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REVIEW

Mechanisms of miRNA expression in regulating glioma invasion

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Glioblastoma (GBM) is the most aggressive, deadliest, and most common brain malignancy in adults. Despite the advances made in surgical techniques, radiotherapy and chemotherapy, the median survival for GBM patients has remained at a mere 14 months. Although anti-angiogenic treatment exerts anti-edematic effect in GBM, unfortunately, tumors progress with acquired increased invasiveness. Therefore, it is an important task to gain a deeper understanding of the intrinsic and post-treatment invasive phenotypes of GBM in hopes that the gained knowledge would lead to novel GBM treatments that are more effective and less toxic. This review will give an overview of some of the microRNAs that have been shown to positively and negatively regulate GBM invasion.

Keywords: Glioblastoma; MicroRNAs; Regulation; Invasion

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Gliomas are primary brain cancers that arise from non-neural cells called glial cells [1]. In the central nervous system (CNS), there are three types of glial cells: astrocytes, oligodendrocytes, and microglial cells. Oligodendrocytes are responsible for myelination while microglial cells are derived from hematopoietic stem cells and phargocytize microbes in the CNS. Astrocytes, the most abundant type of glial cells in the CNS, are star-shaped cells which establish metabolic homeostasis and can shift to a reactive phenotype in response to pathogens or injury in the CNS. This shift is normally a highly regulated process and its dysregulation has been shown to promote malignancy [2, 3].

Gliomas can be categorized based on the type of glial cells they are most histologically similar to, the location of the tumor, and the aggressiveness of the cancer cells. Tumors most similar to astrocytes are specifically called astrocytomas and can be further classified into grades I-IV based on the criteria set by World Health Organization, with a higher grade corresponding to more aggressive tumors. Grades I and II astrocytomas correspond to low-grade tumors that are mostly non-malignant. Grades III and IV astrocytomas are high-grade, malignant tumors. Grade III astrocytomas are also known as anaplastic astrocytomas (Aas) whlie grade IV astrocytomas, commonly referred to as glioblastoma (GBM), are the most aggressive of all gliomas[4, 5].

MicroRNAs (miRNAs) are a class of short (~ 22 nucleotides) non-coding RNA molecules that can regulate gene expression by antisense complementarity to specific mRNA. The importance of miRNAs in tumor development

and progression has become increasingly evident [6]. Recent literatures have shown that certain miRNAs are able to regulate the target genes including oncogenes and tumor suppressor genes in GBM[7]. It is documented that about 253 miRNAs are up-regulated, about 95 are down-regulated and 17 show disputed status in GBM when compared to normal brain tissues [7]. Importantly, about 85% of these miRNAs are not yet functionally characterized [8]. The overexpressed miRNAs include few like miR-10b[9], miR-130b [10], miR-30a-5p [11] and miR-494 [12] that influence processes such as proliferation, in vivo tumor growth, invasiveness and angiogenesis. The miRNAs which can suppress tumor growth are down-regulated in GBM include miR-let-7b/I[13], miR-15b/miR-152 [14], miR-146b-5p [15], miR-410 [16], miR-590-3p [17], miR-661 [18] and miR-34a [19].

Since the high degree of infiltration is one of the hallmarks of GBM, this review will summarize the complex, multi-step process of GBM invasion, molecular pathways that have been reported to facilitate GBM invasion, microRNAs that have been associated with the process, and current therapies with the propensity to inhibit GBM infiltration.

Recently, some studies reported that miRNAs play essential roles in tumor invasion and migration [20, 21]. Among these miRNAs, miR-10b was first reported to induce breast cancer cell invasion and metastasis, which was also found to be associated with tumor invasive potential in hepatic cancer [22], pancreatic cancer [23], glioma [24], esophageal cancer [25] and neurofibromatosis [26]. Moreover, miR-10b inhibited the translation of mRNA encoding HOXD10 (homeobox D10), which further regulated RHOC, a pro-metastasis gene belonging to the Ras homolog gene family. Therefore, the TWIST1-miR-10b-HOXD10-RHOC pathway was crucial for breast cancer cell invasion and metastasis. Tumor invasion and metastasis is a complex and multi-step process: thus, miR-10b may play roles in different steps via different targets. Sun *et al*. [9] showed that miR-10b was over-expressed in glioma samples and directly associated with the glioma's pathological grade and malignancy. It also found that miR-10b induced glioma cell invasion by modulating tumor invasion factors MMP-14 and uPAR expression via the direct target HOXD10. The miR-10b/HOXD10/MMP-14/uPAR signaling pathway might contribute to the invasion of glioma. Accordingly, glioma cells lost their invasive ability when treated with specific antisense oligonucleotides (miR-10b inhibitors), suggesting that miR-10b could be used as a new bio-target to cure glioma.

MicroRNA-130b (miR-130b) has been recognized as an oncogenic miRNA and is implicated in the initiation and development of human cancers. MiR-130b was overexpressed in human colorectal cancer [27], bladder cancer [28], malignant melanoma [29], gastric cancer [30], hepatocellular carcinoma [31] and metastatic renal carcinoma [32]. Zhao *et al*. reported that miR-130b inhibited cell proliferation and invasion by targeting signal transducer and activator of transcription 3 (STAT3) in pancreatic cancer [33]. In endometrial cancer, p53 mutants mediated-miR-130b repression resulted in zinc-finger E-box binding homeobox 1 (ZEB1)-dependent epithelial-mesenchymal transition (EMT) [34]. Malzkorn *et al*. reported that miR-130b was expressed at a significant higher level in primary grade IV gliomas as compared with that in grade II gliomas [35]. Sheng *et al*. reported that miR-103b promoted invasion and migration of glioma cells. Notably, miR-130b regulated peroxisome proliferator-activated receptor gamma (PPAPγ) abundance and epithelial-mesenchymal transition (EMT) in glioma cells. PPAPγ was identified as a functional target of miR-130b in glioma. MiR-130b is an independent prognostic biomarker for indicating survival of glioma patients and promotes glioma cell migration and invasion by targeting PPARγ[10].

MiR-30a-5p was found to be dysregulated in diverse cancers and involved in the regulation of tumor progression [36]. In glioma, miR-30a-5p is overexpressed as compared with normal brain tissue, and its expression level is positively correlated with tumor grade of malignancy [37]. Moreover, inhibition of miR-30a-5p suppresses glioma cell growth [38]. Neural cell adhesion molecule (NCAM/CD56) is a cell-surface molecule in the nervous system and participates in a number of biological processes including cell migration, neurite outgrowth, and synaptic plasticity [39]. In glioma, NCAM expression is decreased and introduction of NCAM into glioma cells inhibits cell growth and invasion[40]. Wang *et al*. showed that miR-30a-5p was activated by Wnt/β-catenin pathway through direct binding of β-catenin/TCF4 to two sites in the promoter region of miR-30a-5p. Moreover, Wnt/β-catenin pathway represses NCAM expression in glioma cells, which depends on miR-30a-5p. Finally, they found that miR-30a-5p promotes glioma cell growth invasion by repressing NCAM, which demonstrated a novel Wnt/β-catenin-miR-30a-5p-NCAM regulatory axis which played important roles in controlling glioma cell invasion and tumorigenesis [11].

MiR-494 was observed to enhance invasion of glioma cell line U-251 cells by activating MMP-2. The miR-494-induced invasive potential was accompanied by, and dependent on, epidermal growth factor receptor (EGFR) upregulation and the activation of its downstream signaling constituents, Akt and ERK. Among the putative target proteins tested, p190B RhoGAP (p190B) was downregulated by miR-494, and its reduced expression was responsible for the increase in EGFR expression. Ectopic expression of p190B suppressed the

miR-494-induced EGFR upregulation and invasion promotion, thereby suggesting that p190B depletion is critical for the invasion-promoting action of miR-494 [12].

The miRNAs of the let-7 family have been demonstrated to reduce GBM cell growth and migration via Ras inhibition [41]. IKBKE (inhibitor of nuclear factor kappa-B kinase subunit epsilon), which is also called IKK$_\varepsilon$ and IKKi, is a member of the IκB kinase (IKK) family [42]. Tian *et al*. reported that IKBKE was overexpressed in human gliomas and that the downregulation of IKBKE markedly inhibits the proliferative and invasive abilities of glioma cells, which was consistent with the results reported by several different research groups. They verified that the microRNAs let-7b and let-7i target IKBKE through luciferase assays and found that let-7b/I mimics can knock down IKBKE and upregulate E-cadherin through western blot analysis. Moreover, the expression levels of let-7b/I were significantly lower in glioma cell lines than that in normal brain tissues, as determined by quantitative real-time PCR. Furthermore, let-7b/I inhibit the invasion and migration of glioma cells, as determined through wound healing and Transwell assays. The above-mentioned data suggest that let-7b/I inhibit the invasive ability of glioma cells by directly downregulating IKBKE and indirectly upregulating E-cadherin [13].

Angiogenesis is essential for tumor growth and metastasis when the tumor reaches 1-2 mm in diameter [43,44]. Capillary-like tube formation is reduced significantly by miR-15b which was reversed by miR-15b inhibition[45]. However, some microRNAs such as miR-152 had no effect on endothelial cell tube formation[45]. Further experiment found that the MEK-ERK pathway is deactivated by both miR-15b and miR-152 via NRP-2 and MMP-3 respectively in 9L cells[14].

MiR-146b-5p is expressed ubiquitously in most human organs, especially in the lung, thymus, and spleen [46]. In papillary thyroid carcinoma and lung cancer, miR-146b-5p is up-regulated, and this up-regulation is associated with a more malignant phenotype [47]. However, in melanoma, breast cancer, prostate cancer, pancreatic cancer, and glioma, miR-146b-5p expression is usually low [48]. Li *et al*. found that decreased miR-146b-5p expression was strongly correlated with chromosome 10q loss in gliomas, especially glioblastomas. The overexpression of miR-146b-5p in glioblastoma cell lines led to MMP16 mRNA silencing, MMP2 inactivation, and the inhibition of tumor cell migration and invasion. Those results suggest that the restoration of miR-146b-5p expression may be a feasible approach for inhibiting the migration and invasion of malignant gliomas [16].

MET is a proto-oncogene that encodes a protein known as hepatocyte growth factor receptor (HGFR) [49]. The MET has been implicated in the development and progression of several human cancers, such as hepatocellular carcinoma, osteosarcoma, colorectal cancer, and GBMs [50]. MET activation, as the consequence of ligand binding, receptor overexpression or interaction with other membrane receptors, which evokes pleiotropic biological responses, is often defined as 'invasive growth': this is a genetic program consisting of rate-limiting steps that takes place physiologically during embryogenesis and tissue repair, and pathologically in oncogenesis [51]. Chen *et al*. showed that miR-410 directly targeted MET in glioma cells. While restoring expression of miR-410 led to proliferation inhibition and reduced invasive capability in glioma cells. They showed that miR-410 played an important role in regulating MET-induced AKT signal transduction. While downregulation of MET by RNAi, which resulted in effects similar to that with miR-410 transfection in glioma cells. Those findings suggest that miR-410, a direct regulator of MET, may function as a tumor suppressor in human gliomas [17].

Pang *et al*. showed that ectopic expression of miR-590-3p suppressed and miR-590-3p-in promoted EMT, migration, and invasion in U87MG and A172 cells. Bioinformatics coupled with luciferase and Western blot assays also revealed that miR-590-3p inhibited expression of ZEB1 and ZEB2, which are master regulator of tumor metastasis. Those indicated that miR-590-3p functions as a suppressor of GBM EMT and metastasis by targeting ZEB1 and ZEB2, and it may be a therapeutic target for metastatic GBM [18].

The overexpression of miR-661 obviously suppressed the proliferation, migration and invasion of glioma cells. MiRNA target prediction algorithms implied that hTERT is a candidate target gene for miR-661. A fluorescent reporter assay confirmed that miR-661 could lead to hTERT gene silencing by recognizing and specifically binding to the predicted site of the hTERT mRNA 3' untranslated region (3'UTR) specifically. Furthermore, hTERT knockdown significantly decreased the growth and viability of glioma cells. These results indicate that miR-661 can inhibit glioma cell proliferation, migration and invasion by targeting hTERT [19].

MicroRNA-34a is found to be expressed in multiple cancer types such as neuroblastoma [50], colon cancer [51], prostate [52] and pancreatic cancer [53]. It was documented to be a tumor suppressor for glioma and is considered as a potential prognostic marker for glioma because its expression negatively correlates with patient survival in grade III and IV glial tumors [19, 54, 55]. A study on miR-34a indicated that

Musashi-1 and platelet-derived growth factor receptor-α (PDGFRA) were identified to be the targets of miR-34a, which may explain the increased PDGF signaling is caused by the loss of miR-34a in GBM[56].

In conclusion, while the current standard first-line regiment has moderately prolonged survival, the problem of tumor recurrence has not been solved. Because GBM is so invasive, these cancer cells can move into normal brain tissue where they escape surgery and/or radiation therapy. Therefore, there is an urgent need for developing new treatment options that can suppress the invasiveness of GBM cells, and the first step is to gain a better understanding of the molecular pathways involved in mediating intrinsic and post-treatment invasion of GBM.

Conflict of interests

The authors have declared that no conflict of interests exists.

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