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Review

Non-coding RNAs: Regulators of glioma cell epithelial-mesenchymal transformation

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ABSTRACT

GBM (glioblastoma multiforme) is the most malignant form of glioma and is the most commonly occurring primary malignant brain tumour. GBM is difficult to completely excise, resulting in an extremely high recurrence rate. The occurrence of an aggressive glioma phenotype depends on EMT (epithelial-mesenchymal transformation), in which epithelial cells transform into mesenchymal cells by losing their cell-cell adhesion and polarity. NcRNAs (non-coding RNAs) play a significant role in the cellular progression from a normal phenotype to a cancerous phenotype. Recently, many studies have shown that there are two essential regulatory ncRNAs, miRNAs (microRNAs) and lncRNAs, which are closely related to EMT. In this review, we conducted a comprehensive investigation of the dysregulated lncRNAs and miRNAs in gliomas with particular attention to the function and regulatory mechanisms of several important lncRNAs and miRNAs, and we discussed their roles as glioma diagnostic and prognostic biomarkers and their potential clinical applications as therapeutic targets.

1. Introduction

Among the most sporadic primary malignant tumours of the brain, gliomas rank at the top and are classified as grade I to IV based on the extent of the malignancy. GBM (glioblastoma multiforme) is one of the most aggressive human tumours [1,2]. The 2016 “World Health Organization Classification of Tumors of the Central Nervous System” defines gliomas as astrocytomas, oligodendrogliomas, ependymomas, or mixed tumours based on their histological subtypes [2,3]. The median survival of patients with GBM was only 10–12 months, despite the use of an invasive treatment strategy with chemotherapy and radiotherapy after the maximum surgical excision was performed [4,5].

The aggressive glioma phenotype depends on EMT (epithelial-mesenchymal transformation), a mechanism by which the cell polarity and cell-cell adhesion of epithelial cells are lost, and cells become mesenchymal cells [6]. The degradation of the underlying basement membrane and the abilities to migrate into and invade the extracellular matrix of epithelial cells are the hallmark consequences of EMT [6,7]. The hypoxic microenvironment was actively involved in the progression of EMT in glioma cells [8,9]. Hypoxic glioblastoma cells release a number of growth factors, including TGF-β (transforming growth factor-β), HGF (hepatocyte growth factor), and EGF (epidermal growth factor) [10]. EMT is induced by a variety of transcription factors that are regulated by growth factors, including Twist, Snail1 (or SNAI1)/Slug (or Snail2/SNAI2), ZEB, WNT/β-catenin, NOTCH and CD44 [10,11]. Epithelial cells undergoing EMT can alter the levels of their differentiation markers, including N-cadherin, fibronectin and vimentin, and the degradation of E-cadherin (CDH1) [7,12]. These disordered proteins result in the acquisition of enhanced migratory and invasive properties. EMT causes the early infiltration of glioma cells into adjacent tissues; therefore, gliomas are difficult to completely excise, resulting in an extremely high recurrence rate. Moreover, EMT is also involved in the formation of tumour chemoresistance [13]. Therefore, the in-depth exploration of the mechanism and the effective inhibition of EMT in GBM will play a vital role in therapeutic strategies for gliomas in the future.

Non-coding RNAs (ncRNAs) were originally thought to be transcriptional noise; however, more evidence points towards ncRNAs having an important role in regulating the cellular progression from a normal phenotype to a cancerous phenotype. According to their size, there are two major regulatory ncRNAs: 1) microRNA (miRNA), a short non-coding RNA with a length of 20–23 nucleotides (nt) [14], and 2) long non-coding RNA (lncRNA) with a length greater than 200 nt [15,16]. It is known that miRNAs control the gene expression of cellular processes, including tumourigenesis, by mediating the translation of mRNA [14]. The relation between miRNA dysregulation and cancer

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was first identified in 2002. Since then, miRNAs that play important roles in the development of cancer are being continuously discovered, and more than 2500 kinds of miRNAs have been identified so far. LncRNAs play a key role in cancer and are involved in chromatin remodelling, transcription, and post-transcriptional regulation. In addition, lncRNAs can also control translation by pairing with translation factors or ribosomal bases or by regulating splicing by binding to splicing factors [17–19]. The functions of lncRNAs are poorly understood compared to those of microRNAs, which have been extensively studied. However, in recent years, considerable progress has been made in the understanding of the function of lncRNAs in tumours.

In recent years, lncRNA and miRNA have been found to be associated with the EMT of glioma cells [20,21]. Therefore, lncRNA and miRNA can be used as biomarkers for the prognosis, diagnosis, and targeted treatment of gliomas [22,23]. In this review, we have tried to recapitulate the recent evidence indicating that lncRNAs and miRNAs regulate EMT in glioma cells, with lncRNAs alone, miRNAs alone, and lncRNAs interacting with miRNAs.

2. Epigenetic regulation of ncRNA expression

Tumorigenesis is the result of epigenetic regulation and genetic abnormalities, and ncRNAs have been shown to play an important role in epigenetics [24], which leads to corresponding phenotypic variation through two main mechanisms :1) DNA methylation and 2) histone modification [25]. Abnormal DNA methylation of some tumor-related gene promoters via DNA methyltransferase (DNMT) leads to tumor formation and development [26,27]. And among various types of histone modifications, the main acetylation is coordinated by HATs and HDACs to maintain histone function and regulate DNA transcription [25].

Numerous studies have shown that miRNAs and lncRNAs can regulate methylation-associated key proteins such as DNMT, methyl CpG binding protein 2 (MeCP2), methyl-CpG binding domain proteins 2 and 4 (MBD2 and MBD4), or chromatin modification complexes (e. g. PRC2) to control DNA methylation [28–30]. In addition, abnormal DNA methylation will result in dysregulation of miRNA. In tumor tissues, both hypermethylation of miRNAs with tumor suppressor function and hypomethylation of onco-miRs promoters promote tumor progression [28]. Similar to DNA methylation, there is a complex regulatory relationship between histone modifications and miRNAs and lncRNAs. Studies have found that in a variety of cancer cells, such as breast cancer [31], prostate cancer [32], dysregulation of HDACs and dysregulation of multiple miRNAs interact to ultimately promote tumor formation and progression. LncRNAs can also bind to chromosomal modifying complexes, inducing different types of histone modifications, such as the combination of overexpressed LncRNA HOTAIR and PRC2 that leads to gene silencing and promotes the metastasis of various cancers [33]. In addition, recent studies have indicated that lncRNAs are involved in the regulation of tumor metabolism, affecting the metabolites of cofactor metabolites necessary for epigenetic modification of complexes, thus indirectly regulating epigenetics [34].

3. LncRNAs involved in the regulation of glioma EMT and their mechanisms

3.1. ZFAS1

ZFAS1 is a newly discovered lncRNA that promotes the growth and metastasis of gastric cancer [35]. According to Xia et al., the upregulation of ZFAS1 and its interaction with miR-150-5p occurs to affect the malignancy of ovarian cancer cells [36]. However, ZFAS1 may act as a suppressor of tumours with downregulated expression in breast cancer [37], while ZFAS1 could act as an oncogene in glioma cells by regulating EMT and the Notch signalling pathway [38].

The upregulation of ZFAS1 was observed in glioma cell lines, and this upregulation was notably correlated with the malignancy of advanced tumours and a lower OS (overall survival) rate. Therefore, ZFAS1 can be used as a therapeutic target [38]. Moreover, in vitro experiments have shown that ZFAS1 impeded glioma cell invasion and migration. In glioma cells with ZFAS1 knocked down, the expression of E-cadherin was upregulated while the expression of the Snail and Notch signal-related proteins Hes-1, NICD and N-cadherin were deregulated, indicating the promotion of the EMT and Notch signalling pathways by ZFAS1 in gliomas [38]. Notch is an induction signal of EMT [11]. After activation by binding to the ligands, Notch produces an active fragment (NIC), which translocates to the nucleus to replace the repressor and to recruit coactivators. Many genes involved in differentiation and survival, such as Hes, cyclin D1 and c-myc, are then activated [39]. Therefore, ZFAS1 promotes the EMT of glioma cells by activating the Notch signalling pathway.

Furthermore, Notch signalling regulates the direction of various tissues and cells in the development process. For example, Notch is the main regulator of glioma stem cells [40].

3.2. PTCSC3

PTCSC3, the papillary thyroid carcinoma susceptibility candidate, is a lncRNA gene present on 14q. 13. 3, which is found mainly in papillary thyroid carcinoma [41]. It has been reported that lncRNA PTCSC3 is a tumour suppressor for thyroid cancer [42]. In glioma cell lines, lncRNA PTCSC3 was significantly downregulated. The overexpression of PTCSC3 in the xenograft model was not associated with the distal site, demonstrating its inhibitory effects on metastasis and invasion [43]. Experiments have shown that E-cadherin was upregulated, while fibrin and the mesenchymal markers Snail and ZEB1 were repressed in cells overexpressing lncRNA PTCSC3 [43]. It has been suggested that lncRNA PTCSC3 can inhibit the EMT of glioma cells.

Mechanistically, PTCSC3 inhibits the EMT of glioma cells by suppressing the Wnt/β-catenin signalling pathway, which can induce EMT [11,44]; LRP (low-density lipoprotein receptor-related protein) acts as a receptor for this pathway to transmit Wnt signals across the membrane [45]. The APC/Axin/GSK/β-catenin protein complex is known as the "deconstruction complex" in Wnt signalling [46] and remains steady under physiological conditions. When LRP6 is inactivated, Axin dissociates, and the nuclear translocation of β-catenin leads to the transcriptional activation of the cyclin D1 and c-myc genes [47]. Previous experiments have demonstrated that the overexpression of lncRNA PTCSC3 inhibited the activity of LRP6 [43], indicating that PTCSC3 inhibited the EMT of glioma cells by suppressing the Wnt/β-catenin signalling pathway. Moreover, the Wnt/β-catenin pathway maintains the stability of stem cells and is involved in therapeutic resistance [48]. Therefore, PTCSC3 is promising as an effective therapeutic target for gliomas in the future.

4. Co-regulating lncRNAs and miRNAs of glioma EMT and their mechanisms

4.1. H19/miR-130a-3p

H19 is a 2. 7 kb gene that is expressed by the maternal line and imprinted by the paternal line; this gene is located near the telomeres of the 11p15. 5 chromosome [60]. Recent studies have elucidated the role of H19 in lung cancer, bladder cancer, breast cancer, among other cancers [61–63]. However, the mechanism in glioma remains to be further explored. Some experiments have shown that H19 is overexpressed in glioma cell lines and tissues and is related to malignancy and survival rate [64]. Thus, H19 can be considered a therapeutic target. Xenograft experiments demonstrated that H19 overexpression can promote cell migration and invasion [64]; the decreased expression of vimentin and N-cadherin in H19-silenced glioma cells shows that H19 expression can induce EMT in glioma cells [64,65]. Furthermore,

Table 1
LncRNAs associated with EMT.

LncRNA	Effect on EMT	Known molecular mechanisms	Reference (s)
AB073614	Positive	Activates Wnt/β-catenin by downregulating SOX7	[49,50]
CCAT2	Positive	Activates the Wnt/β-catenin signalling pathway	[51,52]
LINC00152	Positive	The action of a protein-bound stem-loop	[53]
LINC00599	Negative	–	[54]
LINC00961	Negative	–	[55]
MALAT1	Positive	Upregulates ZEB1	[56]
PTCSC3	Negative	Suppresses the Wnt/β- catenin signalling pathway	[43]
SPRY4-IT1	Positive	Upregulates SKA2	[57,58]
ZEB1-AS1	Positive	Upregulates ZEB1	[59]
ZFAS1	Positive	Activates the Notch signalling pathway	[38]

H19 can also induce EMT through the Wnt/β-catenin pathway [65].

Mechanistically, Sox4 and H19 are the genes targeted by miR-130a-3p. The sponging of miR-130a-3p by H19 eliminates the inhibition of Sox4 by miR-130a-3p [64]. Sox4 is a member of the SoxC transcription factor family and plays a carcinogenic role in a variety of tumours [66–68]. However, the regulation of EMT by Sox4 can be achieved through the Wnt/β-catenin signalling pathway [13]. The relationship between miR-130a-3p and the EMT of glioma cells has not been fully explored. However, some studies have shown that miR-130a-3p could suppress EMT in hepatoma cells, gastric carcinoma cells or nasopharyngeal carcinoma cells by inhibiting Smad4, TBL1XR1 or BACH2, respectively [69–71]. Above all, miR-130a-3p probably indirectly inhibits the Wnt/β-catenin signalling pathway by inhibiting Sox2 and then inhibits the development of EMT in glioma cells (Table 1).

4.2. FOXD2 AS1/miR-185/miR-185-5p

A newly identified lncRNA, lncRNA FOXD2 adjacent opposite strand RNA 1 (FOXD2 AS1), is present on chromosome 1p33 with a 2527 nucleotide long transcript [72]. There are earlier reports that FOXD2 AS1 is upregulated in colorectal cancer and gastric cancer [73,74]. In glioma tissues and cell lines, the upregulated expression of FOXD2 AS1 promotes proliferation, migration and invasion while inhibiting apoptosis. Moreover, FOXD2 AS1 is associated with the malignant grade and poor OS of glioma patients [72,75].

Experiments have shown that FOXD2 AS1 can reduce vimentin and N-cadherin expression and can enhance E-cadherin expression [72,75], indicating that FOXD2 AS1 induces the EMT of glioma cells. The induction of EMT by FOXD2 AS1 mainly depends on the two following axes: FOXD2 AS1/miR-185-5p/cyclin D2 (CCND2) and FOXD2 AS1/miR-185/AKT1 [72,75]. In the FOXD2 AS1/miR-185-5p/CCND2 axis, both FOXD2 AS1 and CCND2 are the target genes of miR-185-5p. MiR-185-5p and CCND2 were repressed and upregulated in glioma cells, respectively, and both were involved in the EMT of glioma cells. The expression of CCND2 was positively correlated with the expression of FOXD2 AS1 in glioma tissues and was negatively correlated with the expression of miR-185-5p [72]. Therefore, FOXD2 AS1 probably induces the process of EMT by relieving the miR-185-5p-mediated inhibition of CCND2 by sponging miR-185-5p. The mode of action of the FOXD2 AS1/miR-185/AKT1 axis is similar to that of the FOXD2 AS1/miR-185-5p/CCND2 axis; that is, FOXD2 AS1 may reduce the miR-185-induced inhibition of AKT1 by sponging miR-185, thus inducing the progression of EMT [75].

4.3. UCA1/miR-204-5p/miR-1/miR-203a

Wang et al. first identified lncRNA UCA1 in bladder carcinoma. UCA1 is located on the positive strand of human chromosome 19p13. 12 with a length of 1. 4 KB [76]. UCA1 plays a carcinogenic role in various malignant tumours, such as bladder cancer, gastric cancer, and colorectal cancer [77–79]. Furthermore, UCA1 is significantly upregulated in glioma cells. In vitro experiments have confirmed that cellular invasion and migration are facilitated by the overexpression of UCA1 [80,81].

UCA1 is an important inducer of EMT. Experiments have demonstrated that the overexpression of UCA1 remarkably upregulates COL5 A1 and fibronectin (EMT-related proteins) in glioma cells [82], indicating the EMT-inducible factor function of UCA1. Many miRNAs have binding sites on UCA1, among which miR-204-5p, miR-1 and miR-203a are closely related to EMT [82,83]; the ZEB protein is a transcription factor of EMT that binds to the E-cadherin promoter region and inhibits its expression, leading to increased motility and the loss of cell-to-cell contact [11] ZEB1 is targeted directly by miR-204-5p and is negatively regulated [82]. Therefore, UCA1 may activate the expression of ZEB1 by acting as a miR-204-5p competitor that regulates the EMT of glioma cells.

TGF-β is involved in the miR-1 and miR-203a interaction with UCA1 [83]. TGF-β is a growth factor that induces transcription factors to regulate EMT in a hypoxic environment [10,11]. UCA1 expression was significantly increased in glioma cells treated with TGF-β [83]. Slug affects downstream TGF-β signal transduction and regulates the EMT of glioma cells [11,84]. LI et al. proved that UCA1 can promote Slug expression by modulating miRNA activity through co-transfection experiments with miR-1 and miR-203a Dicer and UCA1 siRNA [83]. In summary, UCA1 can regulate the EMT progression of glioma cells via the UCA1/miR-204-5p/ZEB1 axis and the TGF-β/UCA1/miR-1/miR-203a/Slug axis.

In glioma cells, most lncRNAs regulate downstream targets by acting as the competent endogenous RNA (ceRNA) of miRNAs(Table 2).

5. MiRNAs involved in the regulation of glioma EMT and their mechanisms

Many recent studies have indicated that miRNAs may also participate in EMT induction in various cancers without the involvement of lncRNAs. MiRNAs have different degrees of expression in different cancers, so miRNAs can be used as diagnostic and prognostic indicators for numerous cancers, including gliomas. MiRNAs control epithelial/mesenchymal plasticity, which enhances some characteristics of gliomas, such as invasion, metastasis, proliferation, and drug resistance, making malignant gliomas extremely easy to relapse.

MiR-130b is upregulated in gliomas and regulates tumour development and EMT. Metadherin (MTDH) is an important oncogene that plays an important role in most cancers [90]. Experiments have shown that MTDH can act as a co-activator of NF-κB to upregulate miR-130b. The target of miR-130b is PTEN, a well-known tumour suppressor that mediates cross-talk with its ceRNAs, PPP2CA and SMAD7, and inhibits EMT-like processes [91]. Peroxisome proliferator-activated receptor gamma (PPARγ) is also targeted directly by miR-130b and participates in the regulation of EMT [92].

The miR-200 family consists of five miRNA sequences that regulate EMT in glioma cells primarily by targeting ZEBs. Experimental analysis

Table 2
LncRNAs act as the ceRNA of miRNAs that are associated with EMT.

LncRNA	Effect on EMT	MiRNA	Effect on EMT	Endogenous targets	Reference (s)
CCAT1	Positive	MiR-181b	Negative	FGFR3 PDGFRα	[85]
Dancer	Positive	MiR-33a-5p	Negative	AXL	[86,87]
FOXD2-AS1	Positive	MiR-185	Negative	AKT1	[75]
FOXD2-AS1	Positive	MiR-185-5p	Negative	CCND2	[72]
H19	Positive	MiR-130a-3p	Negative	Sox4	[64]
HSP90AA1-IT1	Positive	MiR-885-5p	Negative	CDK2	[88]
SNHG6	Positive	MiR-101-3p	Negative	–	[89]
UCA1	Positive	MiR-204-5p	Negative	ZEB1	[82]
	Positive	MiR-1, MiR-203a	Negative	Slug	[83]

Table 3
LncRNAs associated with EMT.

MiRNA	Effect on EMT	Upstream regulator (s)	Downstream regulator (s)	Reference (s)
MiR-205	Negative	TGF-β	ZEB1	[96]
MiR-590-3p	Negative	–	ZEB1, ZEB2	[97]
MiR-663	Negative	–	TGF-β	[98]
MiR-181	Negative	–	TGF-β	[99]
MiR-338	Negative	–	CTBP2	[101]
MiR-16	Negative	–	p-FAK, p-Akt, NF-κB, Slug	[102]
MiR-194	Negative	–	Bmi1	[103]
MiR-211	Negative	H3K27	HMGA2	[104]
MiR-361-5p	Negative	–	Twist1	[105]
MiR-378	Negative	–	IRG1	[106]
MiR-424	Negative	–	KIF23	[107]
MiR-26b	Negative	–	Wee1	[108]
MiR-96	Negative	–	AEG-1	[109]
MiR-101-3p	Negative	–	TRIM44	[110]
MiR-139-5p	Negative	–	Notch1	[111]
MiR-154	Negative	–	Wnt5a	[112]
MiR-181a	Negative	–	Kaiso (ZBTB33)	[113]
MiR-181b	Negative	–	KPNA4, MMP-9	[114]
MiR-203	Negative	–	SNAI2	[115]
MiR-218-5p	Negative	–	LHFPL3	[116]
MiR-34a	Negative	–	Rictor	[117]
MiR-130b	Positive	MTDH	PTEN, PPARγ	[90,91,92]
MiR-200b	Positive	–	ZEB2, ERK5	[93,95]
MiR-200c	Positive	–	ZEB1	[94]
MiR-10b	Positive	–	TGF-β	[100]
MiR-10a	Positive	–	EphA8	[118]
MiR-151-5p, miR-16	Positive	–	ARHGDIA	[119]

of human GBM samples revealed that miR-200b and miR-200c were downregulated in gliomas and that miR-200b and miR-200c regulated EMT by directly targeting ZEB2 and ZEB1, respectively [93,94]. In addition, miR-200b-3p also regulates EMT via directly targeting extracellular-regulated protein kinase 5 (ERK5) [95]. MiR-200c is significantly downregulated in highly amplified EGFR cells, suggesting that EFGR may inhibit the expression of miR-200c [94],

MiR-205 is another miRNA that targets ZEB, which is downregulated in GBM cell lines. ZEB1 is a direct target of miR-205. The overexpression of miR-205 can regulate the Akt/mTOR signalling pathway by downregulating ZEB1, thereby inhibiting the invasion and movement of GBM cells and preventing EMT in GBM cells [96].

MiR-590-3p also directly targets ZEBs. The expression of miR-590-3p was repressed in gliomas, and ZEB1 and ZEB2 were downregulated in A172 and U87MG cell lines that overexpressed miR-590-3p. These results indicate that miR-590-3p is involved in the invasion and metastasis of glioma cells [97].

The genes in the TGF-β pathway are also targets of the miRNAs that are involved in the regulation of EMT. TGF-β represses the growth of a variety of tumours as a tumour suppressor. TGF-β can activate Smad4 in the cytoplasm and translocate to the nucleus as a regulator of site-specific DNA transcription to induce inhibition (occluding, E-calmodulin) or activation (vimentin, Snail, Twist, ZEB and fibronectin), which activates EMT [11]. TGF-β can be targeted by miR-663, which is repressed in glioma cell lines. The overexpression of miR-663 and miR-181 can reduce the downregulation of TGF-β, indicating the successful inhibition of mesenchymal characteristics. In contrast, miR-10b can also target TGF-β, which is upregulated in glioma cells [98,99]. MiR-10b enhances invasion, metastasis, and EMT formation by upregulating TGF-β1 [100].

MiR-338 also regulates EMT and is downregulated in glioma tissues. It represses GBM cell line movement and invasion by negatively regulating eCTBP2 expression. In U87 and T98 G cells transfected with miR-388, Snail, vimentin and fibronectin were downregulated, while E-cadherin was upregulated; this demonstrates that miR-338 inhibits EMT. In addition, the downregulation of CTBP2 can rescue proliferation and invasive changes induced by miR-338-5p inhibitors [101].

6. Conclusion

In this review, we have discussed the lncRNAs and miRNAs involved in the control of epithelial and mesenchymal phenotypes in GBM. LncRNA studies are still in their infancy compared to miRNA studies. Recently, many lncRNAs have been found to be associated with gliomas, but there is little information on the lncRNAs mechanisms of action. Few lncRNAs associated with EMT have been confirmed. In addition to EMT, the relationship between lncRNA and glioma heterogeneity and the roles of lncRNA in the formation of the tumour microenvironment remain to be further studied. At present, advanced treatment methods for malignant glioma are still limited, and lncRNAs may be the most promising targeted therapeutic tools in the future. However, due to the poor stability of lncRNA therapy, current lncRNA-based therapeutic strategies are limited in humans. Therefore, lncRNA needs to be further studied to develop a new strategy for the treatment of glioma.

Bioinformatics prediction and experimental verification analyses have indicated that several miRNAs and their target genes are involved in cancer metastasis (Table 3); however, there are still many defects in the complete mechanism of action of miRNAs. The upstream regulatory factors of many miRNAs are not clear. MiRNAs typically have multiple targets, and bioinformatics analysis of the integration of these potential target mRNAs, proteins, etc. is highly desirable. Improving our understanding of the mechanism of action of miRNAs in glioma cell EMT processes will help to develop personalized prevention and treatment strategies.

Declaration of Competing Interest

None.

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