6

Noncoding RNAs in Glioblastoma

YING ZHANG1 • NICHOLA CRUICKSHANKS1 • MARY PAHUSKI1
FANG YUAN1 • ANINDYA DUTTA2 • DAVID SCHIFF3,4 • BENJAMIN PUROW3,4 • ROGER ABOUNADER1,3,4

1Department of Microbiology, Immunology, and Cancer Biology, University of Virginia, Charlottesville, VA, USA; 2Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA, USA; 3Department of Neurology, University of Virginia, Charlottesville, VA, USA; 4Cancer Center, University of Virginia, Charlottesville, VA, USA

Author for correspondence: Roger Abounader, Department of Microbiology, Immunology, and Cancer Biology, University of Virginia, Old Medical School, Room 4819, PO Box 800168, Charlottesville, VA 22908, USA. E-mail: ra6u@virginia.edu

Doi: http://dx.doi.org/10.15586/codon.glioblastoma.2017.ch6

Abstract: The vast majority of the human genome is transcribed into noncoding RNAs. Among these, microRNAs (miRNA) and long noncoding RNAs (lncRNA) are frequently deregulated in cancer, where they regulate a wide variety of functions. Glioblastoma (GBM) is the most common and the most deadly primary human brain tumor. This chapter reviews the deregulation, functions, mechanisms of action, and clinical applications of miRNAs and lncRNAs in GBM. miRNAs are short noncoding RNAs that broadly and profoundly regulate gene expression. Numerous miRNAs are deregulated in GBM, where their expression levels can serve as diagnostic and prognostic biomarkers. miRNAs can act as oncogenes or tumor suppressors in GBM by regulating the expression of numerous tumor-suppressive or oncogenic proteins. miRNAs regulate all GBM malignancy parameters including tumor cell proliferation, cell survival, invasion, angiogenesis, cancer stem cells, immune escape, and therapy resistance. miRNAs are also secreted in body fluids, where they can be used as biomarkers. Because of...
Noncoding RNAs in glioblastoma

their deep involvement in GBM malignancy, efforts are under way to also exploit miRNAs as therapeutic agents or targets. IncRNAs are a diverse group of noncoding RNAs that are >200 nucleotides long. Several IncRNAs are deregulated in GBM, where their expressions can associate with clinical parameters. IncRNAs regulate GBM functions including tumor cell proliferation, survival, invasion, cancer stem cell differentiation, and therapy resistance. IncRNAs exert their actions via transcriptional, post-transcriptional, and epigenetic mechanisms that are only partly understood. Studying noncoding RNAs is important for the understanding, management, and development of future therapies for GBM.

Key words: Cancer stem cells; Glioblastoma; Glioma; Long noncoding RNA; microRNA

Introduction

The vast majority (>80%) of the human genome is transcribed into RNA. However, only ~2% of RNA is translated into proteins. Consequently, the vast majority of cellular RNAs are noncoding RNAs (ncRNAs). NcRNAs function as crucial regulators of biological, physiological, and pathological processes and are not evolutionary junk as previously thought. In the last decade, the small ncRNAs (microRNAs; 17–22 nucleotides) and long ncRNAs (lncRNAs; >200 nucleotides) have been extensively studied in cancer and have furthered our understanding and knowledge of cancer initiation and progression, and offered new therapeutic avenues. A large number of studies have shown that microRNAs and IncRNAs play important roles in almost every aspect of cancer, including tumor initiation, progression, and resistance to therapy, as well as providing biomarkers for diagnosis and prognosis and serving as therapeutic agents or targets. This chapter reviews the roles of microRNAs and LncRNAs in glioblastoma (GBM).

Glioblastoma

Gliomas are the most common and most malignant primary human brain tumors. They are extremely aggressive tumors that account for the majority of deaths due to primary brain neoplasms (1). Despite the most advanced treatment with combinations of surgery, radiotherapy, and chemotherapy, the most commonly diagnosed grade IV GBM is associated with an average life expectancy of only 14 months. The origin of gliomas is largely unknown, but there is increasing speculation that they might arise from glioma stem cells (GSCs), which might consist of transformed normal neural stem cells (NSCs). GBM malignancy is driven by the deregulation of molecules and pathways that control tumor cell proliferation, survival, invasion, and stem cell differentiation (2). The Cancer Genome Atlas (TCGA) classified these molecular deregulations as belonging to three major pathways: Receptor tyrosine kinase (RTK), p53, and Rb pathways (3). Factors responsible for GBM malignancy and poor prognosis include rapid cell proliferation, resistance to apoptosis, invasion of the surrounding brain, high levels of angiogenesis, immune evasion, and the existence of therapy-resistant GSCs.
MicroRNAs

MicroRNAs (miRNAs) are short, noncoding, endogenous RNAs (17–22 nucleotides) that post-transcriptionally regulate gene expression. More than 3,000 human miRNAs have been identified to date (4, 5). Around two-thirds of miRNA coding genes are located in introns (6, 7). One-third of miRNAs are transcribed as independent single transcriptional units or in clusters (6–8). MiRNA genes are transcribed by RNA polymerase II as pri-miRNA and then processed into pre-miRNA by the RNase III enzyme Drosha and its interacting partner DGCR8 or Pasha. The pre-miRNA is exported to the cytoplasm by exportin-5 and converted into a mature duplex by the Dicer complex (9–11). Mature miRNAs regulate their targets by incorporating into the RNA-induced silencing complex (RISC) and directing it to the targeted mRNA 3′ untranslated region (3′UTR) (12). MiRNAs directly cleave the mRNA or inhibit protein synthesis, according to the degree of complementarities with their targets’ 3′ untranslated regions (3′UTR) (Figure 1). Notably, single miRNAs can regulate the expressions of numerous genes and most genes are regulated by multiple miRNAs. Computational predictions of miRNA targets suggest that more than 60% of human protein expressions are regulated by miRNAs (13). miRNAs are frequently deregulated in human cancers via genetic, epigenetic, transcriptional, and processing mechanisms (14–19). Deregulation of miRNA expression has been associated with cancer initiation, progression, and metastasis (20, 21). By targeting the mRNAs of oncogenes or tumor suppressors, miRNAs can act as tumor suppressors or oncogenes, respectively. miRNAs regulate all aspects of cancer biology including cell cycle, proliferation, death, apoptosis, migration, invasion, metastasis, angiogenesis, tumor microenvironment, tumor immunology, and cancer stem cell biology (5) (Figure 2). Thus, correcting miRNA deficiencies by either antagonizing or restoring miRNA function may provide a therapeutic benefit.

miRNA Deregulation and Association with Clinical Parameters in GBM

Several studies have shown that miRNA expression is deregulated in GBM. Recent reviews (22, 23) summarized the differentially expressed miRNAs in GBM and showed that 256 miRNAs were significantly overexpressed and 95 miRNAs were significantly downregulated in GBM as compared to the normal brain tissue. There follows a brief survey of select deregulated miRNAs in GBM.

MiR-21 was the first miRNA to be linked with glioma malignancy. Most reports describe miR-21 as an oncogenic miRNA. MiR-21 levels are elevated in human glioma cells and tissues as compared to normal glial cells and/or brain (24–26). In addition, miR-21 levels in gliomas correlate with tumor grade, and low miR-21 levels in human tumors are associated with slightly better survival according to the TCGA database (27, 28).

Several reports have implicated miR-221/222 in glioma malignancy. A screening study identified miR-221 as one of the most frequently upregulated miRNAs in human glioma tumors and cell lines (29). MiR-221 upregulation was confirmed in a subsequent study which also found that miR-221 levels are further increased
Figure 1 miRNA biogenesis and functions. Black lines indicate the canonical pathway, with minor pathways depicted in gray lines. Modified with permission from Lee and Dutta (5).
Figure 2 Mechanisms of miRNA deregulation in cancer. Modified with permission from Lee and Dutta (5).
in higher grade tumors (30). TCGA data show that miR-221/222 downregulation in human tumors is associated with a better patient prognosis.

MiR-181a, miR-181b, and miR-181c were reported to be downregulated in GBM cells and tumors (29). miR-181a and, to a greater extent, miR-181b were subsequently described as tumor suppressors (31). Moreover, miR-181b and miR-181c were significantly downregulated in patients who responded to radiation therapy and temozolomide (TMZ) in comparison to patients with progressive disease. It was therefore proposed that expression levels of miR-181b and miR-181c could serve as a predictive marker of response to therapy in GBM patients (32).

Two high-profile publications identified miR-26a as a regulator of the tumor suppressor PTEN in gliomas (33, 34). The first publication showed that miR-26a gene is frequently amplified in human gliomas and that this is associated with monoallelic PTEN loss. The second publication used a multidimensional genomic data set of GBM from TCGA to identify miR-26a as a cooperating component of a frequently occurring amplicon that also contains CDK4 and CENTG1, two oncogenes that regulate the RB1 and PI3K/AKT pathways, respectively.

Analysis of human specimens showed that miR-34a expression is downregulated in GBM tissues compared to normal brain and in mutant p53 gliomas as compared with wild-type p53 gliomas. MiR-34a was also downregulated in GBM cell lines compared to astrocytes. MiR-34a levels in human gliomas were inversely correlated to RTK MET, measured in the same tumors (35).

MiR-148a expression was elevated in human GBM specimens, cell lines, and GSC compared with normal human brain and astrocytes. High expression of miR-148a significantly correlated with survival in TCGA samples. Therefore, miR-148a can serve as a prognostic oncogenic miRNA in GBM (36).

MiR-10b expression was upregulated in glioma samples as compared to non-neoplastic brain tissues, and expression levels were associated with higher grade tumors. Several lines of evidence suggest that miR-10b plays a role in glioma invasion (37, 38).

A recent study identified miR-182 as a prognostic marker for glioma progression and patient survival (39). miR-182 was upregulated in glioma cell lines and primary glioma specimens as compared to normal brain. miR-182 expression levels in the tumors significantly correlated with tumor grade and clinical features. The 5-year survival rates of patients with low miR-182 levels were significantly better than the survival rates of patients with high miR-182 levels. Additional miRNAs that are differentially expressed in GBM are listed in Table 1.

**SECRETED miRNAs AS GBM BIOMARKERS**

GBM cells shed microvesicles with cytoplasmic contents including substantial quantities of miRNAs that are stably preserved to allow quantitation in patient serum and cerebrospinal fluid. The quantification of miRNAs in fluid samples would permit noninvasive determination of GBM features based on miRNA signatures (40, 41). Interestingly, microvesicle shedding by GBM cells enables them to “share” miRNAs with surrounding cells, modifying nearby stromal cells, and essentially terraforming their environment (42). There are many examples of miRNAs released from tumor cells that indicate the importance
### TABLE 1  Deregulated miRNAs with Their Correlations with Survival, Targets, and Functions in Glioblastoma

| miRNA            | Expression in GBM (glioma) | Survival correlation | Targets                         | Function                                                                 |
|------------------|----------------------------|----------------------|--------------------------------|--------------------------------------------------------------------------|
| Let-7            | Down                       |                      | KRAS                           | Migration↓, Proliferation↓, In vivo tumor growth↓                           |
| **Hsa-miR-7**    | Down                       |                      | FAK, EGFR, AKT, PBK, RAF1      | Viability↓, Migration↓, Invasiveness↓, Proliferation↓, In vivo tumor growth↓, Radiosensitivity↓, GSC proliferation and invasion↓ |
| Hsa-miR-9        | Up                         | (Up in high-grade tumor) | CAMTA1                         |                                                                         |
| Hsa-miR-10ab     | Up                         | (Up in TMZ-resistant tumor) | Y HOXD10                        |                                                                         |
| Hsa-miR-15a      | Up                         | (Up in high-grade tumor) |                                |                                                                         |
| Hsa-miR-15b      | (Down in high-grade tumor) |                      | CCNE1                           | Proliferation↑, Proliferation↓                                           |
| Hsa-miR-16       | Up                         | (Up in high-grade tumor) |                                |                                                                         |
| **Hsa-miR-17-92 cluster** | Up                         | (Disputed in high-grade tumor, CD133+ cells) | POLD2, TGFβRII, CTGF, CAMTA1, ATG7 | Angiogenesis↑, Growth↑, GSC apoptosis↑, Proliferation↓, Viability↓, Apoptosis↑, Proliferation↓ |
| Hsa-miR-18a      | Up                         | (Up in low-grade tumor) | Smad4, CTGF                     | Angiogenesis↑, Growth↑, Viability↓, Apoptosis↑, Proliferation↓             |

*Table continued on following page*
| miRNA       | Expression in GBM (glioma) | Survival correlation | Targets                                                                 | Overexpression                                                                 | Anti-miR                                                                 |
|-------------|----------------------------|----------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Hsa-miR-19a | Disputed                   |                      | CTGF                                                                    |                                                                                | Viability↓, Apoptosis↑, Proliferation↓                                        |
| Hsa-miR-20a | Up                        | Up                   | TGFβ-RII, CTGF                                                          | Angiogenesis↑, Growth↑                                                          | Viability↓, Proliferation↓                                                  |
| Hsa-miR-21  | Up                        | Up                   | Y, RECK, TIMP3, APAF1, NP32A, SMARCA4, Spry2, Caspases, PTEN, Cdc25A, HNRPK, Tap63, RRFIP1, PDCD4, p53 | Invasiveness↑                                                                   | Invasiveness↓, Apoptosis↑, Viability↓, Proliferation↓, In vivo tumor growth↓, Chemosensitivity↑, Radiosensitizes↑ |
| Hsa-miR-23a | (Down in high-grade tumor)|                      |                                                                         |                                                                                |                                                                          |
| Hsa-miR-25  | Up                        | Up                   | Mdm2, TSC1                                                              | In vivo tumor growth↓                                                         |                                                                          |
| Hsa-miR-26a | Up                        | Up                   | PTEN, RB1 and MAP3K2/MEKK2                                              | In vivo tumor growth↑                                                         |                                                                          |
| Hsa-miR-28  | Up                        | Up                   |                                                                         |                                                                                |                                                                          |
| Hsa-miR-30bc| Disputed                  |                      | KRAS                                                                    |                                                                                |                                                                          |
| Hsa-miR-34a | Down                      | (Down in GSCs, Down in proneural subtype) | SIRT1, MET, NOTCH1, Msi1, PDGFRA,                                      | Viability↓, Proliferation↓, Apoptosis↑, Invasiveness↓, In vivo tumor growth↓, Differentiation↑, GSC stemness↓ |                                                                          |
| miRNA          | Expression in GBM (glioma) | Survival correlation | Targets                     | Function                                                                 |
|---------------|-----------------------------|----------------------|-----------------------------|--------------------------------------------------------------------------|
| Hsa-miR-93    | Up                          |                      | Integrin-β3                 | Angiogenesis↑, Proliferation↑, *In vivo* tumor growth ↑                  |
| Hsa-miR-96    | Up                          |                      | KRAS                        |                                                                          |
| Hsa-miR-100   | Down                        |                      | ATM                         | Radiosensitivity↑                                                          |
| Hsa-miR-124/137 | Down                      | Y                    | PTBP1, STAT3                | Proliferation↓, Migration↓, Invasiveness↓, Stemness↓, GSC differentiation↑ |
| Hsa-miR-125b  | Down                        |                      | Bmf, MAZ                    | Invasiveness↑, Apoptosis↓, Proliferation↑                                  |
| Hsa-miR-128   | Down                        |                      | WEE1, p70S6K1, Msi1, E2F3a, Bmi-1, EGFR, PDGFRα | Angiogenesis↓, Proliferation↓, *In vivo* tumor growth ↓, inhibition of GSC stemness and self-renewal↓ |
| Hsa-miR-130b  | Up                          | (Up in high-grade tumor) |                            |                                                                          |
| Hsa-miR-133a  | (Down in high-grade tumor)  |                      | KRAS and STAT5B             |                                                                          |
| Hsa-miR-134   | Up                          |                      |                             |                                                                          |

*Table continued on following page*
| miRNA          | Expression in GBM (glioma) | Survival correlation | Targets                  | Function                                                                 |
|---------------|---------------------------|---------------------|--------------------------|--------------------------------------------------------------------------|
| Hsa-miR-135b  | Up (Up in GSCs)           |                     | CDK6, Msi1, Cox-2        | Proliferation↓, Invasiveness↓, Migration↓, In vivo tumor growth↓            |
| Hsa-miR-137   | Down (Down in late-stage tumor) |                     |                          |                                                                          |
| Hsa-miR-140   | Up (Up in high-grade tumor) |                     |                          |                                                                          |
| Hsa-miR-141   | Disputed (UP in GSCs)      |                     |                          |                                                                          |
| Hsa-miR-146b-5p | Down                     |                     | EGFR, MMP16              | Invasiveness↓, Migration↓, Proliferation↓, In vivo tumor growth↓            |
| Hsa-miR-148a  | Up                        | Y                   |                          | Proliferation↑, Apoptosis↓, Angiogenesis↑, In vivo tumor growth↑            |
| Hsa-miR-150   | Down in high-grade tumor   |                     |                          |                                                                          |
| Hsa-miR-153   | Down                      |                     | Bcl-2, Mcl-1, Irs-2      | Proliferation↓, Viability↓, Apoptosis↑                                    |
| Hsa-miR-181abc | Down                     |                     | Bcl-2                    | Proliferation↓, Apoptosis↑, Invasiveness↓, Chemosensitivity and Radiosensitivity↑ |
| miRNA         | Expression in GBM (glioma) | Survival correlation | Targets                        | Function                                      | Overexpression | Anti-miR                          |
|--------------|----------------------------|----------------------|--------------------------------|-----------------------------------------------|----------------|-----------------------------------|
| Hsa-miR-182/183 | Up (Up at late-stage tumor) | Y                    |                                |                                               |                |                                   |
| Hsa-miR-184   | Down (Down in high-grade tumor) |                      | Akt2                           | Apoptosis↑, Invasiveness↓                     |                |                                   |
| Hsa-miR-193   | Up                          |                      | KRAS                           |                                               |                |                                   |
| Hsa-miR-195   | (Up in TMZ resistant)       |                      | CCND3, E2F3, CCND1             | Proliferation↓, Invasiveness↓                 |                | Chemosensitivity, Viability↓      |
| Hsa-miR-196ab | Up                          | Y                    |                                |                                               |                |                                   |
| Hsa-miR-197   | (Down in high-grade tumor)  |                      |                                |                                               |                |                                   |
| Hsa-miR-200c  | Up (High in GSCs)           |                      |                                |                                               |                |                                   |
| Hsa-miR-205   | Disputed (High in GSCs)     |                      | VEGF-A                         | Proliferation↓, Apoptosis↑, Invasiveness↓     |                |                                   |
| Hsa-miR-210   | Up (Up in high-grade tumor) | Y                    | HIF3α                          | Enhanced vasculogenesis, Reduced vascular density and tumor growth in vivo |                |                                   |
| Hsa-miR-218   | Down (Down in mesenchymal subtype) |              | IKK-β, HIF2α                   | Invasiveness↓                                 |                |                                   |
| Hsa-miR-221/222 | Up (Up in high-grade tumor, CD133+ cells) | Y                   | P27, Akt, PUMA, P57, PTPμ BIRC1, XIAP, ICAM-1 | Proliferation↑, Invasiveness↑, In vivo tumor growth↑, Apoptosis↓, Migration↑ |                |                                   |

Table continued on following page
| miRNA          | Expression in GBM (glioma) | Survival correlation | Targets                          | Function                                                                 |
|----------------|-----------------------------|----------------------|----------------------------------|--------------------------------------------------------------------------|
| Hsa-miR-296    | Up                          |                      |                                 |                                                                          |
| Hsa-miR-297    | Down                        |                      |                                 |                                                                          |
| Hsa-miR-301a   | Up (Up in GSCs)             |                      |                                 |                                                                          |
| Hsa-miR-326    | Down                        |                      | NOTCH 1/2, PKM2                  | Proliferation↓, Apoptosis↑, Viability↓, Invasiveness↓, In vivo tumor growth↓, GSC stemness↓ |
| Hsa-miR-328    | (Up in invading cells) Y    |                      | SFRP1, ABCG2                     | Invasiveness↑                                                               |
| Hsa-miR-335    | Up                          |                      | Daam1                           | Proliferation↑, Invasiveness↑                                               |
| Hsa-miR-339-5p | Down (Down in GSCs)         |                      | ICAM-1                           | Proliferation↑, Apoptosis↓                                                 |
| Hsa-miR-363    | Up (Up in GSCs)             |                      | Bim, Caspase3                    | Proliferation↑, Apoptosis↓                                                 |
| Hsa-miR-365a   | (Down in GSCs)              |                      | KRAS, MAX                        | Proliferation↓, Migration↑                                                  |
| Hsa-miR-367-302| Up, (Up in GSCs)            |                      |                                 |                                                                          |
| Hsa-miR-371-373| Up, (Up in GSCs)            |                      |                                 |                                                                          |
| miRNA           | Expression in GBM (glioma) | Survival correlation | Targets     | Overexpression Function                                      | Anti-miR Function         |
|-----------------|---------------------------|----------------------|-------------|---------------------------------------------------------------|---------------------------|
| Hsa-miR-451     | Disputed, (Up in GSCs)    | High with poor survival Y | CAB39       | Proliferation↓, Invasion↓, Stemness↓, Neurosphere formation↓, Sensitized cells to glucose deprivation | Migration↑                |
| Hsa-miR-455     | (Up in TMZ resistant)     |                      |             |                                                               |                           |
| Hsa-miR-497     | (Down in high-grade tumor)|                      |             |                                                               |                           |
| Hsa-miR-548b    | (Down in high-grade tumor)|                      |             |                                                               |                           |
| Hsa-miR-582-5p  | Up, (Up in GSCs)          |                      | Caspase 3/9  | Proliferation↑, Apoptosis↓ | Proliferation↓, Apoptosis↑ |
of their roles in the modulation of the microenvironment in GBM (Table 2). MiR-21 is upregulated (43), while miR-205 is downregulated in patient plasma (44, 45). Many more miRNAs have been described as highly expressed in peripheral blood as compared to normal samples (46). MiR-454-3p was highly expressed in the plasma of GBM patients as compared to healthy controls and was lower in low-grade glioma. Furthermore, miR-454-3p expression in the postoperative plasma is markedly downregulated in comparison to preoperative plasma, and a correlation of worsening prognosis of glioma was observed with increasing miR-454-3p expression (47). MiR-29 levels in serum can serve to distinguish the progression of malignancy from stage I–II to stage III–IV (48). In addition, a huge increase in miR-210 expression was found in serum samples of GBM patients compared to controls and this was associated with tumor grade and poor outcome (48). A study of serum miRNA profiles found a significant difference of miRNA levels between untreated high-grade astrocytomas (grade III–IV) and controls in a genome-wide miRNA analysis. Seven miRNAs (miR-15b*, miR-23a, miR-133a, miR-150*, miR-197, miR-497, and miR-548b-5p) were markedly decreased in grade II–IV patients and showed high specificity (97.87%) and sensitivity (88.00%) for the prediction of malignant astrocytomas (48, 49).

**miRNAs in GSCs**

GSCs are major contributors to therapy resistance in gliomas. It was shown that CD133+ tumor cells, presumably GSCs, represent the cellular population that confers glioma radioresistance and could be the source of tumor recurrence after radiation (50). It was hypothesized that GSCs originate from transformed NSCs. This hypothesis was recently supported by a study that found that gliomas display a miRNA expression profile reminiscent of neural precursor cells (51). Discussed below are select critical miRNAs that have been implicated in the regulation of GSCs (summarized in Figure 3 and Table 1). A study assessed the effects of miR-124 and miR-137 on the differentiation of mouse NSCs, mouse oligodendroglioma-derived stem cells, and human GSCs (26). Transfection of miR-124 or miR-137 induced morphological changes and marker expressions consistent with neuronal differentiation in mouse NSCs, mouse oligodendroglioma-derived stem cells derived from S100β-v-erbB tumors, and CD133+ human GBM-derived stem cells. This study therefore implicated miR-124 and miR-137 in the differentiation of NSCs and GSCs. A subsequent report examined the miRNA profiles of GSC and nonstem cell populations and found that several miRNAs including miR-451, miR-486, and miR-425 were upregulated in the GSCs (53). The expression of miR-451 is regulated by SMADs, which have been previously associated with GSC regulation, through binding to promoter region of miR-451 gene (54). Two studies uncovered critical roles of miRNA-34a in GSCs (35, 55). It was first shown that miR-34a is downregulated in human GBM and exerts potent tumor-suppressive effects in glioma cells and stem cells via direct inhibition of MET, NOTCH1, and NOTCH2 expressions. NOTCH is a critical regulator of normal and cancer stem cell maintenance (56–58). NOTCH pathway activation enhances the stemness, proliferation, and radioresistance of GSCs (57–60). These studies therefore implicated miR-34a in the regulation of GSCs partly via regulation of
| lncRNA       | Expression in GBM (glioma) | Survival correlation | Targets/Mechanisms of action                                                                 | Function                                                                 |
|-------------|---------------------------|---------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| linc-RoR    | Down                      |                     | KLF4                                                                                           | Proliferation↓, Sphere formation↓                                         |
| ADAMTS9-AS2 | Down                      | Y                   | Migration↑                                                                                      | Proliferation↑, Sphere formation↑                                         |
| CRNDE       | Up                        | Y                   | polycomb repressive complex 2 and CoREST complexes, MiR-384, miR-186                             | Cell growth↑, Invasion↑, Apoptosis↓                                        |
| H19         | (Up in high grade)        |                     |                                                                                               | Inversion↑                                                                |
| HOTAIR      | Up                        | Y                   | EZH2, miR-148b-3p                                                                               | Cell cycle↓, in vivo tumor growth↓                                        |
| Xist        |                           |                     |                                                                                               | X-chromosome inactivation↓                                               |
| HOTAIRM1    | Up                        |                     |                                                                                               |                                                                          |
| MEG3        | Down                      |                     | p53                                                                                           | Proliferation↓, Apoptosis↑                                                |
| MALAT1      | (Up at hypoxic conditions)|                     | AIM1, LAYN, HMMR, SLC26A2, CCT4, ROD1, CTHRC1, and FHL1                                       | Migration↓                                                                |
| MIR210HG    | (Up at hypoxic conditions)|                     |                                                                                               | Invasion at hypoxia↑                                                     |
| GAS5        |                           |                     | GR, GREs                                                                                       | Sensitivity GBM cells to erlotinib treatment↑                             |
| PNKY        |                           |                     | PTBP1                                                                                         | Normal neuronal differentiation                                            |

Table continued on following page
| IncRNA       | Expression in GBM (glioma) | Survival corelation | Targets/Mechanisms of action | Function                                      |
|--------------|----------------------------|---------------------|------------------------------|-----------------------------------------------|
| NEAT1        | Up                         |                     | miR-449b-5p                  | Overexpression                                |
| ASLNC22381   | Up                         |                     |                              | Under-expression                              |
| ASLNC2081    | Up                         |                     |                              | GBM recurrence↑                               |
| LOC090937    | Up                         |                     |                              | GBM recurrence↑                               |
| LINC00152    | Up                         |                     |                              |                                               |
| LOC04745     | Up                         |                     |                              |                                               |
| TUNAR        | Down                       |                     |                              | Normal neuronal differentiation                |
| RP11-713C5.1 | Down                      |                     |                              |                                               |
| RP11-123M6.2 | Down                      |                     |                              |                                               |
| LINC00599    | Down                      |                     |                              |                                               |
| LOC27853     | Down (Up in low grade tumor)|                   |                              |                                               |
| RP-32L13.3   | Down (Up in low grade tumor)|                   |                              |                                               |
| IncRNA      | Expression in GBM (glioma) | Survival correlation | Targets/Mechanisms of action | Function |
|------------|----------------------------|----------------------|-----------------------------|----------|
| MIAT       | (Down in low grade tumor)  |                      |                             |          |
| RP11-67704.6| (Down in low grade tumor)  |                      |                             |          |
| TMEM191A   | (Down in low grade tumor)  |                      |                             |          |
| LINC01476  | (Down in migratory GBM cells) |                      |                             |          |
| BTAT10     | (Down in migratory GBM cells) |                      |                             |          |
| SOX2OT     | (Down in migratory GBM cells) |                      |                             |          |
| LOC100192378 | (Up)                     |                      |                             |          |
| LOC100127888 | (Up)                     |                      |                             |          |
| HCG4       | (Down)                    |                      |                             |          |
| FLJ39609   | (Down)                    |                      |                             |          |
NOTCH expression. The miR-17-92 cluster has been implicated in the regulation of GSC differentiation, apoptosis, and proliferation (61). It was first shown that expression of several members of miR-17-92 was significantly higher in primary astrocytic tumors than in the normal brain and significantly increased with tumor grade. A high-level amplification of the miR-17-92 locus was also detected in one GBM specimen, while inhibition of miR-17-92 induced apoptosis and decreased cell proliferation of GSCs.

**Functions and Targets of miRNAs in GBM**

**CELL PROLIFERATION, VIABILITY, AND STEMNESS**

One distinctive characteristic of GBM is uncontrolled proliferation and evasion of programmed cell death. MiRNA deregulation is one mechanism for sustained proliferation and evasion of apoptosis through regulation of the cell cycle, apoptosis, and growth signaling pathways.

AP-1–induced miR-21 downregulates tumor suppressors PDCD4 and PTEN. Inhibition of PDCD4 contributes to an increase in AP-1 activity, revealing an AP-1 autoregulatory mechanism in RAS transformation (62). MiR-21 exerts antiapoptotic effects and enhances tumor formation through targeting of p53 and TGF-β signaling.
and the mitochondrial apoptotic pathway (63). MiR-21 affects apoptosis and the cell cycle by inhibiting heterogeneous nuclear ribonucleoprotein K (HNPRK); the tumor suppressor homologue of p53 (Tap63); programmed cell death 4 (PDCD4); and possibly also EGFR, cyclin D, and Bcl2 (63–65), as well as ANP32A, SMARCA4, SPRY2, IGFBP3, and LRRFIP1 (4, 66–68). MiR-21 is therefore an important miRNA in gliomas that exerts oncogenic effects by regulating cell proliferation and survival.

MiR-221/222 directly targets the tumor suppressor and negative regulator of the cell cycle, p27 (69, 70). miR-221/222 can inhibit apoptosis by targeting p53-upregulated modulator of apoptosis (PUMA), which acts to induce rapid cell death via binding to Bcl-2 and Bcl-xL. Therefore, overexpression of miR-221/222 and subsequent downregulation of PUMA enhance cell survival while knockdown of miR-221/222 induces apoptosis, thereby reducing tumor growth (71, 72).

MiR-26a regulates the major tumor suppressor PTEN in glioma (33, 34). It was shown that miR-26a can transform cells and promote GBM cell growth by decreasing PTEN, RB1, and MAP3K2/MEKK2 protein expression, thereby increasing AKT activation, promoting proliferation, and decreasing c-JUN N-terminal kinase-dependent apoptosis. Overexpression of miR-26a in PTEN-competent and PTEN-deficient GBM cells promoted tumor growth in vivo and increased growth in cells overexpressing CDK4 or CENTG1. MiR-335 is upregulated in GBM and acts to prevent apoptosis and promote cell growth and invasion of astrocytoma cells by targeting the potential tumor suppressor disheveled-associated activator of morphogenesis 1 (DAAM1), as well as regulating RB1 in a p53-dependent manner (73). Inhibition of miR-335 leads to effective suppression of growth and increased apoptosis of astrocytoma cells. Importantly, delivery of a miR-335 antagonist to rat glioma C6 cells prevented tumor growth, resulted in activation of apoptosis, and repressed invasion of astrocytoma xenografts (74).

MiR-34a is a downregulated miRNA in GBM that directly inhibits the expression of MET, NOTCH1, NOTCH2, CDK6, CCND1, and SIRT1 (35, 75–77). MET is a commonly overexpressed and activated RTK in GBM and is responsible for mediating multiple growth-signaling pathways. NOTCH is a critical regulator of cell fate and cancer stem cell maintenance (56–58). CDK6 and CCND1 are well-known cell-cycle regulators. By targeting these important molecules involved in cell proliferation, miR-34a inhibits cell survival, proliferation, and invasion, as well as GSCs self-renewal (35, 55). RTKs are co-deregulated in the majority of GBM. MiR-134 is upregulated in human tumors and GSCs and is regulated by the RTKs, MET, EGFR, and PDGFR (19). MiR-134 inhibits GSCs self-renewal, survival, and xenograft growth and induces GSC differentiation by directly binding to KRAS and STAT5B 3′ UTRs. MiR-134 therefore represents an RTK-regulated tumor-suppressive hub that mediates RTK effects on GBM malignancy.

Many more miRNAs, including the tumor-suppressive miR-181, miR-15b, miR-153, miR-184, miR-326, miR-218, and miR-451 (23, 78–80), inhibit proliferation and/or induce apoptosis in GBM. Additional upregulated oncogenic miRNAs that promote glioma cell viability and proliferation include miR-296 (81), miR-125b (82), miR-196a (83), miR-148a (36), miR-363, and miR-582-5p (84, 52).
MIGRATION AND INVASION

The lethality of GBM is partly attributed to extensive and diffuse tumor cell infiltration throughout the brain. The invasive growth of GBM is driven by the modulation of cell-to-cell and cell-to-matrix interactions, degradation, and remodeling of the extracellular matrix, cytoskeletal reorganization, and gain of migratory behavior (85). These processes are regulated by miRNAs. The oncogenic miR-21 promotes GBM invasiveness through suppression of the expression of matrix metalloprotease (MMP) inhibitors. MMPs are a family of enzymes that function in proteolysis of extracellular matrix components and are critical for the migration and invasion properties of tumor cells. By targeting multiple molecules, such as RECK, TIMP3, ANP32A, and SPRY2, miR-21 can induce the expression and activity of various MMPs, increase Ras/Raf binding, and activate ERK phosphorylation, thereby enhancing the invasive potential of GBM cells (27, 68, 86). Several studies reported that miR-146b and miR-10b can also promote GBM invasion (37, 87–89). MiR-146b inhibits MMP16 and leads the increased invasion in GBM, whereas MiR-10b can enhance GBM invasive growth by indirectly modulating MMP14 as well as uPAR and RhoC through direct binding and inhibits upstream target, HOXD10 (37, 88). When treated with antisense miR-10b, GBM cells display reduced growth, invasion, and angiogenesis, as well as enhanced cell death (38, 88, 89). The let-7 family of tumor-suppressive miRNAs is inhibited by Lin28A, which is normally expressed in development but is also found overexpressed in GBM by TCGA data analysis. There is a strong correlation in GBM between Lin28A expression and expression of the pro-invasive HMGA2 gene targeted by let-7 miRNAs, and an inverse correlation with let-7 family members. Overexpression of let-7g can reverse the invasive phenotype of Lin28A-expressing GSCs (90).

ANGIOGENESIS

One of the primary characteristics of GBM is its ability to create extensive microvascular networks. New blood vessel growth orchestrates the growth of aggressive GBM by supplying a greater quantity of energy and nutrients, in addition to providing infrastructure for invasion. A number of miRNAs have been identified as important regulators of neovascularization in GBM (91). MiR-218 was shown to prevent GBM tumor angiogenesis and cell survival by targeting multiple components of RTK signaling pathways and the hypoxia-inducible factor, HIF2α (92). MiR-125b is downregulated in both human GBM-associated endothelium and in endothelial cells cultured with conditioned medium from GBM cells (82). Myc-associated zinc finger protein (MAZ), a transcription factor that regulates vascular endothelial growth factor (VEGF), is a target of miR-125b that is overexpressed in GBM-associated endothelium and is driven by VEGF. It was reported that miR-296 is a GBM angiogenic miRNA that is upregulated in tumor-associated endothelial cells. Augmented expression of miR-296 is associated with increased endothelial cell tube formation and enhanced vascularization of tumors, while knockdown of miR-296 results in reduced tumor angiogenesis (81). MiR-210-3p is induced under hypoxic growth conditions and directly targets HIF3α, a negative regulator of hypoxic response that acts through downregulation of VEGF.
Therefore, miR-210-3p overexpression induces HIF, VEGF, and CA9 transcriptional activity, enhancing vasculogenesis, while inhibition of miR-210-3p under hypoxia inhibits HIF-mediated induction of VEGF and CA9, reducing vascular density and tumor growth *in vivo* (93). A member of the miR-17 family, miR-93, plays a role in GBM-associated angiogenesis by targeting integrin B8, a tumor suppressor and inhibitor of angiogenesis (94). MiR-93 was sufficient to enhance angiogenesis and tumor growth and drastically reduce survival in a xenograft model of GBM.

**IMMUNE EVASION AND DRUG RESISTANCE**

Increased antitumor immune responses have been linked to enhanced survival in many cancers, including GBM (95–101). MiRNAs regulate immune evasion. MiR-124 inhibits STAT3 to enhance T-cell-mediated immune clearance of glioma (102). Treatment of T cells isolated from GBM with miR-124 reversed a block in T-cell proliferation and also reduced expression of signal transducer and activator of transcription 3 and forkhead box P3—ultimately inhibiting the development of immune-suppressive regulatory T cells (102). MiR-124 delivery in mouse GBM xenograft models prolonged survival but only in immunocompetent mice. Dicer, miR-222, and miR-339 expressions were inversely associated with the expression of intercellular cell adhesion molecule (ICAM-1) and they enhanced the susceptibility of tumor cells to antigen-specific lysis by cytotoxic T-lymphocytes. MiR-222 and miR-339 contribute to GBM evasion of the immune system by targeting ICAM-1, which modulates T-cell responses (103). A major challenge of GBM therapy is the resistance to chemotherapy and/or radiotherapy. A number of miRNAs can influence therapeutic sensitivity by targeting multidrug resistance proteins (104). MiR-21 strongly reduces the effect of TMZ on apoptosis, which is mediated through inhibition of proapoptotic proteins Bax and caspase-3 as well as upregulation of antiapoptotic protein Bcl-2 (105). Inhibition of miR-21 can enhance the chemosensitivity of human GBM cells to TMZ and other drugs including paclitaxel, sunitinib, doxorubicin, and VM-26 (106–110). MiR-195, miR-455-3p, and miR-10a* were also implicated in TMZ resistance as they were upregulated in a TMZ resistant variant of the U251 GBM cell line (111). Knockdown of miR-195 was shown to significantly enhance the effectiveness of TMZ. Two studies examined the link between the miRNA levels (32) and TMZ resistance (112) in GBM. They found that miR-221, miR-222, miR-181b, miR-181c, and miR-128 were significantly downregulated in GBM, while miR-21 was overexpressed. MiR-181b and miR-181c had the strongest correlation with responsiveness to TMZ treatment, indicating their potential as predictive markers for response to TMZ therapy. MiR-125b-2 has also been shown to increase resistance of GSCs to TMZ, whereas peptide nucleic acid (PNA) miR-125b inhibitors increase TMZ-induced GSCs apoptosis via mediation of cytochrome c release from the mitochondria, caspase-3, and PARP activation (113). MiR-328 has been found to sensitize GSCs to chemotherapy through downregulating the expression of ATP-binding cassette subfamily G member 2 (ABCG2), a transporter that regulates shuttling of substrates across the cellular membrane (114). MiR-100 has been reported to increase the sensitivity of glioma cells to ionizing radiation through the downregulation of ataxia telangiectasia mutated (ATM) (115).
miRNA Therapeutics

Because miRNAs regulate all aspects of cancer, they represent promising therapeutic agents or targets. The goal of miRNA therapeutics is to replace tumor suppressor miRNAs or inhibit oncogenic miRNAs. There are a host of possible choices for both the therapeutic payload and the delivery vector. A number of reports in GBM describe preclinical efforts to characterize individual oncogenic and tumor-suppressive miRNA that can be targeted in vitro, with some evidence of efficacy in mouse models; however, none of them has moved on to clinical trials in GBM patients to date.

As described earlier in this chapter, numerous groups have reported oncogenic and tumor-suppressive miRNAs, affecting cell viability in GBM. Therapeutic efforts targeting oncogenic miRNAs have largely focused on delivering stabilized antisense oligonucleotides complementary to the miRNAs sequence. Preclinical studies with GBM tumor-suppressive miRNAs have consisted of forced overexpression of miRNA mimics. Among the GBM oncogenic miRNAs described in multiple studies, miR-21 and miR-10b figure prominently (38, 116–118). Several of these GBM miR-21 and miR-10b studies have demonstrated preclinical efficacy with delivery of miRNA antisense, some of which are dubbed “antagomiRs” (anti-miR); miR-10b may be an especially powerful oncogenic miRNA in GBM. One group has now shown preclinical efficacy in GBM models with a radically different approach to targeting miR-10b; viral delivery of CRISPR/Cas9 elements was used to eliminate miR-10b expression in GBM (119). Even more studies have identified tumor-suppressive microRNAs in GBM and shown their potential for therapeutic delivery. Among these translational studies of tumor-suppressive miRNAs and their therapeutic potential in GBM, miR-34a has received the most attention (35, 55). Others include miR-326, mir-297, miR-128, and miR-182 (120–124). Most of the published work with tumor-suppressive miRNAs in GBM has involved ex vivo transfection prior to GBM cell implantation in the mouse brain, but some studies have reached the higher bar of demonstrating in vivo efficacy with tumor-suppressive miRNA delivery to previously established orthotopic GBM in mice. A number of studies have also shown the potential of miRNA-based therapies to indirectly attack GBM, through its vasculature or through immunotherapeutic effects (82, 92, 94, 102, 103).

The problem of efficient delivery of miRNA-based therapies to GBM remains perhaps the biggest challenge. Numerous approaches tested preclinically have involved local delivery, sometimes with the addition of convection-enhanced delivery (CED) to drive better penetration of the agent into the tumor and the nearby brain. These local delivery approaches have typically used lentivirus, adenovirus, or one of a large variety of nanoparticles as vectors to transfect the GBM cells. While in the occasional report naked miRNA or anti-miRNA has been infused, it is typically more efficient to use a viral or nanoparticle vector to get substantial quantities of the payload into GBM cells. It should also be noted that intravenous delivery of miRNA-based therapeutic vectors might be a possibility for GBM; some reports describe approaches targeted to the brain vasculature or designed to pass through the blood–brain barrier or locally disrupt it (124, 125).

One key question for miRNA-based therapies directly targeting GBM cells is whether it is necessary for the therapeutic vector to reach all or nearly all of the
malignant cells to be highly effective. Some therapies might yield a bystander effect allowing for less-than-perfect delivery, but in general, it is likely that delivery will have to be highly efficient. However, this requirement might well be eased substantially by a biologic phenomenon found to be prominent in GBM cells—intercellular sharing of cytoplasmic contents through exosome shedding and uptake (126). This has been found in GBM cells to allow transduced cells to share cytoplasmic contents such as overexpressed miRNAs with adjacent GBM cells (42), which could dramatically reduce the need to reach the overwhelming majority of the GBM cells with any miRNA-based therapy.

Although there are numerous preclinical studies on miRNA-based therapeutic strategies for GBM, none has yet advanced to clinical trials in patients. However, miRNA-based therapeutics have entered clinical trial testing for other cancers, and GBM might not be far behind. A miRNA-34a therapeutic entered a Phase I trial for certain cancers (NCT01829971), enrolling 47 patients, yielding a partial response and four cases of stable disease, but it was marked by significant inflammatory side effects requiring immunosuppressive steroid premedication (127). This immune reaction may represent yet another challenge with miRNA therapeutics in the clinic, and it is hoped that valuable information will be gleaned from the analysis of this trial.

### Long Noncoding RNAs

LncRNAs are nonprotein coding transcripts that are longer than 200 nucleotides (nt). LncRNAs are emerging as significant regulators of critical biological functions in human disease, including cancer and GBM (128–132). Over 50,000 human LncRNAs have been identified (133–135) and similar catalogs have been generated from various mouse tissues and model organisms (136–140). LncRNAs can regulate gene expression at the transcriptional, post-transcriptional, and epigenetic levels (141). Recent studies indicate that LncRNAs play important roles in glioma development (142, 143) by regulating several tumorigenic processes such as cellular proliferation and apoptosis (144). Differential expression of specific LncRNAs might correlate with disease progression and cancer malignancy and thus could potentially be used as therapeutic targets and biomarkers for prognosis (145–149).

#### LncRNA EXPRESSION AND CORRELATION WITH CLINICAL PARAMETERS IN GLIOMAS

One high throughput screening study of 1308 LncRNAs discovered 654 highly upregulated LncRNA in GBM compared to normal brain tissue (150), among which ASLNC22381 and ASLNC2081 were further investigated and found to be involved in GBM recurrence and malignant progression. Another study (145), using a microarray-mining approach, demonstrated aberrant LncRNA expression patterns in two large public cohorts (151, 152). They identified 127 LncRNAs that were differentially expressed between glioma and nontumoral brain tissues. Their analysis found that LncRNAs, CRNDE and HOTAIRM1, were significantly
upregulated in GBM while MEG3 was downregulated. In a clinical trial–based study, 80 GBM specimens were analyzed and 81 sets of lncRNAs were found to be deregulated (153). Another study found 37 lncRNAs that were upregulated and 44 lncRNAs that were downregulated in GBM specimens compared to nontumoral brain tissues based on the profiling analysis of 30 GBM patient samples and 5 GBM cell lines. They found that 147 out of 2448 lncRNAs were differentially expressed in tumor tissues compared to normal brain, and 213 lncRNAs were differentially expressed in tumor cell lines compared to normal astrocytes. Importantly, certain lncRNAs, including CRNDE, HOTAIRM1, and MEG3, were consistently differentially expressed, indicating that they may play a role early in GBM initiation and tumorigenesis (153, 154) (Table 2).

A recent comprehensive study of global lncRNA expression analyzed over 650 brain tumor and 70 normal brain tissues from TCGA and other public databases (155). A total of 611 induced and 677 repressed lncRNAs were identified in glial tumors relative to normal brains. One frequently reported oncogenic lncRNA, CRNDE, was confirmed to be upregulated over 40-fold in GBM. The lncRNA, TUNAR, was also identified as significantly downregulated (14-fold) in both GBM and LGG. Interestingly, TUNAR was found to act as a crucial positive regulator of neuronal development and differentiation in zebrafish, mice, and humans, suggesting that its downregulation is required for increased oncogenic potential and uncontrolled neuronal cell growth (138, 156).

Specific lncRNAs correlate with patient survival. From TCGA data analysis, approximately 500 lncRNAs were associated with poor prognosis, while 200 lncRNAs correlated with better survival outcomes (155). For example, patients displaying high expression of RP11-334C17.6 had a median survival time of 485 days, while patients with lower expression had a median survival time of 380 days (HR = 0.728, 95% CI = 0.6011–0.883, p = 0.00122). Patients with high versus low expression of BTAT10 had median survival time of 335 and 485 days, respectively (HR = 1.298, 95% CI = 1.0881–1.548, p = 0.00374).

Functions of lncRNAs in GBM

lncRNAs have been implicated in GBM development and malignancy by regulating cell proliferation, apoptosis, GSC self-renewal, differentiation, and response to hypoxic stress (see Table 2).

CELL PROLIFERATION AND APOPTOSIS

MEG3, a lncRNA that is significantly downregulated in GBM (144), acts as a tumor suppressor in GBM cells. Ectopic expression of MEG3 inhibits cell proliferation and via p53 activation. CRNDE, an oncogenic lncRNA in GBM (157) and other cancer types (158), promotes cell proliferation, migration, and invasion while inhibiting apoptosis in GBM cells and GSCs (157, 159, 160). HOTAIr has been shown to regulate cell cycle progression in glioma via interaction with EZH2 (161). Knockdown of HOTAIr or EZH2 leads to cell cycle arrest in GBM cells (161) and inhibition of HOTAIr represses orthotopic GBM tumor growth in vivo (162).
**MIGRATION AND INVASION**

MALAT1 is one lncRNA that was found to regulate cell migration in GBM and lung cancer (163). Although its mechanism in glioma is unclear, initial evidence suggests that MALAT1 regulates cell migration in lung cancer cells through the mediation of several motility-associated molecules, including AIM1, LAYN, HMMR, SL26A2, CCT4, ROD1, CTHRC1, and FHL1 (164). LncRNA SOX2OT is also downregulated in migratory GBM cells, although its exact mechanism of action is unknown. Increased expression of SOX2OT in GBM correlates with better prognosis (165).

**GSC DIFFERENTIATION**

A study discovered 39 lncRNAs that were differentially expressed between GSCs and differentiated GBM cells (166), while another lncRNA screening study identified 33 lncRNAs that were expressed in a unique pattern between glioma cells and GSCs (167). Between these independent studies, six lncRNAs were consistently altered in a similar pattern, with LOC100192378, H19, RP11-112J3.16, and LOC100127888 being upregulated, and HCG4 and FLJ39609 being downregulated in GSCs (167). The effects and mechanism of action of these lncRNAs on the biological properties of GSC remains unknown, although H19 has been reported to play an important role in the maintenance of adult hematopoietic stem cells (168).

**THERAPEUTIC RESPONSE AND RESISTANCE**

Differential expression of lncRNAs has been associated with therapeutic response in GBM patients. Through gene expression profiling of GBM cell lines treated with the EGFR inhibitor erlotinib (ERL), the lncRNA GAS5 was significantly increased after treatment in both ERL-resistant and ERL-sensitive glioma cell lines. Moreover, knockdown of GAS5 sensitized GBM cells to ERL treatment (169). GAS5 is reportedly upregulated in growth-arrested cells and sensitizes mammalian cells to apoptosis, by suppressing genes responsive to glucocorticoid (170). GAS5 may also sensitize mammalian cells to apoptosis through binding to the DNA-binding domain of the glucocorticoid receptor (GR) and competing with target genes of glucocorticoid response elements (GREs).

**MECHANISMS OF ACTION OF LncRNA IN GBM**

Little is known about the regulation of lncRNA expression in GBM. c-Myc, a transcription factor, has been found to induce the expression of the lncRNA H19 in GBM cells (171). Additional transcription factors, c-Myc, NFKB, E2F6, TAF1, and SMAD, which are well-known regulators in GBM (172–175), have been found to possess several binding sites in the promoter region of the lncRNA, CRNDE, which may mediate these important signaling pathways. Similarly, the lncRNA, HOTAIRM1, is highly overexpressed in GBM, and its gene promoter sequence has been bound by NFKB, PU.1, and USF-1 (176). The lncRNA, GASS, functions as a decoy GRE by binding to the DNA-binding domain of the GR and competing with target genes of GREs. Thus, GASS acts to suppress GR-induced transcriptional activity and may
Noncoding RNAs in glioblastoma

Enhance ERL effects in GBM (132, 170). Through interaction with EZH2, IncRNA HOTAIR regulates cell cycle progression in glioma. Proteins with bromodomain and extraterminal (BET) domain are potential therapeutic targets in cancer and GBM, as treatment of GBM samples with a BET inhibitor decreases GBM growth and causes reduced HOTAIR expression. Interestingly, a protein with a BET domain has been found to directly bind the HOTAIR promoter (177). PNKY plays an important role in neuronal differentiation and chromatin-state maps of the PNKY/BRN2 locus in GSCs and shows widespread active chromatin marks at their promoters (178). PNKY can bind to PTBP1, which is upregulated in GBM, and plays a role as a driver gene in GBM tumor growth as well as in the V-SVZ neurogenic lineage (179). CRNDE, an oncogenic IncRNA, induces cell proliferation, migration, and invasion, and inhibits apoptosis in GBM cells and GSCs via the activation of multiple signaling pathways. It functions as a sponge by binding miRNAs, such as miR-384, resulting in the downregulation of piwi-like RNA-mediated gene silencing 4 (PIWIL4) and STAT3 protein in GBM cells (160). CRNDE also upregulates X-linked inhibitor of apoptosis (XIAP) and the evolutionarily conserved serine/threonine protein kinase, PAK7, by binding and inhibiting miR-186, which targets XIAP and PAK7 in GBM cells (159). The IncRNA, nuclear-enriched abundant transcript 1 (NEAT1), is essential for the formation of nuclear body paraspeckles (180) and is upregulated in GBM tissues. Inhibition of NEAT1 reduces cell proliferation, invasion, and migration. NEAT1 exerts its oncogenic effects through the direct binding of miR-449b-5p, leading to upregulation of the RTK MET (180).

Conclusion

MicroRNAs and long noncoding RNAs are frequently deregulated in cancer and GBM, where they regulate all aspects of malignancy, including tumor cell proliferation, survival, migration, and invasion, as well as cancer stem cells, angiogenesis, tumor immune responses, therapy resistance, and the microenvironment. Studying these noncoding RNAs could lead to a better understanding of GBM initiation and progression. MiRNAs and IncRNAs could also be clinically exploited for diagnostic, prognostic, and therapeutic purposes. However, more research is required, especially in the case of IncRNAs, for a better understanding and efficient clinical exploitation of this large and important class of regulatory molecules in cancer and GBM.

Acknowledgment: This article was supported by NIH R01 NS045209 (Roger Abounader).

Conflict of interest: The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this manuscript.

Copyright and permission statement: To the best of our knowledge, the materials included in this chapter do not violate copyright laws. All original sources have been appropriately acknowledged and/or referenced. Where relevant, appropriate permissions have been obtained from the original copyright holder(s).
References

1. Wen PY, Kesari S. Malignant gliomas in adults. N Engl J Med. 2008;359(5):492–507. http://dx.doi.org/10.1056/NEJMra0708126
2. Abounader R, Laterra J. Scatter factor/hepatocyte growth factor in brain tumor growth and angiogenesis. Neuro Oncol. 2005;7(4):436–51. http://dx.doi.org/10.1215/S1152851705000050
3. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008;455(7216):1061–8. http://dx.doi.org/10.1038/nature07385
4. Londin E, Loher P, Telonis AG, Quann K, Clark P, Jing Y, et al. Analysis of 13 cell types reveals evidence for the expression of numerous novel primate- and tissue-specific microRNAs. Proc Natl Acad Sci U S A. 2015;112(10):E1106–15. http://dx.doi.org/10.1073/pnas.1420955112
5. Lee YS, Dutta A. MicroRNAs in cancer. Annu Rev Pathol. 2009;4:199–227. http://dx.doi.org/10.1146/annurev.pathol.4.110807.092222
6. Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. Nature. 1998;391(6669):806–11. http://dx.doi.org/10.1038/35888
7. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. Science. 2001;294(5543):853–8. http://dx.doi.org/10.1126/science.1064921
8. Lee RC, Ambros V. An extensive class of small RNAs in Caenorhabditis elegans. Science. 2001;294(5543):862–4. http://dx.doi.org/10.1126/science.1065329
9. Lau NC, Lim LP, Weinstein EG, Bartel DP. An abundant class of tiny RNAs with probable regulatory roles in Caenorhabditis elegans. Science. 2001;294(5543):858–62. http://dx.doi.org/10.1126/science.1065062
10. Bentwich I, Avniel A, Karov Y, Aharonov R, Gilad S, Barad O, et al. Identification of hundreds of conserved and nonconserved human microRNAs. Nat Genet. 2005;37(7):766–70. http://dx.doi.org/10.1038/ng1590
11. Berezikov E, Guriev V, van de Belt J, Wienholds E, Plasterk RH, Cuppen E. Phylogenetic shadowing and computational identification of human microRNA genes. Cell. 2005;120(1):21–4. http://dx.doi.org/10.1016/j.cell.2004.12.031
12. Yu J, Wang F, Yang GH, Wang FL, Ma YN, Du ZW, et al. Human microRNA clusters: Genomic organization and expression profile in leukemia cell lines. Biochem Biophys Res Commun. 2006;349(1):59–68. http://dx.doi.org/10.1016/j.bbrc.2006.07.207
13. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell. 2005;120(1):15–20. http://dx.doi.org/10.1016/j.cell.2005.03.035
14. Dews M, Homayouni A, Yu D, Murphy D, Sevignani C, Wentzel E, et al. Augmentation of tumor angiogenesis by a Myc-activated microRNA cluster. Nat Genet. 2006;38(9):1060–5. http://dx.doi.org/10.1038/ng1855
15. Sylvestre Y, De Guire V, Querido E, Mukhopadhyay UK, Bourdeau V, Major F, et al. An E2F/miR-20a autoregulatory feedback loop. J Biol Chem. 2007;282(4):2135–43. http://dx.doi.org/10.1074/jbc.M608939200
16. Hafner M, Renwick N, Brown M, Mihailovic A, Holoch D, Lin C, et al. RNA-ligase-dependent biases in miRNA representation in deep-sequenced small RNA cDNA libraries. RNA. 2011;17(9):1697–712. http://dx.doi.org/10.1216/rna.2011.17.9.2799511
17. Hermeking H. p53 enters the microRNA world. Cancer Cell. 2007;12(5):414–8. http://dx.doi.org/10.1016/j.ccr.2007.10.028
18. He L, He X, Lim LP, de Stanchina E, Xuan Z, Liang Y, et al. A microRNA component of the p53 tumour suppressor network. Nature. 2007;447(7148):1130–4. http://dx.doi.org/10.1038/nature05939
19. Zhang Y, Kim J, Mueller AC, Dey B, Yang Y, Lee DH, et al. Multiple receptor tyrosine kinases converge on microRNA-134 to control KRAS, STAT5B, and glioblastoma. Cell Death Differ. 2014;21(5):720–34. http://dx.doi.org/10.1038/cdd.2013.196
Noncoding RNAs in glioblastoma

20. Melo SA, Esteller M. Dysregulation of microRNAs in cancer: Playing with fire. FEBS Lett. 2011;585(13):2087–99. http://dx.doi.org/10.1016/j.febslet.2010.08.009

21. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci U S A. 2004;101(9):2999–3004. http://dx.doi.org/10.1073/pnas.0307323101

22. Moller HG, Rasmussen AP, Andersen HH, Johnsen KB, Henriksen M, Duroux M. A systematic review of microRNA in glioblastoma multiforme: Micro-modulators in the mesenchymal mode of migration and invasion. Mol Neurobiol. 2013;47(1):131–44. http://dx.doi.org/10.1007/s12035-012-8349-7

23. Shea A, Harish V, Alzal Z, Chijoke J, Kedir H, Dumatava S, et al. MicroRNAs in glioblastoma multiforme pathogenesis and therapeutics. Cancer Med. 2016;5(8):1917–46. http://dx.doi.org/10.1002/cam4.775

24. Conti A, Aguennouz M, La Torre D, Tomasello C, Cardali S, Anglieri FF, et al. MicroRNAs in glioblastoma multiforme pathogenesis and therapeutics. Cancer Med. 2016;5(8):1917–46. http://dx.doi.org/10.1002/cam4.775

25. Chan JA, Krichevsky AM, Kosik KS. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. Cancer Res. 2005;65(14):6029–33. http://dx.doi.org/10.1158/0008-5472.CAN-05-0137

26. Silber J, Lim DA, Petritsch C, Persson AI, Maunakea AK, Yu M, et al. miR-124 and miR-137 inhibit proliferation of glioblastoma multiforme cells and induce differentiation of brain tumor stem cells. BMC Med. 2008;6:14. http://dx.doi.org/10.1186/1741-7015-6-14

27. Gabriely G, Wurdinger T, Kesari S, Esau CC, Burchard J, Linsley PS, et al. MicroRNA 21 promotes glioma invasion by targeting matrix metalloproteinase regulators. Mol Cell Biol. 2008;28(17):5369–80. http://dx.doi.org/10.1128/MCB.00479-08

28. Malzkorn B, Wolter M, Liesenberg F, Grzendowski M, Stuhler K, Meyer HE, et al. Identification and functional characterization of microRNAs involved in the malignant progression of gliomas. Brain Pathol. 2010;20(3):539–50. http://dx.doi.org/10.1111/j.1750-3639.2009.00328.x

29. Ciafre SA, Galardi S, Mangiola A, Ferracin M, Liu CG, Sabatino G, et al. Extensive modulation of a set of microRNAs in primary glioblastoma. Biochem Biophys Res Commun. 2005;334(4):1351–8. http://dx.doi.org/10.1016/j.bbrc.2005.07.030

30. Conrad ME, Barton JC. Factors affecting the absorption and excretion of lead in the rat. Gastroenterology. 1978;74(4):731–40.

31. Shi L, Cheng Z, Zhang J, Li R, Zhao P, Fu Z, et al. hsa-mir-181a and hsa-mir-181b function as tumor suppressors in human glioma cells. Brain Res. 2008;1236:185–93. http://dx.doi.org/10.1016/j.brainres.2008.07.085

32. Slaby O, Lakomy R, Fadrus P, Hrstka R, Kren L, Lzicarova E, et al. MicroRNA-181 family predicts response to concomitant chemoradiotherapy with temozolomide in glioblastoma patients. Neoplasma. 2010;57(3):264–9. http://dx.doi.org/10.4149/neo_2010_03_264

33. Huse JT, Brennan C, Hambardzumyan D, Wee B, Pena J, Rouhanifard SH, et al. The PTEN-regulating microRNA miR-26a is amplified in high-grade glioma and facilitates gliomagenesis in vivo. Genes Dev. 2009;23(11):1327–37. http://dx.doi.org/10.1101/gad.1777409

34. Kim H, Huang W, Jiang X, Pennicooke B, Park PJ, Johnson MD. Integrative genome analysis reveals an oncomir/oncogene cluster regulating glioblastoma survivalship. Proc Natl Acad Sci U S A. 2010;107(5):2183–8. http://dx.doi.org/10.1073/pnas.090896107

35. Li Y, Guessous F, Zhang Y, Dipierro C, Kefas B, Johnson E, et al. MicroRNA-34a inhibits glioblastoma growth by targeting multiple oncogenes. Cancer Res. 2009;69(19):7569–76. http://dx.doi.org/10.1158/0008-5472.CAN-09-0529

36. Kim J, Zhang Y, Skalski M, Hayes J, Kefas B, Schiff D, et al. microRNA-148a is a prognostic oncomiR that targets MIG6 and BIM to regulate EGFR and apoptosis in glioblastomas. Cancer Res. 2014;74(5):1541–53. http://dx.doi.org/10.1158/0008-5472.CAN-13-1449

37. Sasayama T, Nishihara M, Kondoh T, Hosoda K, Kohmura E. MicroRNA-10b is overexpressed in malignant glioma and associated with tumor invasive factors, uPAR and RhoC. Int J Cancer. 2009;125(6):1407–13. http://dx.doi.org/10.1002/ijc.24522

38. Guessous F, Alvarado-Velez M, Marcinikiewicz L, Zhang Y, Kim J, Heister S, et al. Oncogenic effects of miR-10b in glioblastoma stem cells. J Neurooncol. 2013;112(2):153–63. http://dx.doi.org/10.1007/s11060-013-1047-0
39. Jiang L, Mao P, Song L, Wu J, Huang J, Lin C, et al. miR-182 as a prognostic marker for glioma progression and patient survival. Am J Pathol. 2010;177(1):29–38. http://dx.doi.org/10.2353/ajpath.2010.090812
40. Akers JC, Ramakrishnan V, Kim R, Skog J, Nakano I, Pingle S, et al. MiR-21 in the extracellular vesicles (EVs) of cerebrospinal fluid (CSF): A platform for glioblastoma biomarker development. PLoS One. 2013;8(10):e78115. http://dx.doi.org/10.1371/journal.pone.0078115
41. Teplyuk NM, Mollenhauer B, Gabriely G, Giese A, Kim E, Smolsky M, et al. MicroRNAs in cerebrospinal fluid identify glioblastoma and metastatic brain cancers and reflect disease activity. Neuro Oncol. 2012;14(6):689–700. http://dx.doi.org/10.1093/neuonc/nos074
42. Li CC, Eaton SA, Young PE, Lee M, Shuttleworth R, Humphreys DT, et al. Glioma microvesicles carry selectively packaged coding and non-coding RNAs which alter gene expression in recipient cells. RNA Biol. 2013;10(8):1333–44. http://dx.doi.org/10.4161/rna.25281
43. Wang Q, Li P, Li A, Jiang W, Wang H, Wang J, et al. Plasma specific miRNAs as predictive biomarkers for diagnosis and prognosis of glioma. J Exp Clin Cancer Res. 2012;31:97. http://dx.doi.org/10.1186/1756-9966-31-97
44. Sun J, Liao K, Wu X, Huang J, Zhang S, Lu X. Serum microRNA-128 as a biomarker for diagnosis of glioma. Int J Clin Exp Med. 2015;8(1):456–63.
45. Yue X, Lan F, Hu M, Pan Q, Wang Q, Wang J. Downregulation of serum microRNA-205 as a potential diagnostic and prognostic biomarker for human glioma. J Neurosurg. 2016;124(1):122–8. http://dx.doi.org/10.3171/2015.1.JNS141577
46. Barciszewska AM. MicroRNAs as efficient biomarkers in high-grade gliomas. Folia Neuropathol. 2016;54(4):369–74. http://dx.doi.org/10.5114/fn.2016.64812
47. Shao N, Wang L, Xue L, Wang R, Lan Q. Plasma miR-454-3p as a potential prognostic indicator in human glioma. Neurol Sci. 2015;36(2):309–13. http://dx.doi.org/10.1007/s10072-014-1938-7
48. Yu X, Li Z. Serum microRNAs as potential noninvasive biomarkers for glioma. Tumour Biol. 2016;37(2):1407–10. http://dx.doi.org/10.1007/s13277-015-4515-7
49. Yang C, Wang C, Chen X, Chen S, Zhang Y, Zhi F, et al. Identification of seven serum microRNAs from a genome-wide serum microRNA expression profile as potential noninvasive biomarkers for malignant astrocytomas. Int J Cancer. 2013;132(1):116–27. http://dx.doi.org/10.1002/ijc.27657
50. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, et al. Glioma stem cells promote radioreistance by preferential activation of the DNA damage response. Nature. 2006;444(7120):756–60. http://dx.doi.org/10.1038/nature05349
51. Fan X, Matsui W, Khaki L, Stearns D, Chun J, Li YM, et al. NOTCH pathway inhibition depletes stem-like cells and blocks engraftment in embryonal brain tumors. Cancer Res. 2006;66(15):7445–52. http://dx.doi.org/10.1158/0008-5472.CAN-06-0858
52. Shih AH, Holland EC. Notch signaling enhances nestin expression in gliomas. Neoplasia. 2006;8(12):1072–82. http://dx.doi.org/10.1593/neo.060526
53. Fan X, Khaki L, Zhu TS, Soules ME, Talsma CE, Gul N, et al. NOTCH pathway blockade depletes CD133-positive glioblastoma cells and inhibits growth of tumor neurospheres and xenografts. Stem Cells. 2010;28(1):5–16.
59. Wang J, Wakeman TP, Lathia JD, Hjelmeland AB, Wang XF, White RR, et al. Notch promotes radioreistance of glioma stem cells. Stem Cells. 2010;28(1):17–28.

60. Zhang XP, Zheng G, Zou L, Liu HL, Hou LH, Zhou P, et al. Notch activation promotes cell proliferation and the formation of neural stem cell-like colonies in human glioma cells. Mol Cell Biochem. 2008;307(1–2):101–8.

61. Ernst A, Campos B, Meier J, Devens F, Liesenberg F, Wolter M, et al. De-repression of CTGF via the miR-17-92 cluster upon differentiation of human glioblastoma spheroid cultures. Oncogene. 2010;29(23):3411–22. http://dx.doi.org/10.1038/onc.2010.83

62. Talotta F, Cimmino A, Matarazzo MR, Casalino L, De Vita G, D’Esposito M, et al. An autoregulatory loop mediated by miR-21 and PDCD4 controls the AP-1 activity in RAS transformation. Oncogene. 2009;28(1):73–84. http://dx.doi.org/10.1038/onc.2008.370

63. Papagiannakopoulos T, Shapiro A, Kosik KS. MicroRNA-21 targets a network of key tumor-suppressive pathways in glioblastoma cells. Cancer Res. 2008;68(19):8164–72. http://dx.doi.org/10.1158/0008-5472.CAN-08-1305

64. Chen Y, Liu W, Chao T, Zhang Y, Yan X, Gong Y, et al. MicroRNA-21 down-regulates the expression of tumor suppressor PDCD4 in human glioblastoma cell T98G. Cancer Lett. 2008;272(2):197–205. http://dx.doi.org/10.1016/j.canlet.2008.06.034

65. Zhou X, Ren Y, Moore L, Mei M, You Y, Xu P, et al. Downregulation of miR-21 inhibits EGFR pathway and suppresses the growth of human glioma cells independent of PTEN status. Lab Invest. 2010;90(2):144–55. http://dx.doi.org/10.1038/lab.2009.126

66. Gaur AB, Holbeck SL, Colburn NH, Israel MA. Downregulation of Pdc4 by mir-21 facilitates glioblastoma proliferation in vivo. Neuro Oncol. 2011;13(6):580–90. http://dx.doi.org/10.1093/neuonc/ nor033

67. Yang CH, Yue J, Pfeffer SR, Fan M, Paulus E, Hosni-Ahmed A, et al. MicroRNA-21 promotes glioblastoma tumorigenesis by down-regulating insulin-like growth factor-binding protein-3 (IGFBP3). J Biol Chem. 2014;289(36):25079–87. http://dx.doi.org/10.1074/jbc.M114.593863

68. Kwak HJ, Kim YJ, Chun KR, Woo YM, Park SJ, Jeong JA, et al. Downregulation of Spry2 by miR-21 triggers malignancy in human gliomas. Oncogene. 2011;30(21):2433–42. http://dx.doi.org/10.1038/onc.2010.620

69. Gillies JK, Lorimer IA. Regulation of p27Kip1 by miRNA 221/222 in glioblastoma. Cell Cycle. 2007;6(16):2005–9. http://dx.doi.org/10.4161/cc.6.16.4526

70. Zhang C, Kang C, You Y, Pu P, Yang W, Zhao P, et al. Co-suppression of miR-221/222 cluster suppresses human glioma cell growth by targeting p27Kip1 in vitro and in vivo. Int J Oncol. 2009;34(6):1653–60.

71. Zhang CZ, Zhang JX, Zhang AL, Shi ZD, Han L, Jia ZF, et al. MiR-221 and miR-222 target PUMA to induce cell survival in glioblastoma. Mol Cancer. 2010;9:229. http://dx.doi.org/10.1186/1476-4598-9-229

72. Chen L, Zhang J, Han L, Zhang A, Zhang C, Zheng Y, et al. Downregulation of miR-221/222 sensitizes glioma cells to temozolomide by regulating apoptosis independently of p53 status. Oncol Rep. 2012;27(3):854–60.

73. Shu M, Zheng X, Wu S, Lu H, Leng T, Zhu W, et al. Targeting oncogenic miR-335 inhibits growth and invasion of malignant astrocytoma cells. Mol Cancer. 2011;10:59. http://dx.doi.org/10.1186/1476-4598-10-59

74. Shu M, Zhou Y, Zhu W, Wu S, Zheng X, Yan G. Activation of a pro-survival pathway IL-6/JAK2/STAT3 contributes to glial fibrillary acidic protein induction during the cholera toxin-induced differentiation of C6 malignant glioma cells. Mol Oncol. 2011;5(3):265–72. http://dx.doi.org/10.1016/j.molonc.2011.03.003

75. Sun F, Fu H, Liu Q, Tie Y, Zhu J, Xing R, et al. Downregulation of CCND1 and CDK6 by miR-34a induces cell cycle arrest. FEBS Lett. 2008;582(10):1564–8. http://dx.doi.org/10.1016/j.febslet.2008.03.057

76. Bueno MJ, Malumbres M. MicroRNAs and the cell cycle. Biochim Biophys Acta. 2011;1812(5):592–601. http://dx.doi.org/10.1016/j.bbadis.2011.02.002

77. Luan S, Sun L, Huang F. MicroRNA-34a: A novel tumor suppressor in p53-mutant glioma cell line U251. Arch Med Res. 2010;41(2):67–74. http://dx.doi.org/10.1016/j.arcmed.2010.02.007
78. Zhang JM, Sun CY, Yu SZ, Wang Q, An TL, Li YY, et al. [Relationship between miR-218 and CDK6 expression and their biological impact on glioma cell proliferation and apoptosis]. Zhonghua bing li xue za zhi Chin J Pathol. 2011;40(7):454–9.

79. Xia H, Yan Y, Hu M, Wang Y, Wang Y, Dai Y, et al. MiR-218 sensitizes glioma cells to apoptosis and inhibits tumorigenicity by regulating ECOP-mediated suppression of NF-kappaB activity. Neuro Oncol. 2013;15(4):413–22. http://dx.doi.org/10.1093/neuonc/nos296

80. Nan Y, Han L, Zhang A, Wang G, Jia Z, Yang Y, et al. MiRNA-451 plays a role as tumor suppressor in human glioma cells. Brain Res. 2010;1359:14–21. http://dx.doi.org/10.1016/j.brainres.2010.08.074

81. Wurdinger T, Tannous BA, Saydam O, Skog J, Grau S, Soutschek J, et al. MiR-296 regulates growth factor receptor overexpression in angiogenic endothelial cells. Cancer Cell. 2008;14(5):382–93. http://dx.doi.org/10.1016/j.ccr.2008.10.005

82. Smits M, Wurdinger T, van het Hof B, Dreuxhage JA, Geerts D, Wesseling P, et al. Myc-associated zinc finger protein (MAZ) is regulated by miR-125b and mediates VEGF-induced angiogenesis in glioblastoma. FASEB J. 2012;26(6):2639–47. http://dx.doi.org/10.1096/fj.11-202820

83. Yang G, Han D, Chen X, Zhang D, Wang L, Shi C, et al. MiR-196a exerts its oncogenic effect in glioblastoma multiforme by inhibition of IkappaBalpha both in vitro and in vivo. Neuro Oncol. 2014;16(5):652–61. http://dx.doi.org/10.1093/neuonc/not307

84. Floyd DH, Zhang Y, Dey BK, Kefas B, Breit H, Marks K, et al. Novel anti-apoptotic microRNAs 582-5p and 363 promote human glioblastoma stem cell survival via direct inhibition of caspase 3, caspase 9, and Bim. PLoS One. 2014;9(5):e96239. http://dx.doi.org/10.1371/journal.pone.0096239

85. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest. 2009;119(6):1420–8. http://dx.doi.org/10.1172/JCI39104

86. Schramedei K, Morbt N, Peifer G, Lauter J, Rosolowski M, Tomm JM, et al. MicroRNA-21 targets tumor suppressor genes ANP32A and SMARCA4. Oncogene. 2011;30(26):2975–85. http://dx.doi.org/10.1038/onc.2011.15

87. Li Y, Wang Y, Yu L, Sun C, Cheng D, Yu S, et al. miR-146b-5p inhibits glioma migration and invasion by targeting MMP16. Cancer Lett. 2013;339(2):260–9. http://dx.doi.org/10.1016/j.canlet.2013.06.018

88. Sun L, Yan Y, Wang Y, Sun G, Luo H, Zhang J, et al. MicroRNA-10b induces glioma cell invasion by modulating MMP-14 and uPAR expression via HOXD10. Brain Res. 2011;1389:9–18. http://dx.doi.org/10.1016/j.brainres.2011.03.013

89. Lin J, Teo S, Lam DH, Jeyaseelan K, Wang S. MicroRNA-10b pleiotropically regulates invasion, angiogenicity and apoptosis of tumor cells resembling mesenchymal subtype of glioblastoma multiforme. Cell Death Dis. 2012;3:e398. http://dx.doi.org/10.1038/cddis.2012.134

90. Mao XG, Hutt-Cabezaz M, Otr BA, Weingart M, Taylor I, Rajan AK, et al. LIN28A facilitates the transformation of human neural stem cells and promotes glioblastoma tumorigenesis through a pro-invasive genetic program. Oncotarget. 2013;4(7):1050–64. http://dx.doi.org/10.18632/oncotarget.1131

91. Wang S, Olson EN. AngiomiRs--key regulators of angiogenesis. Curr Opin Genet Dev. 2009;19(3):205–11. http://dx.doi.org/10.1016/j.gde.2009.04.002

92. Mathew L, Skuli N, Mucaj V, Lee SS, Zinn PO, Sathyan P, et al. miR-218 opposes a critical RTK-HIF pathway in mesenchymal glioblastoma. Proc Natl Acad Sci U S A. 2014;111(1):291–6. http://dx.doi.org/10.1073/pnas.1314341111

93. Agrawal R, Pandey P, Jha P, Dwivedi V, Sarkar C, Kulshreshtha R. Hypoxic signature of microRNAs in glioblastoma: Insights from small RNA deep sequencing. BMC Genomics. 2014;15:686. http://dx.doi.org/10.1186/1471-2164-15-686

94. Fang L, Deng Z, Shatseva T, Yang J, Peng C, Du WW, et al. MicroRNA Mr-93 promotes tumor growth and angiogenesis by targeting integrin-beta8. Oncogene. 2011;30(7):806–21. http://dx.doi.org/10.1038/onc.2010.465

95. Brooks WH, Markesbery WR, Gupta GD, Roszman TL. Relationship of lymphocyte invasion and survival of brain tumor patients. Ann Neurol. 1978;4(3):219–24. http://dx.doi.org/10.1002/ana.410040305

96. Jacobs JF, Idena AJ, Bol KE, Grotenhuis JA, de Vries IJ, Wesseling P, et al. Prognostic significance and mechanism of Treg infiltration in human brain tumors. J Neuroimmunol. 2010;225(1–2):195–9. http://dx.doi.org/10.1016/j.jneuroim.2010.05.020
97. Kong LY, Wu AS, Doucette T, Wei J, Priewe W, Fuller GN, et al. Intratumoral mediated immunosuppression is prognostic in genetically engineered murine models of glioma and correlates to immunotherapeutic responses. Clin Cancer Res. 2010;16(23):5722–33. http://dx.doi.org/10.1158/1078-0432.CCR-10-1693

98. Palma L, Di Lorenzo N, Guidetti B. Lymphocytic infiltrates in primary glioblastomas and recidivous gliomas. Incidence, fate, and relevance to prognosis in 228 operated cases. J Neurosurg. 1978;49(6):854–61. http://dx.doi.org/10.3171/jns.1978.49.6.0854

99. Safdari H, Hochberg FH, Richardson EP, Jr. Prognostic value of round cell (lymphocyte) infiltration in malignant gliomas. Surg Neurol. 1985;23(3):221–6. http://dx.doi.org/10.1016/0090-3019(85)90086-2

100. von Hanwehr RI, Hofman FM, Taylor CR, Apuzzo ML. Mononuclear lymphoid populations infiltrating the microenvironment of primary CNS tumors. Characterization of cell subsets with monoclonal antibodies. J Neurosurg. 1984;60(6):1138–47. http://dx.doi.org/10.3171/jns.1984.60.6.1138

101. Yang I, Tihan T, Han SJ, Wrensch MR, Wiencke J, Sughrue ME, et al. CD8+ T-cell infiltrate in newly diagnosed glioblastoma is associated with long-term survival. J Clin Neurosci. 2010;17(11):1381–5. http://dx.doi.org/10.1016/j.jocn.2010.03.031

102. Wei J, Wang F, Kong LY, Xu S, Doucette T, Ferguson SD, et al. miR-124 inhibits STAT3 signaling to enhance T cell-mediated immune clearance of glioma. Cancer Res. 2013;73(13):3913–26. http://dx.doi.org/10.1158/0008-5472.CAN-12-4318

103. Ueda R, Kohanbash G, Sasaki K, Fujita M, Zhu X, Kastenhuber ER, et al. Dicer-regulated microRNAs 222 and 339 promote resistance of cancer cells to cytotoxic T-lymphocytes by down-regulation of ICAM-1. Proc Natl Acad Sci U S A. 2009;106(26):10746–51. http://dx.doi.org/10.1073/pnas.0811817106

104. Hassan A, Mosley J, Singh S, Zinn PO. A comprehensive review of genomics and noncoding RNA in gliomas. Top Magn Reson Imaging. 2017;26(1):3–14. http://dx.doi.org/10.1097/01.mri.0000000000000111

105. Shi L, Chen J, Yang J, Pan T, Zhang S, Wang Z. MiR-21 protected human glioblastoma U87MG cells from chemotherapeutic drug temozolomide induced apoptosis by decreasing Bax/Bcl-2 ratio and caspase-3 activity. Brain Res. 2010;1352:255–64. http://dx.doi.org/10.1016/j.brainres.2010.07.009

106. Li Y, Li W, Yang Y, Lu Y, He C, Hu G, et al. MicroRNA-21 targets LRRFIP1 and contributes to VM-26 resistance in glioblastoma multiforme. Brain Res. 2009;1286:13–8. http://dx.doi.org/10.1016/j.brainres.2009.06.053

107. Costa PM, Cardoso AL, Nobrega C, Pereira de Almeida LF, Bruce JN, Canoll P, et al. MicroRNA-21 silencing enhances the cytotoxic effect of the antiangiogenic drug sunitinib in glioblastoma. Hum Mol Genet. 2013;22(5):904–18. http://dx.doi.org/10.1093/hmg/ddq496

108. Wong ST, Zhang XQ, Zhuang JT, Chan HL, Li CH, Leung GK. MicroRNA-21 inhibition enhances in vitro chemosensitivity of temozolomide-resistant glioblastoma cells. Anticancer Res. 2012;32(7):2835–41.

109. Barker CA, Chang M, Chou JF, Zhang Z, Beal K, Gutin PH, et al. Radiotherapy and concomitant temozolomide may improve survival of elderly patients with glioblastoma. J Neurooncol. 2012;109(2):391–7. http://dx.doi.org/10.1007/s11060-012-0906-4

110. Ren Y, Zhou X, Mei M, Yuan XB, Han L, Wang GX, et al. MicroRNA-21 inhibitor sensitizes human glioblastoma cells U251 (PTEN-mutant) and LN229 (PTEN-wild type) to taxol. BMC Cancer. 2010;10:27. http://dx.doi.org/10.1186/1471-2407-10-27

111. Ujifuku K, Mitsutake N, Takakura S, Matsuse M, Saenko V, Suzuki K, et al. miR-195, miR-455-3p and miR-10a(*) are implicated in acquired temozolomide resistance in glioblastoma multiforme cells. Cancer Lett. 2010;296(2):241–8. http://dx.doi.org/10.1016/j.canlet.2010.04.013

112. Zhang S, Han L, Wei J, Shi Z, Pu P, Zhang J, et al. Combination treatment with doxorubicin and microRNA-21 inhibitor synergistically augments anticancer activity through upregulation of tumor suppressing genes. Int J Oncol. 2015;46(4):1589–600. http://dx.doi.org/10.3892/ijo.2015.2841

113. Shi L, Zhang S, Feng K, Wu F, Wan Y, Wang Z, et al. MicroRNA-125b-2 confers human glioblastoma stem cells resistance to temozolomide through the mitochondrial pathway of apoptosis. Int J Oncol. 2012;40(1):119–29.

114. Turri E, Haenisch S, Laechelt S, Diewock T, Bruhn O, Cascorbi I. MicroRNA profiling in K-562 cells under imatinib treatment: Influence of miR-212 and miR-328 on ABCG2 expression. Pharmacogenet Genomics. 2012;22(3):198–205. http://dx.doi.org/10.1097/FPC.0b013e328350012b
115. Ng WL, Yan D, Zhang X, Mo YY, Wang Y. Over-expression of miR-100 is responsible for the low-expression of ATM in the human glioma cell line: M059J. DNA repair. 2010;9(11):1170–5. http://dx.doi.org/10.1016/j.dnarep.2010.08.007

116. Krichhevsky AM, King KS, Donahue CP, Khrapko K, Kosik KS. A microRNA array reveals extensive regulation of microRNAs during brain development. RNA. 2003;9(10):1274–81. http://dx.doi.org/10.1261/rna.5980303

117. Lee TJ, Yoo JY, Shu D, Li H, Zhang J, Yu JG, et al. RNA nanoparticle-based targeted therapy for glioblastoma through inhibition of oncogenic miR-21. Mol Ther. 2017;25(7):1544–55. http://dx.doi.org/10.1016/j.molther.2016.11.016

118. Gabriely G, Yi M, Narayan RS, Niers JM, Wurdinger T, Imitola J, et al. Human glioma growth is controlled by microRNA-10b. Cancer Res. 2011;71(10):3563–72. http://dx.doi.org/10.1158/0008-5472.CAN-10-3568

119. El Fatimy R, Subramanian S, Uhlmann EJ, Krichhevsky AM. Genome editing reveals glioblastoma addiction to microRNA-10b. Mol Ther. 2017;25(2):368–78. http://dx.doi.org/10.1016/j.molther.2016.11.004

120. Kefas B, Comeau L, Erdle N, Montgomery E, Amos S, Purow B. Pyruvate kinase M2 is a target of the tumor-suppressive microRNA-326 and regulates the survival of glioma cells. Neuro Oncol. 2010;12(11):1102–12. http://dx.doi.org/10.1093/neuonc/noq080

121. Godlewski J, Nowicki MO, Bronisz A, Williams S, Otsuki A, Nuovo G, et al. Targeting of the Bmi-1 oncogene/stem cell renewal factor by microRNA-128 inhibits glioma proliferation and self-renewal. Cancer Res. 2008;68(22):9125–30. http://dx.doi.org/10.1158/0008-5472.CAN-08-2629

122. Kefas B, Floyd DH, Comeau L, Frisbee A, Dominguez C, Dipierro CG, et al. A miR-297/hypoxia/DGKa alpha axis regulating glioblastoma survival. Neuro Oncol. 2013;15(12):1652–63. http://dx.doi.org/10.1093/neuonc/not118

123. Godlewski J, Nowicki MO, Bronisz A, Williams S, Otsuki A, Nuovo G, et al. Targeting of the Bmi-1 oncogene/stem cell renewal factor by microRNA-128 inhibits glioma proliferation and self-renewal. Cancer Res. 2008;68(22):9125–30. http://dx.doi.org/10.1158/0008-5472.CAN-08-2629

124. Kefas B, Floyd DH, Comeau L, Frisbee A, Dominguez C, Dipierro CG, et al. A miR-182 integrates apoptosis, growth, and differentiation programs in glioblastoma. Genes Dev. 2015;29(7):732–45. http://dx.doi.org/10.1011/gad.257394.114

125. Skog J, Wurdinger T, van Rijn S, Meijer DH, Gainche L, Sena-Esteves M, et al. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. Nat Cell Biol. 2008;10(12):1470–1476. http://dx.doi.org/10.1038/ncb1800

126. Beg MS, Brenner AJ, Sachdev J, Borad M, Kang YK, Stoudemire J, et al. Phase I study of MRX34, a liposomal miR-34a mimic, administered twice weekly in patients with advanced solid tumors. Invest New Drugs. 2017;35(2):180–8. http://dx.doi.org/10.1007/s10637-016-0407-y

127. Rinn JL, Chang HY. Genome regulation by long noncoding RNAs. Annu Rev Biochem. 2012;81:145–66. http://dx.doi.org/10.1146/annurev-biochem-051410-092902

128. Batista PJ, Chang HY. Long noncoding RNAs: Cellular address codes in development and disease. Cell. 2013;152(6):1298–307. http://dx.doi.org/10.1016/j.cell.2013.02.012

129. Mercer TR, Mattick JS. Structure and function of long noncoding RNAs in epigenetic regulation. Nat Struct Mol Biol. 2013;20(3):300–7. http://dx.doi.org/10.1038/nsmb.2480

130. Heo JB, Lee YS, Sung S. Epigenetic regulation by long noncoding RNAs in plants. Chromosome Res. 2013;21(6–7):685–93. http://dx.doi.org/10.1007/s10577-013-9392-6

131. Ramos AD, Attenollo FJ, Lim DA. Uncovering the roles of long noncoding RNAs in neural development and glioma progression. Neurosci Lett. 2016;625:70–9. http://dx.doi.org/10.1016/j.neulet.2015.12.025

132. Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, et al. The landscape of long noncoding RNAs in the human transcriptome. Nat Genet. 2015;47(3):199–208SS.

133. Cabili MN, Trapnell C, Goff L, Koziol M, Tazon-Vega B, Regev A, et al. Integrative annotation of large intergenic noncoding RNAs reveals global properties and specific subclasses. Gene Dev. 2011;25(18):1915–27. http://dx.doi.org/10.1101/gad.17446611
135. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgher H, et al. The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression. Genome Res. 2012;22(9):1775–89. http://dx.doi.org/10.1101/gr.132159.111

136. Mercer TR, Qureshi IA, Gokhan S, Dinger ME, Li GY, Mattick JS, et al. Long noncoding RNAs in neuronal-glia fate specification and oligodendrocyte lineage maturation. BMC Neurosci. 2010;11:14. http://dx.doi.org/10.1186/1471-2202-11-14

137. Belgard TG, Marques AC, Oliver PL, Aibaan HO, Sirey TM, Hoerder-Suabedissen A, et al. A transcriptomic atlas of mouse neocortical layers. Neurosci. 2011;71(4):605–16. http://dx.doi.org/10.1016/j.neuron.2011.06.039

138. Ulitsky I, Shkumatava A, Jan CH, Sive H, Bartel DP. Conserved function of lincRNAs in vertebrate embryonic development despite rapid sequence evolution. Cell. 2011;147(7):1537–50. http://dx.doi.org/10.1016/j.cell.2011.11.055

139. Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature. 2009;458(7235):223–7. http://dx.doi.org/10.1038/nature07672

140. Ramos AD, Diaz A, Nellore A, Delgado RN, Park KY, Gondalez-Roybal G, et al. Integration of genome-wide approaches identifies lncRNAs of adult neural stem cells and their progeny in vivo. Cell Stem Cell. 2013;12(5):616–28. http://dx.doi.org/10.1016/j.stem.2013.03.003

141. Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: Insights into functions. Nat Rev Genet. 2009;10(3):155–9. http://dx.doi.org/10.1038/nrg2521

142. Bian EB, Li J, Xie YS, Zong G, Li J, Zhao B. LncRNAs: New players in gliomas, with special emphasis on the interaction of lncRNAs with EZH2. J Cell Physiol. 2015;230(3):496–503. http://dx.doi.org/10.1002/jcp.24549

143. Sun YZ, Wang Z, Zhou D. Long non-coding RNAs as potential biomarkers and therapeutic targets for gliomas. Med Hypotheses. 2013;81(2):319–21. http://dx.doi.org/10.1016/j.mehy.2013.04.010

144. Wang PJ, Ren QZ, Sun PY. Overexpression of the long non-coding RNA MEG3 impairs in vitro glioma cell proliferation. J Cell Biochem. 2012;113(6):1868–74. http://dx.doi.org/10.1002/jcb.24055

145. Zhang XQ, Sun S, Pu JKS, Tsang ACO, Lee D, Man VOY, et al. Long non-coding RNA expression profiles predict clinical phenotypes in glioma. Neurobiol Dis. 2012;48(1):1–8. http://dx.doi.org/10.1016/j.nbd.2012.06.004

146. Amit D, Matouk IJ, Lavon I, Birman T, Galula J, Abu-Lail R, et al. Transcriptional targeting of glioblastoma by diphtheria toxin-A driven by both H19 and IGF2-P4 promoters. Int J Clin Exp Med. 2012;5(2):124–35.

147. Qi P, Du X. The long non-coding RNAs, a new cancer diagnostic and therapeutic gold mine. Modern Pathol. 2013;26(2):155–65. http://dx.doi.org/10.1038/modpathol.2012.160

148. Spizzo R, Almeida MI, Colombatti A, Calin GA. Long non-coding RNAs and cancer: A new frontier of translational research? Oncogene. 2012;31(43):4577–87. http://dx.doi.org/10.1038/onc.2011.621

149. Wahlestedt C. Targeting long non-coding RNA to therapeutically upregulate gene expression. Nat Rev Drug Discov. 2013;12(6):433–46. http://dx.doi.org/10.1038/nrd4018

150. Han L, Zhang KL, Shi ZD, Zhang JX, Zhu SJ, et al. LncRNA profile of glioblastoma reveals the potential role of lncRNAs in contributing to glioblastoma pathogenesis. Int J Oncol. 2012;40(6):2004–12.

151. Gravendeel L, Kouwenhoven M, Gevaert O, de Rooi J, Stubbs A, Duijnm J, et al. Intrinsic gene expression profiles of gliomas are a better predictor of survival than histology. Neuro Oncol. 2009;11(5):602. http://dx.doi.org/10.1177/1460207209337727

152. Sun LX, Hui AM, Su Q, Vortmeyer A, Kotliarov Y, Pastorino S, et al. Neuronal and glia-derived stem cell factor induces angiogenesis within the brain. Cancer Cell. 2006;9(4):287–300. http://dx.doi.org/10.1016/j.ccr.2006.03.003

153. Murat A, Migliavacca E, Gorlia T, Lambiv WL, Shay T, Hamou MF, et al. Stem cell-related “Self-Renewal” signature and high epidermal growth factor receptor expression associated with resistance to concomitant chemoradiotherapy in glioblastoma. J Clin Oncol. 2008;26(18):3015–24. http://dx.doi.org/10.1200/JCO.2007.15.7164
154. Grzmil M, Morin PJ, Lino MM, Merlo A, Frank S, Wang YH, et al. MAP kinase-interacting kinase 1 regulates SMAD2-dependent TGF-beta signaling pathway in human glioblastoma. Cancer Res. 2011;71(6):2392–402. http://dx.doi.org/10.1158/0008-5472.CAN-10-3112

155. Reon BJ, Anaya J, Zhang Y, Mandell J, Purow B, Abounader R, et al. Expression of lncRNAs in low-grade gliomas and glioblastoma multiforme: An in silico analysis. PLoS Med. 2016;13(12):e1002192. http://dx.doi.org/10.1371/journal.pmed.1002192

156. Lin NW, Chang KY, Li ZH, Gates K, Rana ZA, Dang JS, et al. An evolutionarily conserved long non-coding RNA TUNA controls pluripotency and neural lineage commitment. Mol Cell. 2014;53(6):1005–19. http://dx.doi.org/10.1016/j.molcel.2014.01.021

157. Zheng J, Liu XB, Wang P, Xue YX, Ma J, Qu CB, et al. CRNDE promotes malignant progression of glioma by attenuating miR-384/PIWIL4/STAT3 axis. Mol Ther. 2016;24(7):1199–215. http://dx.doi.org/10.1038/mt.2016.71

158. Graham LD, Pedersen SK, Brown GS, Ho T, Kassir Z, Moynihan AT, et al. Colorectal neoplasia differentially expressed (CRNDE), a novel gene with elevated expression in colorectal adenomas and adenocarcinomas. Genes Cancer. 2011;2(8):829–40. http://dx.doi.org/10.1177/1947601911431081

159. Zheng J, Li XD, Wang P, Liu XB, Xue YX, Hu Y, et al. CRNDE affects the malignant biological characteristics of human glioma stem cells by negatively regulating miR-186. Oncotarget. 2015;6(28):25339–55. http://dx.doi.org/10.18632/oncotarget.4509

160. Wang Y, Wang Y, Li J, Zhang Y, Yin H, Han B. CRNDE, a long-non-coding RNA, promotes glioma cell growth and invasion through mTOR signaling. Cancer Lett. 2015;367(2):122–8. http://dx.doi.org/10.1016/j.canlet.2015.03.027

161. Zhang K, Sun X, Zhou X, Han L, Chen L, Shi Z, et al. Long non-coding RNA HOTAIR promotes glioblastoma cell cycle progression in an EZH2 dependent manner. Oncotarget. 2015;6(1):537–46.

162. Tano K, Mizuno R, Okada T, Rakwal R, Shibato J, Masuo Y, et al. MALAT-1 enhances cell motility of lung adenocarcinoma cells by influencing the expression of motility-related genes. FEBS Lett. 2010;584(22):4575–80. http://dx.doi.org/10.1016/j.febslet.2010.10.008

163. Gutschner T, Hammerle M, Eissmann M, Hsu J, Kim Y, Hung G, et al. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res. 2013;73(3):1180–9. http://dx.doi.org/10.1158/0008-5472.CAN-12-2850

164. Aldaz B, Sagardoy A, Nogueira L, Guruceaga E, Grande L, Huse JT, et al. Involvement of miRNAs in the differentiation of human glioblastoma multiforme stem-like cells. PLoS One. 2013;8(10):e77098. http://dx.doi.org/10.1371/journal.pone.0077098

165. Venkatraman A, He XC, Thorvaldsen JL, Sugimura R, Perry JM, Tao F, et al. Maternal imprinting at the H19-Igf2 locus maintains adult haematopoietic stem cell quiescence. Nature. 2013;500(7462):345–9. http://dx.doi.org/10.1038/nature12303

166. Kino T, Hurt DE, Ichijo T, Nader N, Chrousos GP. Noncoding RNA gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. Sci Signal. 2010;3(107):ra8. http://dx.doi.org/10.1126/scisignal.2000568

167. Garcia-Claver A, Lorente M, Mur P, Campos-Martin Y, Mollejo M, Velasco G, et al. Gene expression changes associated with erlotinib response in glioma cell lines. Eur J Cancer. 2013;49(7):1641–53. http://dx.doi.org/10.1016/j.ejca.2013.01.002

168. Kino T, Hurt DE, Ichijo T, Nader N, Chrousos GP. Noncoding RNA gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. Sci Signal. 2010;3(107):ra8. http://dx.doi.org/10.1126/scisignal.2000568

169. Barsyte-Lovejoy D, Lau SK, Boutros PC, Khosravi F, Jurisica I, Andrulis IL, et al. The c-Myc oncogene directly induces the H19 noncoding RNA by allele-specific binding to potentiate tumorigenesis. Cancer Res. 2006;66(10):5330–7. http://dx.doi.org/10.1158/0008-5472.CAN-06-0037
172. Atkinson GP, Nozell SE, Benveniste ET. NF-kappaB and STAT3 signaling in glioma: Targets for future therapies. Expert Rev Neurother. 2010;10(4):575–86. http://dx.doi.org/10.1586/ern.10.21

173. Herms JW, von Loewenich FD, Behnke J, Markakis E, Kretzschmar HA. c-myc oncogene family expression in glioblastoma and survival. Surg Neurol. 1999;51(5):536–42. http://dx.doi.org/10.1016/S0090-3019(98)00028-7

174. Moustakas A, Souchelnytskyi S, Heldin CH. Smad regulation in TGF-beta signal transduction. J Cell Sci. 2001;114(Pt 24):4359–69.

175. ten Dijke P, Hill CS. New insights into TGF-beta-Smad signalling. Trends Biochem Sci. 2004;29(5):265–73. http://dx.doi.org/10.1016/j.tibs.2004.03.008

176. Yang JH, Li JH, Jiang S, Zhou H, Qu LH. ChIPBase: A database for decoding the transcriptional regulation of long non-coding RNA and microRNA genes from ChIP-Seq data. Nucleic Acids Res. 2013;41(Database issue):D177–87. http://dx.doi.org/10.1093/nar/gks1060

177. Pastori C, Kapranov P, Penas C, Peschansky V, Volmar CH, Sarkaria JN, et al. The Bromodomain protein BRD4 controls HOXAIR, a long noncoding RNA essential for glioblastoma proliferation. Proc Natl Acad Sci U S A. 2015;112(27):8326–31. http://dx.doi.org/10.1073/pnas.1424220112

178. Suva ML, Rheinbay E, Gillespie SM, Patel AP, Wakimoto H, Rabkin SD, et al. Reconstructing and reprogramming the tumor-propagating potential of glioblastoma stem-like cells. Cell. 2014;157(3):580–94. http://dx.doi.org/10.1016/j.cell.2014.02.030

179. Ferrarese R, Harsh GRt, Yadav AK, Bug E, Maticzka D, Reichardt W, et al. Lineage-specific splicing of a brain-enriched alternative exon promotes glioblastoma progression. J Clin Invest. 2014;124(7):2861–76. http://dx.doi.org/10.1172/JCI68836

180. Zhen L, Yun-Hui L, Hong-Yu D, Jun M, Yi-Long Y. Long noncoding RNA NEAT1 promotes glioma pathogenesis by regulating miR-449b-5p/c-Met axis. Tumour Biol. 2016;37(1):673–83. http://dx.doi.org/10.1007/s13277-015-3843-y