/CCR2 axis, inhibiting their phagocytosis and promoting their growth. In comparison to the sole application of radiotherapy, the suppression of exosomes has been found to markedly curtail the proliferation of glioblastoma cells that have been exposed to radiation within a zebrafish model (Ubanako et al., 2024).The sponge effect between circATP8B4 and miR-766 may be involved in radiation resistance in glioma (Zhang et al., 2024).Similarly,exosomal circMETRN has been

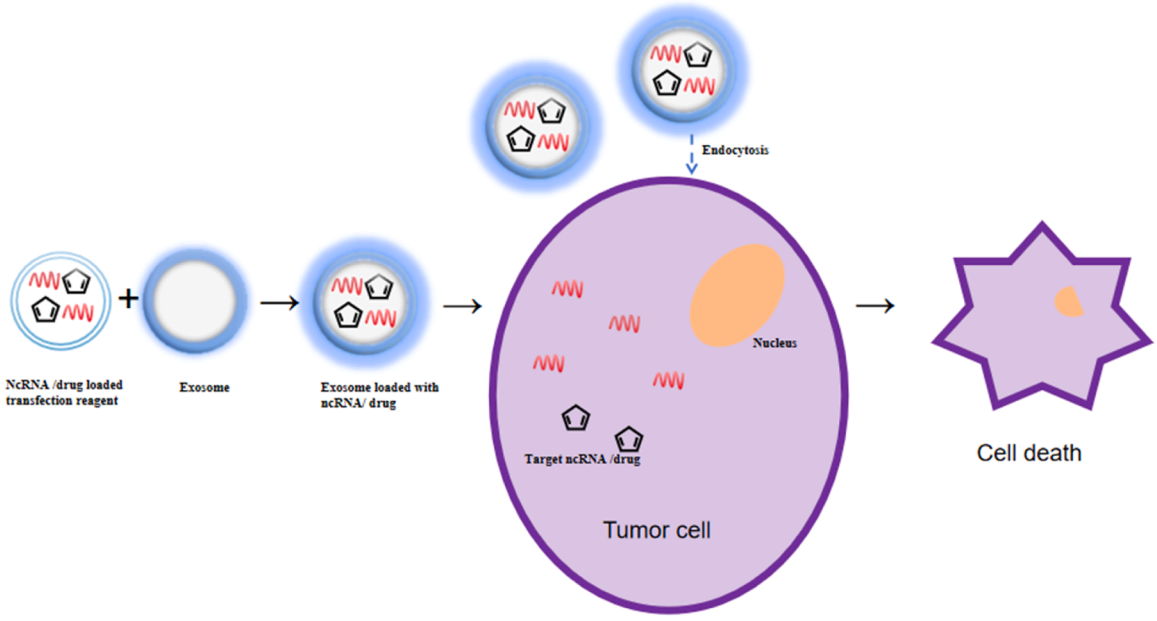

Fig. 3. The process of using exosomes to deliver drugs or ncRNA for targeted treatment.

identified to participate in the radiation resistance of glioblastoma. Further research has elucidated its specific mechanism to be the regulatory effect of circMETRN on the miR-4709–3p/GRB14/PDGFRα axis (Teng et al., 2022). These exosomal circRNAs may be an effective entry point for clinical improvement of radiation resistance.

2.2. Exosomal ncRNAs and personalized treatment

The inherent properties of exosomes make them highly promising in therapeutic applications. Genetically modifying exosomes, which involves transferring their contents to specific targets, can endow exosomes with high selectivity. The presence of membrane proteins allows exosome components to evade degradation by proteases and RNA hydrolases, thereby enhancing the stability of exosomes. Good tissue compatibility corresponds to low toxicity of exosomes. Lastly, their nanoscale size facilitates the penetration of the blood-brain barrier, making exosomes as carriers more promising for the treatment of gliomas,provide targeted treatment strategies (Rana and Devi, 2025).

Exploring the role of exosomes as carriers in the treatment of gliomas , the research mainly focuses on two directions: one is to load drugs onto exosomes, including temozolomide O6-benzylguanine dual receptor exosomes (Cunha Silva and Branco, 2024), doxorubicin, and paclitaxel (Yang et al., 2015).The other one is a genetic engineering approach that guides exosomes carrying specific gene sequences to target cells(The specific process is shown in Fig. 3).Exosomes derived from glioma stem cells(gsc) containing miRNAs play a key role in the treatment of gliomas. Exosomes derived from gsc containing miR-944 can inhibit the expression of VEGFC, interfere with the information transmission of the AKT/ERK signaling axis, and block the angiogenesis process of gliomas, serving as a targeted therapeutic effect (Jiang et al., 2021).MiR-29a-3p acts as a tumor suppressor with reduced levels in glioma tissues, inhibiting glioma angiogenesis and migration by targeting ROBO1. Based on this mechanism, Zhang's team utilized human mesenchymal stem cells (MSCs) to prepare exosomes overexpressing miR-29a-3p, ultimately confirming that these exosomes can exert a definite therapeutic effect on glioma (Yang et al., 2024).Expert Lang also uses mesenchymal stem cells as a factory for preparing exosomes carrying specific genes, producing exosomes enriched with miR-124a, which can inhibit tumor cell vitality and proliferation effects after acting on gliomas (Hu et al., 2024).miR-512–5p has also been extensively studied for its tumor suppressive effects. Exosomes derived from BMSCs carrying miR-512–5p act on the glioma U87 cell line, targeting and downregulating JAG1 to induce cell cycle arrest (Peng et al., 2021).Exosomes derived from mesenchymal stem cells transfected with microRNA-584 also play a therapeutic role, as these microRNA-584-loaded exosomes can promote the apoptosis of glioma cells and inhibit their invasion (Song et al., 2024).Looking forward to the future, engineered exosomes equipped with non-coding RNA will become a promising entry point for precision targeted therapy for glioma, and targeted therapy will be used to accurately intervene in glioma. It is also possible to make exosomes a tool to carry chemotherapy drugs through more complete means, so that chemotherapy drugs can play a greater role through the blood-brain barrier.

3. Conclusion and future outlook

In summary, we have elucidated the characteristics of various exosomal ncRNAs, summarized the targets and signaling pathways regulating glioma apoptosis, angiogenesis, proliferation, migration, and invasion mediated by exosomal non-coding RNAs, and introduced the mechanisms of exosomal non-coding RNAs in glioma therapy and drug resistance. Our understanding of the types and functions of exosomal ncRNAs continues to expand, and our knowledge of their roles in the development of glioma is becoming more profound. Exosomal ncRNAs can serve as diagnostic biomarkers or prognostic evaluation indicators. After clarifying their targets and mechanisms of action, targeted interventions for specific ncRNAs can be developed. Based on current research, exosomal ncRNAs are a promising target in the field of glioma therapy, but achieving clinical application remains a challenging task.

CRediT authorship contribution statement

Jin Peng: Writing – original draft. **Bai Xue:** Supervision.

Declaration of Competing Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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