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Chapter 6

# Critical Molecular and Genetic Markers in Primary Brain Tumors with Their Clinical Importance

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Additional information is available at the end of the chapter

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**Abstract**

Classification of primary brain tumors is based mainly on histopathological characteristics. Due to the peculiarity of the central nervous system (CNS), the location of the tumor is also used in the naming of the CNS tumors. These features, histopathology, and location determine the main prognostic factors in these tumors. Updated molecular and genetic findings in the last two decades accumulated vast amount of knowledge about the biological behavior, response to the treatment, and consequently the prognosis of CNS tumors. After the clinical use of these data, a recent classification is proposed by the International Society of Neuropathology named as "integrated diagnosis."

This classification considers the histopathological classification, World Health Organization (WHO) grade along with the molecular information. The emerging molecular-genetic data about the CNS tumors will allow the translational researchers to deliberately understand the oncogenic mechanisms involved in the evolution of these tumors and judge the optional treatment strategies.

Evaluating the check points of cell cycle and apoptosis provides valuable information about the tumor biology (tumorigenesis). These mechanisms (pathways) also play an exclusive role in CNS tumors. Knowledge concerning the gene repressors and gene activators or some epigenetic changes in proliferative and antiproliferative pathways that regarded gliomas may yield new individualized treatment options.

In this chapter, we will review the basic and translational research molecular-genetic data of gliomas with special interest on proliferative and antiproliferative pathways. Further emerging treatment options and treatment responses in gliomas will be

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critically evaluated with regard to their histopathology, anatomical location, and molecular-genetic fingerprints.

**Keywords:** gliomas, proliferation, apoptosis, cell cycle, gene

## 1. Introduction

Primary brain tumors are a distinct group of pathologies due to their location, low incidence compared to other human tumors, histopathologic diversities, and unexpected response to treatment methods mainly caused by their peculiar genetic and molecular characteristics. Evaluating new important biomarkers which affect the etiopathogenesis of brain tumors may also help clinicians in consulting patients about prognosis, potential clinical studies, and following response to the treatment strategies [1]. Nowadays, the value of early detection of various types of cancer before metastasis has become a very significant issue. This approach may increase life expectancy and the quality of life in these patients [2]. It is known that one of the best management strategies of cancer is to predict its prognosis and response to the updated therapeutic procedures. In order to achieve this, it is significant to consider the blood, serum, plasma, or tissue biomarkers. Although the value of liquid biopsy in different human tumors is established, there is a lack of data regarding primary brain tumors [3]. Confluence of information suggested that genetic, epigenetic, functional or compositional heterogeneity of diseased and healthy tissues presented a major challenge to strategies to improve clinical outcome. [4]. Many molecules found in various fluids, tissues, and cell lines are produced either by the tumor itself, other tissues, or tumor microenvironment, in response to the presence of cancer or other associated conditions including inflammation. The scientists study on cancer search for proper candidate tumor markers and for identifying patients who face different diagnosis or clinical stages of cancer. This type of biomarkers must have some characteristics which can be used to estimate tumor volume, determine response to treatment, and assess disease recurrence through monitoring. Recent advancements have shown that amplifications/translocations, genetic mutations and changes in microarray-generated profiles (genetic signatures) are contributory in cancer development, metastasis and development of resistance against different therapeutics. These genetic signatures are referred according to the type of tumor marker or profile and may be associated with clinical outcomes or good prognosis or enhanced quality of life [3,4]. An ideal tumor marker is described as easily measurable, reliable, and cost-effective by use of an assay with high analytical sensitivity and specificity. Although we have developed a deeper understanding of the underlying mechanisms, there are only a few markers which have been used in routine applications and only a limited number of them can be used to identify patients or monitor progression of cancer types and clinical staging.

Gene overexpression is described as increase in copy number of genes or chromosomes (i.e., gene amplification) through increased transcriptional activity. It is known that imbalance between the gene repressors and gene activators or some epigenetic changes as DNA methylation or chromosomal translocations can alter transcriptional activity of the gene [3,4].

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## 2. Defined molecular markers which changed our clinical attitude

The use of biomarkers in glioblastoma (GBM) has been evaluated in a recent survey by neuro-oncologists [5]. Current evidences indicate that MGMT, EGFR, 1p/19q, EGFR, p53, phosphatase and tensin homolog (PTEN) mutation or deletion, EGFRvIII, IDH1/2, PDGFR, and PIK3CA are the most commonly used markers. But, use of these biomarkers claimed to be prognostic in GBM cases is still debated. There exist significantly varying clinical representations and cases of GBM, and the structure of the signaling molecules is highly complex, and therefore, use of these markers is not very common as of now. In addition, glioblastoma, still a heterogeneous disease, also possesses additional difficulties such as having limited biomarkers to diagnosis and monitoring and therapeutic options, having poorly understood pathogenesis, and requiring individualized treatments. On the other hand, the discovery of new biomarkers together with currently used markers can enable us to better stratify patients regarding treatment paradigms and clinical trials (**Figure 1**) [6,7].

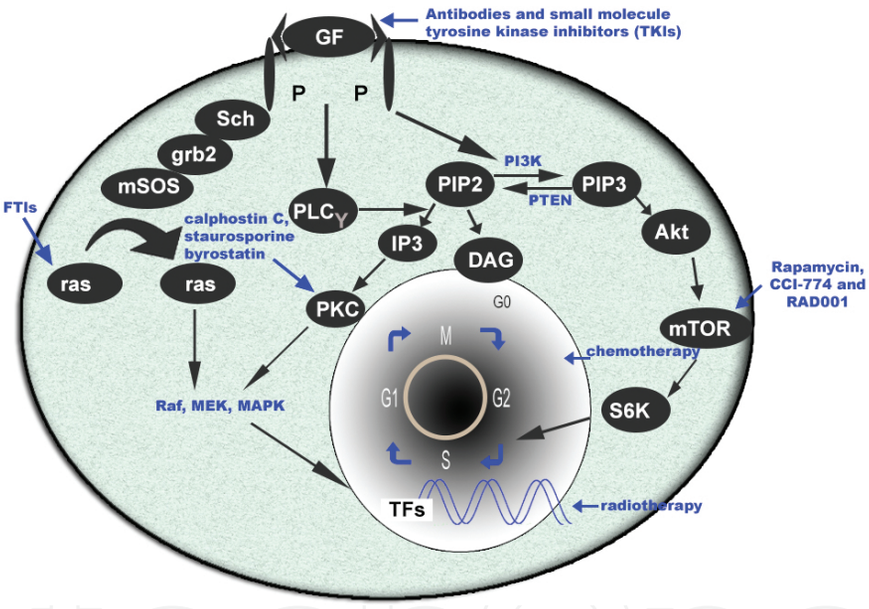



**Figure 1.** Some signaling pathways with therapeutic implications in gliomas [7]. Some abbreviations are shown below. EGF: epidermal growth factor; PIP2, phosphatidylinositol phosphate-2; PIP3, phosphatidylinositol phosphate-2; PKC, protein kinase C; Grb2, growth factor receptor-bound protein-2; VEGF, vascular endothelial growth factor; S6K, p70 S6 kinase; mTOR, mammalian target of rapamycin; TF, transcription factors; SOS, son of sevenless molecule.

## 3. Proliferative and antiproliferative pathways and their roles in gliomas

As more and more detailed studies into intracellular signaling cascades and modulators that regulate these pathways are published, intricacy of the fine-balance between celluar survival and death is revealed. A revolution in the signaling cascades has provided near complete resolution of how physiologically important signaling proteins interact with extracellular cues to trigger proliferation. More detailed understanding of the regulatory and activation

processes of uncontrolled cellular proliferation is proving to be a key in identification of newer approaches to improve the efficacy of existing therapeutics. The homeostasis of mitogenic signaling is tactfully controlled by multiple mechanisms. The past several years have seen a dramatic leap in our understanding of how Receptor tyrosine kinase (RTK) mediated signaling is rewired during tumorigenesis to support the transformed phenotype. Activation of RTK results in receptor dimerization and autophosphorylation. More importantly, docking sites are created for different adaptor protein complexes such as Grb2/SOS. Mutant Ras is reportedly involved in 50% of all human tumors. There are direct pieces of evidence emphasizing on role of mutant Ras in gliomas. High Ras-GTP levels in advanced astrocytomas have been reported [8, 9].

Epidermal growth factor receptor (EGFR), coded as a cell-surface-bound receptor, is another important molecule involved in cell proliferation with potential effects on clinical prognosis of GBM. It is known that approximately <10% of secondary GBMs and 50% of primary GBMs have EGFR mutations [10]. The presence of EGFR variant III mutation (EGFRvIII) is known to upregulate mitogenic signaling pathways. There is a deletion of the regulator N-terminal domain ( ▪ 6–273) of EGFR in this pattern of EGFR. About 10–60% of the patients with GBM have EGFRvIII which can be detected in the peripheral blood of brain tumors. The detection of this mutation in brain cancer patients has great importance for anti-EGFRvIII therapies and patients can be monitored to track their response to these therapies [11,12]. Better and deeper knowledge of mechanistic insights that cause EGFR heterogeneity in GBM will prove to be helpful in identification of drugs with maximum efficacy. *EGFRvIII* mutation to identify patients for treatments such as erlotinib therapy for non-small cell lung cancer or RNA-directed treatments and vaccine therapies [13]. As of now, we still have a limited knowledge about downstream signaling pathways for EGFR and whether *EGFR* mutations affect these downstream signaling pathways, such as AKT, MAPK, and STAT3. On the other hand, it has been suggested that the clinical utility of this biomarker and its use for targeted treatment are complicated [1].

Platelet-derived growth factor receptor (PDGFR), a cell-surface tyrosine kinase, plays role in GBM proliferation and stem cell renewal. There are multiple isoforms of PDGFR, mutated in up to 30% of GBMs. One of them, the most significant one regarding GBM, is PDGFRA. The other isoform is also PDGFRAD (with a deletion of exons 8 and 9), seen in 40% of GBMs, and leads to constitutive activation [14,15]. According to the Cancer Genome Atlas, PDGFRA has a crucial role in the proneural subtype of GBM; however, no changes were observed in prognosis of the evaluated patients [16].

The phosphatidylinositol 3-kinase (PI3K)/AKT (PI3K/AKT) pathway is known as a crucial intracellular signaling pathway, taking role in regulating cell proliferation, migration, quiescence, proliferation, cancer, and longevity [17]. PI3K is an enzyme which phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3) at the cell inner membrane. This activation process leads to recruit and upregulate various downstream pathways including AKT, a molecule localized in the plasma membrane [18].

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Phosphatase and tensin homolog (PTEN) is known as a natural inhibitor of PI3K/AKT pathway. It has been shown to inhibit transduction of signals to downstream effectors via dephosphorylation of $PIP_3$ to $PIP_2$ [19]. It has been reported that an increased PI3K/Akt/mTOR signaling is seen in ~88% of all glioblastomas [20,21]. All of these biological pathways has been related to genetic alterations of key regulatory molecules involved in mitogenic signaling in RTKs and also in the PI3K-PTEN-Akt signaling axis.

Some regulatory and effector molecules play important role in classical cell death networks of both extrinsic (death receptor-mediated) and intrinsic (mitochondria-dependent) apoptosis signaling pathways [22]. Since the discovery of TNF (Tumor Necrosis Factor) family members, a new milestone in apoptosis-inducing cancer therapies has emerged. TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) is a protein reportedly involved in selective killing of cancer cells while leaving normal cells intact. The major biological role of this 281-amino acid-type II transmembrane protein is apoptosis induction after interacting with its receptors to trigger extrinsically and intrinsically controlled pathways. Four different homologous human TRAIL receptors have been categorized into TRAIL-R1/DR4, TRAIL-R2/DR5 also known as Killer, TRAIL-R3 or DcR1, and TRAIL-R4 or DcR2. Substantial fraction of information has been added into the existing pool of knowledge related to TRAIL biology and known that different cancers are resistant to TRAIL-based therapeutics. Mechanistically it has been shown that downregulation of death receptors considerably impaired TRAIL-induced apoptosis in cancer cells. In the upcoming section, we briefly summarize advancements in our understanding related to the underlying mechanisms of resistance against TRAIL-induced apoptosis. We also discuss how TRAIL has shown as a potent anticancer agent in xenografted mice. Natural products have also added more options in the armory against brain tumor. Detailed mechanistic insights have provided a near complete resolution of protein network TRAIL-resistant glioblastoma and increasingly it is being realized that imbalance of stoichiometric ratios of proapoptotic and antiapoptotic proteins modulates response of cancer cells to TRAIL. Previously, it has been convincingly revealed that Znf domain of A20 E3 ligase ubiquitinated RIP1 through a K63-linked polyUB chain that structurally interacted with p18 domain of caspase-8 and blocked its dimerization and cleavage. Functionally inactive caspase-8 was unable to proteolytically process downstream effectors that resulted in impairment of TRAIL-induced apoptosis in glioblastoma [23]. Adeno-associated virus (AAV) vectors are being used to efficiently deliver secreted, soluble TRAIL in different preclinical studies. Additionally, these are also used in combination with TRAIL-sensitizing cardiac glycoside, lanatoside C (lan C). Tumor growth was considerably reduced in intracranial U87 tumor-bearing mice treated with AAV-sTRAIL and lanatoside C [24]. Mesenchymal stem cells (MSCs) have the ability to migrate toward intracranial glioma xenografts. Experimentally verified data indicated that MSCs expressing firefly luciferase (fluc) injected into the left hemisphere migrated rapidly toward right, tumor-bearing region of the brain. Results revealed that 11% of implanted MSCs were noted to be localized in right hemisphere within 2 hours after MSC inoculation. Coculture of GBM43 and U87 glioma cells with MSCs-TRAIL displayed notable rise in caspase-3 activity. Survival rate of tumor-bearing mice was enhanced intranasally delivered with MSCs-TRAIL [25]. Carbenoxolone (CBX), a derivative of 18-glycyrrhetinic acid, has been shown to effectively enhance killing activity of TRAIL-express-

ing MSCs. CBX considerably upregulated cell-surface expression of DR5 in CBX-treated ΔGli36 and U87MG cells. CBX also inhibited gap junction (GJ) communication via modulation of connexin (Cx43). CBX remarkably reduced expression levels of Cx43 in U87MG and ΔGli36 cells after 72 hours. Results revealed that TRAIL-induced apoptosis was markedly higher in cells transfected with Cx43-siRNA [26] .

Antibody-based anticancer therapies have attracted considerable attention and different structural variations are being tested for efficacies which involve smaller antibody fragments such as ScFvs, Fabs, and nanobodies. Single-chain Fv fragment (scFv) consists of a variable light-chain (VL) and variable heavy-chain (VH) domains, which contains whole antigen-binding site.

Multidrug resistance protein 3 (MRP3) is frequently overexpressed in glioblastoma multiforme cells. scFvM58-sTRAIL is an engineered protein formed by fusion of MRP3-specific scFv antibody M58 with N-terminus of soluble TRAIL. scFvM58-sTRAIL was effective against MRP3-positive GBM cells. Expectedly, scFvM58-sTRAIL did not show significant activity against MRP3-negative Jurkat cells. These results indicated that scFvM58-sTRAIL was effective against MRP3-positive cancer cells [27].

Various bivalent EGFR-targeting nanobodies (ENbs) have been designed and noted to be effective. Neural stem cells (NSC) are potent agents to deliver ENbs. Preclinical study revealed that tumor regression was significantly higher in xenografted mice treated with NSC-ENb2-TRAIL. Xenografted mice survived for 51 days upon treatment with control NSC-ENb2 and 80% of mice survived for 80 days after treatment with NSC-ENb2-TRAIL. These findings indicated that tumoritropic NSC-releasing ENb2 inhibited growth of glioblastoma and effectiveness of ENb2-based therapy was markedly improved by NSC-releasing ENb2-TRAIL [28].

Diethylamino-curcumin mimics with substituted triazolyl groups have previously been synthesized and reported to effectively sensitize resistant CRT-MG astroglioma cells to TRAIL [29].

Gingerol, a major bioactive component of ginger, has been shown to trigger expression of DR5 in a p53-dependent manner in U87 glioblastoma cells. Digitoxin (DT), a clinically approved cardiac glycoside, has been observed to overcome resistance against TRAIL in resistant U87MG glioblastoma cells. Digitoxin effectively enhanced DR5 expression on cell surface of resistant cancer cells [30].

## 4. Natural products mediated targeting of proliferative protein network in glioblastoma

Crude hydromethanolic extracts produced by maceration of *Spartium junceum* flowers and *Onopordum acanthium* leaves were tested for anticancer activity against glioblastoma U-373 cancer cells. *O. acanthium* was effective against glioblastoma cells and induced apoptosis [31] .

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Aqueous extract of *Ruta graveolens* L. notably enhanced phosphorylated ERK1/2 and Akt levels in glioma cells. The results indicated that *Ruta graveolens* exerted inhibitory effects via activation of ERK1/2 and Akt-induced signaling pathways [32].

Triterpenoid saponins from *Albizia lebbeck* (L.) showed activity against TG1 and U-87 MG cancer cells with $IC_{50}$ values of 2.10 and 2.24 μM for compound 2 and 3.46 and 1.36 μM for compound 1 [33].

Isocitrate Dehydrogenase 1 and 2 (IDH1/2) are two important enzymes involved in the Krebs cycle and oxidatively decarboxylate isocitrate to produce a-ketoglutarate and $CO_2$. IDH1 is a cytosolically located protein. IDH2 encodes a mitochondrial protein. Parsons et al. reported that IDH1/2 was mutated in approximately 60–80% of secondary gliomas and 5% of primary gliomas [34]. There are two common IDH mutation (IDH1R132H and IDH2172 mutations) types. It has been reported that these mutations are seen in GBM (>90% samples with IDH1/2 mutation). These mutations lead to increased production of the oncometabolite D-2-hydroxyglutarate. This metabolite has previously been noted to modify DNA methylation patterns in GBM and transcriptional activity of different target genes [35]. *IDH1* mutation may be correlated with several clinical factors such as younger patient age and frontal location. It has also been reported that additional survival benefit (median survival 9.75 years) was achieved from greater tumor resection (<5 $cm^3$ residual) in *IDH1* mutants, except for wild-type *IDH1*. It has also been suggested that the presence of *IDH1/2* mutation supports increased therapeutic efficacy with chemoradiotherapy and greater resection [1]. When IDH mutations occur, enzymatic activities of some important molecules can be altered. While alpha-ketoglutarate ($\alpha$-KG) is decreased, produced 2-hydroxyglutarate (2-HG) can inhibit the activity of some enzymes. These enzymes play a significant role in regulating DNA and histone methylation ($\alpha$-KG-dependent dioxygenase), including histone demethylases and the TET family of 5mC hydroxylases [36–38].

TET proteins are described as a new class of enzymes which can alter the methylation status of the DNA by converting 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC). The biological function of 5hmC is not clear. It has been suggested that it is an intermediate in DNA demethylation process. 5hmC offers remarkable reduction in human gliomas as compared to normal brain. An inverse relationship has been reported between 5hmC levels and cell proliferation [39,40].

p53 is a very important protein involved in many physiological and pathological process in the regulation of cell viability in terms of cell cycle, apoptosis, cell differentiation, and other mechanisms of cell regulation during exposure to DNA-damaging agents (e.g., ultraviolet radiation, toxins, chemotherapeutic agents) [1]. It has been reported that P53 gene is mutated in 28% of primary GBMs [41]. There are three patterns regarding p53 dysfunction. One is called loss of function. This pattern may describe a lot of endogenous growth inhibitor effects of wild-type p53. The other is gain of function. This means that mutant p53 upregulates a distinct subset of genes from wild-type p53. The last one is dominant-negative effects of p53. It is associated with a tetramer pattern of mutant p53/wild-type p53 and leads to downregulate activity [42]. It is known that some other mechanisms of p53 inactivation include mutations of its modulators including MDM2 inhibitor or deletion of p14ARF [43,44]. Whether there

is a correlation between p53 and GBM prognosis is still unclear due to the complexity of the p53 signaling pathway. P53 pathway includes many important regulators and the heterogeneity of p53 mutation types can also affect the p53 molecule. Because of those mentioned, therapies targeting P53 have been limited in this field [42].

The deletion of 1p and 19q, occurring early in tumorigenesis, is known as an important genetic signature. The deletion is seen in 50–70% of patients with low-grade oligodendrogliomas. This can be predictive for the tumor's chemosensitivity to some agents [46,47]. It has been reported that *P190RhoGAP*, localized on 19q13.3, can be one of the candidate genes as a tumor suppressor [48]. A large-scale genomic analysis by array CGH has reported two different patterns about 1p deletion for prognostic factors. One of them is the whole 1p (associated with the deletion of the whole 19q). This may be associated with a good prognosis for oligodendrogliomas. Another is 1p deletion (not associated with 19q loss). This deletion has a negative prognostic value and improves progression-free survival (PFS) and overall survival (OS). It is mostly associated with astrocytomas [49]. It is also related to the response to chemotherapy and radiation in oligodendroglioma. Data obtained from EORTC 26951 and RTOG 9402 trials showed an improvement in OS with the addition of radiation to procarbazine/lomustine/vincristine chemotherapy in anaplastic oligodendroglioma with 1p/19q mutation [50]. There are some studies correlated with these similar findings, In GBM, similar findings have been demonstrated in some studies [51,52], but not in others [53,54]. It has also been reported that codeletion of 1p and 19q is related with *IDH1* mutation and *MGMT* hypermethylation [47,55].

O-6-Methylguanine-DNA-methyltransferase (MGMT) is involved in removal of alkylation at the O6 position of guanine. Hypermethylation of *MGMT* transcriptionally down-regulated its expression. This situation results in impaired repair capability response to chemotherapeutic agents and radiation. Some clinical trials have confirmed the prognostic and predictive roles of *MGMTm* [56]. It has been suggested that patients with *MGMTm* are responsive to chemotherapy. However, *MGMT* status was not distinguished between patients with glioblastoma (GBM) and those with anaplastic astrocytoma (AA) and this restricts interpretation of the study. The European Organisation for Research and Treatment of Cancer (EORTC) 26981/22981 and National Cancer Institute of Canada (NCIC) trials also indicates increased responsiveness to temozolomide for patients with MGMTm [57]. It has been suggested that a standard marker both following prognosis and identifying patients for clinical trials, in which alkylation therapies and/or radiation therapy are applied, may be used for MGMTm [1].

## 5. Epigenetics in human gliomas with some details

Acetylation of lysine residues is a post-tranlational modification controlled by the opposing action of histone deacetylases (HDACs) and histone acetyl transferases (HATs) [58–60]. Histone methylation may generally occur on the side chains of lysines and arginines, which can alter the activity of effector proteins of the transcriptional machinery [58–60]. It has been

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reported that some mutations in some regulatory genes such as HDACs (HDAC2 and HDAC9), histone demethylases (JMJD1A and JMJD1B), and histone methyltransferases (SET7, SETD7, MLL, MLL3, and MLL4) have been detected to a large extent in genomic analysis of GBM samples [34]. However, it is still unclear whether histone modifications play significant roles in gliomas and their potential can serve as biomarkers and/or therapeutic targets. Noncoding RNAs are known to play an important role in the epigenetic regulation of gene expression [61,62].

One group of RNAs are described as microRNAs (miRNAs). miRNAs are important regulators for gene expression. miRNAs post-transcriptionally regulate expression of target genes. miRNAs are double-stranded RNA molecules of approximately 22 nucleotides (nt) in length. miRNA binds to specific recognition sequences within the 3′-untranslated region (3′-UTR) of target mRNAs [61–63]. miRNAs are characterized functionally into tumor suppressors and oncogenic miRNAs. Tumor suppressor miRNAs are frequently down-regulated in gliomas as compared to normal brain [64–67]. In contrast, some miRNAs are defined as oncogenes with enhanced expression in glioma such as miR-21, targeting regulators, miR-10b and miR-221, targeting cell cycle inhibitors, miR-30e, and targeting IjBa [68–71]. It has been suggested that there is a link between miRNAs and well-known stem cell-regulating proteins [72]. It has also been reported that miR-17-92 plays a critical role in regulation of glioma stem cell (GSC) differentiation, apoptosis, and proliferation [73]. miR-451 expression reduced notably in cancer cells kept in low glucose conditions. Results revealed that cancer cells kept in low glucose conditions had reduced cell proliferation but an enhanced rate of cell migration and survival in glioblastomas. Glucose sufficiency induced upregulation of miR-451 notably inhibited LKB1/AMPK pathway activation [74]. miR-128, downregulated in glioblastoma tissue, has a tumor-suppressive function. Both in vitro and in vivo, miR-128 expression significantly reduces glioma cell proliferation via downregulation of *Bmi-1 oncogene*, a component of the polycomb repressor complex (PRC). In addition, miR-128 inhibits GSC self-renewal [75]. The PRC has been shown to induce normal and cancer stem cell self-renewal and plays role in GSC regulation [76]. When miR-124 has overexpression, it can inhibit the CD133+ cell subpopulation of the neurosphere and downregulate stem cell markers, such as *BMI1*, *Nanog*, and *Nestin* [77]. Both miR-124 and miR-137 are up-regulated during adult neural stem cell differentiation and down-regulated in high-grade gliomas [78]. Although there are comprehensive studies about miRNa in gliomas, it should not be forgotten that one miRNA can affect the expression of various target genes. It must be reconsidered in terms of several important aspects before miRNAs may be used therapeutically [79].

LncRNAs which have more than 200 nucleotides and are up to 100 kb in length are described as an important RNA molecule that plays role in some biological cellular actions such as stemness, development, and cell survival [80–82]. Maternally expressed gene 3 (*MEG3*) is a maternally expressed imprinted gene that can also act as an lncRNA. Its expression in glioma tissues is lower than that in normal adjacent tissues [83]. The tumor-suppressive role of *MEG3* is confirmed by the fact that it can associate with p53. It is known that this association is needed for p53 activation [84].

## 6. Possible relationships between location and genetic signature in primary brain tumors

A unique finding is that the location of certain primary brain tumors determines their genetic characteristics. Cranial base meningiomas are less malignant compared to the non-cranial base meningiomas [85]. The frequencies of grade II and III cranial base and non-cranial base meningiomas are 3.5 and 12.1%, respectively. These findings origin from a clinical-pathological observation. The biological, molecular, and genetic basis of this fact requires further explanation. A simple answer would be the diverse embryological origins of the dura mater in various locations of human skull [86]. A recently published paper showed (utmost) intriguing data about meningioma biology, which is going to help our understanding of this tumor, of which 85–90% is classified as benign (grade I), but has in certain locations an aggressive course. Meningiomas regarding their genetic origin are divided as NF2 and non-NF2 meningiomas. The non-NF2 meningiomas behave clinically different and are generally always benign, with chromosomal stability, and originate from the medial skull base. In contrast to these findings, meningiomas with mutant NF2 and/or chromosome 22 loss are more likely to be atypical and demonstrate genomic instability and are localized to the cerebral and cerebellar hemispheres. This group concludes their study: "Collectively, these findings identify distinct meningioma subtypes, suggesting avenues for targeted therapeutics" [87]. There is a mutational profile of a meningioma, which can be predicted based on its anatomical location in human calvarium. This finding may provide a unique treatment strategy for midline tumors, which may have a response to medical treatment like hedgehog inhibitors. There are treatment-resistant meningiomas, which are surgically unresectable, recurrent, or invasive. In these patients one can reserve surgery or irradiation, bearing in mind that there is an independent risk factor for progression of these generally benign considered primary brain tumors. This location-based molecular and genetic data provides an updated information about prognosis and treatment response of meningiomas. This update research, which is collected over 300 meningiomas, is a valuable finding, regarding designing personalized management strategies for meningiomas.

Another fact about meningioma is that there is a subgroup of meningiomas, which are histopathologically classified as grade I meningioma, but recurs during follow-up in a short distance unexpectedly as grade II and later as grade III meningiomas. Although the malignant progression of gliomas is considerably well defined and researched entity, there is lack of scientific data about meningiomas, regarding which one is going to transform malignantly. Al-Mefty et al. explained this clinical observation with their FISH analysis of primary and recurring meningiomas with malignant progression in their series. They studied 175 recurrent meningiomas and found that 11 tumors showed histopathologically verified progression to a higher grade. In this study, the cytogenetic analysis with FISH showed deletions of 22, 1p, and 14q. The interesting finding was that in all but one case, these aberrations have been shown to be also present in the previous specimen despite their lower histopathological grades [88].

The conclusion of this translational paper from 2004 was defined: "Tumors that present with complex genetic alterations, even those with a benign histopathological grade are potentially aggressive and require closer follow-up." After 12 years this sentence is still valid for meningiomas and other primary brain tumors, which are genetically prone to upgrade. The designated malignant progression of primary brain tumors is an important issue for designing molecular-genetic-based therapeutic approaches in the near future. The finding that oligodendrogliomas show allelic deletions on 19q and 1p has been defined in 1994 by Reifenberger et al. [89]. Clinical relevance and its implication in changing management strategies followed this genetic finding. The chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas were explained with the over-mentioned genetic background [90]. Its relationship with better prognosis and response to chemotherapy is today an established fact and will be considered in the update "integrated-layered" classification of central nervous system tumors after Haarlem consensus [91]. The location of oligodendrogliomas and its relationship with 1p19q deletion further changed our direction in a phylogenetic explanation of primary brain tumor development and coexisting molecular-genetic mechanisms. Frontal location of oligodendroglioma was suggested to be a favorable prognostic factor. The accumulated data clearly demonstrated that frontal location was strongly correlated with 1p19q deletion [92]. Prognostic variables in oligodendroglial tumors: a single-institution study of 95 cases. This translational information eased (helped) to predict the prognosis of these peculiar tumors. The embryological developmental basis of oligodendroglioma and its molecular-genetic relationship are other issues, which require further investigation.

Lucius Annaeus Seneca, known as Seneca the Younger (c. 4 BC–AD 65), stated: "No one can wear a mask for very long." We can further apply this wise quote to our update neuro-oncological approach, which requires redefinition in the coming decades: "No tumor can wear a mask for very long." The molecular-genetic data and determining its relationship with primary brain tumors will further relieve "the mask" of the primary brain tumors. The upcoming new WHO classification of central nervous system tumors will consider this issue.

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## References

[1] Karsy M, Neil JA, Guan J, Mahan MA, Colman H, Jensen RL: A practical review of prognostic correlations of molecular biomarkers in glioblastoma. Neurosurg Focus. 2015;38(3):E4. doi: 10.3171/2015.1.FOCUS14755.

[2] Etzioni R, Urban N, Ramsey S, McIntosh M, Schwartz S, Reid B, Radich J, Anderson G, Hartwell L: The case for early detection. Nat Rev Cancer. 2003;3(4):243–252.

[3] Kulasingam V, Diamandis EP: Strategies for discovering novel cancer biomarkers through utilization of emerging technologies. Nat Clin Pract Oncol. 2008;5:588–599.

[4] Hayes DF, Bast RC, Desch CE, Fritsche H Jr, Kemeny NE, Jessup JM, Locker GY, Macdonald JS, Mennel RG, Norton L, Ravdin P, Taube S, Winn RJ: Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst. 1996;88(20):1456–1466.

[5] Holdhoff M, Ye X, Blakeley JO, Blair L, Burger PC, Grossman SA, et al: Use of personalized molecular biomarkers in the clinical care of adults with glioblastomas. J Neurooncol. 2012;110:279–285.

[6] Westhoff MA, Karpel-Massler G, Brühl O, Enzenmüller S, La Ferla-Brühl K, Siegelin MD, Nonnenmacher L Debatin KM: A critical evaluation of PI3K inhibition in glioblastoma and neuroblastoma therapy. Mol Cell Ther. 2014;2:32.

[7] Rao RD, James CD: Altered molecular pathways in gliomas: an overview of clinically relevant issues. Semin Oncol. 2004;31(5):595–604

[8] Guha A, Feldkamp MM, Lau N, Boss G, Pawson A: Proliferation of human malignant astrocytomas is dependent on Ras activation. Oncogene. 1997;15:2755–2765.

[9] Pandey V, Bhaskara VK, Babu PP: Implications of mitogen-activated protein kinase signaling in glioma. J Neurosci Res. 2016;94:114–127. doi: 10.1002/jnr.23687.

[10] Wong AJ, Ruppert JM, Bigner SH, Grzeschik CH, Humphrey PA, Bigner DS, et al: Structural alterations of the epidermal growth factor receptor gene in human gliomas. Proc Natl Acad Sci U S A. 1992;89:2965–2969.

[11] Frederick L, Wang XY, Eley G, James CD: Diversity and frequency of epidermal growth factor receptor mutations in human glioblastomas. Cancer Res. 2000;60:1383–1387.

[12] Salkeni MA, Zarzour A, Ansay TY, McPherson CM, Warnick RE, Rixe O, et al: Detection of EGFRvIII mutant DNA in the peripheral blood of brain tumor patients. J Neurooncol. 2013;115:27–35

[13] Taylor TE, Furnari FB, Cavenee WK: Targeting EGFR for treatment of glioblastoma: molecular basis to overcome resistance. Curr Cancer Drug Targets. 2012;12:197–209.

[14] Brennan C, Momota H, Hambardzumyan D, Ozawa T, Tandon A, Pedraza A, et al: Glioblastoma subclasses can be defined by activity among signal transduction pathways and associated genomic alterations. PLoS ONE. 2009;4:e7752.

[15] Ozawa T, Brennan CW, Wang L, Squatrito M, Sasayama T, Nakada M, et al: PDGFRA gene rearrangements are frequent genetic events in PDGFRA-amplified glioblastomas. Genes Dev. 2010;24:2205–2218.

[16] Verhaak RGW, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, et al: Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell. 2010;17:98–110.

[17] Sami A, Karsy M: Targeting the PI3K/AKT/mTOR signaling pathway in glioblastoma: novel therapeutic agents and advances in understanding. Tumour Biol. 2013;34:1991–2002.

[18] King D, Yeomanson D, Bryant HE: PI3King the lock: targeting the PI3K/Akt/mTOR pathway as a novel therapeutic strategy in neuroblastoma. J Pediatr Hematol Oncol. 2015;37:245–251.

[19] Rafalski VA, Brunet A: Energy metabolism in adult neural stem cell fate. Prog Neurobiol. 2011;93(2):182–203. doi: 10.1016/j.pneurobio.2010.10.007. PMID 21056618.

[20] Network CGAR: Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008;455:1061–1068.

[21] Fan QW, Weiss WA: Targeting the RTK–PI3K–mTOR axis in malignant glioma: overcoming resistance. Curr Top Microbiol Immunol. 2010;347:279–296.

[22] Lavrik IN, Golks A, and Krammer PH: Caspases: pharmacological manipulation of cell death. J Clin Invest. 2005;115:2665–2672.

[23] Bellail AC, Olson JJ, Yang X, Chen ZJ, Hao C: A20 ubiquitin ligase-mediated polyubiquitination of RIP1 inhibits caspase-8 cleavage and TRAIL-induced apoptosis in glioblastoma. Cancer Discov. 2012;2(2):140–155.

[24] Crommentuijn MH, Maguire CA, Niers JM, Vandertop WP, Badr CE, Würdinger T, Tannous BA: Intracranial AAV–sTRAIL combined with lanatoside C prolongs survival in an orthotopic xenograft mouse model of invasive glioblastoma. Mol Oncol. 2015;11. pii: S1574-7891(15)00226-4.

[25] Balyasnikova IV, Prasol MS, Ferguson SD, Han Y, Ahmed AU, Gutova M, Tobias AL, Mustafi D, Rincón E, Zhang L, Aboody KS, Lesniak MS: Intranasal delivery of mesenchymal stem cells significantly extends survival of irradiated mice with experimental brain tumors. Mol Ther. 2014;22(1):140–148.

[26] Yulyana Y, Endaya BB, Ng WH, Guo CM, Hui KM, Lam PY, Ho IA: Carbenoxolone enhances TRAIL-induced apoptosis through the upregulation of death receptor 5 and

inhibition of gap junction intercellular communication in human glioma. Stem Cells Dev. 2013;22(13):1870–1882.

[27] Wang LH, Ni CW, Lin YZ, Yin L, Jiang CB, Lv CT, Le Y, Lang Y, Zhao CY, Yang K, Jiao BH, Yin J: Targeted induction of apoptosis in glioblastoma multiforme cells by an MRP3-specific TRAIL fusion protein in vitro. Tumour Biol. 2014;35(2):1157–1168.

[28] van de Water JA, Bagci-Onder T, Agarwal AS, Wakimoto H, Roovers RC, Zhu Y, Kasmieh R, Bhere D, Van Bergen en Henegouwen PM, Shah K: Therapeutic stem cells expressing variants of EGFR-specific nanobodies have antitumor effects. Proc Natl Acad Sci U S A. 2012;109(41):16642–16647

[29] Ahn Y, Oh S, Lee SJ, Park BG, Park YS, Shin WS, Jang HJ, Park JH, Kwon D, Lee S: Synthesis of diethylamino-curcumin mimics with substituted triazolyl groups and their sensitization effect of TRAIL against brain cancer cells. Bioorg Med Chem Lett. 2014;24(15):3346–3350.

[30] Lee DH, Lee CS, Kim DW, Ae JE, Lee TH: Digitoxin sensitizes glioma cells to TRAIL-mediated apoptosis by upregulation of death receptor 5 and downregulation of survivin. Anticancer Drugs. 2014;25(1):44–52.

[31] Abusamra YA, Scuruchi M, Habibatni S, Maammeri Z, Benayache S, D'Ascola A, Avenoso A, Campo GM, Spina E: Evaluation of putative cytotoxic activity of crude extracts from *Onopordum acanthium* leaves and Spartium junceum flowers against the U-373 glioblastoma cell line. Pak J Pharm Sci. 2015;28(4):1225–1232.

[32] Gentile MT, Ciniglia C, Reccia MG, Volpicelli F, Gatti M, Thellung S, Florio T, Melone MA, Colucci-D'Amato L: *Ruta graveolens* L. induces death of glioblastoma cells and neural progenitors, but not of neurons, via ERK 1/2 and AKT activation. PLoS One. 2015;10(3):e0118864.

[33] Noté OP, Jihu D, Antheaume C, Zeniou M, Pegnyemb DE, Guillaume D, Chneiwess H, Kilhoffer MC, Lobstein A: Triterpenoid saponins from *Albizia lebbeck* (L.) Benth and their inhibitory effect on the survival of high grade human brain tumor cells. Carbohydr Res. 2015;404:26–33.

[34] Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Siu IM, Gallia GL, Olivi A, McLendon R, Rasheed BA, Keir S, Nikolskaya T, Nikolsky Y, Busam DA, Tekleab H, Diaz LA Jr, Hartigan J, Smith DR, Strausberg RL, Marie SK, Shinjo SM, Yan H, Riggins GJ, Bigner DD, Karchin R,Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW: An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321:1807–1812. doi: 10.1126/science.1164382.

[35] Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP, et al: Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer Cell. 2010;17:510–522.

[36] Lu C, Ward PS, Kapoor GS, Rohle D, Turcan S, Abdel-Wahab O, Edwards CR, Khanin R, Figueroa ME, Melnick A, Wellen KE, O'Rourke DM, Berger SL, Chan TA, Levine RL,

Mellinghoff IK, Thompson CB: IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature. 2012;483:474–478.

[37] Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, Fantin VR, Jang HG, Jin S, Keenan MC, Marks KM, Prins RM, Ward PS, Yen KE, Liau LM, Rabinowitz JD, Cantley LC, Thompson CB, Vander Heiden MG, Su SM: Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2010;465:966.

[38] Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, Ito S, Yang C, Wang P, Xiao MT, Liu LX, Jiang WQ, Liu J, Zhang JY, Wang B, Frye S, Zhang Y, Xu YH, Lei QY, Guan KL, Zhao SM, Xiong Y: Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. Cancer Cell. 2011;19:17–30.

[39] Jin SG, Jiang Y, Qiu R, Rauch RA, Wang Y, Schackert G, Krex D, Lu Q, Pfeifer GP: 5-Hydroxymethylcytosine is strongly depleted in human cancers but its levels do not correlate with IDH1 mutations. Cancer Res. 2011;71:7360–7365.

[40] Kraus TF, Globisch D, Wagner M, Eigenbrod S, Widmann D, Munzel M, Muller M, Pfaffeneder T, Hackner B, Feiden W, Schuller U, Carell T, Kretzschmar HA: Low values of 5-hydroxymethylcytosine (5hmC), the "sixth base," are associated with anaplasia in human brain tumors. Int J Cancer. 2012, http://dx.doi.org/10.1002/ijc.27429.

[41] Ohgaki H, Kleihues P: Genetic profile of astrocytic and oligodendroglial gliomas. Brain Tumor Pathol. 2011;28:177–183.

[42] England B, Huang T, Karsy M: Current understanding of the role and targeting of tumor suppressor p53 in glioblastoma multiforme. Tumour Biol. 2013;34:2063–2074.

[43] Biernat W, Kleihues P, Yonekawa Y, Ohgaki H: Amplification and overexpression of MDM2 in primary (de novo) glioblastomas. J Neuropathol Exp Neurol. 1997;56:180–185.

[44] Nakamura M, Watanabe T, Klangby U, Asker C, Wiman K, Yonekawa Y, et al: p14ARF deletion and methylation in genetic pathways to glioblastomas. Brain Pathol. 2001;11:159–168.

[45] Blough MD, Beauchamp DC, Westgate MR, Kelly JJ, Cairncross JG: Effect of aberrant p53 function on temozolomide sensitivity of glioma cell lines and brain tumor initiating cells from glioblastoma. J Neurooncol. 2011;102:1–7.

[46] Ino Y, Betensky RA, Zlatescu MC, Sasaki H, Macdonald DR, Stemmer-Rachamimov AO, Ramsay DA, Cairncross JG, Louis DN: Molecular subtypes of anaplastic oligodendroglioma: implications for patient management at diagnosis. Clin Cancer Res. 2001;7:839–845.

[47] Jeuken JW, von Deimling A, Wesseling P: Molecular pathogenesis of oligodendroglial tumors. J Neurooncol. 2004;70:161–181.

[48] Wolf RM, Draghi N, Liang X, Dai C, Uhrbom L, Eklof C, Westermark B, Holland EC, Resh MD: p190RhoGAP can act to inhibit PDGF induced gliomas in mice: a putative

tumor suppressor encoded on human chromosome 19q13.3. Genes Dev. 2003;17:476–487.

[49] Idbaih A, Marie Y, Pierron G, Brennetot C, Hoang-Xuan K, Kujas M, Mokhtari K, Sanson M, Lejeune J, Aurias A, Delattre O, Delattre JY: Two types of chromosome 1p losses with opposite significance in gliomas. Ann Neurol. 2005;58:483– 487.

[50] Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, et al: Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol. 2013;31:337–343.

[51] Boots-Sprenger SHE, Sijben A, Rijntjes J, Tops BBJ, Idema AJ, Rivera AL, et al: Significance of complete 1p/19q codeletion, IDH1 mutation and MGMT promoter methylation in gliomas: use with caution. Mod Pathol. 2013;26:922–929.

[52] Schmidt MC, Antweiler S, Urban N, Mueller W, Kuklik A, Meyer-Puttlitz B, et al: Impact of genotype and morphology on the prognosis of glioblastoma. J Neuropathol Exp Neurol. 2002;61:321–328.

[53] Hartmann C, Hentschel B, Simon M, Westphal M, Schackert G, Tonn JC, et al: Long-term survival in primary glioblastoma with versus without isocitrate dehydrogenase mutations. Clin Cancer Res. 2013;19:5146–5157.

[54] Laxton RC, Popov S, Doey L, Jury A, Bhangoo R, Gullan R, et al: Primary glioblastoma with oligodendroglial differentiation has better clinical outcome but no difference in common biological markers compared with other types of glioblastoma. Neuro Oncol. 2013;15:1635–1643.

[55] SongTao Q, Lei Y, Si G, YanQing D, HuiXia H, XueLin Z, et al: IDH mutations predict longer survival and response to temozolomide in secondary glioblastoma. Cancer Sci. 2012;103:269–273.

[56] Wick W, Hartmann C, Engel C, Stoffels M, Felsberg J, Stockhammer F, Sabel MC, Koeppen S, Ketter R, Meyermann R, Rapp M, Meisner C, Kortmann RD,Pietsch T, Wiestler OD, Ernemann U, Bamberg M, Reifenberger G, von Deimling A, Weller M: NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol. 2009;27(35):5874–5880. doi: 10.1200/JCO.2009.23.6497.

[57] Gorlia T, van den Bent MJ, Hegi ME, Mirimanoff RO, Weller M, Cairncross JG, Eisenhauer E, Belanger K, Brandes AA, Allgeier A, Lacombe D, Stupp R.: Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. Lancet Oncol. 2008;9:29–38.

[58] Karlic R, Chung HR, Lasserre J, Vlahovicek K, Vingron M: Histone modification levels are predictive for gene expression. Proc Natl Acad Sci U S A. 2010;107:2926–2931.

[59] Bannister AJ, Kouzarides T: Regulation of chromatin by histone modifications. Cell Res. 2011;21:381–395.

[60] Santos-Rosa H, Schneider R, Bannister AJ, Sherriff J, Bernstein BE, Emre NC, Schreiber SL, Mellor J, Kouzarides T: Active genes are tri-methylated at K4 of histone H3. Nature. 2002;419:407–411.

[61] Costa FF: Non-coding RNAs, epigenetics and complexity. Gene. 2008;410:9–17.

[62] Esteller M: Non-coding RNAs in human disease. Nat Rev Genet. 2011;12:861–874.

[63] Mendell JT: MicroRNAs: critical regulators of development, cellular physiology and malignancy. Cell Cycle. 2005;4:1179–1184.

[64] Li Y, Guessous F, Zhang Y, diPierro C, Kefas B, Johnson E, Marcinkiewicz L, Jiang J, Yang Y, Schmittgen TD, Lopes B, Schiff D, Purow B, Abounader R: MicroRNA-34a inhibits glioblastoma growth by targeting multiple oncogenes. Cancer Res. 2009;69:7569–7576.

[65] Mei J, Bachoo R, Zhang CL: MicroRNA-146a inhibits glioma development by targeting Notch1. Mol Cell Biol. 2011;31:3584–3592.

[66] Kefas B, Godlewski J, Comeau L, Li Y, Abounader R, Hawkinson M, Lee J, Fine H, Chiocca EA, Lawler S, Purow B: MicroRNA-7 inhibits the epidermal growth factor receptor and the Akt pathway and is down-regulated in glioblastoma. Cancer Res. 2008;68:3566–3572.

[67] Zhang QQ, Xu H, Huang MB, Ma LM, Huang QJ, Yao Q, Zhou H, Qu LH: MicroRNA-195 plays a tumor-suppressor role in human glioblastoma cells by targeting signaling pathways involved in cellular proliferation and invasion. Neuro Oncol. 2012;14:278–287.

[68] Gabriely G, Yi M, Narayan RS, Niers JM, Wurdinger T, Imitola J, Ligon KL, Kesari S, Esau C, Stephens RM, Tannous BA, Krichevsky AM: Human glioma growth is controlled by microRNA-10b. Cancer Res. 2011;71;3563–3572.

[69] Gabriely G, Wurdinger T, Kesari S, Esau CC, Burchard J, Linsley PS, Krichevsky AM: MicroRNA 21 promotes glioma invasion by targeting matrix metalloproteinase regulators. Mol Cell Biol. 2008;28:5369–5380.

[70] Jiang L, Lin C, Song L, Wu J, Chen B, Ying Z, Fang L, Yan X, He M, Li J, Li M: MicroRNA-30e_ promotes human glioma cell invasiveness in an orthotopic xenotransplantation model by disrupting the NF-kappaB/IkappaBalpha negative feedback loop. J Clin Invest. 2012;122:33–47.

[71] Zhang CZ, Zhang JX, Zhang AL, Shi ZD, Han L, Jia ZF, Yang WD, Wang GX, Jiang T, You YP, Pu PY, Cheng JQ, Kang CS: MiR-221 and miR-222 target PUMA to induce cell survival in glioblastoma. Mol Cancer. 2010;9;229.

[72] Piccirillo SG, Reynolds BA, Zanetti N, Lamorte G, Binda E, Broggi G, et al: Bone morphogenetic proteins inhibit the tumorigenic potential of human brain tumour-initiating cells. Nature. 2006;444:761–765. doi: 10.1038/nature 05349.

[73] 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;29:3411–3422. doi: 10.1038/onc.2010.83.

[74] Godlewski J, Nowicki MO, Bronisz A,Nuovo G, Palatini J, DeLay M, et al: MicroRNA-451regulates LKB1/AMPKsignalingandallows adaptation to metabolic stress in glioma cells. Mol Cell. 2010;37:620–632. doi: 10.1016/j.molcel.2010.02.018.

[75] Godlewski J, Nowicki MO, Bronisz A, Williams S, Otsuki A, Nuovo G, et al: Targeting of the Bmi-1 oncogene/stemcell renewal factor by microRNA-128 inhibits glioma proliferation and self-renewal. Cancer Res. 2008;68:9125–9130. doi: 10.1158/0008-5472.CAN-08-2629.

[76] Natsume A, Ito M, Katsushima K,Ohka F, Hatanaka A,Shinjo K, et al: Chromatin regulator PRC2Is a key regulator of epigenetic plasticity in glioblastoma. Cancer Res. 2013;73:4559–4570.

[77] Xia H, Cheung WK, Ng SS, Jiang X, Jiang S, Sze J, et al: Loss of brain-enriched miR-124 microRNA enhances stem-like traits and invasiveness of glioma cells. J Biol Chem. 2012. 287:9962–9971. doi: 10.1074/jbc.M111.332627

[78] 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. doi: 10.1186/1741-7015-6-14.

[79] Kreth S, Thon N, Kreth FW: Epigenetics in human gliomas. Cancer Lett. 2014;342:185–192

[80] Mercer TR, Dinger ME, Mattick JS: Long non-coding RNAs: insights into functions. Nat Rev Genet. 2009;10:155–159. doi: 10.1038/nrg2521

[81] Koziol MJ, Rinn JL: RNA traffic control of chromatin complexes. Curr Opin Genet Dev. 2010;20:142–148. doi: 10.1016/j.gde.2010.03.003.

[82] Zhang H, Chen Z, Wang X, Huang Z, He Z, Chen Y. Long non-coding RNA:a new player in cancer. J Hematol Oncol. 2013;6:37. doi: 10.1186/1756-8722-6-37.

[83] Wang P, Ren Z, Sun P: Overexpression of the long non-coding RNA MEG3 impairs in vitro glioma cell proliferation. J Cell Biochem. 2012;113:1868–1874. doi: 10.1002/jcb. 24055

[84] Lu KH, Li W, Liu XH, Sun M, Zhang ML, Wu WQ, et al: Long non-coding RNA MEG3 inhibits NSCLC cells proliferation and induces apoptosis by affecting p53 expression. BMC Cancer. 2013;13:461. doi: 10.1186/1471-2407-13-461.

[85] Sade B, Chahlavi A, Krishnaney A, Nagel S, Choi E, Lee JH: World Health Organization grades II and III meningiomas are rare in the cranial base and spine. Neurosurgery. 2007;61:1194–1198.

[86] O'Rahilly R, Muller F: The meninges in human development. J Neuropathol Exp Neurol. 1986;45:588–608.

[87] Clark VE, Erson-Omay EZ, Serin A, Jun Yin J, Cotney J, Ozduman K, et al: Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science. 2013;339(6123)1077–1080.

[88] Al-Mefty O, Kadri P, Pravdenkova S, Sawyer JR, Stangeby C, Husain M: Malignant progression in meningioma: documentation of a series and analysis of cytogenetic findings. J Neurosurg. 2004;101:210–218.

[89] Reifenberger J, Reifenberger G, Liu L, James CD, Wechsler W, Collins VP: Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. Am J Pathol. 1994;145(5):1175–1190.

[90] Cairncross JG, Ueki K, Zlatescu MC, Lisle DK, Finkelstein DM, Hammond RR, Silver JS, Stark PC, Macdonald DR, Ino Y, Ramsay DA, Louis DN: Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst. 1998;90:1473–1479.

[91] Louis DN, Perry A, Burger P, Ellison DW, Reifenberger G, von Deimling A, Aldape K, Brat D, Collins VP, Eberhart C et al.International society of neuropathology-haarlem consensus guidelines for nervous system tumor classification and grading. Brain Pathol. 2014;24:429–435.

[92] Scheie D, Meling TR, Cvancarova M, Skullerud K, Mørk S, Lote K, Eide TJ, Helseth E, Beiske K. Prognostic variables in oligodendroglial tumors: a single-institution study of 95 cases. Neuro Oncol. 2011;13:1225–1233.

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