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miRNAs and related genetic biomarkers according to the WHO glioma classification: From diagnosis to future therapeutic targets

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ABSTRACT

In the 2021 WHO classification of Tumors of the Central Nervous System, additional molecular characteristics have been included, defining the following adult-type diffuse glioma entities: Astrocytoma IDH-mutant, Oligodendroglioma IDH-mutant and 1p/19q-codeleted, and Glioblastoma IDH-wildtype. Despite advances in genetic analysis, precision oncology, and targeted therapy, malignant adult-type diffuse gliomas remain "hard-to-treat tumors", indicating an urgent need for better diagnostic and therapeutic strategies.

In the last decades, miRNA analysis has been a hotspot for researching and developing diagnostic, prognostic, and predictive biomarkers for various disorders, including brain cancer. Scientific interest has recently been directed towards therapeutic applications of miRNAs, with encouraging results.

Databases such as NCBI, PubMed, and Medline were searched for a selection of articles reporting the relationship between deregulated miRNAs and genetic aberrations used in the latest WHO CNS classification.

The current review discussed the recommended molecular biomarkers and genetic aberrations based on the 2021 WHO classification in adult-type diffuse gliomas, along with associated deregulated miRNAs. Additionally, the study highlights miRNA-based treatment advancements in adults with gliomas.

1. Introduction

Malignant primary brain tumors are among the most difficult to treat, with a high recurrence rate and low overall survival (OS) of patients. The 2021 fifth edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) emphasized the role of integrated diagnosis [1]. In the last decades, the classification of CNS tumors mainly based on histological and, in some cases, immunohistochemical analyses has proven to be incomplete. The introduction of molecular biomarkers has significantly improved diagnostic accuracy. High-throughput molecular analyses have provided a lot of evidence regarding the crucial role of molecular changes, leading to the integration of numerous aberrant genes in CNS classification. Combining molecular markers with histological assessment could enhance tumor grading and prognosis [2].

The current standard of care, consisting of surgical resection, radiotherapy, and chemotherapy, has resulted in only modest improvements in OS for malignant gliomas. This underscores the urgent need for the development of more effective diagnostic biomarkers and alternative therapeutic approaches.

miRNAs are small non-coding RNAs (ncRNA) of 18–25 nucleotides in length. They can bind to messenger RNA (mRNA) molecules and regulate post-transcriptional gene expression. Each miRNA can target multiple mRNAs, and each mRNA can be targeted by multiple miRNAs.

miRNAs play critical roles in various physiological and biological processes, including cell cycle and division, differentiation, growth, apoptosis, proliferation, and migration [3]. MiRNAs regulate neurogenesis, synaptic plasticity, and neuronal networks. So, miRNA are essential for normal brain development and have been involved in neurodevelopmental disorders [3]. Moreover, immune response to pathogens and cell metabolism have also been influenced by miRNAs. More than 60 % of all human protein-coding genes are post-transcriptionally regulated by miRNAs [4], mainly recognizing 3′-untranslated regions (3′-UTR) of targeted mRNA [5].

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miRNA synthesis starts in the cell nucleus, and RNA polymerase II generates primary miRNA (pri-MiRNA) encoded by DNA. In the next step, ribonuclease Drosha processes pri-miRNA into the precursor miRNA (pre-miRNA) with 60–70 nt in length. The final step is the cleavage by Dicer (RNA ribonuclease III) of pre-miRNA into mature double-stranded miRNA in the cytoplasm. The mature miRNA forms an RNA-induced silencing complex (RISC) [6]. Binding to the 3′–UTR of the target mRNA, miRNA post-transcriptionally suppresses the gene expression, either by translation repression or by mRNA degradation [5]. Many miRNAs are highly conserved across different species, indicating their fundamental importance.

Dysregulation of miRNA expression has been associated with a wide range of diseases, including cancer [7–11]. MiRNAs may function as oncogenes (oncomiRs) or tumor suppressors by regulating the expression of corresponding genes. OncomiRs downregulate tumor suppressor genes typically involved in cell cycle regulation, DNA repair, and apoptosis, resulting in increased expression and uncontrolled cell growth, leading to the development of cancer. Conversely, tumor suppressor miRNAs inhibit the expression of oncogenes, and their loss or downregulation leads to cell proliferation and cancer progression. MiRNAS are also involved in epithelial-to-mesenchymal transition (EMT), angiogenesis, and drug resistance [10].

Given the importance of miRNAs, they have become a subject of significant research interest. MiRNAs exhibit stability in various tissues and biofluids, making them promising candidates as biomarkers and therapeutic targets. Researchers have investigated the use of miRNA mimics to replace downregulated tumor suppressor miRNAs and anti-miRNA oligonucleotides to inhibit incomiRs as potential anti – cancer strategies [8,10]. Recent research has demonstrated the potential therapeutic applications of deregulated miRNAs in patients with brain tumors [2].

In the current review, we discuss the relationship between deregulated miRNAs and genetic biomarkers used in adult-type glioma classification.

2. Classification of adult-type diffuse gliomas

The fifth edition of the WHO classification of CNS (CNS5) was based on additional molecular markers along with histopathological characteristics [1]. Gliomas, neuronal tumors, and glioneuronal tumors are divided into six families, including adult-type diffuse gliomas, pediatric-type diffuse low- and high - grade gliomas, circumscribed astrocytic gliomas, glioneuronal and neuronal tumors, and ependymomas. The subject of our review is adult-type diffuse gliomas, comprising the majority of adult primary brain tumors.

Adult-type diffuse gliomas are further classified (Table 1) using the Layered Report Structure for a comprehensive, final integrated diagnosis of CNS WHO grade and entity [1].

2.1. Glioblastoma, IDH-wildtype

The CNS5 WHO classification recommended the algorithm for diagnosis (Fig. 1) of "Glioblastoma, *IDH*-wildtype". Even in the absence of histological findings such as microvascular proliferation and necrosis, the presence of genetic aberrations, including TERT promoter mutations, EGFR amplification, or gain of chromosome 7 and loss of chromosome 10 (+7/-10), can serve as sufficient markers for diagnosis [12]. The implementation of up-to-date molecular diagnostic techniques might accurately determine the grade even when the tumor appears to have a lower histological grade [13].

Table 1
The WHO CNS5 revised tumor types for adult-type diffuse gliomas. The term "anaplastic" is removed, and arabic numbers are used to standardize CNS grading. IDH - isocitrate dehydrogenase.

CNS WHO terms	Grades
Astrocytoma, *IDH*-mutant	2, 3, 4
Oligodendroglioma, *IDH*-mutant and *1p/19q*-codeleted	2, 3
Glioblastoma, *IDH*-wildtype	4

2.2. Astrocytoma, IDH-mutant

In the 2021 classification "Astrocytoma, *IDH*-mutant", CNS WHO grades 2, 3, and 4 have been used instead of previous diffuse astrocytic tumors. *IDH* mutations have been associated with favorable prognosis, but the presence of cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B)* homozygous deletion is a negative prognostic marker related to poor patient outcomes [14].

2.3. Oligodendroglioma, IDH-mutant, 1p/19q codeleted

Oligodendrogliomas are among the diffuse neuroglial brain tumors in adults with longer OS and progression-free survival (PFS) [15]. This tumor entity harbors *IDH* mutation, *1p/19q* codeletion, which is present exclusively in oligodendroglioma [16], and *TERT* promoter mutations. Mutations in the tumor suppressors *Capicua transcriptional repressor (CIC)* and *Far Upstream element Binding Protein 1* (*FUBP1),* as well as mutations in the *NOTCH1* are also included [17]. Disturbances in these genes lead to cell proliferation [18], malignant transformation [19,20], disease progression, and shorter OS [21].

3. Molecular markers for classification of adult-type diffuse glioma

The main reported disturbed cell pathways in gliomas have been RTK (receptor tyrosine kinase), RB (retinoblastoma), and P53 [22]. Various molecular assays could be used to detect the altered genes listed in Table 2 [13].

3.1. IDH

Isocitrate dehydrogenase (IDH) 1 and 2 catalyze the conversion of isocitrate into α-ketoglutarate in cytoplasm and peroxisomes (IDH1), and in mitochondria (IDH2 and 3) [23]. Mutations in each gene decrease the enzyme affinity for the substrate but increase its affinity for nicotinamide adenine dinucleotide phosphate (NADPH). The last leads to an accumulation of the toxic and oncogenic product 2-hydroxyglutarate (2HG), which disturbs the citric acid cycle and cell metabolism. Furthermore, 2HG inhibited certain DNA demethylases, leading to CpG hypermethylation and suppression of crucial cellular processes [24]. *IDH* mutations have been observed in a variety of tumors [23] and are also vital for glioma classification [1], serving as prognostic biomarkers [14].

3.2. TERT promoter

Mutations in the promoter of the *TERT* gene are associated with increased telomerase activity and the survival of cancer cells. Furthermore, *TERT* promoter disturbance is observed in various cancers and is linked to tumor diagnosis and treatment [25]. These mutations have been described in up to 80 % of adult gliomas, mainly in patients with glioblastoma, followed by oligodendrogliomas (60–70 %) and astrocytomas (35–55 %) [26]. *TERT* promoter mutations serve as prognostic markers for poor patient survival and can predict the risk of radiotherapy resistance [27]. The most frequent *TERT* promoter mutations include C228T, followed by C250T [28].

3.3. Gain of chromosome 7 and loss of chromosome 10

Some identified genes on chromosome 7 that impact malignization are Platelet Derived Growth Factor Subunit A (PDGFA) and Epidermal

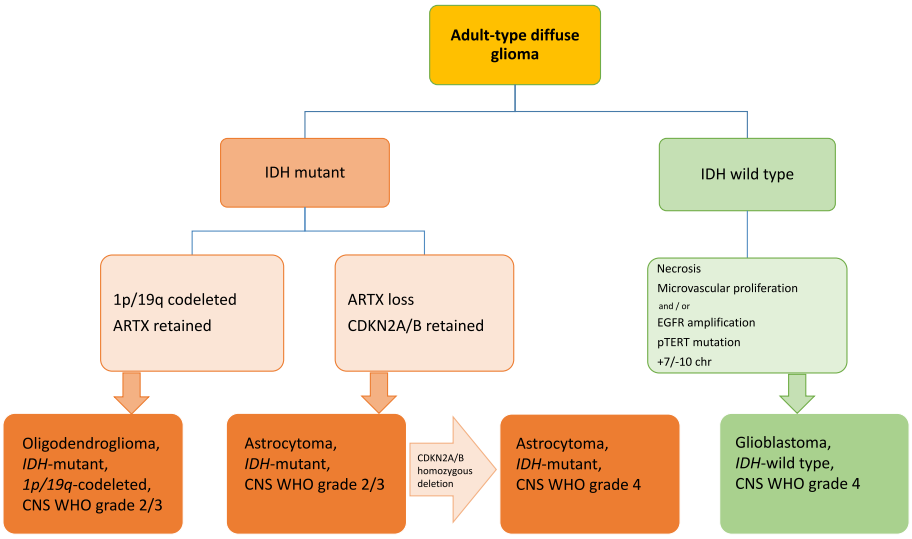

Fig. 1. The WHO recommended an algorithm for adult-type diffuse glioma classification. *ATRX* loss is mutually exclusive with *1p/19q* codeletion and can be used as molecular diagnostic marker instead of *1p/19q* codeletion.

Table 2
Altered genes according to the WHO CNS5 classification in adult-type diffuse gliomas. Epidermal Growth Factor Receptor – EGFR; Telomerase Reverse Transcriptase – TERT; Tumor Protein 53 – TP53; Alpha thalassemia/mental retardation syndrome X – ATRX; Cyclin-Dependent Kinase Inhibitor 2A/B – CDKN2A/B; Capicua transcriptional repressor – CIC; Notch Receptor 1 – NOTCH1; Far Upstream Element Binding Protein 1 – FUBP1.

Tumor type	Altered genes	Aberrations
Glioblastoma, *IDH*-wildtype	*IDH*-wild type	wildtype
	chromosomes 7/10	amplification/deletion
	EGFR	amplification, mutation
	TERT promoter	mutation
Astrocytoma, *IDH*-mutant	*IDH1/IDH2*	mutations
	TP53	deletion
	ATRX	mutation
	CDKN2A/B	deletion
Oligodendroglioma, *IDH*-mutant *1p/19q*-codeleted	*IDH1*, *IDH2*	mutations
	1p/19q	codeletion
	TERT promoter	mutation
	CIC	deletion, mutations
	NOTCH1	mutations
	FUBP1	deletion, mutations

Growth Factor Receptor (EGFR). The gain of chromosome 7 (+7) mainly increased PDGFA mRNA levels. Ozawa et al. have speculated that *PDGFA* is the primary disturbed gene due to gaining additional copies of chromosome 7, while the second disturbed chromosome, a loss of 10 (−10) has led to disturbance in the tumor suppressors - Phosphatase and Tensin homolog (PTEN), O-6-methylguanine-DNA methyltransferase (MGMT), and others [29].The detection of +7/-10 chromosomes has been linked to poor patient survival and might be used as potential therapeutic targets. Amplification of +7 with the *EGFR* locus and deletion of −10, with *PTEN* are frequently altered chromosomal regions in glioblastoma [30]. Oncogenesis might be triggered if *PTEN* is deleted or inhibited [31]. *PTEN* inhibits the PI3K-AKT pathway, leading to apoptosis by cell cycle arrest [32]. In nearly 25 % of glioblastoma patients, *PTEN* deletion or mutation has induced activation of the PI3K-AKT pathway and promotion of oncogenesis [33].

3.4. EGFR

EGFR is a member of the receptor tyrosine kinase (RTK) family of cell surface receptors. RTK family also includes Platelet-Derived Growth Factor Receptor (PDGFR), Vascular Endothelial Growth Factor Receptor (VEGFR), Fibroblast Growth Factor Receptor (FGFR), and Insulin-like Growth Factor 1 Receptor (IGF-1R). All receptors are vital components of mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinases (ERK), and phosphoinositide-3-kinase (PI3K)/V-AKT murine thymoma viral oncogene homolog (AKT) cell signaling systems. These signaling pathways regulate various cellular processes, including the cell cycle, differentiation, cell division, metastasis, and apoptosis [34]. Thus, activated *EGFR* can trigger multiple pathways [35], leading to oncogenesis [31].

EGFR gene amplification in *IDH*-wildtype diffuse and astrocytic gliomas serves as a diagnostic biomarker for glioblastoma CNS WHO grade 4 [1]. Additionally, *EGFR* variants, including *EGFRvIII, EGFRvI*, *EGFRvII*, *EGFRvIV,* and *EGFRvV*, are frequently co-expressed alongside *EGFR* amplification. These genetic aberrations significantly influence glioma proliferation and aggressiveness [36].

3.5. CDKN2A/B

CDKN2A/B genes on chromosome 9p21 are frequently mutated or deleted in a wide variety of tumors. The *CDKN2A* gene encodes proteins p16(INK4A) and p14(ARF) involved in cell growth and apoptosis, by regulating p53 and RBs [37]. Homozygous deletion of *CDKN2A* or Mdm2/4 amplification resulted in the degradation of the p53 tumor suppressor [38].

CDKN2B encodes p15/INK4B, which inactivates cyclin-dependent kinase (CDK) 4 and 6 (CDK4/CDK6) and regulates cell proliferation [37]. *CDKN2A/B* homozygous deletion is a negative prognostic marker indicating shorter median OS and shorter PFS [39,40].

3.6. TP53

TP53 (tumor protein 53) is a tumor suppressor gene encoding the p53 protein. This protein is responsible for regulating cell cycle arrest, apoptosis, DNA reparation, and protecting cells from tumorigenesis. Half of the reported cancers showed mutations in p53, making it one of the most frequently mutated genes and highlighting its crucial role in oncogenesis [41]. Mutations in *TP53* are predominantly found mainly in astrocytomas, with an occurrence rate ranging from 50 % to 75 %, and to a lesser extent in oligodendroglioma, observed in approximately 10–34 % [42]. Mutant p53 interacts with oncoproteins and triggers neoplastic processes. Therefore, *TP53* mutations serve as a prognostic marker associated with increased OS and PFS in patients undergoing chemotherapy [41].

3.7. ATRX

Telomere and chromatin structure maintenance involves the alpha thalassemia/mental retardation syndrome X-linked (ATRX) protein by binding to G-rich tandem repeats [43]. Mutations in *ATRX* have been related to DNA destabilization and the activation of a mechanism known as alternative lengthening of telomeres (ALT). ALT is typically inactive in healthy cells [44] but becomes active in cancer cells [45]. In adult diffuse gliomas, *ATRX* mutations have also been reported [46], particularly in patients with *IDH*-mutated, *TP53*-mutated astrocytomas, and secondary GBM [16]. Patients with mutations in *IDH* and *ATRX* loss have been observed to exhibit improved OS and PFS [47].

4. Deregulated miRNAs

miRNAs regulate neurodevelopment in the CNS, and their dysregulation has caused crucial brain cell functions to be affected [48]. It is known that miRNAs could act as tumor suppressors or oncomiRs, and their dysfunction led to the dysregulation of signaling pathways and cell neoplasia [49]. Moreover, cancer cells communicate with nearby and distant cells using extracellular vesicles (EVs) carried by biological fluids. EVs contain various signaling molecules, including miRNAs that regulate the tumor microenvironment and promote tumorigenesis [50]. miRNA stability in different biological fluids highlighted their diagnostic, prognostic, and predictive biomarker potential [51]. Monitoring miRNAs in plasma, blood, urine [52], and other non-invasive samples would enable better post-surgery patient monitoring with multiple samplings and relapse control [53].

Most of the studies have discussed the relationship between miRNAs and regulated targets in gliomas, while our review aims to focus on the recommended WHO molecular genetic markers in adult-type gliomas and the corresponding deregulated miRNAs with potential implications for brain tumor monitoring and future therapy (Fig. 2).

4.1. miRNA and IDH

Limited data are available regarding the relationship between deregulated miRNAs and the *IDH* status of brain cancer patients. It has been reported that mutant *IDH*, by generating 2-HG, can lead to the methylation of promoters for certain miRNAs, resulting in a decrease in their expression. For instance, the tumor suppressor miR-148A has been decreased due to promoter hypermethylation. The presence of 2-HG influences the level of 5-hydroxymethylcytosine (5-hmC) [54]. MiR-148a regulates cellular differentiation, development and also plays a role in neuronal development. Deregulation of its levels has been observed in various tumors, which correlates to patient prognosis [55].

A study has identified miRNAs associated with mutated *IDH* in low grade gliomas, including miR-106b, miR-130b, miR-98-3p, miR-185, and miR-7d-3p. The authors have observed that the deregulated signature could discriminate low-grade glioma from healthy individuals [56]. These miRNAS are studied as oncomiRs and tumor suppressors involved in tumorigenesis, proliferation, invasion, migration, and metastases [56–58].

In another study, downregulation of miR- 1-3p, miR-26a-1-3p, and miR-487b-3p have been observed in patients' serum, corresponding to *IDH* mutations. The signature was more downregulated in *IDH*-wildtype samples compared to *IDH*-mutant or in controls with normal *IDH*. Given that the three miRNAs are tumor suppressors, the authors reported that their levels were informative for OS and PFS [59].

Zhang et al., 2018 investigated the relationship between the *IDH1 R132H* mutation, miRNAs and insulin-like growth factor 1 receptor (IGF1R). They observed that the *IDH1 R132H* mutation has decreased expression of miR-141-3p, miR-7-5p, and miR-223-3p. The three miRNAs have suppressed malignization and metastasis and their deregulation was related to increased expression of IGF1R [60]. Increased IGF1R is frequently observed in many cancers and is related to proliferative and aggressive tumor phenotype [61].

Another study has observed that the high level of 2-HG has been

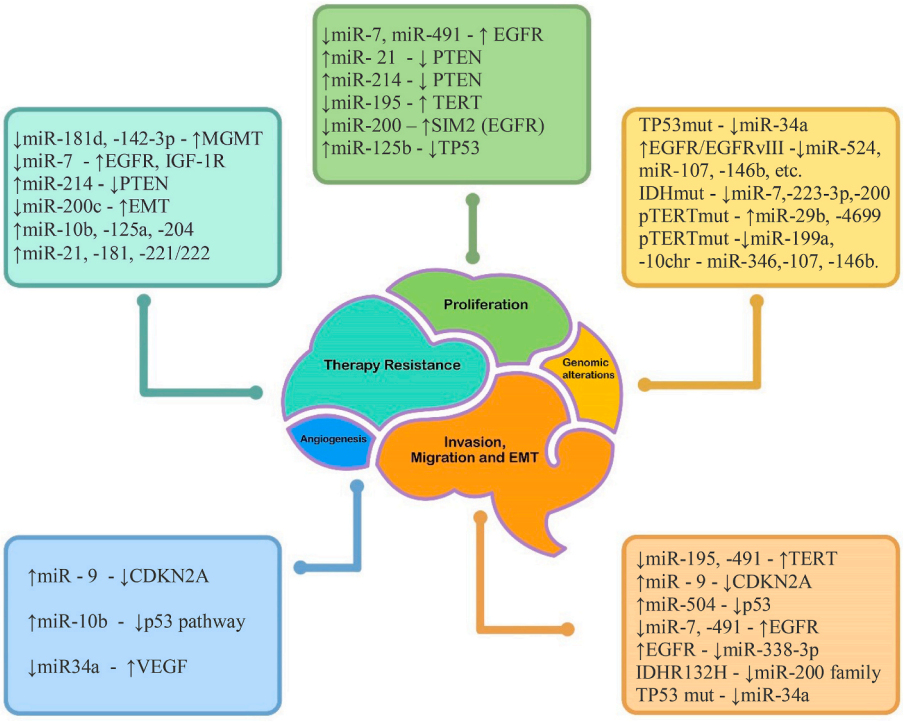

Fig. 2. Some of the deregulated miRNAs and corresponding genetic biomarkers, involved in glioma pathogenesis and therapy. Epidermal Growth Factor Receptor – EGFR; Telomerase Reverse Transcriptase – TERT; Tumor Protein 53 – TP53; Vascular Endothelial Growth Factor Receptor – VEGF, O-6-Methylguanine-DNA Methyltransferase – MGMT; Insulin-like Growth Factor 1 Receptor – IGF-1R; Cyclin-Dependent Kinase Inhibitor 2A – CDKN2A; Isocitrate dehydrogenase – IDH; Phosphatase and Tensin homolog – PTEN; single-minded homolog 2 – SIM2; *epithelial*–mesenchymal transition – *EMT; - 10 chr – loss of chromosome 10.*

associated with EMT, by deregulating miR-200b and miR-200c and up-regulating the ZEB1. Interestingly, inhibition of the IDH mutation has reversed EMT properties [62].

4.2. miRNA and TERT promoter mutations

TERT has been reported as a target of tumor suppressor miR-491. This miRNA has been down-regulated in ovarian, glioblastoma, hepatocellular carcinoma (HCC), and brain metastases [8,63–65]. Regulating the PI3K/AKT pathway, miRNA-491 has inhibited cell invasion and migration in gliomas and other cancers [63,64]. Moreover, miRNA-491 targeting EGFR, CDK6, and Bcl has suppressed glioblastoma proliferation, invasion, and induced apoptosis [64]. Another study has observed that miR-491 along with miR-133a, miR-342, and let-7g, directly targeted TERT and inhibited telomerase activity, the Wnt pathway, and cell division [66]. These miRs act as tumor suppressors and have been involved in the regulation of cell proliferation, migration, metastases, and drug resistance [67,68].

In patients with mutated *TERT* promoter miR-199a has been down-regulated, while miRNA-29b-1 and miRNA-4699 have been up-regulated. It has been reported that miR-199a, as a tumor suppressor, has regulated cell cycle and cancer progression [69]. MiR-29b-1 acts as oncomiR and has been observed to activate EMT in oral squamous cell carcinoma [70].

Other miRNAs regulating TERT are miR-195, suppressing tumorigenesis in thyroid cancer [71] and a widely reported oncomiR – miRNA-21 in patients with GBM [72]. MiR-195 regulates critical signaling pathways such as MAPK, PI3K/AKT, TNF, Wnt/β-Catenin, JAK/STAT, and Notch. As a tumor suppressor, miR-195 is frequently downregulated in various cancers. This miRNA was related to inhibition of cell proliferation, migration, chemoresistance and activation of apoptosis [71,73]. MiR-21 regulates a plethora of biological processes and diseases, including development, cardiovascular diseases, inflammation, and cancer. It is a widely studied oncomiR with elevated expression in various tumors, including gliomas [8,74,75]. Some of the confirmed targets of miR-21 are some tumor suppressor genes, such as *PTEN, Bcl2, PDCD4* [76]. Upregulation of miR-21 in glioblastoma cells increased TERT expression mediated by STAT3, promoting glioma growth. Otherwise, the downregulation of miR-21 suppressed TERT expression [72].

Some TERT-targeting miRs have been reported to possess prognostic value. For example, the down-regulation of miR-1207, miR-1182, miR-532, and miR-3064 has been related to poor clinical outcomes in patients with different tumors [77,78]. MiR-1182 has inhibited proliferation, invasion and metastasis [77,78]. Furthermore, miR-1182 has induced chemosensitivity to cisplatin by inhibition of TERT in bladder cancer [78].

Downregulation of miR-532 and miR-3064 was related to higher tumor stage and metastasis, by up-regulation of Slug and down-regulation of Bax and E-cadherin [64]. These miRNAs predominantly act as tumor suppressors and may be investigated for future clinical applications.

4.3. miRNA and +7/-10 chromosomes

The gain of chromosome 7 might increase the levels of encoded miRNAs, while the deletion of chromosome 10 decreases the levels of miRNAs located there. Deregulated miRNAs are strongly associated with the disturbed genes. The loss of chromosome 10 promotes glioma growth, due to deletion of the *PTEN* tumor suppressor gene and low expression of miRNAs located on this chromosome, including miR-107, miR-146b-5p, miR-346, and miR-1287–5p. Downregulation of these miRNAs was related to overexpression of *CDK6*, *EGFR*, *TERT*, and *SEMA6A* genes involved in glioma growth and proliferation [79]. These miRNAs have also been disturbed and deregulated in various cancers [79]. *PTEN* has been frequently deleted in various cancers and appeared to be directly regulated by miR-21 in hepatocellular carcinoma (HCC) [80], as well as miR-19a, and miR-214 [76,81]. As a tumor suppressor, *PTEN* inhibits cell proliferation by the PI3K-AKT pathway [30].

MiR-214 has suppressed expression of PTEN leading to cell proliferation and survival [76,81]. Furthermore, *PTEN* deletion or suppression by miRNAs is also related to drug resistance. For instance, in ovarian cancer, miR-214 has induced cisplatin resistance and cell malignization, by inhibiting PTEN [81].

The *PTEN* loss was related to the amplification of miR-26a and gliomagenesis [82]. Interestingly, the last miRNAs (−21 and −26a) have shown diagnostic and prognostic value in high-grade glioma [82].

4.4. miRNA and EGFR

EGFR overexpression has been reported in various cancers, including breast, colon, lung cancers and glioblastoma, related to poor patient's prognosis [36,83,84].

Notably, *EGFR* overexpression, along with *EGFRvIII* variant, has been found to suppress miR-524-3p and miR-524 by histone modifications [84]. These two miRNAs, miR-524-5p and miR-524-3p play a pivotal role in malignization by targeting Smad2, Hes1, and Tead1, which subsequently inhibit the oncogenic C-myc protein. Interestingly, C-myc upregulated EGFR or EGFRvIII variant expression by binding to their promoter [84]. These findings indicate the significance of the miR-524/EGFR/EGFRvIII/C-myc axis in gliomagenesis. Moreover, both miRNAs have been associated with longer OS in glioma patients. Their restoration has demonstrated therapeutic potential, effectively inhibiting glioma proliferation, migration and tumorigenesis [84]. MiR-524 exhibits tumor suppressor activity by targeting PTEN, BRAF and ERK2 [85,86] inhibiting the growth of various cancers [84–86]. MiR-524-5p further has targeted SMAD4 and ZEB2, contributing to EMT and cancer metastasis [87].

In addition, *EGFR* amplification has been linked to the inhibition of the tumor suppressor miR-338-3p, leading to EMT and metastasis [83,88]. By targeting ZEB2 and Akt signaling, miR-338-3p inhibited EMT [88]. The selection of genetic alterations, such as *EGFR* overexpression in adult gliomas, has been shown to enhance cell growth and migration by upregulating the levels of the oncoprotein EYA transcriptional coactivator and phosphatase 2 (EYA2). The restoration of miR-338-3p and inhibition of EYA2 represent potential therapeutic alternatives for metastatic tumors [83]. Moreover, miR-338-3p has been reported to be downregulated in various tumors, and its low expression is associated with poor clinical outcomes [88].

miR-7, a tumor suppressor miRNA, plays a vital role in regulating fundamental cellular processes, including cell division, differentiation, migration, and apoptosis. Downregulated miR-7 has been observed in a plethora of cancers, including brain tumors [89,90]. In glioblastoma, low miR-7 expression has been linked to elevated levels of its confirmed target, EGFR [91]. Restoration of miR-7 expression has demonstrated its potential in reducing proliferation, survival, and invasiveness in cultured glioma cells [92]. MiR-7 targeted PI3K mediators, AKT activity, the insulin receptor, and decreased miR-7 levels have been associated with increased activity in these pathways [91]. Additionally, mir-7 suppression by promoter methylation has been observed in cancer stem cells, while Hepatitis B virus (HBV) protein HBx and hepatocyte growth factor can upregulate miR-7 expression through EGFR in certain cell types [93].

EGFR has been targeted by miR-133b, regulating cell invasion and division in colorectal cancer [94]. Reduced expression of miR-133b has been associated with increased levels of EGFR, leading to poor patient survival and metastases in various cancers [94].

miR-200a-3p, a member of the miRNA 200 family, has been decreased in gliomas. As a result, Gαi1 protein has activated EGFR and PI3K-Akt pathways, promoting cell proliferation and inhibiting apoptosis [95,96]. The miRNA-200 family, including miR-141, miR-200b, miR-200c, miR-429, plays a crucial role in glioma

development, progression, and metastasis [95,97]. Some of the targets of miR-200a include single-minded homolog 2-short form (SIM2-s), which regulates cell invasion and migration, as well as TGF – β2, which plays a role in proliferation, differentiation, and migration [98].

4.5. miRNA and CDKN2A/2B

The product of the *CDKN2A* gene, namely p16 protein, probably plays a more important role in cancer suppression than p53. P16 is involved in cell cycle arrest, cell proliferation, the occurrence of various cancers [39].

Increased expression of miR-9 has been linked to reduced expression of its target, p16, influencing cell growth, angiogenesis, and metastasis in patients with osteosarcoma [99]. MiR-9 has been deregulated in lung cancer, bladder cancer, osteosarcoma, ovarian cancer, nasopharyngeal carcinoma, glioblastoma, etc. [100]. In glioblastoma, miR-9 has inhibited proliferation by targeting CAMP response element-binding protein (CREB) and promoted migration by targeting neurofibromin 1 (NF1) [100].

Interestingly, the human herpes simplex virus (HSV-2) encoded miRNA, H4-5p, has been shown to bind to the 3′–UTR of CDKN2A and inhibit its expression, leading to reduced apoptosis [101].

In leukemia cells, decreased expression of miR-497 and miR-195 has been related to intensive deletion of *CDKN2A/B* and lower PFS. Furthermore, authors observed tumor recurrence when miR-195 and miR-497 have been suppressed. These miRNas have targeted cyclin-dependent kinase 4 (CDK4) and cyclin-D3 (CCND3), controlling cell cycle and inhibiting B-cell precursor acute lymphoblastic leukemia progression [102]. Interestingly, the presence of normal *CDKN2A/2B* in combination with high expression of miR-497 and miR-195 have demonstrated a better outcome, indicating their potential as therapeutic targets. Both miRNAs have been observed to function as tumor suppressors in various cancers [71,102,103]. The expression of miR-497 and miR-195 is epigenetically suppressed by promoter methylation in some types of cancers [102].

4.6. miRNA and TP53

Several miRs have been identified as key regulators of p53 levels and its associated functions in apoptosis and cell cycle arrest.

In contrast, miR-34a indirectly upregulates p53 activity through downregulation of sirtuin 1 (SIRT1). SIRT1 is a negative regulator of p53 by its deacetylation and inhibits cell apoptosis. Furthermore, p53 can directly regulate the expression of the miR-34 family by binding to their promoters and activating their transcription [104]. In glioma, patients with mutant p53 showed lower miR-34 expression, which correlated with a poor prognosis and a higher tumor grade [105]. The loss of miR-34 could promote tumorigenesis and this miRNA has been reported to be down-regulated in various tumors [104–106]. Furthermore, mutations in the *TP53* gene (*R175H* and *R273H*) might influence the activity of Drosha and decrease the levels of miR-16-1, miR-143, and miR-145.

The P53 pathway has been controlled by miRNA-10b, which is overexpressed in gliomas and brain metastases [8,107]. Upregulation of miR-10b has been associated with cell proliferation, angiogenesis, and migration. Its levels have been linked to a poor prognosis in glioma patients, promoting cell invasion and migration [108–110]. Interestingly, Epstein-Barr virus latent membrane protein 1 (LMP1) activated the expression of TWIST-1 and NF-kB, increasing the levels of miR-10b, which is critical for EMT [111]. MiR-10 has shown potential not only as a diagnostic and prognostic biomarker but also as a therapeutic target. Decreased expression of miR-10b is associated with improved response to neoadjuvant therapy and increased survival [107].

MiR-125b and miR-504 have directly targeted the 3′-UTR region of p53 and downregulated its expression levels [112,113]. MiR125 is a brain-enriched miRNA which is upregulated in glioma cells. This miRNA has interacted with Bmf, inducing glioma proliferation and inhibiting cell apoptosis [114]. MiR-504 overexpression has suppressed migration, invasion, EMT, and stemness in glioblastoma [112].

4.7. miRNA and MGMT

MGMT plays a crucial role in DNA repair, particularly in the removal of alkyl groups from the O-6 position of guanine. Methylation of MGMT promoter leads to the accumulation of DNA damage and increases the cytotoxicity of alkylating chemotherapy. Epigenetic silencing of *MGMT* through promoter methylation has been observed in nearly 45 % of GBM patients and is a predictive marker for better response to adjuvant temozolomide (TMZ) therapy as well as better patient outcomes [115].

Some miRNAs have emerged as key regulators of MGMT and have been shown to predominantly enhance TMZ sensitivity in glioblastoma. For example, miR-181d and miR-142-3p have targeted MGMT directly, leading to increased chemosensitivity towards the alkylating agent TMZ. Therefore, together with MGMT, miR-181d might be used as a predictive biomarker, correlated with improved OS [116]. Interestingly, the low expression of miR-181b and miR-181c in glioblastoma has been related to a better TMZ response [116].

Other direct regulators of the 3′UTR of MGMT are miR-198, miR-221/222, miR-767-3p, and miR-648 which have also increased the sensitivity to TMZ [117,118]. Moreover, miR-221/222, which are frequently up-regulated in glioma, increase chromosomal aberrations and are correlated with poor patient survival [118].

miRNAs play a significant role in regulating MGMT promoter methylation and expression, which, in turn, influence the response to alkylating chemotherapy in cancer [119]. DNA methyltransferases (DNMTs), which include the DNMT1, DNMT2, and DNMT3 family of enzymes, catalyze the methylation of the CpG islands in the promoter regions. In high-grade astrocytic tumors, DNMT1 overexpression has been correlated with a reduction in MGMT protein expression. Some miRNAs associated with DNMT overexpression include miR-143, miR-153, miR-148 [119,120]. MiR-143 and miR-148 have been down-regulated in various cancers, including gliomas [118]. Overexpression of miR-143 and miR-148 inhibited angiogenesis, migration, and invasion. Moreover, miR-143 has been shown to sensitize glioma cells to TMZ, presumably by indirectly regulating MGMT promoter methylation and expression [121].

Understanding the intricate interplay between miRNAs and MGMT offers valuable insights into the development of personalized treatment strategies and the identification of predictive biomarkers. Further research in this field holds promise for improving the effectiveness of alkylating chemotherapy and enhancing outcomes for cancer patients.

4.8. miRNA and BRAF

Mutations in v-raf murine viral oncogene homolog B1 (BRAF) play a significant role in various types of cancer, including brain tumors [85,122]. The most common *BRAF* mutation, p.V600E, involves a specific change in the *BRAF* gene, resulting in the substitution of valine (V) with glutamic acid (E) at position 600 in the BRAF protein. This genetic alteration leads to the constitutive activation of the *BRAF*, leading to the uncontrolled activation of the MAPK pathway and cell proliferation, division, apoptosis inhibition, and cell survival.

These signaling events contribute to the formation and growth of brain tumors, even in the absence of external growth signals. The most common BRAF alterations, p.V600E and *BRAF-KIAA1549* fusions, involving exon 16 in *KIAA1549* and 9 in *BRAF*, are observed in adult-type glioma (3–5%), although they are most commonly associated with pediatric low-grade gliomas and pleomorphic xanthoastrocytomas [122,123]. *KIAA1*549-BRAF fusions are also found in various other malignancies, including melanoma, spindle cell neoplasms, sarcomas, breast carcinoma, thyroid and lung cancer.

BRAF mutation, p.V600E, is targeted by FDA-approved therapy,

while additional inhibitors against other BRAF aberrations are under development. Targeted therapies using BRAF inhibitors, have been developed and show promise in treating *BRAF V600E*-mutated brain tumors [124,125]. However, ongoing research is essential to address resistance mechanisms and optimize treatment strategies for these tumors.

Several miRNAs have been identified as regulators of BRAF or components of the BRAF signaling pathway. For example, down-regulation of miR-31 has been associated with increased BRAF expression and activation of the MAPK signaling pathway. Conversely, miR-31 has been significantly up-regulated and associated with advanced CRC with the *BRAF V600E* mutation, compared to wild-type *BRAF*. Therefore, this miR showed potential as a prognostic and therapeutic marker [126].

By specifically targeting the 3′-UTR of BRAF and ERK2, miR-524p has been shown to inhibit the development of oncogenic BRAF melanoma. MiR-524 efficiently blocks MAPK/ERK signaling, influencing tumor growth, proliferation, and cell motility [85].

A number of studies have already reported the contribution of miRNAs to the resistance to BRAF inhibitors [127–129]. Some miRNAs have shown the ability to inhibit the growth of BRAF-resistant tumors, while others play a role in the selection and survival of cell populations that have developed resistance to BRAF inhibitors.

For example, miR-7 has been found to counteract resistance to BRAF inhibitors by targeting EGFR, IGF-1R, CRAF and suppressing MAPK and PI3K/Akt pathways. The authors have reported inhibition of tumor growth using miR-7 mimics and underlined the role of this miR as a potential therapeutic agent in BRAF-resistant melanoma [127]. MiR-524 has also shown the ability to suppress the development of melanoma resistant to BRAF inhibitors [85,130].

Conversely, miR-125a, miR-204, and miR-211 have contributed to increased BRAF resistance, primarily acting through MAPK and PI3K/Akt pathways [128]. Additionally, miR-200c has been observed to regulate EMT, leading to the acquisition of resistance to BRAF inhibitors. The upregulation of miR-200c has resulted in inhibition of melanoma growth, especially in resistant cells to BRAF inhibitors [129].

5. Therapeutic applications

The current standard of treatment for malignant brain tumors involves surgical resection, radio- and chemotherapy. Surgical resection has been recommended to be performed in high-volume medical centers with highly-trained specialists to avoid surgical morbidity, errors in biopsy sampling, and adverse outcomes [131]. Since the improvement in patient outcome, OS, and PFS is minimal, new therapy strategies and molecular markers for monitoring are urgently needed. The diagnosis and treatment of patients with GBM are still challenging. Even though glioma accounts for approximately 1 % of global cancer cases, it has a low survival rate, frequent recurrence, and treatment resistance [32,132].

The recommended genetic markers for therapy decisions have been updated in the WHO CNS5 classification. Notably, molecular testing should be performed on the most recent tumor sample, as cancers may change and their molecular profiles might alter over time [1,133].

Most treatments for malignant brain tumors have had a limited impact on the tumor's growth and the patient's survival. Non-invasive biomarker discovery has been a "hot" topic in brain tumor management [52]. miRNA-based circulating biomarkers are among the most tested due to their stability in biofluids and disturbance in cancer [134]. The suffix NOS in glioma classification is sometimes related to a difficult prognosis. For example, in patients with *IDH* NOS glioma, establishing a miRNA signature can improve the accuracy of the prognosis. Additionally, studies Performed over the recent years have confirmed their role in developing radio- and chemotherapy resistance in brain tumors [2,135–137]. Certain miRNAs can sensitize tumor cells to radiation or chemotherapy, making them more susceptible to these treatments.

Some miRNAs have been associated with TMZ resistance in GBM [135,138–140] and can be used as predictive biomarkers and therapeutic targets. For example, miR-21 promotes cell survival, tumor growth, chemo- and radioresistance. Inhibition of miR-21 in GBM by antisense oligonucleotides (ASO) resulted in cell death and apoptosis due to the restoration of caspase-3 activity and the Bax/Bcl2 ratio. Furthermore, this resulted in radiosensitization of U373 and U87 cells, whereas overexpression of miR-21 led to a decrease in radiosensitivity. This has resulted in a better TMZ response [139]. In another study, high miRNA-9 expression levels have been associated with increased glioma TMZ sensitivity, and its expression might be used for TMZ treatment monitoring [135]. Another study reported that miR-210-3p induced chemoresistance to TMZ in glioma cell lines via upregulation of the TGF-β under hypoxic conditions [141]. MiR-181 family and miR-221/222 have been related to chemoresistance and their down-regulation in cell lines caused an increase in sensitivity to TMZ and apoptosis [138].

MiRNAs have also exhibited a crucial role in the development of radiotherapy resistance. For instance, some miRNAs promoted GBM radiosensitivity, including microRNAs-26a, −124, −128, −103a, −145, −153, −181a/b, −203, −221/222, −223, −224, −320, - 524, −590, -640, etc [142,143]. For example, miR-524-5p increased the radiosensitivity of glioma cells by suppressing autophagy. Up-regulation of miR-7 has led to downregulation of the EGFR-AKT signaling network [127] and radiosensitivity in glioma cell lines cell [144]. These miRNAS might be further explored for enhancement of the effect of radiotherapy.

Conversely, miR-96, -135b, −21, −155, −210, −320b, and −212 have been related to radioresistance [142,145]. These miRNA regulate radiation-related signaling pathways such as apoptosis, proliferation, DNA repair, and cell cycle arrest. Therefore, knockdown of the radioresistant miRNAs represents a prospective opportunity for better radiotherapy.

Additionally, miRNAs can be used as predictive biomarkers for glioma therapy. For example, miR-21 and miR-181c have stratified patients according to the relapse time after TMZ therapy, while let-7a, miR-539, miR-1305, miR-1260, and miR-3163 have been deregulated between patients with short- and long-time survival [146]. Thus, miRNA-based therapies can be combined with traditional chemotherapy or radiotherapy to enhance treatment outcomes.

The perspective for miRNA-based therapy applications is based on their stability and small size. However, miRNA's ability to target multiple genes has been a limiting factor for their therapeutic use. For this reason, miRNA-loaded nanoparticles, protecting miRNAs from nuclease degradation, have been pointed out as a possible effective delivery of miRNAs across the blood–brain barrier to the tumor site. This approach enhances therapeutic efficacy, reduces off-target effects, and facilitates interactions with nearby healthy cells [147].

Moreover, GBM-specific surface receptors function as recognition targets, guaranteeing that miRNA is transported to the specific tumor cells and the targeted gene [148]. Experimental *in vitro* analyses using nanoparticles for miR-21 inhibition result in increased tumor apoptosis and OS in glioblastoma cells [149]. Some deregulated miRNAs might be used as adjuvant therapy in TMZ-resistant patients. Interestingly, suppressing miR-10b has inhibited proliferation and growth only in glioma cells but not nearby normal cells [109,150]. Restoration of miR-7 has decreased tumor volume and survival in mice by suppressing EGFR/-PI3K/AKT pathways [151].

Several promising miRNA-based therapeutic approaches have entered clinical trials (Table 3). There are currently no miRNAs in clinical trials for patients with diffuse gliomas. However, significant attention has been focused on miRNA-based therapy and resistance due to EGFR activation or PTEN inhibition, which have often been disrupted in gliomas [31].

MiRNA-based therapeutic approaches are still in the early stages of development and require further preclinical and clinical studies to determine their safety and efficacy. For successful miRNA-based

Table 3
MiRNA-based drugs that have entered clinical trials.

miRNA	Disease	Clinical stage	Company/drug name	Study number
miR-155	treatment of amyotrophic lateral sclerosis (ALS)	preclinical trial	miRagen Therap., Inc./MRG-107	completed a preclinical trial
miR-34a	treatment of different types of cancers	I	miRNATherapeutics/MRX34	NCT03713320
miR-17	treatment of polycystic kidney disease	I	Regulus Therapeutics/RGLS4326	NCT04536688
miR-16	treatment of recurrent malignant pleural mesothelioma and non-small cell lung cancer	I	Asbestos Diseases Research Foundation/ TargomiRs	NCT02369198
miR-21	prevent alport syndrome (nephropathy)	I	Genzyme/Lademirsen	NCT03373786
miR-92a	blood vessel growth and to control ischemia	I	miRagen Therap. Inc./MRG-110	NCT03603431
miR-103, miR-107	Non Alcoholic Steatohepatitis (NASH) in patients with type 2 diabetes	I/IIa	AstraZeneca/AZD4076 (RG-125)	NCT02826525
miR-155	cutaneous T-cell lymphoma (CTCL)	II	miRagen Therap., Inc./MRG-106	NCT03713320
miR-29	treatment of fibrosis (cutaneous, idiopathic pulmonary fibrosis etc.)	II	miRagen Therap., Inc./MRG-201	NCT03601052
miR-122	treatment of hepatitis C virus (HCV)	II	SantarisPharma/Miravirsen (SPC3649)	NCT01200420

therapy, the delivery system should be more cancer-specific. The use of engineered exosomes [152], viral vectors, or plasmids [153] offer a non-invasive and cell-specific delivery method with promising therapeutic application. Nevertheless, these strategies hold significant potential for advancing the treatment of brain tumors and other types of cancer.

These studies emphasize the potential use of miRNAs and the currently recommended biomarkers for glioma diagnosis and treatment. Furthermore, miRNA profiling could also be used to stratify patients and determine the best course of treatment.

6. Conclusions

The study highlights the role of deregulated miRNAs related to the recommended molecular aberrations in adult diffuse glial tumors according to the 2021 WHO CNS classification. Since miRNAs contribute to the dysregulation of cell cycle control, cell proliferation, apoptosis, and other critical processes, their biomarker potential could improve brain tumor monitoring. Finally, we outline the potential of personalized miRNA therapy for more effective treatment and patient outcome improvement. Continued research and clinical trials are essential to translate genetic aberrations and deregulated miRNAs into effective treatments, paving the way for a future of precision medicine for patients with gliomas.

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Availability of data and material

All data collected during the preparation of the study are included in this published article.

CRediT authorship contribution statement

Emiliya Nikolova: Conceptualization, Writing – original draft. **Lili Laleva:** Visualization. **Milko Milev:** Writing – review & editing. **Toma Spiriev:** Writing – review & editing, Resources. **Stoycho Stoyanov:** he was responsible for Resources gahtering (information selectoin). **Vanyo Mitev:** Writing revision. **Albena Todorova:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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References

[1] D.N. Louis, A. Perry, P. Wesseling, D.J. Brat, I.A. Cree, D. Figarella-Branger, C. Hawkins, H.K. Ng, S.M. Pfister, G. Reifenberger, R. Soffietti, A. von Deimling, D.W. Ellison, The 2021 WHO classification of tumors of the central nervous system: a summary, Neuro Oncol. 23 (2021) 1231–1251, https://doi.org/10.1093/neuonc/noab106.
[2] A.A. Balachandran, L.M. Larcher, S. Chen, R.N. Veedu, Therapeutically significant MicroRNAs in primary and metastatic brain malignancies, Cancers 12 (2020), https://doi.org/10.3390/cancers12092534.
[3] M. Ha, V.N. Kim, Regulation of microRNA biogenesis, Nat. Rev. Mol. Cell Biol. 15 (2014) 509–524, https://doi.org/10.1038/nrm3838.
[4] P.J. Dexheimer, L. Cochella, MicroRNAs: from mechanism to organism, Front. Cell Dev. Biol. 8 (2020) 409, https://doi.org/10.3389/fcell.2020.00409.
[5] T.X. Lu, M.E. Rothenberg, MicroRNA, J. Allergy Clin. Immunol. 141 (2018) 1202–1207, https://doi.org/10.1016/j.jaci.2017.08.034.
[6] J. O'Brien, H. Hayder, Y. Zayed, C. Peng, Overview of MicroRNA biogenesis, mechanisms of actions, and circulation, Front. Endocrinol. 9 (2018) 402, https://doi.org/10.3389/fendo.2018.00402.
[7] D.J. Erstad, B.C. Fuchs, K.K. Tanabe, Molecular signatures in hepatocellular carcinoma: a step toward rationally designed cancer therapy, Cancer 124 (2018) 3084–3104, https://doi.org/10.1002/cncr.31257.
[8] E. Nikolova, C. Georgiev, L. Laleva, M. Milev, T. Spiriev, S. Stoyanov, T. Taseva-Mineva, V. Mitev, A. Todorova, Diagnostic, grading and prognostic role of a restricted miRNAs signature in primary and metastatic brain tumours. Discussion on their therapeutic perspectives, Mol. Genet. Genom. 297 (2022) 357–371, https://doi.org/10.1007/s00438-021-01851-5.
[9] E. Eskandari, J. Motalebzadeh, Transcriptomics-based screening of molecular signatures associated with patients overall survival and their key regulators in subtypes of breast cancer, Cancer Genet 239 (2019) 62–74, https://doi.org/10.1016/j.cancergen.2019.09.004.
[10] A.A. Svoronos, D.M. Engelman, F.J. Slack, OncomiR or tumor suppressor? The duplicity of MicroRNAs in cancer, Cancer Res. 76 (2016) 3666–3670, https://doi.org/10.1158/0008-5472.CAN-16-0359.
[11] G. Marziali, M. Buccarelli, A. Giuliani, R. Ilari, S. Grande, A. Palma, Q. G. D'Alessandris, M. Martini, M. Biffoni, R. Pallini, L. Ricci-Vitiani, A three-microRNA signature identifies two subtypes of glioblastoma patients with different clinical outcomes, Mol. Oncol. 11 (2017) 1115–1129, https://doi.org/10.1002/1878-0261.12047.
[12] C.M.S. Tesileanu, L. Dirven, M.M.J. Wijnenga, J.A.F. Koekkoek, A.J.P.E. Vincent, H.J. Dubbink, P.N. Atmodimedjo, J.M. Kros, S.G. van Duinen, M. Smits, M.J. B. Taphoorn, P.J. French, M.J. van den Bent, Survival of diffuse astrocytic glioma, IDH1/2 wildtype, with molecular features of glioblastoma, WHO grade IV: a confirmation of the cIMPACT-NOW criteria, Neuro Oncol. 22 (2020) 515–523, https://doi.org/10.1093/neuonc/noz200.
[13] F. Sahm, S. Brandner, L. Bertero, D. Capper, P.J. French, D. Figarella-Branger, F. Giangaspero, C. Haberler, M.E. Hegi, B.W. Kristensen, K.M. Kurian, M. Preusser, B.B.J. Tops, M. van den Bent, W. Wick, G. Reifenberger, P. Wesseling, Molecular diagnostic tools for the World Health Organization (WHO) 2021 classification of gliomas, glioneuronal and neuronal tumors; an EANO guideline, Neuro Oncol. (2023), https://doi.org/10.1093/neuonc/noad100 noad100.
[14] P. Śledzińska, M.G. Bebyn, J. Furtak, J. Kowalewski, M.A. Lewandowska, Prognostic and predictive biomarkers in gliomas, Int. J. Mol. Sci. 22 (2021), https://doi.org/10.3390/ijms221910373.
[15] J.E. Eckel-Passow, D.H. Lachance, A.M. Molinaro, K.M. Walsh, P.A. Decker, H. Sicotte, M. Pekmezci, T. Rice, M.L. Kosel, I. V Smirnov, G. Sarkar, A.A. Caron, T.M. Kollmeyer, C.E. Praska, A.R. Chada, C. Halder, H.M. Hansen, L.S. McCoy, P.

M. Bracci, R. Marshall, S. Zheng, G.F. Reis, A.R. Pico, B.P. O'Neill, J.C. Buckner, C. Giannini, J.T. Huse, A. Perry, T. Tihan, M.S. Berger, S.M. Chang, M.D. Prados, J. Wiemels, J.K. Wiencke, M.R. Wrensch, R.B. Jenkins, Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors, N. Engl. J. Med. 372 (2015) 2499–2508, https://doi.org/10.1056/NEJMoa1407279.

[16] X.-Y. Liu, N. Gerges, A. Korshunov, N. Sabha, D.-A. Khuong-Quang, A. M. Fontebasso, A. Fleming, D. Hadjadj, J. Schwartzentruber, J. Majewski, Z. Dong, P. Siegel, S. Albrecht, S. Croul, D.T.W. Jones, M. Kool, M. Tonjes, G. Reifenberger, D. Faury, G. Zadeh, S. Pfister, N. Jabado, Frequent ATRX mutations and loss of expression in adult diffuse astrocytic tumors carrying IDH1/IDH2 and TP53 mutations, Acta Neuropathol. 124 (2012) 615–625, https://doi.org/10.1007/s00401-012-1031-3.

[17] C. Bettegowda, N. Agrawal, Y. Jiao, M. Sausen, L.D. Wood, R.H. Hruban, F. J. Rodriguez, D.P. Cahill, R. McLendon, G. Riggins, V.E. Velculescu, S.M. Oba-Shinjo, S.K.N. Marie, B. Vogelstein, D. Bigner, H. Yan, N. Papadopoulos, K. W. Kinzler, Mutations in CIC and FUBP1 contribute to human oligodendroglioma, Science 333 (2011) 1453–1455, https://doi.org/10.1126/science.1210557.

[18] L. Ajuria, C. Nieva, C. Winkler, D. Kuo, N. Samper, M.J. Andreu, A. Helman, S. González-Crespo, Z. Paroush, A.J. Courey, G. Jiménez, Capicua DNA-binding sites are general response elements for RTK signaling in Drosophila, Development 138 (2011) 915–924, https://doi.org/10.1242/dev.057729.

[19] M.J. van den Bent, M. Smits, J.M. Kros, S.M. Chang, Diffuse infiltrating oligodendroglioma and astrocytoma, J. Clin. Oncol. 35 (2017) 2394–2401, https://doi.org/10.1200/JCO.2017.72.6737.

[20] R.B. Jenkins, H. Blair, K. V Ballman, C. Giannini, R.M. Arusell, M. Law, H. Flynn, S. Passe, S. Felten, P.D. Brown, E.G. Shaw, J.C. Buckner, A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma, Cancer Res. 66 (2006) 9852–9861, https://doi.org/10.1158/0008-5472.CAN-06-1796.

[21] K. Aoki, H. Nakamura, H. Suzuki, K. Matsuo, K. Kataoka, T. Shimamura, K. Motomura, F. Ohka, S. Shiina, T. Yamamoto, Y. Nagata, T. Yoshizato, M. Mizoguchi, T. Abe, Y. Momii, Y. Muragaki, R. Watanabe, I. Ito, M. Sanada, H. Yajima, N. Morita, I. Takeuchi, S. Miyano, T. Wakabayashi, S. Ogawa, A. Natsume, Prognostic relevance of genetic alterations in diffuse lower-grade gliomas, Neuro Oncol. 20 (2018) 66–77, https://doi.org/10.1093/neuonc/nox132.

[22] W. Szopa, T.A. Burley, G. Kramer-Marek, W. Kaspera, Diagnostic and therapeutic biomarkers in glioblastoma: current status and future perspectives, 2017, BioMed Res. Int. (2017), 8013575, https://doi.org/10.1155/2017/8013575.

[23] H.-Q. Ju, J.-F. Lin, T. Tian, D. Xie, R.-H. Xu, NADPH homeostasis in cancer: functions, mechanisms and therapeutic implications, Signal Transduct. Targeted Ther. 5 (2020) 231, https://doi.org/10.1038/s41392-020-00326-0.

[24] K. Ichimura, Molecular pathogenesis of IDH mutations in gliomas, Brain Tumor Pathol. 29 (2012) 131–139, https://doi.org/10.1007/s10014-012-0090-4.

[25] A.J. Colebatch, A. Dobrovic, W.A. Cooper, TERT gene: its function and dysregulation in cancer, J. Clin. Pathol. 72 (2019), https://doi.org/10.1136/jclinpath-2018-205653, 281 LP – 284.

[26] P.J. Killela, C.J. Pirozzi, P. Healy, Z.J. Reitman, E. Lipp, B.A. Rasheed, R. Yang, B. H. Diplas, Z. Wang, P.K. Greer, H. Zhu, C.Y. Wang, A.B. Carpenter, H. Friedman, A.H. Friedman, S.T. Keir, J. He, Y. He, R.E. McLendon, J.E. 2nd Herndon, H. Yan, D.D. Bigner, Mutations in IDH1, IDH2, and in the TERT promoter define clinically distinct subgroups of adult malignant gliomas, Oncotarget 5 (2014) 1515–1525, https://doi.org/10.18632/oncotarget.1765.

[27] K. Gao, G. Li, Y. Qu, M. Wang, B. Cui, M. Ji, B. Shi, P. Hou, TERT promoter mutations and long telomere length predict poor survival and radiotherapy resistance in gliomas, Oncotarget 7 (2016) 8712–8725, https://doi.org/10.18632/oncotarget.6007.

[28] C.D. Hurst, F.M. Platt, M.A. Knowles, Comprehensive mutation analysis of the TERT promoter in bladder cancer and detection of mutations in voided urine, Eur. Urol. 65 (2014) 367–369, https://doi.org/10.1016/j.eururo.2013.08.057.

[29] T. Ozawa, M. Riester, Y.-K. Cheng, J.T. Huse, M. Squatrito, K. Helmy, N. Charles, F. Michor, E.C. Holland, Most human non-GCIMP glioblastoma subtypes evolve from a common proneural-like precursor glioma, Cancer Cell 26 (2014) 288–300, https://doi.org/10.1016/j.ccr.2014.06.005.

[30] D. Koul, PTEN signaling pathways in glioblastoma, Cancer Biol. Ther. 7 (2008) 1321–1325, https://doi.org/10.4161/cbt.7.9.6954.

[31] E.Y.H.P. Lee, W.J. Muller, Oncogenes and tumor suppressor genes, Cold Spring Harb. Perspect. Biol. 2 (2010) a003236, https://doi.org/10.1101/cshperspect.a003236.

[32] I. Crespo, A.L. Vital, M. Gonzalez-Tablas, M. del C. Patino, A. Otero, M.C. Lopes, C. de Oliveira, P. Domingues, A. Orfao, M.D. Tabernero, Molecular and genomic alterations in glioblastoma multiforme, Am. J. Pathol. 185 (2015) 1820–1833, https://doi.org/10.1016/j.ajpath.2015.02.023.

[33] H. Ohgaki, P. Kleihues, Genetic pathways to primary and secondary glioblastoma, Am. J. Pathol. 170 (2007) 1445–1453, https://doi.org/10.2353/ajpath.2007.070011.

[34] C.M. Croce, K. Zhang, Y. Wei, Announcing signal transduction and targeted therapy, Signal Transduct. Targeted Ther. 1 (2016), 15006, https://doi.org/10.1038/sigtrans.2015.6.

[35] R.J. Roskoski, Small molecule inhibitors targeting the EGFR/ErbB family of protein-tyrosine kinases in human cancers, Pharmacol. Res. 139 (2019) 395–411, https://doi.org/10.1016/j.phrs.2018.11.014.

[36] Z. An, O. Aksoy, T. Zheng, Q.-W. Fan, W.A. Weiss, Epidermal growth factor receptor and EGFRvIII in glioblastoma: signaling pathways and targeted therapies, Oncogene 37 (2018) 1561–1575, https://doi.org/10.1038/s41388-017-0045-7.

[37] D.N. Louis, P. Wesseling, K. Aldape, D.J. Brat, D. Capper, I.A. Cree, C. Eberhart, D. Figarella-Branger, M. Fouladi, G.N. Fuller, C. Giannini, C. Haberler, C. Hawkins, T. Komori, J.M. Kros, H. Ng, B.A. Orr, S. Park, W. Paulus, A. Perry, T. Pietsch, G. Reifenberger, M. Rosenblum, B. Rous, F. Sahm, C. Sarkar, D. A. Solomon, U. Tabori, M.J. Bent, A. Deimling, M. Weller, V.A. White, D. W. Ellison, cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading, Brain Pathol. 30 (2020) 844–856, https://doi.org/10.1111/bpa.12832.

[38] R. Fontana, M. Ranieri, G. La Mantia, M. Vivo, Dual role of the alternative reading frame ARF protein in cancer, Biomolecules 9 (2019), https://doi.org/10.3390/biom9030087.

[39] L.E. Huang, Impact of CDKN2A/B homozygous deletion on the prognosis and biology of IDH-mutant glioma, Biomedicines 10 (2022), https://doi.org/10.3390/biomedicines10020246.

[40] V.M. Lu, K.P. O'Connor, A.H. Shah, D.G. Eichberg, E.M. Luther, R.J. Komotar, M. E. Ivan, The prognostic significance of CDKN2A homozygous deletion in IDH-mutant lower-grade glioma and glioblastoma: a systematic review of the contemporary literature, J. Neuro Oncol. 148 (2020) 221–229, https://doi.org/10.1007/s11060-020-03528-2.

[41] A. Binayke, S. Mishra, P. Suman, S. Das, H. Chander, Awakening the "guardian of genome": reactivation of mutant p53, Cancer Chemother. Pharmacol. 83 (2019) 1–15, https://doi.org/10.1007/s00280-018-3701-x.

[42] E. Gillet, A. Alentorn, B. Doukouré, E. Mundwiller, H.F. van Thuijl, J. C. Reijneveld, J.A.M. Medina, A. Liou, Y. Marie, K. Mokhtari, K. Hoang-Xuan, M. Sanson, J.-Y. Delattre, A. Idbaih, TP53 and p53 statuses and their clinical impact in diffuse low grade gliomas, J. Neuro Oncol. 118 (2014) 131–139, https://doi.org/10.1007/s11060-014-1407-4.

[43] M.J. Law, K.M. Lower, H.P.J. Voon, J.R. Hughes, D. Garrick, V. Viprakasit, M. Mitson, M. De Gobbi, M. Marra, A. Morris, A. Abbott, S.P. Wilder, S. Taylor, G. M. Santos, J. Cross, H. Ayyub, S. Jones, J. Ragoussis, D. Rhodes, I. Dunham, D. R. Higgs, R.J. Gibbons, ATR-X syndrome protein targets tandem repeats and influences allele-specific expression in a size-dependent manner, Cell 143 (2010) 367–378, https://doi.org/10.1016/j.cell.2010.09.023.

[44] C.M. Heaphy, A.P. Subhawong, S.-M. Hong, M.G. Goggins, E.A. Montgomery, E. Gabrielson, G.J. Netto, J.I. Epstein, T.L. Lotan, W.H. Westra, I.-M. Shih, C. A. Iacobuzio-Donahue, A. Maitra, Q.K. Li, C.G. Eberhart, J.M. Taube, D. Rakheja, R.J. Kurman, T.C. Wu, R.B. Roden, P. Argani, A.M. De Marzo, L. Terracciano, M. Torbenson, A.K. Meeker, Prevalence of the alternative lengthening of telomeres telomere maintenance mechanism in human cancer subtypes, Am. J. Pathol. 179 (2011) 1608–1615, https://doi.org/10.1016/j.ajpath.2011.06.018.

[45] S.T. Durant, Telomerase-independent paths to immortality in predictable cancer subtypes, J. Cancer 3 (2012) 67–82, https://doi.org/10.7150/jca.3965.

[46] D.N. Nguyen, C.M. Heaphy, R.F. de Wilde, B.A. Orr, Y. Odia, C.G. Eberhart, A. K. Meeker, F.J. Rodriguez, Molecular and morphologic correlates of the alternative lengthening of telomeres phenotype in high-grade astrocytomas, Brain Pathol. 23 (2013) 237–243, https://doi.org/10.1111/j.1750-3639.2012.00630.x.

[47] H.E. Leeper, A.A. Caron, P.A. Decker, R.B. Jenkins, D.H. Lachance, C. Giannini, IDH mutation, 1p19q codeletion and ATRX loss in WHO grade II gliomas, Oncotarget 6 (2015) 30295–30305, https://doi.org/10.18632/oncotarget.4497.

[48] N. Zolboot, J.X. Du, F. Zampa, G. Lippi, MicroRNAs instruct and maintain cell type diversity in the nervous system, Front. Mol. Neurosci. 14 (2021), 646072, https://doi.org/10.3389/fnmol.2021.646072.

[49] B. Liu, J. Li, M.J. Cairns, Identifying miRNAs, targets and functions, Briefings Bioinf. 15 (2014) 1–19, https://doi.org/10.1093/bib/bbs075.

[50] A.B. Ghaemmaghami, M. Mahjoubin-Tehran, A. Movahedpour, K. Morshedi, A. Sheida, S.P. Taghavi, H. Mirzaei, M.R. Hamblin, Role of exosomes in malignant glioma: microRNAs and proteins in pathogenesis and diagnosis, Cell Commun. Signal. 18 (2020) 120, https://doi.org/10.1186/s12964-020-00623-9.

[51] T. Kinoshita, K.W. Yip, T. Spence, F.-F. Liu, MicroRNAs in extracellular vesicles: potential cancer biomarkers, J. Hum. Genet. 62 (2017) 67–74, https://doi.org/10.1038/jhg.2016.87.

[52] L. Gatto, E. Franceschi, V. Di Nunno, A. Tosoni, R. Lodi, A.A. Brandes, Liquid biopsy in glioblastoma management: from current research to future perspectives, Oncol. 26 (2021) 865–878, https://doi.org/10.1002/onco.13858.

[53] A.B. Díaz Méndez, E. Tremante, G. Regazzo, S. Brandner, M.G. Rizzo, Time to focus on circulating nucleic acids for diagnosis and monitoring of gliomas: a systematic review of their role as biomarkers, Neuropathol. Appl. Neurobiol. 47 (2021) 471–487, https://doi.org/10.1111/nan.12691.

[54] T. Li, C.D. Cox, B.H. Ozer, N.T. Nguyen, H.N. Nguyen, T.J. Lai, S. Li, F. Liu, H. I. Kornblum, L.M. Liau, P.L. Nghiemphu, T.F. Cloughesy, A. Lai, D-2-Hydroxyglutarate is necessary and sufficient for isocitrate dehydrogenase 1 mutant-induced MIR148A promoter methylation, Mol. Cancer Res. 16 (2018) 947–960, https://doi.org/10.1158/1541-7786.MCR-17-0367.

[55] Y. Li, X. Deng, X. Zeng, X. Peng, The role of mir-148a in cancer, J. Cancer 7 (2016) 1233–1241, https://doi.org/10.7150/jca.14616.

[56] S. Ebrahimkhani, F. Vafaee, S. Hallal, H. Wei, M.Y.T. Lee, P.E. Young, L. Satgunaseelan, H. Beadnall, M.H. Barnett, B. Shivalingam, C.M. Suter, M. E. Buckland, K.L. Kaufman, Deep sequencing of circulating exosomal microRNA allows non-invasive glioblastoma diagnosis, npj Precis. Oncol. 2 (2018) 28, https://doi.org/10.1038/s41698-018-0071-0.

[57] L. Jia, B. Lei, H. Gao, L. Jia, D. Luo, J. Han, B. Jia, miR-130b suppresses the invasion and migration of prostate cancer via inhibiting DLL1 and regulating the PI3K/Akt pathways, Exp. Ther. Med. 23 (2022) 98, https://doi.org/10.3892/etm.2021.11021.

[58] J.S. Imam, K. Buddavarapu, J.S. Lee-Chang, S. Ganapathy, C. Camosy, Y. Chen, M.K. Rao, MicroRNA-185 suppresses tumor growth and progression by targeting the Six1 oncogene in human cancers, Oncogene 29 (2010) 4971–4979, https://doi.org/10.1038/onc.2010.233.

[59] A.B. Díaz Méndez, A. Sacconi, E. Tremante, V. Lulli, V. Caprara, L. Rosanò, F. Goeman, M. Carosi, M. Di Giuliani, G. Vari, A. Silvani, B. Pollo, C. Garufi, S. Ramponi, G. Simonetti, E. Ciusani, C. Mandoj, S. Scalera, V. Villani, A. Po, E. Ferretti, G. Regazzo, M.G. Rizzo, A diagnostic circulating miRNA signature as orchestrator of cell invasion via TKS4/TKS5/EFHD2 modulation in human gliomas, J. Exp. Clin. Cancer Res. 42 (2023) 66, https://doi.org/10.1186/s13046-023-02639-8.

[60] L. Zhang, M. Qi, T. Feng, J. Hu, L. Wang, X. Li, W. Gao, H. Liu, M. Jiao, Z. Wu, X. Bai, Y. Bie, L. Liu, B. Han, IDH1R132H promotes malignant transformation of benign prostatic epithelium by dysregulating MicroRNAs: involvement of igf1r-AKT/STAT3 signaling pathway, Neoplasia 20 (2018) 207–217, https://doi.org/10.1016/j.neo.2017.12.001.

[61] J. Wu, E. Yu, Insulin-like growth factor receptor-1 (IGF-IR) as a target for prostate cancer therapy, Cancer Metastasis Rev. 33 (2014) 607–617, https://doi.org/10.1007/s10555-013-9482-0.

[62] A.R. Grassian, F. Lin, R. Barrett, Y. Liu, W. Jiang, M. Korpal, H. Astley, D. Gitterman, T. Henley, R. Howes, J. Levell, J.M. Korn, R. Pagliarini, Isocitrate dehydrogenase (IDH) mutations promote a reversible ZEB1/microRNA (miR)-200-dependent epithelial-mesenchymal transition (EMT), J. Biol. Chem. 287 (2012) 42180–42194, https://doi.org/10.1074/jbc.M112.417832.

[63] C. Denoyelle, B. Lambert, M. Meryet-Figuière, N. Vigneron, E. Brotin, C. Lecerf, E. Abeilard, F. Giffard, M.-H. Louis, P. Gauduchon, P. Juin, L. Poulain, miR-491-5p-induced apoptosis in ovarian carcinoma depends on the direct inhibition of both BCL-XL and EGFR leading to BIM activation, Cell Death Dis. 5 (2014) e1445, https://doi.org/10.1038/cddis.2014.389. –e1445.

[64] Y. Zhou, Y. Li, J. Ye, R. Jiang, H. Yan, X. Yang, Q. Liu, J. Zhang, MicroRNA-491 is involved in metastasis of hepatocellular carcinoma by inhibitions of matrix metalloproteinase and epithelial to mesenchymal transition, Liver Int. Off. J. Int. Assoc. Study Liver. 33 (2013) 1271–1280, https://doi.org/10.1111/liv.12190.

[65] X. Li, Y. Liu, K.J. Granberg, Q. Wang, L.M. Moore, P. Ji, J. Gumin, E.P. Sulman, G. A. Calin, H. Haapasalo, M. Nykter, I. Shmulevich, G.N. Fuller, F.F. Lang, W. Zhang, Two mature products of MIR-491 coordinate to suppress key cancer hallmarks in glioblastoma, Oncogene 34 (2015) 1619–1628, https://doi.org/10.1038/onc.2014.98.

[66] R. Hrdličková, J. Nehyba, W. Bargmann, H.R.J. Bose, Multiple tumor suppressor microRNAs regulate telomerase and TCF7, an important transcriptional regulator of the Wnt pathway, PLoS One 9 (2014), e86990, https://doi.org/10.1371/journal.pone.0086990.

[67] D.M. Cittelly, P.M. Das, N.S. Spoelstra, S.M. Edgerton, J.K. Richer, A.D. Thor, F. E. Jones, Downregulation of miR-342 is associated with tamoxifen resistant breast tumors, Mol. Cancer 9 (2010) 317, https://doi.org/10.1186/1476-4598-9-317.

[68] S. Volinia, M. Galasso, S. Costinean, L. Tagliavini, G. Gamberoni, A. Drusco, J. Marchesini, N. Mascellani, M.E. Sana, R. Abu Jarour, C. Desponts, M. Teitell, R. Baffa, R. Aqeilan, M. V Iorio, C. Taccioli, R. Garzon, G. Di Leva, M. Fabbri, M. Catozzi, M. Previati, S. Ambs, T. Palumbo, M. Garofalo, A. Veronese, A. Bottoni, P. Gasparini, C.C. Harris, R. Visone, Y. Pekarsky, A. de la Chapelle, M. Bloomston, M. Dillhoff, L.Z. Rassenti, T.J. Kipps, K. Huebner, F. Pichiorri, D. Lenze, S. Cairo, M.-A. Buendia, P. Pineau, A. Dejean, N. Zanesi, S. Rossi, G. A. Calin, C.-G. Liu, J. Palatini, M. Negrini, A. Vecchione, A. Rosenberg, C. M. Croce, Reprogramming of miRNA networks in cancer and leukemia, Genome Res. 20 (2010) 589–599, https://doi.org/10.1101/gr.098046.109.

[69] P. Liu, P. Xia, Q. Fu, C. Liu, Q. Luo, L. Cheng, P. Yu, T. Qin, H. Zhang, miR-199a-5p inhibits the proliferation of hepatocellular carcinoma cells by regulating CDC25A to induce cell cycle arrest, Biochem. Biophys. Res. Commun. 571 (2021) 96–103, https://doi.org/10.1016/j.bbrc.2021.07.035.

[70] M. Kurihara-Shimomura, T. Sasahira, H. Shimomura, C. Nakashima, T. Kirita, The oncogenic activity of miR-29b-1-5p induces the epithelial-mesenchymal transition in oral squamous cell carcinoma, J. Clin. Med. 8 (2019), https://doi.org/10.3390/jcm8020273.

[71] Z. Liu, L. Zhang, W. Chen, F. Yuan, Z. Yang, S. Liu, F. Le, miR-195-5p regulates cell proliferation, apoptosis, and invasion of thyroid cancer by targeting telomerase reverse transcriptase, Bioengineered 12 (2021) 6201–6209, https://doi.org/10.1080/21655979.2021.1963908.

[72] Y.-Y. Wang, G. Sun, H. Luo, X.-F. Wang, F.-M. Lan, X. Yue, L.-S. Fu, P.-Y. Pu, C.-S. Kang, N. Liu, Y.-P. You, MiR-21 modulates hTERT through a STAT3-dependent manner on glioblastoma cell growth, CNS Neurosci. Ther. 18 (2012) 722–728, https://doi.org/10.1111/j.1755-5949.2012.00349.x.

[73] Q. Xu, J.-L. Xu, W.-Q. Chen, W.-X. Xu, Y.-X. Song, W.-J. Tang, D. Xu, M.-P. Jiang, J. Tang, Roles and mechanisms of miR-195–5p in human solid cancers, Biomed. Pharmacother. 150 (2022), 112885, https://doi.org/10.1016/j.biopha.2022.112885.

[74] R. Kumarswamy, I. Volkmann, T. Thum, Regulation and function of miRNA-21 in health and disease, RNA Biol. 8 (2011) 706–713, https://doi.org/10.4161/rna.8.5.16154.

[75] A. Conti, M. Aguennouz, D. La Torre, C. Tomasello, S. Cardali, F.F. Angileri, F. Maio, A. Cama, A. Germanò, G. Vita, F. Tomasello, miR-21 and 221 upregulation and miR-181b downregulation in human grade II–IV astrocytic tumors, J. Neuro Oncol. 93 (2009) 325–332, https://doi.org/10.1007/s11060-009-9797-4.

[76] M.G. Pezzolesi, P. Platzer, K.A. Waite, C. Eng, Differential expression of PTEN-targeting microRNAs miR-19a and miR-21 in Cowden syndrome, Am. J. Hum. Genet. 82 (2008) 1141–1149, https://doi.org/10.1016/j.ajhg.2008.04.005.

[77] L. Bai, H. Wang, A.-H. Wang, L.-Y. Zhang, J. Bai, MicroRNA-532 and microRNA-3064 inhibit cell proliferation and invasion by acting as direct regulators of human telomerase reverse transcriptase in ovarian cancer, PLoS One 12 (2017), e0173912, https://doi.org/10.1371/journal.pone.0173912.

[78] J. Zhou, W. Dai, J. Song, miR-1182 inhibits growth and mediates the chemosensitivity of bladder cancer by targeting hTERT, Biochem. Biophys. Res. Commun. 470 (2016) 445–452, https://doi.org/10.1016/j.bbrc.2016.01.014.

[79] M. Wolter, T. Werner, B. Malzkorn, G. Reifenberger, Role of microRNAs located on chromosome arm 10q in malignant gliomas, Brain Pathol. 26 (2016) 344–358, https://doi.org/10.1111/bpa.12294.

[80] F. Meng, R. Henson, H. Wehbe-Janek, K. Ghoshal, S.T. Jacob, T. Patel, MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer, Gastroenterology 133 (2007) 647–658, https://doi.org/10.1053/j.gastro.2007.05.022.

[81] H. Yang, W. Kong, L. He, J.-J. Zhao, J.D. O'Donnell, J. Wang, R.M. Wenham, D. Coppola, P.A. Kruk, S. V Nicosia, J.Q. Cheng, MicroRNA expression profiling in human ovarian cancer: miR-214 induces cell survival and cisplatin resistance by targeting PTEN, Cancer Res. 68 (2008) 425–433, https://doi.org/10.1158/0008-5472.CAN-07-2488.

[82] J.T. Huse, C. Brennan, D. Hambardzumyan, B. Wee, J. Pena, S.H. Rouhanifard, C. Sohn-Lee, C. le Sage, R. Agami, T. Tuschl, E.C. Holland, The PTEN-regulating microRNA miR-26a is amplified in high-grade glioma and facilitates gliomagenesis in vivo, Genes Dev. 23 (2009) 1327–1337, https://doi.org/10.1101/gad.1777409.

[83] Y. Liang, X. Xu, T. Wang, Y. Li, W. You, J. Fu, Y. Liu, S. Jin, Q. Ji, W. Zhao, Q. Song, L. Li, T. Hong, J. Huang, Z. Lyu, Q. Ye, The EGFR/miR-338-3p/EYA2 axis controls breast tumor growth and lung metastasis, Cell Death Dis. 8 (2017) e2928, https://doi.org/10.1038/cddis.2017.325. –e2928.

[84] K. Zhao, Q. Wang, Y. Wang, K. Huang, C. Yang, Y. Li, K. Yi, C. Kang, EGFR/c-myc axis regulates TGFβ/Hippo/Notch pathway via epigenetic silencing miR-524 in gliomas, Cancer Lett. 406 (2017) 12–21, https://doi.org/10.1016/j.canlet.2017.07.022.

[85] S.-M. Liu, J. Lu, H.-C. Lee, F.-H. Chung, N. Ma, miR-524-5p suppresses the growth of oncogenic BRAF melanoma by targeting BRAF and ERK2, Oncotarget 5 (2014) 9444–9459, https://doi.org/10.18632/oncotarget.2452.

[86] M. Zhuang, X. Qiu, D. Cheng, C. Zhu, L. Chen, MicroRNA-524 promotes cell proliferation by down-regulating PTEN expression in osteosarcoma, Cancer Cell Int. 18 (2018) 114, https://doi.org/10.1186/s12935-018-0612-1.

[87] P.N.N. Nguyen, K.B. Choo, C.-J. Huang, S. Sugii, S.K. Cheong, T. Kamarul, miR-524-5p of the primate-specific C19MC miRNA cluster targets TP53IPN1- and EMT-associated genes to regulate cellular reprogramming, Stem Cell Res. Ther. 8 (2017) 214, https://doi.org/10.1186/s13287-017-0666-3.

[88] N. Huang, Z. Wu, L. Lin, M. Zhou, L. Wang, H. Ma, J. Xia, J. Bin, Y. Liao, W. Liao, MiR-338-3p inhibits epithelial-mesenchymal transition in gastric cancer cells by targeting ZEB2 and MACC1/Met/Akt signaling, Oncotarget 6 (2015) 15222–15234, https://doi.org/10.18632/oncotarget.3835.

[89] D. Bhere, N. Arghiani, E.R. Lechtich, Y. Yao, S. Alsaab, F. Bei, M.M. Matin, K. Shah, Simultaneous downregulation of miR-21 and upregulation of miR-7 has anti-tumor efficacy, Sci. Rep. 10 (2020) 1779, https://doi.org/10.1038/s41598-020-58072-w.

[90] H. Xiao, MiR-7-5p suppresses tumor metastasis of non-small cell lung cancer by targeting NOVA2, Cell. Mol. Biol. Lett. 24 (2019) 60, https://doi.org/10.1186/s11658-019-0188-3.

[91] Z. Liu, Z. Jiang, J. Huang, S. Huang, Y. Li, S. Yu, S. Yu, X. Liu, miR-7 inhibits glioblastoma growth by simultaneously interfering with the PI3K/ATK and Raf/MEK/ERK pathways, Int. J. Oncol. 44 (2014) 1571–1580, https://doi.org/10.3892/ijo.2014.2322.

[92] B. Kefas, J. Godlewski, L. Comeau, Y. Li, R. Abounader, M. Hawkinson, J. Lee, H. Fine, E.A. Chiocca, S. Lawler, B. Purow, microRNA-7 inhibits the epidermal growth factor receptor and the Akt pathway and is down-regulated in glioblastoma, Cancer Res. 68 (2008) 3566–3572, https://doi.org/10.1158/0008-5472.CAN-07-6639.

[93] P. Korać, M. Antica, M. Matulić, MiR-7 in cancer development, Biomedicines 9 (2021) 325, https://doi.org/10.3390/biomedicines9030325.

[94] J. Zhou, L. Lv, C. Lin, G. Hu, Y. Guo, M. Wu, B. Tian, X. Li, Combinational treatment with microRNA-133b and cetuximab has increased inhibitory effects on the growth and invasion of colorectal cancer cells by regulating EGFR, Mol. Med. Rep. 12 (2015) 5407–5414, https://doi.org/10.3892/mmr.2015.4046.

[95] Y.-Y. Liu, M.-B. Chen, L. Cheng, Z.-Q. Zhang, Z.-Q. Yu, Q. Jiang, G. Chen, C. Cao, microRNA-200a downregulation in human glioma leads to Gαi1 over-expression, Akt activation, and cell proliferation, Oncogene 37 (2018) 2890–2902, https://doi.org/10.1038/s41388-018-0184-5.

[96] C. Cao, X. Huang, Y. Han, Y. Wan, L. Birnbaumer, G.-S. Feng, J. Marshall, M. Jiang, W.-M. Chu, Galpha(i1) and Galpha(i3) are required for epidermal growth factor-mediated activation of the Akt-mTORC1 pathway, Sci. Signal. 2 (2009) ra17, https://doi.org/10.1126/scisignal.2000118.

[97] P.A. Gregory, A.G. Bert, E.L. Paterson, S.C. Barry, A. Tsykin, G. Farshid, M. A. Vadas, Y. Khew-Goodall, G.J. Goodall, The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1, Nat. Cell Biol. 10 (2008) 593–601, https://doi.org/10.1038/ncb1722.

[98] Y. Su, Q. He, L. Deng, J. Wang, Q. Liu, D. Wang, Q. Huang, G. Li, MiR-200a impairs glioma cell growth, migration, and invasion by targeting SIM2-s,

Neuroreport 25 (2014) 12–17, https://doi.org/10.1097/WNR.0000000000000032.
[99] S. Gao, J. Wang, S. Tian, J. Luo, miR-9 depletion suppresses the proliferation of osteosarcoma cells by targeting p16, Int. J. Oncol. 54 (2019) 1921–1932, https://doi.org/10.3892/ijo.2019.4783.
[100] M. Khafaei, E. Rezaie, A. Mohammadi, P. Shahnazi Gerdehsang, S. Ghavidel, S. Kadkhoda, A. Zorrieh Zahra, N. Forouzanfar, H. Arabameri, M. Tavallaie, miR-9: from function to therapeutic potential in cancer, J. Cell. Physiol. 234 (2019) 14651–14665, https://doi.org/10.1002/jcp.28210.
[101] Y. Zhao, J. Yang, Y. Liu, J. Fan, H. Yang, HSV-2-encoded miRNA-H4 regulates cell cycle progression and act-D-induced apoptosis in HeLa cells by targeting CDKL2 and CDKN2A, Virol. Sin. 34 (2019) 278–286, https://doi.org/10.1007/s12250-019-00101-8.
[102] E. Boldrin, E. Gaffo, A. Niedermayer, J.M. Boer, M. Zimmermann, D. Weichenhan, R. Claus, V. Münch, Q. Sun, S. Enzenmüller, F. Seyfried, S. Demir, J. Zinngrebe, G. Cario, M. Schrappe, M.L. Den Boer, C. Plass, K.-M. Debatin, G. Te Kronnie, S. Bortoluzzi, L.H. Meyer, MicroRNA-497/195 is tumor suppressive and cooperates with CDKN2A/B in pediatric acute lymphoblastic leukemia, Blood 138 (2021) 1953–1965, https://doi.org/10.1182/blood.2020007591.
[103] R. Lakomy, J. Sana, S. Hankeova, P. Fadrus, L. Kren, E. Lzicarova, M. Svoboda, H. Dolezelova, M. Smrcka, R. Vyzula, J. Michalek, M. Hajduch, O. Slaby, MiR-195, miR-196b, miR-181c, miR-21 expression levels and O-6-methylguanine-DNA methyltransferase methylation status are associated with clinical outcome in glioblastoma patients, Cancer Sci. 102 (2011) 2186–2190, https://doi.org/10.1111/j.1349-7006.2011.02092.x.
[104] H. Tazawa, N. Tsuchiya, M. Izumiya, H. Nakagama, Tumor-suppressive miR-34a induces senescence-like growth arrest through modulation of the E2F pathway in human colon cancer cells, Proc. Natl. Acad. Sci. U.S.A. 104 (2007) 15472–15477, https://doi.org/10.1073/pnas.0707351104.
[105] H. Gao, H. Zhao, W. Xiang, Expression level of human miR-34a correlates with glioma grade and prognosis, J. Neuro Oncol. 113 (2013) 221–228, https://doi.org/10.1007/s11060-013-1119-1.
[106] C.M. Lopez, P.Y. Yu, X. Zhang, A.S. Yilmaz, C.A. London, J.M. Fenger, MiR-34a regulates the invasive capacity of canine osteosarcoma cell lines, PLoS One 13 (2018), e0190086, https://doi.org/10.1371/journal.pone.0190086.
[107] P. Sheedy, Z. Medarova, The fundamental role of miR-10b in metastatic cancer, Am. J. Cancer Res. 8 (2018) 1674–1688. http://www.ncbi.nlm.nih.gov/pubmed/30323962.
[108] C. Ma, F. Wei, H. Xia, H. Liu, X. Dong, Y. Zhang, Q. Luo, Y. Liu, Y. Li, MicroRNA-10b mediates TGF-β1-regulated glioblastoma proliferation, migration and epithelial-mesenchymal transition, Int. J. Oncol. 50 (2017) 1739–1748, https://doi.org/10.3892/ijo.2017.3947.
[109] G. Gabriely, M. Yi, R.S. Narayan, J.M. Niers, T. Wurdinger, J. Imitola, K.L. Ligon, S. Kesari, C. Esau, R.M. Stephens, B.A. Tannous, A.M. Krichevsky, Human glioma growth is controlled by MicroRNA-10b, Cancer Res. 71 (2011) 3563–3572, https://doi.org/10.1158/0008-5472.CAN-10-3568.
[110] L. Sun, W. Yan, Y. Wang, G. Sun, H. Luo, J. Zhang, X. Wang, Y. You, Z. Yang, N. Liu, MicroRNA-10b induces glioma cell invasion by modulating MMP-14 and uPAR expression via HOXD10, Brain Res. 1389 (2011) 9–18, https://doi.org/10.1016/j.brainres.2011.03.013.
[111] C.W. Dawson, R.J. Port, L.S. Young, The role of the EBV-encoded latent membrane proteins LMP1 and LMP2 in the pathogenesis of nasopharyngeal carcinoma (NPC), Semin. Cancer Biol. 22 (2012) 144–153, https://doi.org/10.1016/j.semcancer.2012.01.004.
[112] M.T.N. Le, C. Teh, N. Shyh-Chang, H. Xie, B. Zhou, V. Korzh, H.F. Lodish, B. Lim, MicroRNA-125b is a novel negative regulator of p53, Genes Dev. 23 (2009) 862–876, https://doi.org/10.1101/gad.1767609.
[113] W. Hu, C.S. Chan, R. Wu, C. Zhang, Y. Sun, J.S. Song, L.H. Tang, A.J. Levine, Z. Feng, Negative regulation of tumor suppressor p53 by microRNA miR-504, Mol. Cell. 38 (2010) 689–699, https://doi.org/10.1016/j.molcel.2010.05.027.
[114] M. Yuan, A.C.A.L. Da Silva, A. Arnold, L. Okeke, H. Ames, L.S. Correa-Cerro, M. A. Vizcaino, C.-Y. Ho, C.G. Eberhart, F.J. Rodriguez, MicroRNA (miR) 125b regulates cell growth and invasion in pediatric low grade glioma, Sci. Rep. 8 (2018), 12506, https://doi.org/10.1038/s41598-018-30942-4.
[115] M.E. Hegi, A.-C. Diserens, T. Gorlia, M.-F. Hamou, N. de Tribolet, M. Weller, J. M. Kros, J.A. Hainfellner, W. Mason, L. Mariani, J.E.C. Bromberg, P. Hau, R. O. Mirimanoff, J.G. Cairncross, R.C. Janzer, R. Stupp, MGMT gene silencing and benefit from temozolomide in glioblastoma, N. Engl. J. Med. 352 (2005) 997–1003, https://doi.org/10.1056/NEJMoa043331.
[116] O. Slaby, R. Lakomy, P. Fadrus, R. Hrstka, L. Kren, E. Lzicarova, M. Smrcka, M. Svoboda, H. Dolezalova, J. Novakova, D. Valik, R. Vyzula, J. Michalek, MicroRNA-181 family predicts response to concomitant chemoradiotherapy with temozolomide in glioblastoma patients, Neoplasma 57 (2010) 264–269, https://doi.org/10.4149/neo_2010_03_264.
[117] E. Nie, X. Jin, W. Wu, T. Yu, X. Zhou, Z. Shi, J. Zhang, N. Liu, Y. You, MiR-198 enhances temozolomide sensitivity in glioblastoma by targeting MGMT, J. Neuro Oncol. 133 (2017) 59–68, https://doi.org/10.1007/s11060-017-2425-9.
[118] C. Quintavalle, D. Mangani, G. Roscigno, G. Romano, A. Diaz-Lagares, M. Iaboni, E. Donnarumma, D. Fiore, P. De Marinis, Y. Soini, M. Esteller, G. Condorelli, MiR-221/222 target the DNA methyltransferase MGMT in glioma cells, PLoS One 8 (2013), e74466, https://doi.org/10.1371/journal.pone.0074466.
[119] A. Kirstein, T.E. Schmid, S.E. Combs, The role of miRNA for the treatment of MGMT unmethylated glioblastoma multiforme, Cancers 12 (2020), https://doi.org/10.3390/cancers12051099.
[120] R.-K. Lin, Y.-C. Wang, Dysregulated transcriptional and post-translational control of DNA methyltransferases in cancer, Cell Biosci. 4 (2014) 46, https://doi.org/10.1186/2045-3701-4-46.
[121] L. Wang, Z.-M. Shi, C.-F. Jiang, X. Liu, Q.-D. Chen, X. Qian, D.-M. Li, X. Ge, X.-F. Wang, L.-Z. Liu, Y.-P. You, N. Liu, B.-H. Jiang, MiR-143 acts as a tumor suppressor by targeting N-RAS and enhances temozolomide-induced apoptosis in glioma, Oncotarget 5 (2014) 5416–5427, https://doi.org/10.18632/oncotarget.2116.
[122] A. Mackay, A. Burford, D. Carvalho, E. Izquierdo, J. Fazal-Salom, K.R. Taylor, L. Bjerke, M. Clarke, M. Vinci, M. Nandhabalan, S. Temelso, S. Popov, V. Molinari, P. Raman, A.J. Waanders, H.J. Han, S. Gupta, L. Marshall, S. Zacharoulis, S. Vaidya, H.C. Mandeville, L.R. Bridges, A.J. Martin, S. Al-Sarraj, C. Chandler, H.-K. Ng, X. Li, K. Mu, S. Trabelsi, D.H.-B. Brahim, A.N. Kisljakov, D.M. Konovalov, A.S. Moore, A.M. Carcaboso, M. Sunol, C. de Torres, O. Cruz, J. Mora, L.I. Shats, J. N. Stavale, L.T. Bidinotto, R.M. Reis, N. Entz-Werle, M. Farrell, J. Cryan, D. Crimmins, J. Caird, J. Pears, M. Monje, M.-A. Debily, D. Castel, J. Grill, C. Hawkins, H. Nikbakht, N. Jabado, S.J. Baker, S.M. Pfister, D.T.W. Jones, M. Fouladi, A.O. von Bueren, M. Baudis, A. Resnick, C. Jones, Integrated molecular meta-analysis of 1,000 pediatric high-grade and diffuse intrinsic pontine glioma, Cancer Cell 32 (2017) 520–537.e5, https://doi.org/10.1016/j.ccell.2017.08.017.
[123] K.C. Schreck, S.A. Grossman, C.A. Pratilas, BRAF mutations and the utility of RAF and MEK inhibitors in primary brain tumors, Cancers 11 (2019), https://doi.org/10.3390/cancers11091262.
[124] T. Nicolaides, K.J. Nazemi, J. Crawford, L. Kilburn, J. Minturn, A. Gajjar, K. Gauvain, S. Leary, G. Dhall, M. Aboian, G. Robinson, J. Long-Boyle, H. Wang, A.M. Molinaro, S. Mueller, M. Prados, Phase I study of vemurafenib in children with recurrent or progressive BRAF(V600E) mutant brain tumors: pacific Pediatric Neuro-Oncology Consortium study (PNOC-002), Oncotarget 11 (2020) 1942–1952, https://doi.org/10.18632/oncotarget.27600.
[125] S. Perreault, V. Larouche, U. Tabori, C. Hawkin, S. Lippé, B. Ellezam, J.-C. Décarie, Y. Théoret, M.-É. Métras, S. Sultan, É. Cantin, M.-È. Routhier, M. Caru, G. Legault, É. Bouffet, L. Lafay-Cousin, J. Hukin, C. Erker, N. Jabado, A phase 2 study of trametinib for patients with pediatric glioma or plexiform neurofibroma with refractory tumor and activation of the MAPK/ERK pathway: TRAM-01, BMC Cancer 19 (2019) 1250, https://doi.org/10.1186/s12885-019-6442-2.
[126] K. Nosho, H. Igarashi, M. Nojima, M. Ito, R. Maruyama, S. Yoshii, T. Naito, Y. Sukawa, M. Mikami, W. Sumioka, E. Yamamoto, S. Kurokawa, Y. Adachi, H. Takahashi, H. Okuda, T. Kusumi, M. Hosokawa, M. Fujita, T. Hasegawa, K. Okita, K. Hirata, H. Suzuki, H. Yamamoto, Y. Shinomura, Association of microRNA-31 with BRAF mutation, colorectal cancer survival and serrated pathway, Carcinogenesis 35 (2014) 776–783, https://doi.org/10.1093/carcin/bgt374.
[127] X. Sun, J. Li, Y. Sun, Y. Zhang, L. Dong, C. Shen, L. Yang, M. Yang, Y. Li, G. Shen, Y. Tu, J. Tao, miR-7 reverses the resistance to BRAFi in melanoma by targeting EGFR/IGF-1R/CRAF and inhibiting the MAPK and PI3K/AKT signaling pathways, Oncotarget 7 (2016) 53558–53570, https://doi.org/10.18632/oncotarget.10669.
[128] M. Díaz-Martínez, L. Benito-Jardón, L. Alonso, L. Koetz-Ploch, E. Hernando, J. Teixidó, miR-204-5p and miR-211-5p contribute to BRAF inhibitor resistance in melanoma, Cancer Res. 78 (2018) 1017–1030, https://doi.org/10.1158/0008-5472.CAN-17-1318.
[129] S. Liu, M.T. Tetzlaff, T. Wang, R. Yang, L. Xie, G. Zhang, C. Krepler, M. Xiao, M. Beqiri, W. Xu, G. Karakousis, L. Schuchter, R.K. Amaravadi, W. Xu, Z. Wei, M. Herlyn, Y. Yao, L. Zhang, Y. Wang, L. Zhang, X. Xu, miR-200c/Bmi1 axis and epithelial-mesenchymal transition contribute to acquired resistance to BRAF inhibitor treatment, Pigment Cell Melanoma Res 28 (2015) 431–441, https://doi.org/10.1111/pcmr.12379.
[130] M.-H.T. Nguyen, C.-H. Lin, S.-M. Liu, A. Miyashita, H. Ihn, H. Lin, C.H. Ng, J.-C. Tsai, M.-H. Chen, M.-S. Tsai, I.-Y. Lin, S.-C. Liu, L.-Y. Li, S. Fukushima, J. Lu, N. Ma, miR-524-5p reduces the progression of the BRAF inhibitor-resistant melanoma, Neoplasia 22 (2020) 789–799, https://doi.org/10.1016/j.neo.2020.10.009.
[131] M. Williams, P. Treasure, D. Greenberg, A. Brodbelt, P. Collins, on behalf of the (Uk) N.C.I.N.B.T. Group, Surgeon volume and 30 day mortality for brain tumours in England, Br. J. Cancer 115 (2016) 1379–1382, https://doi.org/10.1038/bjc.2016.317.
[132] F.G. Davis, T.A. Dolecek, B.J. McCarthy, J.L. Villano, Toward determining the lifetime occurrence of metastatic brain tumors estimated from 2007 United States cancer incidence data, Neuro Oncol. 14 (2012) 1171–1177, https://doi.org/10.1093/neuonc/nos152.
[133] Y.Z. Kim, C.-Y. Kim, D.H. Lim, The overview of practical guidelines for gliomas by KSNO, NCCN, and EANO, Brain Tumor Res. Treat. 10 (2022) 83–93, https://doi.org/10.14791/btrt.2022.0001.
[134] L. Valihrach, P. Androvic, M. Kubista, Circulating miRNA analysis for cancer diagnostics and therapy, Mol. Aspect. Med. 72 (2020), 100825, https://doi.org/10.1016/j.mam.2019.10.002.
[135] Q. Li, Y. Chang, L. Mu, Y. Song, MicroRNA-9 enhances chemotherapy sensitivity of glioma to TMZ by suppressing TOPO II via the NF-κB signaling pathway, Oncol. Lett. 17 (2019) 4819–4826, https://doi.org/10.3892/ol.2019.10158.
[136] G.-B. Wang, J.-H. Liu, J. Hu, K. Xue, MiR-21 enhanced glioma cells resistance to carmustine via decreasing Spry2 expression, Eur. Rev. Med. Pharmacol. Sci. 21 (2017) 5065–5071, https://doi.org/10.26355/eurrev_201711_13819.
[137] Y. Chen, R. Li, M. Pan, Z. Shi, W. Yan, N. Liu, Y. You, J. Zhang, X. Wang, MiR-181b modulates chemosensitivity of glioblastoma multiforme cells to temozolomide by targeting the epidermal growth factor receptor, J. Neuro Oncol. 133 (2017) 477–485, https://doi.org/10.1007/s11060-017-2463-3.

[138] B.K. Ahir, H. Ozer, H.H. Engelhard, S.S. Lakka, MicroRNAs in glioblastoma pathogenesis and therapy: a comprehensive review, Crit. Rev. Oncol. Hematol. 120 (2017) 22–33, https://doi.org/10.1016/j.critrevonc.2017.10.003.

[139] J.A. Chan, A.M. Krichevsky, K.S. Kosik, MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells, Cancer Res. 65 (2005) 6029–6033, https://doi.org/10.1158/0008-5472.CAN-05-0137.

[140] L. Shi, J. Chen, J. Yang, T. Pan, S. Zhang, Z. Wang, 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. 1352 (2010) 255–264, https://doi.org/10.1016/j.brainres.2010.07.009.

[141] H. Liu, C. Chen, J. Zeng, Z. Zhao, Q. Hu, MicroRNA-210-3p is transcriptionally upregulated by hypoxia induction and thus promoting EMT and chemoresistance in glioma cells, PLoS One 16 (2021), e0253522, https://doi.org/10.1371/journal.pone.0253522.

[142] E.A. Toraih, A. El-Wazir, H.Y. Abdallah, M.A. Tantawy, M.S. Fawzy, Deregulated MicroRNA signature following glioblastoma irradiation, Cancer Control 26 (2019), 1073274819847226, https://doi.org/10.1177/1073274819847226.

[143] J. Gu, N. Mu, B. Jia, Q. Guo, L. Pan, M. Zhu, W. Zhang, K. Zhang, W. Li, M. Li, L. Wei, X. Xue, Y. Zhang, W. Zhang, Targeting radiation-tolerant persister cells as a strategy for inhibiting radioresistance and recurrence in glioblastoma, Neuro Oncol. 24 (2022) 1056–1070, https://doi.org/10.1093/neuonc/noab288.

[144] B. Jia, W. Liu, J. Gu, J. Wang, W. Lv, W. Zhang, Q. Hao, Z. Pang, N. Mu, W. Zhang, Q. Guo, MiR-7-5p suppresses stemness and enhances temozolomide sensitivity of drug-resistant glioblastoma cells by targeting Yin Yang 1, Exp. Cell Res. 375 (2019) 73–81, https://doi.org/10.1016/j.yexcr.2018.12.016.

[145] W. Yang, J. Wei, T. Guo, Y. Shen, F. Liu, Knockdown of miR-210 decreases hypoxic glioma stem cells stemness and radioresistance, Exp. Cell Res. 326 (2014) 22–35, https://doi.org/10.1016/j.yexcr.2014.05.022.

[146] M. Niyazi, F. Zehentmayr, O.M. Niemöller, S. Eigenbrod, H. Kretzschmar, K. Schulze-Osthoff, J.-C. Tonn, M. Atkinson, S. Mörtl, C. Belka, MiRNA expression patterns predict survival in glioblastoma, Radiat. Oncol. 6 (2011) 153, https://doi.org/10.1186/1748-717X-6-153.

[147] H. Sela, H. Cohen, P. Elia, R. Zach, Z. Karpas, Y. Zeiri, Spontaneous penetration of gold nanoparticles through the blood brain barrier (BBB), J. Nanobiotechnol. 13 (2015) 71, https://doi.org/10.1186/s12951-015-0133-1.

[148] S. Zhang, Z. Cheng, Y. Wang, T. Han, The risks of miRNA therapeutics: in a drug target perspective, Drug Des. Dev. Ther. 15 (2021) 721–733, https://doi.org/10.2147/DDDT.S288859.

[149] T.J. Lee, J.Y. Yoo, D. Shu, H. Li, J. Zhang, J.-G. Yu, A.C. Jaime-Ramirez, M. Acunzo, G. Romano, R. Cui, H.-L. Sun, Z. Luo, M. Old, B. Kaur, P. Guo, C. M. Croce, RNA nanoparticle-based targeted therapy for glioblastoma through inhibition of oncogenic miR-21, Mol. Ther. 25 (2017) 1544–1555, https://doi.org/10.1016/j.ymthe.2016.11.016.

[150] N.M. Teplyuk, E.J. Uhlmann, G. Gabriely, N. Volfovsky, Y. Wang, J. Teng, P. Karmali, E. Marcusson, M. Peter, A. Mohan, Y. Kraytsberg, R. Cialic, E. A. Chiocca, J. Godlewski, B. Tannous, A.M. Krichevsky, Therapeutic potential of targeting microRNA-10b in established intracranial glioblastoma: first steps toward the clinic, EMBO Mol. Med. 8 (2016) 268–287, https://doi.org/10.15252/emmm.201505495.

[151] D. Bhere, K. Tamura, H. Wakimoto, S.H. Choi, B. Purow, J. Debatisse, K. Shah, microRNA-7 upregulates death receptor 5 and primes resistant brain tumors to caspase-mediated apoptosis, Neuro Oncol. 20 (2018) 215–224, https://doi.org/10.1093/neuonc/nox138.

[152] Y. Qi, C. Jin, W. Qiu, R. Zhao, S. Wang, B. Li, Z. Zhang, Q. Guo, S. Zhang, Z. Gao, S. Zhao, Z. Pan, Y. Fan, Z. chen, H. Wang, J. Xu, L. Deng, S. Ni, J. Wang, H. Xue, F. Xue, G. Li, The dual role of glioma exosomal microRNAs: glioma eliminates tumor suppressor miR-1298-5p via exosomes to promote immunosuppressive effects of MDSCs, Cell Death Dis. 13 (2022) 426, https://doi.org/10.1038/s41419-022-04872-z.

[153] F.F. Lang, C. Conrad, C. Gomez-Manzano, W.K.A. Yung, R. Sawaya, J.S. Weinberg, S.S. Prabhu, G. Rao, G.N. Fuller, K.D. Aldape, J. Gumin, L.M. Vence, I. Wistuba, J. Rodriguez-Canales, P.A. Villalobos, C.M.F. Dirven, S. Tejada, R.D. Valle, M. M. Alonso, B. Ewald, J.J. Peterkin, F. Tufaro, J. Fueyo, Phase I study of DNX-2401 (Delta-24-RGD) oncolytic adenovirus: replication and immunotherapeutic effects in recurrent malignant glioma, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 36 (2018) 1419–1427, https://doi.org/10.1200/JCO.2017.75.8219.