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REVIEW

Genetic and epigenetic contribution to astrocytic gliomas pathogenesis

Pouria Khani*†, Farzad Nasri‡, Fateme Khani Chamani§, Farzane Saeidi¶, Javid Sadri Nahand**, Alireza Tabibkhooei†† and Hamed Mirzaei‡‡

*Department of Medical Genetics and Molecular Biology, Faculty of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran

†Student Research Committee, Iran University of Medical Sciences, Tehran, Iran

‡Department of Medical Immunology, Faculty of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran

§Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

¶Department of Medical Genetics, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran

**Department of Virology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran

††Department of Neurosurgery, Iran University of Medical Sciences, Tehran, Iran

‡‡Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran

Abstract

Astrocytic gliomas are the most common and lethal form of intracranial tumors. These tumors are characterized by a significant heterogeneity in terms of cytopathological, transcriptional, and (epi)genomic features. This heterogeneity has made these cancers one of the most challenging types of cancers to study and treat. To uncover these complexities and to have better understanding of the disease initiation and progression, identification, and characterization of underlying cellular and molecular pathways related to (epi)genetics of astrocytic gliomas is crucial. Here, we discuss and summarize molecular and (epi)genetic mechanisms that provide clues as to the pathogenesis of astrocytic gliomas.

Keywords: astrocytic glioma, molecular mechanism, therapy.

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Gliomas are the most common type of tumors among CNS neoplasms derived from glial cells. They comprise about 40–45% of the total intracranial tumors (Russel and Rubinstein 1989). Based on the tumor morphological features and tissue structure, gliomas are divided into several subgroups, the most important of which include oligodendroglial tumors, ependymal tumors, astrocytic tumors, and mixed gliomas (oligo-astrocytoma) (Kibirige *et al.* 1989).

Primary glioma tumors can be formed without any syndromic background or are created because of certain syndromes as secondary tumors (Vieregge *et al.* 1987; Kibirige *et al.* 1989). Studies have shown that familial glioma, which has nothing to do with a specific genetic syndrome, can occur as well. However, these types of gliomas are rare and there is very little possibility of seeing more than two first-degree relatives with glioma. Vieregge and colleagues investigated the familial glioma in their

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Address correspondence and reprint requests to Assistant Prof. Alireza Tabibkhooei, Department of Neurosurgery, Iran University of Medical Sciences, Tehran, Iran. Email: alireza.tabibkhooei@gmail.com (or) Hamed Mirzaei, Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran; Email: mirzaei-h@kaums.ac.ir

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Abbreviations used: Cdk4, cyclin-dependent kinase 4; CNS, central nervous system; CT, computed tomography; DMBT1, deleted in malignant brain tumors 1; EGFR, epidermal growth factor receptor; GBM, glioblastoma multiforme; IDH, isocitrate dehydrogenase; MDM2, murine double minute 2; MGMT, methyl-guanine methyl transferase; MiRNA, microRNA; MRI, magnetic resonance imaging; NADPH, nicotinamide adenine dinucleotide phosphate; NF1, neurofibromatosis type I; NF2, neurofibromatosis type II; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol 3′ kinase; *RTKs*, receptor tyrosine kinases; TS, Turcot syndrome.

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studies. By examining 39 cases of familial gliomas, they found that 60% of them were suffering sisters and brothers (Vieregge *et al.* 1987).

The presence of a genetic predisposition can play a significant role in the emergence and development of gliomas. For example, neurofibromatosis type I (NF1) and NF2, Li-Fraumeni syndrome, ataxia-telangiectasia, Turcot syndrome, tuberous sclerosis, Maffucci syndrome, and Gorlin syndrome can contribute to the occurrence and development of gliomas. Gliomas can be detected by the specific features of the created glioma and the position of its formation. For example, pylocytic astrocytoma of the optic nerve is common in neurofibromatosis type I. However, in neurofibromatosis type II, spinal cord ependymoma is more likely to occur (Lewis and Ketcham 1973; Kibirige *et al.* 1989).

The neurofibromine protein resulting from the expression of the *NF1* gene as a potent tumor suppressor plays a role in the negative regulation of the signal transduction of RAS and mTOR in astrocytes. *NF1* gene mutations are more common in mesenchymal glioblastoma subtypes (Hamilton *et al.* 1995; Zhu *et al.* 2005). Gliomas are seen in Turcot syndrome that main characteristic of which is the creation of primary neuroepithelial tumors of the central nervous system. However, the somatic mutations of the APC gene are rare in primary brain tumors so that no somatic mutations were detected in 91 cases of neuroepithelial tumors including gliomas (Mori *et al.* 1994). Glioblastomas produced in patients with Turcot syndrome, which are caused by mismatch repair gene mutations, can have high survival (Iuzzolino *et al.* 1994). There is no any clinical trial or case report where knowledge of a particular mutation or epigenetic modification has had therapeutic value for the patient.

Astrocytoma and glioblastoma

Definition and features of tissue pathology

In terms of definition, astrocytoma is a general term which is used for diffused infiltrated tumors, including differentiated neoplastic astrocytes (Hayat 2012). Astrocytomas or astrocytic gliomas can be divided into two main groups including: (i) a group which is more prevalent and consists of diffused infiltrated tumors. Astrocytoma, anaplastic astrocytoma and glioblastoma are included in this group, and (ii) a group which is less prevalent and consists of growth-restricted tumors. Pilocytic astrocytoma, pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, and Turcot syndrome are included in this group (Gladson *et al.* 2010; Hayat 2012).

Despite the slow growth of astrocytomas, since these tumors tend to infiltrate and diffuse around the brain, even the types in which the cells are well differentiated (grade II of histology) tend to recur. Malignant anaplastic astrocytoma exhibits an anaplastic diffused process. Increased cellularity, pleomorphism, unusual nucleus, and mitotic activities are some evidences for this claim (astrocytoma is responsible for creating grade III of histology).

Glioblastoma, which is known as the most common primary malignant tumor of the brain, as well as the most malign and most common type of glioma (about 50% of the total gliomas), annually affects about 10 000 people. The average survival rate of these persons is between 12 and 15 months (Weary *et al.* 1972; Kibirige *et al.* 1989; Russel and Rubinstein 1989).

Glioblastomas are anaplastic tumors, which often have cells with very small differentiation, conic, round or pleomorphic shapes and sometimes have multi-nucleus giant cells. The presence of parameters such as prominent angiogenesis or necrosis is essential for histological diagnosis of these tumors. Histologically, glioblastomas are responsible for creating grade IV (Weary *et al.* 1972).

The incidence of astrocytoma and glioblastoma in adults is higher compared to children. These tumors in adults have about 17% of the brain's primary tumors. However, this is only 4% in children (Weary *et al.* 1972). As noted above, glioblastomas can occur at different ages, but the incidence rate varies in different ages. The highest incidence of glioblastomas is between the ages of 45 and 60 years. Using computed tomography and magnetic resonance imaging, these tumors have a ring-like structure with a low density (necrotic) center surrounded by a ring of contrast-enhancing vital tumor tissue and edema (Burger and Green 1987; Kleihues *et al.* 2002).

Macroscopic appearance of typical glioblastomas is like large necrotic masses with a peripheral area of the fleshy gray tumor tissue. Intra-tumor bleeding is common in them. Since glioblastomas can display a range of cell and tissue differentiation patterns, the differentiation of these tumors is very difficult or even impossible in histology aspect. However, genetically, they can be divided into distinct primary and secondary tumors. Primary glioblastomas are more common in older people (usually older than 50). Usually, after a short clinical history (less than 3 months), without clinical and tissue evidence of a less malignant precursor lesion, they appear to be a new phenomenon. However, the incidence of secondary glioblastomas in younger patients (usually less than 45 years) is higher. They are associated with the progression of malignancy from grade II or III of astrocytoma. The duration of tumor progression can vary between a period of less than 1–10 years (with a mean interval of 4–5 years) (Kleihues *et al.* 2002). Clinical prognosis of patients with glioblastoma is very poor and the average survival time after surgery is only 12 months (Burger and Green 1987).

Molecular genetics of astrocytic gliomas

Several molecular mechanisms can lead to the development of gliomas and the formation of more malignant tissue features as well as the recurrence of the disease. Some of these mechanisms include gene amplification, rearrangement, and deletions. The outcome of these mechanisms is the dominant activity of oncogenes, as well as the recessive inactivation of suppressive genes.

EGFR

One of the most common genes that is over-expressed in primary glioblastomas is epidermal growth factor receptor (EGFR) gene. Over-expression of this gene has been observed in 60% of cases and amplification of gene occurs in 40% of cases (Ekstrand *et al.* 1992). EGFR abnormalities are specifically associated with glioblastoma multiforme (GBM), and EGFR amplification is associated with a decrease in the average survival rate of patients (Hurt *et al.* 1992). The gene encoding EGFR is located on chromosome 7. A frequent observation of trisomy 7 in glioblastoma can be an evidence for the link between EGFR amplification and GBM (Agosti *et al.* 1992).

EGFR is structurally a transmembrane protein with tyrosine kinase activity that contains an extracellular domain attached to EGF and transforming growth factor alpha (Fig. 1). The autocrine interaction of this receptor with its ligand can lead to increased cell proliferation (Agosti *et al.* 1992; Hurt *et al.* 1992; Sjöström *et al.* 2010). Meanwhile, EGFR VIII is concurrently expressed as a mutated receptor in 50% of glioblastomas with amplification of EGFR (Ekstrand *et al.* 1992; Aldape *et al.* 2004; Mellinghoff *et al.* 2005). This EGFR variant powerfully and continuously contributes to the activation of signaling pathway of the phosphatidylinositol 3′ kinase (Fig. 1) (Choe *et al.* 2003; Li *et al.* 2004; Sordella *et al.* 2004).

In a study on tumors of 58 patients with glioblastoma, von Deimling *et al.* showed that EGFR gene amplification is only observed in tumors which lack chromosome 10. This suggests that the lack of chromosome 10 can be a cause for the incidence of EGFR abnormality in the tumor progression process (Louis *et al.* 1992). In addition to over-expression and amplification of the EGFR gene, rearrangements and deletions of this gene can also be one of the causes of the ligand's abnormal connection (Ekstrand *et al.* 1991; Wu *et al.* 1993).

Most of the rearrangements are the deletions which involve the 5′ end of the gene. This part of the gene encodes the extracellular domain of protein. The 3′ end of the gene that encodes the intracellular domain is rarely affected (Louis *et al.* 1993). The most common rearrangement is an 801 bp inframe deletion which results in an incorrect splicing of exons 1–8. As a result of this false splicing, the receptor molecule is incompletely expressed. The resulting receptor lacked some sections of the extracellular domain that are necessary for binding to the ligand. The functional feature of this type of EGFR is the continuous activity of tyrosine kinase, which is likely to increase tumorigenesis in human glioma cells (Collins 1995).

One potential explanation for the failure of EGFR and platelet derived growth factor receptor alpha inhibitors to exert remarkable clinical effects is that other receptor tyrosine kinases may crosstalk to make an integrated signaling threshold that is not effectively mitigated through the inactivation of any single receptor tyrosine kinase (Lu *et al.* 2009; De Witt Hamer 2010). In a study on pilocytic astrocytoma (the most common type of astrocytic tumors in children), there was no change in the EGFR gene and absence of alleles in chromosomes 10, 17p, and 19q was reported (von Deimling *et al.* 1993).

Murine double minute 2

Over-expression and amplification of the murine double minute 2 (MDM2) gene were reported in a number of primary glioblastomas. The product of this gene can form a complex with P53 and inhibit its function (Fig. 1) (Finlay 1993; Biernat *et al.* 1997; Wang *et al.* 2011). In their studies on 157 primary brain tumors, Reifenberger *et al.* found that MDM2 gene is amplified and over-expressed in 8–10% of the anaplastic astrocytomas and glioblastomas. In addition to examining this mutation, the *TP53* gene was also studied. No mutation in TP53 gene or LOH in 17p was detected in these tumors. This suggests that the amplification of the *MDM2* gene may be an alternative mechanism for abnormally regulated growth control by P53 protein (Reifenberger *et al.* 1993; Schiebe *et al.* 2000; Wang *et al.* 2011).

Reifenberger *et al.* also showed that 15% of glioblastomas and astrocytomas have chromosomal amplification of 12q13-14. Another major finding of their research was that some tumors that did not have *MDM2* gene amplification in their genome, had genetic amplification for the *CDK4* and *SAS* genes (Reifenberger *et al.* 1994). It was reported that *MDM4* gene is genetically amplified in gliomas which lack both *TP53* mutation and *MDM2* gene amplification (Riemenschneider *et al.* 1999).

P53

P53 tumor suppressing gene (Fig. 1) mutations and over-expression of platelet-derived growth factor ligands in secondary glioblastomas have been observed (Kleihues *et al.* 2002). The presence of P53 mutation in mild astrocytomas causes tumor tendency for progressive and aggressive growth (Ohgaki *et al.* 1993; England *et al.* 2013). The survival rate estimated by Kaplan–Meier method for patients with P53 mutation was 21% 5 years after diagnosis, whereas it was 46% for patients with tumors lacking P53 immunoreactivity. (Ohgaki *et al.* 1993).

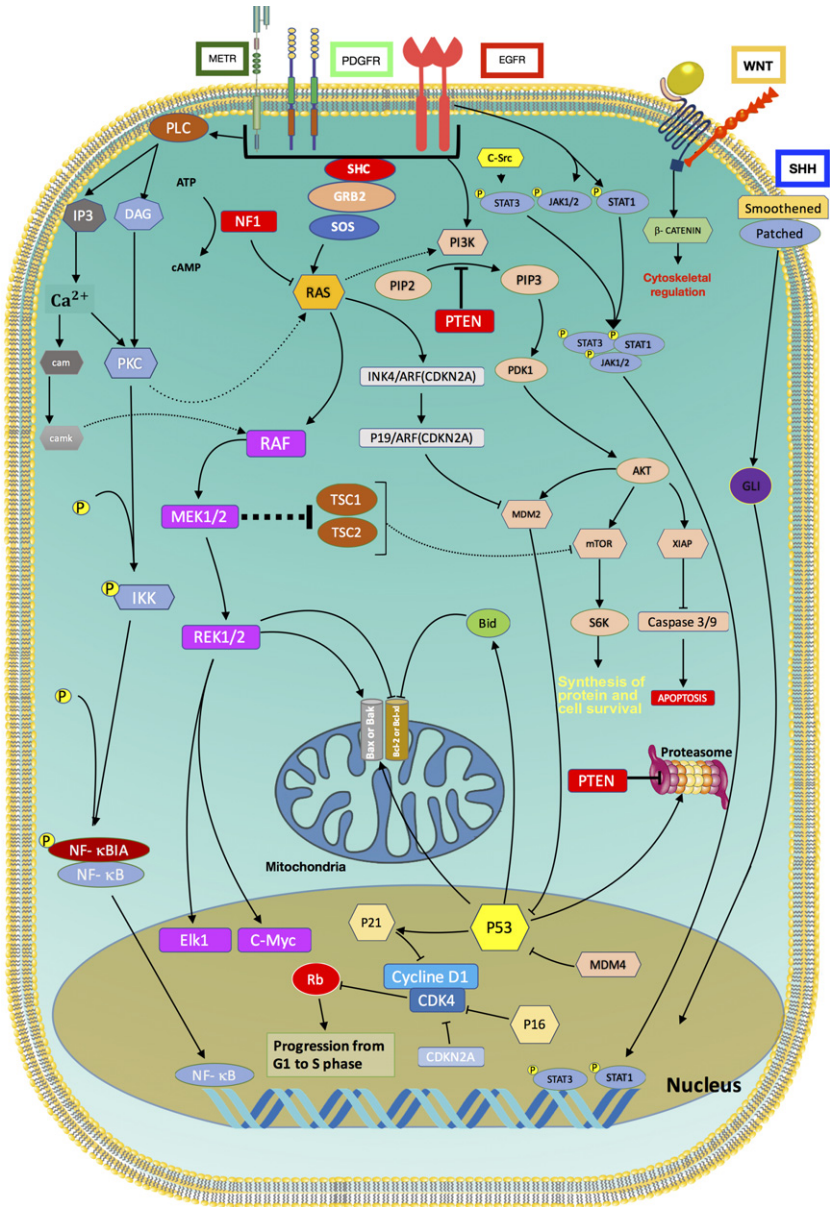

Fig. 1 Different signaling pathways involved in glioblastom. This figure represents different signaling pathways including EGFR, PDGFR, METR, WNT, and SHH signaling as well as their downstream molecules and their connection with each other. Disturbing the balance of these pathways can cause gliomas.

MGMT (methyl-guanine methyl transferase) and methylation

Methyl-guanine methyl transferase (*MGMT*) gene, located on the chromosome 10q26, is involved in the removal of alkyl groups from the O6 position of guanine by the production of a protein involved in DNA repair. Thus, the high activity of MGMT reduces the therapeutic effects of alkylating agents. The lack of expression of MGMT can be caused by epigenetic silencing of MGMT gene promoter *via* methylation (Taylor and Schiff 2015). In a study on 206 glioblastomas, the promoter methylation of this gene occurred in 45% of cases, which led to the promoter's silencing of the gene and consequently its lack of expression. This change led to a significant increase in the overall survival rate from 12.2 months (in patients without promoter methylation) to 18.2 months (in patients with promoter methylation). In addition to the benefit of increasing the survival rate, patients with *MGMT* methylated promoters benefit from a combination of chemotherapy (by an alkylating agent such as temozolomide) and radiotherapy (with an survival of 21.7 months) compared with radiotherapy alone (with an average survival of 15.3 months) (Hegi *et al.* 2005; De Salvo *et al.* 2011; Juratli *et al.* 2012; Johnson *et al.* 2014).

MicroRNAs

Among several factors which are involved in the initiation and progression stages of astrocytic gliomas, microRNAs (miRNAs) have emerged as epigenetic regulators and play key roles in the pathogenesis of many diseases such as

astrocytic gliomas (Sato *et al.* 2011; Nikaki *et al.* 2012) (Gholamin *et al.* 2016, 2018; Mirzaei *et al.* 2016a,c,e, 2018a,b; Mirzaei 2017; Rashidi *et al.* 2017a,b; Hoseini *et al.* 2018; Jamali *et al.* 2018; Moridikia *et al.* 2018; Rabieian *et al.* 2018). miRNAs are short non-coding RNAs which are involved in many biological processes such as growth, development, angiogenesis, and differentiation (Fathullahzadeh *et al.* 2016; Mirzaei *et al.* 2016b, 2017b; Mohammadi *et al.* 2016; Saadatpour *et al.* 2016; Salarinia *et al.* 2016; Keshavarzi *et al.* 2017a,b; Golabchi *et al.* 2018; Keshavarz *et al.* 2018; Mashreghi *et al.* 2018). Increasing evidence has indicated that miRNAs are associated with the initiation and progression of several diseases such as cardiovascular disease, stroke, diabetes, and cancer (Mirzaei *et al.* 2016d, 2017a; Banikazemi *et al.* 2018; Golabchi *et al.* 2018; Jafari *et al.* 2018; Masoudi *et al.* 2018; Saeedi Borujeni *et al.* 2018; Simonian *et al.* 2018; Tavakolizadeh *et al.* 2018). Previously, we showed that a variety of miRNAs are involved in glioblastoma pathogenesis (Masoudi *et al.* 2018). It has been revealed that deregulation of miRNAs in various cells associated (i.e., astrocytes, and microglia) with gliomas could contribute to the progression of astrocytic gliomas (Malzkorn *et al.* 2010; Yang *et al.* 2014). In a study, Conti *et al.* (2009) assessed the expression levels of various miRNAs (i.e., miR-21,miR-221, miR-128a, miR-128b, miR-128c, miR-181a, miR-181b, and miR-181c) in human astrocytic tumors. Their results indicated that miR-21 and miR-221 are up-regulated in glioma samples, while miR-181b is down-regulated when compared with normal brain tissue. Moreover, miR-21 was up-regulated in all tumor samples, whereas higher levels of miR-221 were observed in high-grade gliomas. These results suggested that the deregulation of various miRNAs could be associated with different stages of astrocytic gliomas (Conti *et al.* 2009).

Recently, Mao *et al.* (2017) reported a molecular classification of astrocytic tumors. Their results indicated that there are 11 795 DNA methylation sites, 3627 genes, 3334 lncRNAs, and 136 miRNAs that are involved in astrocytic tumors. Moreover, they observed that some genes (i.e., ANK3, TSPYL5, RAB3A, and ABCA2) are hypermethylated which lead to their decreased expression in astrocytic tumors (Mao *et al.* 2017).

Other genetics alteration

Astrocytic tumors, like other tumors, show genetic heterogenity. Different genetic factors from chromosomal changes to molecular changes have been identified in astrocytic tumors. These factors are grouped by chromosome in Table 1, Fig. 2.

Mutation in isocitrate dehydrogenase (*IDH*) is one of major molecular alterations which involved in the pathogenesis of grade glioma. *IDH1* or *IDH2* mutation is observed that have occurred in more 90% of astrocytomas and oligodendrogliomas. Besides *IDH, ATRX* gene mutation is other important mutations which could be detected employing immunohistochemistry as loss of nuclear ATRX expression (Chatterjee *et al.* 2018). In a study, Chatterjee *et al.* (2018), assessed the frequency of *IDH*1, *ATRX*, and *BRAF* V600E mutations in 80 patients (including 25 diffuse astrocytoma, 25 glioblastoma, 15 pilocytic astrocytoma, and 15 anaplastic astrocytoma) with grade astrocytomas and their prognostic value. Their results indicated that all patients with pilocytic astrocytoma and primary glioblastoma were negative for *IDH1* mutation. Moreover, low expression of nuclear ATRX was observed in 87% (20/23) and 100% (14/14) DA and AA patients, respectively. *BRAF* V600E mutation was not diagnosed in any astrocytic tumor. Their findings proposed that *IDH1* and *ATRX* mutations are commonly associated with diffuse astrocytoma and anaplastic astrocytoma, while they are rarely observed in patients with pilocytic astrocytoma and glioblastoma (Chatterjee *et al.* 2018).

In a study, Chen *et al.* (2016), indicated that mutations or epigenetic modifications of IDH1 can provide a survival advantage to glioma patients. Their results demonstrated that these mutations improve overall patient survival though decreasing the ability of cells to produce nicotinamide adenine dinucleotide phosphate, and consequently lowers the capacity of the cell to scavenge oxygen species. These events could make the tumor cells more susceptible to irradiation and chemotherapy (Chen *et al.* 2016).

CDKN2/p16 is main deletion which is observed in various gliomas tumors. P16 is an important regulator which is able to control a cell cycle cascade and includes cyclin-dependent kinase 4 (cdk4), cyclin D1, and pRb. It has been observed that deregulation of each of these proteins are associated with primary human GBM or in GBM cell lines (Purkait *et al.* 2015). In a study, Miettinen *et al.* (1999), assessed the association of CDKN2/p16 expression and cell proliferation activity and survival rate of patient with oligodendrogliomas and astrocytomas. They showed that expression of CDKN2/p16 was reduced in grade II and anaplastic oligodendrogliomas (17/42) and low CDKN2/p16 expression was related to high histologic cancer grade. Moreover, they indicated that protein levels of CDKN2/p16 were reduced in glioblastomas (9/10), anaplastic astrocytomas (5/9), grade II astrocytomas (3/10) and in none of pilocytic astocytomas (0/7). Their results revealed that low expression of CDKN2/p16 was also related to high cell proliferation activity and poor survival rate in patient with astrocytomas. Their findings proposed that loss of CDKN2/p16 expression could have main roles in the progression of oligodendrogliomas and CDKN2/p16 immunocytochemistry could be employed as a biomarker in oligodendrogliomas and low-grade astrocytomas (Miettinen *et al.* 1999).

The Deleted in Malignant Brain Tumors 1 (DMBT1) is other gene which involved in astrocytic gliomas pathogensis. DMBT1 is a region of chromosome 10q25.3-q26.1 and its

Table 1 Cytogenetic and molecular genetics of astrocytic gliomas

Chromosome	Gene	Product	Features	References
1	MDM4 Fig. 1	Murine double minute 4	• p53 regulator • Amplified in gliomas lacking TP53 mutations with lacking MDM2 amplification	Riemenschneider *et al.* (1999) and Furgason *et al.* (2015)
2q	IDH1 Fig. 2	Isocitrate dehydrogenase 1	• Encodes an enzyme in the citric acid cycle • Somatic mutations have been seen in 12% of glioblastoma multiforme (GBM) tumors • Mutations: ○ Uncommon (5%) in primary adult GBMs ○ Present in 85% of secondary glioblastomas ○ Have been reported in Pediatric gliomas (rarely) ○ The earliest detectable genetic change in precursor of low-grade diffuse astrocytomas ○ Early event of transformation in tumors that gain either p53 mutations or deletions of 1p and 19q	Balss *et al.* (2008), Capper *et al.* (2009), Hartmann *et al.* (2009, 2010) and Ohgaki and Kleihues (2013)
4q	PDGFRα Fig. 1	Platelet-derived growth factor receptor alpha	• Initiates signal of mitogensis • Amplification in up to 17% of GBMs • Detected in all four subtypes • Changes are more common in the proneural subtype	Fomchenko *et al.* (2011) and Lokker *et al.* (2002)
7	EGFR(7p) Fig. 1	Epidermal growth factor receptor	• Chromosome 7 amplification is the most common change in glioblastomas (increase copy number of EGFR) • Detected in 50–60% of GBM tumors • EGFRvIII: a aberrantly active version of EGFR with evades degradation and contributes to instability of genome • Alterations in EGFR are observed in all four tumor subtypes • EGFR change is a hallmark of the classic subtype	Burger and Fuller (1991), Howe *et al.* (1989), Verhaak *et al.* (2010), Li *et al.* (2014) and Furgason *et al.* (2015)
	CDK6(7q) Fig. 1	Cyclin-dependent kinase 6	• Commonly up-regulated in gliomas • Amplification and over-expression or activation of Cdk6 related with human glioblastoma	Zhu *et al.* (2013) and Raub *et al.* (2015)
	MET (7q) Fig. 1	MET proto-oncogene (receptor tyrosine kinase)	• The expression of MET associates with tumor grade • Amplifications of MET in glioma tumors are far less common than those of EGFR • *In vivo* inhibition of MET by antibodies resulted in reduction of tumor growth	Kong *et al.* (20090, Wu *et al.* (2011), Eckerich *et al.* (2007) and Martens *et al.* (2006)

(continued)

Table 1. (continued)

Chromosome	Gene	Product	Features	References
			• Higher expression is related with a shorter time to recurrence of tumor • MET signaling contributes to drug resistance • May be critical to cancer stem cells	
9p	CDKN2A (MTS1) Fig. 1	p16 (p16INK4a)	• Mutations of CDKN2A have been recognized in astrocytoma, glioblastoma and melanoma • Deletions of one or two CDKN2A gene copies frequently take place in Glioblastomas • CDKN2A homozygous deletion in 41% and hemizygous CDKN2A loss in 28% of primary glioblastomas have been observed • In glioblastoma cell lines, the incidence of homozygous CDKN2A is even higher (up to 70%) • CDKN2A inactivation by point mutation or through methylation of 5′ CpG island has been found in some glioblastomas • Deletions of chromosome 9p may occur in oligodendrogliomas and lower grade astrocytomas as well as malignant astrocytomas • The tumor cells with lack CDKN2A mutations characteristically have RB1mutations • Analysis of molecular subtype of tumors reveals CDKN2A gene deletion is common (70%) • CDKN2A gene deletion take place in 95% of tumors with the classic subtype	Liggett and Sidransky (1998), Greene (1999), Schmidt *et al.* (1994), Ranjit *et al.* (2015), Urbschat *et al.* (2017), Sippl *et al.* (2018), Cerchietti and Melnick (2017) and He *et al.* (1994)
10	Monosomy 10		• Frequently detected in glioma tumors • Monosomy 10 is characteristically related with a more malignant histologic type • The incidence range of chromosome 10 loss in glioblastoma tumors in different studies is from 60% to more than 90% of the cases • Primary glioblastomas are characterized by loss of heterozygosity on entire chromosome 10, while secondary glioblastomas often illustrate LOH on chromosome 10q. • Loss of heterozygosity (LOH) on chromosome 10 is occurred in up to 80% of cases	Karlbom *et al.* (1993), Schrock *et al.* (1994), Yadav *et al.* (2009), Nakamura *et al.* (2000), Albarosa *et al.* (1996) and Fujisawa *et al.* (2000)

(continued)

Table 1. (continued)

Chromosome	Gene	Product	Features	References
			• LOH on chromosome 10 is less common (approximately 40%) in anaplastic astrocytomas	
	DMBT1	Deleted in malignant brain tumors 1	• Located at distal 10q • Intragenic homozygous deletions in DMBT1 were found in about 23% of glioblastomas	Mollenhauer *et al.* (1997) and Sasaki *et al.* (2002)
	MXI1		• Candidate gene that located at distal 10q • Negatively regulate MYC oncoprotein function • MXI1 is a gene with potential tumor suppressor activity • Mutations of MXI1 have been discovered in prostate cancer	Eagle *et al.* (1995) and Wechsler *et al.* (1997)

	PTEN Fig. 1		• PTEN somatic mutations have been discovered in about 1/3 of glioblastoma tumors
			• Chromosome 10 deletions in region that containing the PTEN gene, frequently occur in tumors with EGFR amplifications
			• Mutations of PTEN are detected in 60% of glioblastoma multiforme (GBM)
			• Deletions in the gene region are:
			  ○ Far more common (occur in 85% of tumors)
			  ○ Less common in the proneural subtype
			• Loss-of-function mutations of PTEN are typically related with increased drug resistance and invasive actions
				Benitez *et al.* (2017), Furnari *et al.* (2007), Mellinghoff *et al.* (2005), Nagata *et al.* (2004), Bianco *et al.* (2003) and Bostrom *et al.* (1998)

	ANXA7	Tumor supressor gene annexin 7	• Located at 10q22–23 region • Ca^{2+} and phospholipid-binding protein • Lack of expression of Anxa7 is associated with GBM tumors in late-stage • The relatively higher Anxa7 levels potentially lead to longer survival for patients with GBM • Deletions in ANXA7 occur in 77% of tumors • Mutations are detected in 6%	Guo *et al.* (2013), Yadav *et al.* (2009), Bello *et al.* (1994)
11p			• Loss of heterozygosity of markers in 11p have been shown in malignant astrocytomas (except HRAS gene) • Loss is identified in low-grade and high-grade glioma tumors • Probably these events plays a role in early tumorigenesis	Fults *et al.* (1992)

(continued)

Table 1. (continued)

Chromosome	Gene	Product	Features	References
12	CDK4 Fig. 1	Cyclin-dependent kinase 4	• CDK4 amplification and over-expression are observed in glioblastoma tumors • Amplification has been detected in 15% of malignant gliomas • Tumors with wild type CDK4 are more probably to comprise RB1 mutations • Usage inhibitor of CDK4 kinase has potential for treating primary tumors of central nervous system such as glioblastoma	Furgason *et al.* (2015), Raub *et al.* (2015), Choi *et al.* (1970) and Reifenberger *et al.* (1996)
	MDM2 Fig. 1	Murine double minute 2	• A negative regulator of tumor suppressor p53 • Amplification and over-expression of *MDM2* gene have seen in 8–10% of glioblastomas and anaplastic astrocytomas • Associate with worse survival	Bello *et al.* (1995), Toledo and Wahl (2007) and Reifenberger *et al.* (1993b)
	GLI Fig. 1		• Transcription factor • Krüppel-like zinc finger protein • Activated by amplification • Gli1 modulates the expression of stemness genes and the self-renewal of CD133(+) glioma stem cells (GSCs)	Santoni *et al.* (2013), Yao *et al.* (2014) and Kinzler *et al.* (1987)
13	RB1 Fig. 1	Retinoblastoma protein	• The RB signaling network is often disrupted in GBMs • Mutations in RB1 were observed in glioblastomas, particularly when tumors are wild type of cyclin dependent kinases • Chromosomal deletions in the region as the location RB gene are a common event in GBM (44%), but are less frequent in the classic subtype • Hypermethylation of promoter have been observed significantly more common in secondary glioblastomas than in primary glioblastomas	Cairncross *et al.* (1998), Badiali *et al.* (1993), Nakamura *et al.* (2001) and Gonzalez-Gomez *et al.* (2003)
14q	NFKBIA Fig. 1	NFKB inhibitor alpha	• Constitutive activation of NF-κB is frequently observed in GBMs • Monoallelic deletions in the chromosome 14q are detected in nearly 1/4 of GBM tumors • NFKBIA have a role in glioblastoma tumor suppression. • Because of the existence of *NFKBIA* deletions in some cancer stem cells of glioblastoma, these deletions may have occurred early in the glioblastoma pathogenesis.	Consortium, E. C. T. S (1993), Josefa Bello *et al.* (1994) and Bredel *et al.* (2011)

(continued)

Table 1. (continued)

Chromosome	Gene	Product	Features	References
			• Loss of *NFKBIA* can be related with progression of disease and recurrence of tumor	

17	TP53(17p) Fig. 1		• Chromosome 17p loss is an early and common event in astrocytomas
			• Losses are frequently accompanied by TP53 gene mutation
			• Mutations of *TP53*:
			  ○ Are the earliest detectable genetic change and most common to formation of secondary glioblastoma
			  ○ Present in 60% of precursor low-grade astrocytomas.
			  ○ Are well recognized in glioblastoma multiform (GBMs) tumors (specifically tumors lacking amplification of EGFR and from a proneural subtype)
			• Glial tumors incidence in the patients with Li–Fraumeni syndrome proposed the important role of the TP53 gene in the formation of sporadic gliomas
			• TP53 inactivation may not be an mandatory step in tumor development
			• Aberrant expression or increased of p53 has been detected in many astrocytic tumors (29% of grade 2 tumors and 49% of grade 3–4 astrocytomas)
				Kyritsis *et al.* (1994), Sameshima *et al.* (1992), van Meyel *et al.* (1994), Karamitopoulou *et al.* (1993), Ohgaki and Kleihues (2007) and Chung *et al.* (1991)

	NF1(17q) Fig. 1	Neuro fibromin 1	• Neurofibromin 1 (NF1) Loss leads to RAS hyperactivation • Mutations are found in 17% of GBMs • 15% to 20% of affected persons with Neurofibromatosis 1 develop astrocytomas	Obremski *et al.* (1998), See *et al.* (2012) and Lau *et al.* (2000)
19			• Loss of heterozygosity on chromosome 19p is a frequent change in astrocytomas • Alterations on chromosome 19q (involving 19q13.2–q13.4) are less frequently related to the astrocytomas development	Ritland *et al.* (1995), Nakamura *et al.* (2000) and von Deimling *et al.* (1994)
22			• Chromosome 22 gain and loss have been found in malignant gliomas • In chromosome 22q12 region a novel amplification site was mapped • Two separate loci affected by regional gains have been identified by array-CGH analysis that contained two candidate genes: *TOP3B* and *TAFA5*	Neumann *et al.* (1992), Bigner *et al.* (1990) and de Ståhl *et al.* (2005)

DMBT1, deleted in malignant brain tumors 1; EGFR, epidermal growth factor receptor; GBM, glioblastoma multiforme; IDH, isocitrate dehydrogenase, MDM2, murine double minute 2; PDGFRα, platelet derived growth factor receptor alpha.

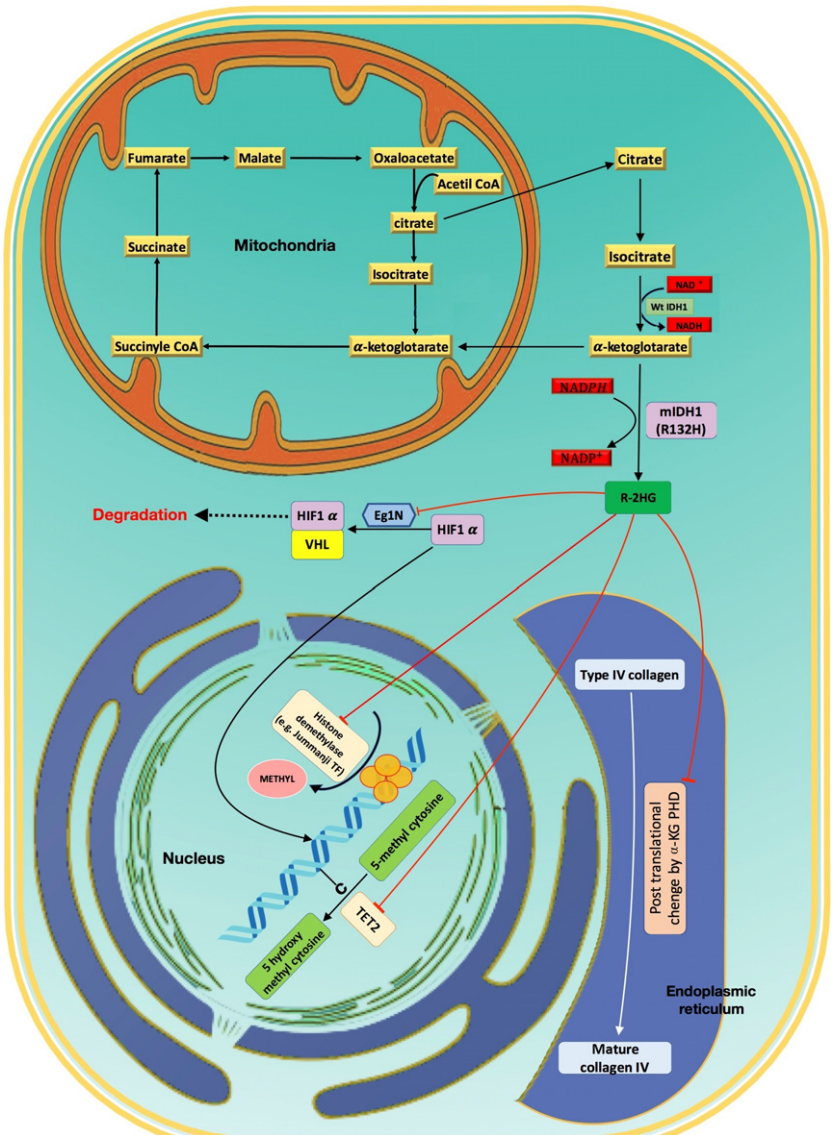

Fig. 2 Production of R-2HG as a result of activity of IDH1 mutated gene and the effects of activity R-2HG on various cellular functions. Mechanisms involved in tumorigenesis induced by the mutation of IDH1. Wild type of IDH1 (wtIDH1) isoform presents in the cytosol and in a normal conditions, convert cytosolic isocitrate into α-KG. Converting of wt IDH1 to mutant IDH1 (mIDH1) can be resulted in α-KG conversion to R-enantiomer of 2-hydroxyglutarate (R-2HG). In addition, this mutation can decrease the affinity of active site of IDH1 enzyme for isocitrate and increases it for nicotinamide adenine dinucleotide phosphate and α-KG. R-2-HG as an 'onco-metabolite' encourages tumorigenesis process through three pathways. (1) R-2HG by inhibiting Eg1N (an α-KG dependent prolyl hydroxylases (PHD) that causes the hydroxylation of proline residues in HIF1- α and its degradation by von-Hippel Lindau protein (VHL)) resulted in persistence of HIF1- α and transcription of factors induces by it.(2) Other changes caused by R-2HG are epigenetic alterations. These modifications can be made at two levels: DNA and Histones. Tet methylcytosin dioxygenase 2 (TET2) is a DNA modifying enzyme that is α-KG -dependent and its inhibition may cause DNA hypermethylation (DNA level). Some of the histone demethylases are α-KG -dependent. R-2HG as a competitive inhibitor causes histones hypermethylation (Histone level). (3) The process of changing immature type IV collagen to mature collagen requires α-KG –dependent PHD for post-translational modifications. Inhibition of this reaction can cause accretion of misfolded collagen in the ER and activating an ER stress response. Moreover, deficiency of perivascular type IV collagen may encourage failure of the physiological BBB in gliomas with mutated IDH1.

homologous deletions and lack of expression in various malignancies such as medulloblastoma, glioblastoma multiforme, lung, and gastrointestinal cancers, has introduced it as a tumor suppressor gene (Wu *et al.* 1999).

In a study, Mueller *et al.* (2002) indicated that the rare mutations in DMBT1 are associated with astrocytic gliomas. They used mutational analysis of coding region of DMBT1, using direct DNA sequencing and single-

stranded conformation polymorphism analysis 79 patients with astrocytic gliomas. Their results revealed that there were five somatic mutations which two of them led to an amino acid exchange. One pilocytic astrocytoma had two missense mutations and another pilocytic astrocytoma carried a somatic mutation which not affecting the presumed protein. Moreover, there were observed 21 of the 27 single nucleotide polymorphisms in patients with astrocytic gliomas. These results suggested that mutation in DMBT1 could be related to appearance of astrocytic gliomas (Mueller *et al.* 2002).

Conclusion

Astrocytic gliomas among the most important CNS tumors and are associated with a significant disease burden worldwide. Astrocytic glioma is a complex disease and a variety of internal and external risk factors could be related to its initiation and progression. Among various risk factors, deregulation of various mechanisms which could lead to up/down regulation of genes such as p53, MGMT, EGFR, and MDM2, has a critical role in the progression of astrocytic gliomas. It seems that identification of underlying molecular mechanisms related to astrocytic gliomas could contribute to a better understanding of the pathogenesis and identification of more effective therapeutic strategies.

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References

Agosti R. M., Leuthold M., Gullick W. J., Yasargil M. G. and Wiestler O. D. (1992) Expression of the epidermal growth factor receptor in astrocytic tumours is specifically associated with glioblastoma multiforme. *Virchows Arch. A Pathol. Anat. Histopathol.* **420**, 321–325.

Albarosa R., Colombo B. M., Roz L. *et al.* (1996) Deletion mapping of gliomas suggest the presence of two small regions for candidate tumor-suppressor genes in a 17-cM interval on chromosome 10q. *Am. J. Hum. Genet.* **58**, 1260.

Aldape K. D., Ballman K., Furth A., Buckner J. C., Giannini C., Burger P. C., Scheithauer B. W., Jenkins R. B. and James C. D. (2004) Immunohistochemical detection of EGFRvIII in high malignancy grade astrocytomas and evaluation of prognostic significance. *J. Neuropathol. Exp. Neurol.* **63**, 700–707.

Badiali M., Iolascon A., Loda M., Scheithauer B., Basso G., Trentini G. and Giangaspero F. (1993) p53 gene mutations in medulloblastoma. Immunohistochemistry, gel shift analysis, and sequencing. *Diagn. Mol. Pathol.* **2**, 23–28.

Balss J., Meyer J., Mueller W., Korshunov A., Hartmann C. and von Deimling A. (2008) Analysis of the IDH1 codon 132 mutation in brain tumors. *Acta Neuropathol.* **116**, 597–602.

Banikazemi Z., Haji H. A., Mohammadi M. *et al.* (2018) Diet and cancer prevention: dietary compounds, dietary MicroRNAs, and dietary exosomes. *J. Cell. Biochem.* **119**, 185–196.

Bello M. J., Vaquero J., de Campos J. M., Kusak M. E., Sarasa J. L., Saez-Castresana J., Pestana A. and Rey J. A. (1994) Molecular analysis of chromosome 1 abnormalities in human gliomas reveals frequent loss of 1p in oligodendroglial tumors. *Int. J. Cancer* **57**, 172–175.

Bello M. J., Leone P. E., Vaquero J., de Campos J. M., Kusak M. E., Sarasa J. L., Pestana A. and Rey J. A. (1995) Allelic loss at 1p and 19q frequently occurs in association and may represent early oncogenic events in oligodendroglial tumors. *Int. J. Cancer* **64**, 207–210.

Benitez J. A., Ma J., D'Antonio M. *et al.* (2017) PTEN regulates glioblastoma oncogenesis through chromatin-associated complexes of DAXX and histone H3. 3. *Nat. Commun.* **8**, 15223.

Bianco R., Shin I., Ritter C. A. *et al.* (2003) Loss of PTEN/MMAC1/TEP in EGF receptor-expressing tumor cells counteracts the antitumor action of EGFR tyrosine kinase inhibitors. *Oncogene* **22**, 2812–2822.

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

Bigner S. H., Mark J. and Bigner D. D. (1990) Cytogenetics of human brain tumors. *Cancer Genet. Cytogenet.* **47**, 141–154.

Bostrom J., Cobbers J. M., Wolter M., Tabatabai G., Weber R. G., Lichter P., Collins V. P. and Reifenberger G. (1998) Mutation of the PTEN (MMAC1) tumor suppressor gene in a subset of glioblastomas but not in meningiomas with loss of chromosome arm 10q. *Cancer Res.* **58**, 29–33.

Bredel M., Scholtens D. M., Yadav A. K. *et al.* (2011) NFKBIA deletion in glioblastomas. *N. Engl. J. Med.* **364**, 627–637.

Burger P. and Fuller G. (1991) Pathology–trends and pitfalls in histologic diagnosis, immunopathology, and applications of oncogene research. *Neurol. Clin.* **9**, 249–271.

Burger P. C. and Green S. B. (1987) Patient age, histologic features, and length of survival in patients with glioblastoma multiforme. *Cancer* **59**, 1617–1625.

Cairncross J. G., Ueki K., Zlatescu M. C. *et al.* (1998) Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J. Natl Cancer Inst.* **90**, 1473–1479.

Capper D., Zentgraf H., Balss J., Hartmann C. and von Deimling A. (2009) Monoclonal antibody specific for IDH1 R132H mutation. *Acta Neuropathol.* **118**, 599.

Cerchietti L. and Melnick A. (2017) DNA methylation–based biomarkers. *J. Clin. Oncol.* **35**, 793–795.

Chatterjee D., Radotra B. D., Kumar N., Vasishta R. K. and Gupta S. K. (2018) IDH1, ATRX, and BRAFV600E mutation in astrocytic tumors and their significance in patient outcome in north Indian population. *Surg. Neurol. Int.* **9**, 29.

Chen J. R., Yao Y., Xu H. Z. and Qin Z. Y. (2016) Isocitrate dehydrogenase (IDH)1/2 mutations as prognostic markers in patients with glioblastomas. *Medicine* **95**, e2583.

Choe G., Horvath S., Cloughesy T. F. *et al.* (2003) Analysis of the phosphatidylinositol 3′-kinase signaling pathway in glioblastoma patients in vivo. *Can. Res.* **63**, 2742–2746.

Choi N. W., Schuman L. M. and Gullen W. H. (1970) Epidemiology of primary central nervous system neoplasms. II. Case-Control Study. *Am. J. Epidemiol.* **91**, 467–485.

Chung R., Whaley J., Kley N. *et al.* (1991) TP53 gene mutations and 17p deletions in human astrocytomas. *Genes Chromosom. Cancer* **3**, 323–331.

Collins V. (1995) Gene amplification in human gliomas. *Glia* **15**, 289–296.

Consortium, E. C. T. S (1993) Identification and characterization of the tuberous sclerosis gene on chromosome 16. *Cell* **75**, 1305–1315.

Conti A., Aguennouz M., La Torre D. *et al.* (2009) miR-21 and 221 upregulation and miR-181b downregulation in human grade II-IV astrocytic tumors. *J. Neurooncol.* **93**, 325–332.

De Salvo M., Maresca G., D'agnano I. *et al.* (2011) Temozolomide induced c-Myc-mediated apoptosis via Akt signalling in MGMT expressing glioblastoma cells. *Int. J. Radiat. Biol.* **87**, 518–533.

De Witt Hamer P. C. (2010) Small molecule kinase inhibitors in glioblastoma: a systematic review of clinical studies. *Neuro Oncol.* **12**, 304–316.

von Deimling A., Louis D. N., Menon A. G., von Ammon K., Petersen I., Ellison D., Wiestler O. D. and Seizinger B. R. (1993) Deletions on the long arm of chromosome 17 in pilocytic astrocytoma. *Acta Neuropathol.* **86**, 81–85.

von Deimling A., Nagel J., Bender B., Lenartz D., Schramm J., Louis D. N. and Wiestler O. D. (1994) Deletion mapping of chromosome 19 in human gliomas. *Int. J. Cancer* **57**, 676–680.

Eagle L. R., Yin X., Brothman A. R., Williams B. J., Atkin N. B. and Prochownik E. V. (1995) Mutation of the MXI1 gene in prostate cancer. *Nat. Genet.* **9**, 249–255.

Eckerich C., Zapf S., Fillbrandt R., Loges S., Westphal M. and Lamszus K. (2007) Hypoxia can induce c-Met expression in glioma cells and enhance SF/HGF-induced cell migration. *Int. J. Cancer* **121**, 276–283.

Ekstrand A. J., James C. D., Cavenee W. K., Seliger B., Pettersson R. F. and Collins V. P. (1991) Genes for epidermal growth factor receptor, transforming growth factor α, and epidermal growth factor and their expression in human gliomas in vivo. *Can. Res.* **51**, 2164–2172.

Ekstrand A. J., Sugawa N., James C. D. and Collins V. P. (1992) Amplified and rearranged epidermal growth factor receptor genes in human glioblastomas reveal deletions of sequences encoding portions of the N-and/or C-terminal tails. *Proc. Natl Acad. Sci.* **89**, 4309–4313.

England B., Huang T. and Karsy M. (2013) Current understanding of the role and targeting of tumor suppressor p53 in glioblastoma multiforme. *Tumor Biol.* **34**, 2063–2074.

Fathullahzadeh S., Mirzaei H., Honardoost M. A., Sahebkar A. and Salehi M. (2016) Circulating microRNA-192 as a diagnostic biomarker in human chronic lymphocytic leukemia. *Cancer Gene Ther.* **23**, 327–332.

Finlay C. A. (1993) The mdm-2 oncogene can overcome wild-type p53 suppression of transformed cell growth. *Mol. Cell. Biol.* **13**, 301–306.

Fomchenko E. I., Dougherty J. D., Helmy K. Y., Katz A. M., Pietras A., Brennan C., Huse J. T., Milosevic A. and Holland E. C. (2011) Recruited cells can become transformed and overtake PDGF-induced murine gliomas in vivo during tumor progression. *PLoS ONE* **6**, e20605.

Fujisawa H., Reis R. M., Nakamura M., Colella S., Yonekawa Y., Kleihues P. and Ohgaki H. (2000) Loss of heterozygosity on chromosome 10 is more extensive in primary (de novo) than in secondary glioblastomas. *Lab. Invest.* **80**, 65.

Fults D., Petronio J., Noblett B. D. and Pedone C. A. (1992) Chromosome 11p15 deletions in human malignant astrocytomas and primitive neuroectodermal tumors. *Genomics* **14**, 799–801.

Furgason J. M., Koncar R. F., Michelhaugh S. K., Sarkar F. H., Mittal S., Sloan A. E., Barnholtz-Sloan J. S. and Bahassi E. M. (2015) Whole genome sequence analysis links chromothripsis to EGFR, MDM2, MDM4, and CDK4 amplification in glioblastoma. *Oncoscience* **2**, 618.

Furnari F. B., Fenton T., Bachoo R. M. *et al.* (2007) Malignant astrocytic glioma: genetics, biology, and paths to treatment. *Genes Dev.* **21**, 2683–2710.

Gholamin S., Pasdar A., Khorrami M. S., Mirzaei H., Mirzaei H. R., Salehi R., Ferns G. A., Ghayour-Mobarhan M. and Avan A. (2016) The potential for circulating microRNAs in the diagnosis of myocardial infarction: a novel approach to disease diagnosis and treatment. *Curr. Pharm. Des.* **22**, 397–403.

Gholamin S., Mirzaei H., Razavi S. M., Hassanian S. M., Saadatpour L., Masoudifar A., ShahidSales S. and Avan A. (2018) GD2-targeted immunotherapy and potential value of circulating microRNAs in neuroblastoma. *J. Cell. Physiol.* **233**, 866–879.

Gladson C. L., Prayson R. A. and Liu W. M. (2010) The pathobiology of glioma tumors. *Annu. Rev. Pathol. Mech. Dis.* **5**, 33–50.

Golabchi K., Soleimani-Jelodar R., Aghadoost N., Momeni F., Moridikia A., Nahand J. S., Masoudifar A., Razmjoo H. and Mirzaei H. (2018) MicroRNAs in retinoblastoma: potential diagnostic and therapeutic biomarkers. *J. Cell. Physiol.* **233**, 3016–3023.

Gonzalez-Gomez P., Bello M., Alonso M., Arjona D., Lomas J., De Campos J., Isla A. and Rey J. (2003) CpG island methylation status and mutation analysis of the RB1 gene essential promoter region and protein-binding pocket domain in nervous system tumours. *Br. J. Cancer* **88**, 109.

Greene M. H. (1999) The genetics of hereditary melanoma and nevi. *Cancer* **86**, 2464–2477.

Guo C., Liu S., Greenaway F. and Sun M. Z. (2013) Potential role of annexin A7 in cancers. *Clin. Chim. Acta* **423**, 83–89.

Hamilton S. R., Liu B., Parsons R. E. *et al.* (1995) The molecular basis of Turcot's syndrome. *N. Engl. J. Med.* **332**, 839–847.

Hartmann C., Meyer J., Balss J. *et al.* (2009) Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. *Acta Neuropathol.* **118**, 469–474.

Hartmann C., Hentschel B., Wick W. *et al.* (2010) Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol.* **120**, 707–718.

Hayat M. A. (2012) *Tumors of the Central Nervous System*. Springer, Berlin, Germany.

He J., Allen J. R., Collins V. P., Allalunis-Turner M. J., Godbout R., Day R. S., 3rd and James C. D. (1994) CDK4 amplification is an alternative mechanism to p16 gene homozygous deletion in glioma cell lines. *Cancer Res.* **54**, 5804–5807.

Hegi M. E., Diserens A.-C., Gorlia T. *et al.* (2005) MGMT gene silencing and benefit from temozolomide in glioblastoma. *N. Engl. J. Med.* **352**, 997–1003.

Hoseini Z., Sepahvand F., Rashidi B., Sahebkar A., Masoudifar A. and Mirzaei H. (2018) NLRP3 inflammasome: its regulation and involvement in atherosclerosis. *J. Cell. Physiol.* **233**, 2116–2132.

Howe G. R., Burch J. D., Chiarelli A. M., Risch H. A. and Choi B. C. (1989) An exploratory case-control study of brain tumors in children. *Can. Res.* **49**, 4349–4352.

Hurt M. R., Moossy J., Donovan-Peluso M. and Locker J. (1992) Amplification of epidermal growth factor receptor gene in gliomas: histopathology and prognosis. *J. Neuropathol. Exp. Neurol.* **51**, 84–90.

Iuzzolino P., Ghimenton C., Nicolato A., Giorgiutti F., Fina P., Doglioni C. and Barbareschi M. (1994) p53 protein in low-grade

astrocytomas: a study with long-term follow-up. *Br. J. Cancer* **69**, 586.

Jafari S. H., Saadatpour Z., Salmaninejad A., Momeni F., Mokhtari M., Nahand J. S., Rahmati M., Mirzaei H. and Kianmehr M. (2018) Breast cancer diagnosis: imaging techniques and biochemical markers. *J. Cell. Physiol.* **233**, 5200–5213.

Jamali L., Tofigh R., Tutunchi S. *et al.* (2018) Circulating microRNAs as diagnostic and therapeutic biomarkers in gastric and esophageal cancers. *J. Cell. Physiol.* **233**, 8538–8550.

Johnson B. E., Mazor T., Hong C. *et al.* (2014) Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. *Science* **343**, 189–193.

Josefa Bello M., Pestaña A., Rey J. A., De Campos J. M., Vaquero J., Elena Kusak M. and Sarasa J. L. (1994) Molecular and cytogenetic analysis of chromosome 9 deletions in 75 malignant gliomas. *Genes Chromosom. Cancer* **9**, 33–41.

Juratli T., Kirsch M., Geiger K. *et al.* (2012) The prognostic value of IDH mutations and MGMT promoter status in secondary high-grade gliomas. *J. Neurooncol.* **110**, 325–333.

Karamitopoulou E., Perentes E. and Diamantis I. (1993) p53 protein expression in central nervous system tumors: an immunohistochemical study with CM1 polyvalent and DO-7 monoclonal antibodies. *Acta Neuropathol.* **85**, 611–616.

Karlbom A. E., James C. D., Boethius J., Cavenee W. K., Collins V. P., Nordenskjold M. and Larsson C. (1993) Loss of heterozygosity in malignant gliomas involves at least three distinct regions on chromosome 10. *Hum. Genet.* **92**, 169–174.

Keshavarz M., Dianat-Moghadam H., Sofiani V. H. *et al.* (2018) miRNA-based strategy for modulation of influenza A virus infection. *Epigenomics* **10**, 829–844.

Keshavarzi M., Darijani M., Momeni F., Moradi P., Ebrahimnejad H., Masoudifar A. and Mirzaei H. (2017a) Molecular imaging and oral cancer diagnosis and therapy. *J. Cell. Biochem.* **118**, 3055–3060.

Keshavarzi M., Sorayayi S., Jafar Rezaei M., Mohammadi M., Ghaderi A., Rostamzadeh A., Masoudifar A. and Mirzaei H. (2017b) MicroRNAs-based imaging techniques in cancer diagnosis and therapy. *J. Cell. Biochem.* **118**, 4121–4128.

Kibirige M., Birch J. M., Campbell R. H., Gattamaneni H. and Blair V. (1989) A review of astrocytoma in childhood. *Pediatr. Hematol. Oncol.* **6**, 319–329.

Kinzler K. W., Bigner S. H., Bigner D. D., Trent J. M., Law M. L., O'Brien S. J., Wong A. J. and Vogelstein B. (1987) Identification of an amplified, highly expressed gene in a human glioma. *Science* **236**, 70–73.

Kleihues P., Louis D. N., Scheithauer B. W., Rorke L. B., Reifenberger G., Burger P. C. and Cavenee W. K. (2002) The WHO classification of tumors of the nervous system. *J. Neuropathol. Exp. Neurol.* **61**, 215–225.

Kong D. S., Song S. Y., Kim D. H. *et al.* (2009) Prognostic significance of c-Met expression in glioblastomas. *Cancer* **115**, 140–148.

Kyritsis A. P., Bondy M. L., Xiao M., Berman E. L., Cunningham J. E., Lee P. S., Levin V. A. and Saya H. (1994) Germline p53 gene mutations in subsets of glioma patients. *J. Natl Cancer Inst.* **86**, 344–349.

Lau N., Feldkamp M. M., Roncari L., Loehr A. H., Shannon P., Gutmann D. H. and Guha A. (2000) Loss of neurofibromin is associated with activation of RAS/MAPK and PI3-K/AKT signaling in a neurofibromatosis 1 astrocytoma. *J. Neuropathol. Exp. Neurol.* **59**, 759–767.

Lewis R. J. and Ketcham A. S. (1973) Maffucci's syndrome: functional and neoplastic significance. Case report and review of the literature. *J. Bone Joint Surg. Am.* **55**, 1465–1479.

Li B., Yuan M., Kim I.-A., Chang C.-M., Bernhard E. J. and Shu H.-K. G. (2004) Mutant epidermal growth factor receptor displays increased signaling through the phosphatidylinositol-3 kinase/AKT pathway and promotes radioresistance in cells of astrocytic origin. *Oncogene* **23**, 4594.

Li S., Gao Y., Ma W., Guo W., Zhou G., Cheng T. and Liu Y. (2014) EGFR signaling-dependent inhibition of glioblastoma growth by ginsenoside Rh2. *Tumor Biol.* **35**, 5593–5598.

Liggett W. H., Jr and Sidransky D. (1998) Role of the p16 tumor suppressor gene in cancer. *J. Clin. Oncol.* **16**, 1197–1206.

Lokker N. A., Sullivan C. M., Hollenbach S. J., Israel M. A. and Giese N. A. (2002) Platelet-derived growth factor (PDGF) autocrine signaling regulates survival and mitogenic pathways in glioblastoma cells: evidence that the novel PDGF-C and PDGF-D ligands may play a role in the development of brain tumors. *Can. Res.* **62**, 3729–3735.

Louis D., Petersen I., Wiestler O. and Seizinger B. (1992) Evidence for a tumor suppressor gene on chromosome 19q associated with human astrocytomas, oligodendrogliomas, and mixed gliomas. *Can. Res.* **52**, 4277–4279.

Louis D. N., Von Deimling A., Chung R. Y. *et al.* (1993) Comparative study of p53 gene and protein alterations in human astrocytic tumors. *J. Neuropathol. Exp. Neurol.* **52**, 31–38.

Lu K. V., Zhu S., Cvrljevic A. *et al.* (2009) Fyn and SRC are effectors of oncogenic epidermal growth factor receptor signaling in glioblastoma patients. *Can. Res.* **69**, 6889–6898.

Malzkorn B., Wolter M., Liesenberg F., Grzendowski M., Stühler K., Meyer H. E. and Reifenberger G. (2010) Identification and functional characterization of microRNAs involved in the malignant progression of gliomas. *Brain Pathol.* **20**, 539–550.

Mao C. X., Yin J. Y., Zhang Y. *et al.* (2017) The molecular classification of astrocytic tumors. *Oncotarget* **8**, 96340–96350.

Martens T., Schmidt N.-O., Eckerich C., Fillbrandt R., Merchant M., Schwall R., Westphal M. and Lamszus K. (2006) A novel one-armed anti-c-Met antibody inhibits glioblastoma growth in vivo. *Clin. Cancer Res.* **12**, 6144–6152.

Mashreghi M., Azarpara H., Bazaz M. R., Jafari A., Masoudifar A., Mirzaei H. and Jaafari M. R. (2018) Angiogenesis biomarkers and their targeting ligands as potential targets for tumor angiogenesis. *J. Cell. Physiol.* **233**, 2949–2965.

Masoudi M. S., Mehrabian E. and Mirzaei H. (2018) MiR-21: a key player in glioblastoma pathogenesis. *J. Cell. Biochem.* **119**, 1285–1290.

Mellinghoff I. K., Wang M. Y., Vivanco I. *et al.* (2005) Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. *N. Engl. J. Med.* **353**, 2012–2024.

van Meyel D. J., Ramsay D. A., Chambers A. F., Macdonald D. R. and Cairncross J. G. (1994) Absence of hereditary mutations in exons 5 through 9 of the p53 gene and exon 24 of the neurofibromin gene in families with glioma. *Ann. Neurol.* **35**, 120–122.

Miettinen H., Kononen J., Sallinen P. *et al.* (1999) CDKN2/p16 predicts survival in oligodendrogliomas: comparison with astrocytomas. *J. Neurooncol.* **41**, 205–211.

Mirzaei H. (2017) Stroke in women: risk factors and clinical biomarkers. *J. Cell. Biochem.* **118**, 4191–4202.

Mirzaei H., Gholamin S., Shahidsales S., Sahebkar A., Jaafari M. R., Mirzaei H. R., Hassanian S. M. and Avan A. (2016a) MicroRNAs as potential diagnostic and prognostic biomarkers in melanoma. *Eur. J. Cancer* **53**, 25–32.

Mirzaei H., Khataminfar S., Mohammadparast S. *et al.* (2016b) Circulating microRNAs as potential diagnostic biomarkers and therapeutic targets in gastric cancer: current status and future perspectives. *Curr. Med. Chem.* **23**, 4135–4150.

Mirzaei H., Naseri G., Rezaee R. *et al.* (2016c) Curcumin: a new candidate for melanoma therapy? *Int. J. Cancer* **139**, 1683–1695.

Mirzaei H., Yazdi F., Salehi R. and Mirzaei H. R. (2016d) SiRNA and epigenetic aberrations in ovarian cancer. *J. Cancer. Res. Ther.* **12**, 498–508.

Mirzaei H. R., Sahebkar A., Mohammadi M. *et al.* (2016e) Circulating microRNAs in hepatocellular carcinoma: potential diagnostic and prognostic biomarkers. *Curr. Pharm. Des.* **22**, 5257–5269.

Mirzaei H., Ferns G. A., Avan A. and Mobarhan M. G. (2017a) Cytokines and MicroRNA in coronary artery disease. *Adv. Clin. Chem.* **82**, 47–70.

Mirzaei H., Sahebkar A., Jaafari M. R., Goodarzi M. and Mirzaei H. R. (2017b) Diagnostic and therapeutic potential of exosomes in cancer: the beginning of a new tale? *J. Cell. Physiol.* **232**, 3251–3260.

Mirzaei H., Fathullahzadeh S., Khanmohammadi R. *et al.* (2018a) State of the art in microRNA as diagnostic and therapeutic biomarkers in chronic lymphocytic leukemia. *J. Cell. Physiol.* **233**, 888–900.

Mirzaei H., Momeni F., Saadatpour L. *et al.* (2018b) MicroRNA: relevance to stroke diagnosis, prognosis, and therapy. *J. Cell. Physiol.* **233**, 856–865.

Mohammadi M., Goodarzi M., Jaafari M. R., Mirzaei H. R. and Mirzaei H. (2016) Circulating microRNA: a new candidate for diagnostic biomarker in neuroblastoma. *Cancer Gene Ther.* **23**, 371–372.

Mollenhauer J., Wiemann S., Scheurlen W., Korn B., Hayashi Y., Wilgenbus K. K., von Deimling A. and Poustka A. (1997) DMBT1, a new member of the SRCR superfamily, on chromosome 10q25.3-26.1 is deleted in malignant brain tumours. *Nat. Genet.* **17**, 32–39.

Mori T., Nagase H., Horii A. *et al.* (1994) Germ-line and somatic mutations of the APC gene in patients with turcot syndrome and analysis of APC mutations in brain tumors. *Genes Chromosom. Cancer* **9**, 168–172.

Moridikia A., Mirzaei H., Sahebkar A. and Salimian J. (2018) MicroRNAs: potential candidates for diagnosis and treatment of colorectal cancer. *J. Cell. Physiol.* **233**, 901–913.

Mueller W., Mollenhauer J., Stockhammer F., Poustka A. and von Deimling A. (2002) Rare mutations of the DMBT1 gene in human astrocytic gliomas. *Oncogene* **21**, 5956–5959.

Nagata Y., Lan K. H., Zhou X. *et al.* (2004) PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. *Cancer Cell* **6**, 117–127.

Nakamura M., Yang F., Fujisawa H., Yonekawa Y., Kleihues P. and Ohgaki H. (2000) Loss of heterozygosity on chromosome 19 in secondary glioblastomas. *J. Neuropathol. Exp. Neurol.* **59**, 539–543.

Nakamura M., Yonekawa Y., Kleihues P. and Ohgaki H. (2001) Promoter hypermethylation of the RB1 gene in glioblastomas. *Lab. Invest.* **81**, 77.

Neumann H., Eggert H., Scheremet R. *et al.* (1992) Central nervous system lesions in von Hippel-Lindau syndrome. *J. Neurol. Neurosurg. Psychiatry* **55**, 898–901.

Nikaki A., Piperi C. and Papavassiliou A. G. (2012) Role of microRNAs in gliomagenesis: targeting miRNAs in glioblastoma multiforme therapy. *Expert Opin. Investig. Drugs* **21**, 1475–1488.

Obremski V. J., Hall A. M. and Fernandez-Valle C. (1998) Merlin, the neurofibromatosis type 2 gene product, and β1 integrin associate in isolated and differentiating Schwann cells. *J. Neurobiol.* **37**, 487–501.

Ohgaki H. and Kleihues P. (2007) Genetic pathways to primary and secondary glioblastoma. *Am. J. Pathol.* **170**, 1445–1453.

Ohgaki H. and Kleihues P. (2013) The definition of primary and secondary glioblastoma. *Clin. Cancer Res.* **19**, 764–772.

Ohgaki H., Eibl R. H., Reichel M. B. *et al.* (1993) Mutations of the p53 tumor suppressor gene in neoplasms of the human nervous system. *Mol. Carcinog.* **8**, 74–80.

Purkait S., Sharma V., Jha P., Sharma M. C., Suri V., Suri A., Sharma B. S. and Sarkar C. (2015) EZH2 expression in gliomas: correlation with CDKN2A gene deletion/p16 loss and MIB-1 proliferation index. *Neuropathology* **35**, 421–431.

Rabieian R., Boshtam M., Zareei M., Kouhpayeh S., Masoudifar A. and Mirzaei H. (2018) Plasminogen Activator Inhibitor Type-1 as a Regulator of Fibrosis. *J. Cell. Biochem.* **119**, 17–27.

Ranjit M., Motomura K., Ohka F., Wakabayashi T. and Natsume A. (2015) Applicable advances in the molecular pathology of glioblastoma. *Brain Tumor Pathol.* **32**, 153–162.

Rashidi B., Hoseini Z., Sahebkar A. and Mirzaei H. (2017a) Anti-Atherosclerotic Effects of Vitamins D and E in Suppression of Atherogenesis. *J. Cell. Physiol.* **232**, 2968–2976.

Rashidi B., Malekzadeh M., Goodarzi M., Masoudifar A. and Mirzaei H. (2017b) Green tea and its anti-angiogenesis effects. *Biomed. Pharmacother.* **89**, 949–956.

Raub T. J., Wishart G. N., Kulanthaivel P. *et al.* (2015) Brain exposure of two selective dual CDK4 and CDK6 inhibitors and the antitumor activity of CDK4 and CDK6 inhibition in combination with temozolomide in an intracranial glioblastoma xenograft. *Drug Metab. Dispos.* **43**, 1360–1371.

Reifenberger G., Liu L., Ichimura K., Schmidt E. E. and Collins V. P. (1993) Amplification and overexpression of the MDM2 gene in a subset of human malignant gliomas without p53 mutations. *Can. Res.* **53**, 2736–2739.

Reifenberger G., Reifenberger J., Ichimura K., Meltzer P. S. and Collins V. P. (1994) Amplification of multiple genes from chromosomal region 12q13-14 in human malignant gliomas: preliminary mapping of the amplicons shows preferential involvement of CDK4, SAS, and MDM2. *Can. Res.* **54**, 4299–4303.

Reifenberger G., Ichimura K., Reifenberger J., Elkahloun A. G., Meltzer P. S. and Collins V. P. (1996) Refined mapping of 12q13-q15 amplicons in human malignant gliomas suggests CDK4/SAS and MDM2 as independent amplification targets. *Cancer Res.* **56**, 5141–5145.

Riemenschneider M. J., Büschges R., Wolter M., Reifenberger J., Boström J., Kraus J. A., Schlegel U. and Reifenberger G. (1999) Amplification and overexpression of the MDM4 (MDMX) gene from 1q32 in a subset of malignant gliomas without TP53 mutation or MDM2 amplification. *Can. Res.* **59**, 6091–6096.

Ritland S. R., Ganju V., Jenkins D. and Robert B. (1995) Region-specific loss of heterozygosity on chromosome 19 is related to the morphologic type of human glioma. *Genes Chromosom. Cancer* **12**, 277–282.

Russel D. and Rubinstein L. (1989) Pathology of tumors of the nervous system, in *Tumours of Central Neuroepithelial Origin*, 5th edn (Esiri M., ed), pp. 83–246. Williams and Wilkins, Baltimore.

Saadatpour L., Fadaee E., Fadaei S., Nassiri Mansour R., Mohammadi M., Mousavi S. M., Goodarzi M., Verdi J. and Mirzaei H. (2016) Glioblastoma: exosome and microRNA as novel diagnosis biomarkers. *Cancer Gene Ther.* **23**, 415–418.

Saeedi Borujeni M. J., Esfandiary E., Taheripak G., Codoner-Franch P., Alonso-Iglesias E. and Mirzaei H. (2018) Molecular aspects of diabetes mellitus: resistin, microRNA, and exosome. *J. Cell. Biochem.* **119**, 1257–1272.

Salarinia R., Sahebkar A., Peyvandi M. *et al.* (2016) Epi-Drugs and Epi-miRs: moving Beyond Current Cancer Therapies. *Curr. Cancer Drug Targets* **16**, 773–788.

Sameshima Y., Tsunematsu Y., Watanabe S. *et al.* (1992) Detection of novel germ-line p53 mutations in diverse-cancer-prone families identified by selecting patients with childhood adrencortical carcinoma. *J. Natl Cancer Inst.* **84**, 703–707.

Santoni M., Burattini L., Nabissi M., Morelli M. B., Berardi R., Santoni G. and Cascinu S. (2013) Essential role of Gli proteins in glioblastoma multiforme. *Curr. Protein Pept. Sci.* **14**, 133–140.

Sasaki H., Betensky R. A., Cairncross J. G. and Louis D. N. (2002) DMBT1 polymorphisms: relationship to malignant glioma tumorigenesis. *Cancer Res.* **62**, 1790–1796.

Sato F., Tsuchiya S., Meltzer S. J. and Shimizu K. (2011) MicroRNAs and epigenetics. *FEBS J.* **278**, 1598–1609.

Schiebe M., Ohneseit P., Hoffmann W., Meyermann R., Rodemann H.-P. and Bamberg M. (2000) Analysis of mdm2 and p53 gene alterations in glioblastomas and its correlation with clinical factors. *J. Neurooncol.* **49**, 197–203.

Schmidt E. E., Ichimura K., Reifenberger G. and Collins V. P. (1994) CDKN2 (p16/MTS1) gene deletion or CDK4 amplification occurs in the majority of glioblastomas. *Can. Res.* **54**, 6321–6324.

Schrock E., Thiel G., Lozanova T. *et al.* (1994) Comparative genomic hybridization of human malignant gliomas reveals multiple amplification sites and nonrandom chromosomal gains and losses. *Am. J. Pathol.* **144**, 1203–1218.

See W. L., Tan I.-L., Mukherjee J., Nicolaides T. and Pieper R. O. (2012) Sensitivity of glioblastomas to clinically available MEK inhibitors is defined by neurofibromin 1 deficiency. *Can. Res.* **72**, 3350–3359.

Simonian M., Mosallayi M. and Mirzaei H. (2018) Circulating miR-21 as novel biomarker in gastric cancer: diagnostic and prognostic biomarker. *J. Cancer. Res. Ther.* **14**, 475.

Sippl C., Urbschat S., Kim Y. J., Senger S., Oertel J. and Ketter R. (2018) Promoter methylation of RB1, P15, P16, and MGMT and their impact on the clinical course of pilocytic astrocytomas. *Oncol. Lett.* **15**, 1600–1606.

Sjöström S., Andersson U., Liu Y. *et al.* (2010) Genetic variations in EGF and EGFR and glioblastoma outcome. *Neuro Oncol.* **12**, 815–821.

Sordella R., Bell D. W., Haber D. A. and Settleman J. (2004) Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. *Science* **305**, 1163–1167.

de Ståhl T. D., Hartmann C., De Bustos C., Piotrowski A., Benetkiewicz M., Mantripragada K. K., Tykwinski T., von Deimling A. and Dumanski J. P. (2005) Chromosome 22 tiling-path array–CGH analysis identifies germ-line-and tumor-specific aberrations in patients with glioblastoma multiforme. *Genes Chromosom. Cancer* **44**, 161–169.

Tavakolizadeh J., Roshanaei K., Salmaninejad A. *et al.* (2018) MicroRNAs and exosomes in depression: potential diagnostic biomarkers. *J. Cell. Biochem.* **119**, 3783–3797.

Taylor J. W. and Schiff D. (2015) Treatment considerations for MGMT-unmethylated glioblastoma. *Curr. Neurol. Neurosci. Rep.* **15**, 507.

Toledo F. and Wahl G. M. (2007) MDM2 and MDM4: p53 regulators as targets in anticancer therapy. *Int. J. Biochem. Cell Biol.* **39**, 1476–1482.

Urbschat S., Sippl C., Engelhardt J., Kammers K., Oertel J. and Ketter R. (2017) Importance of biomarkers in glioblastomas patients receiving local BCNU wafer chemotherapy. *Mol. Cytogenet.* **10**, 16.

Verhaak R. G., Hoadley K. A., Purdom E. *et al.* (2010) Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell* **17**, 98–110.

Vieregge P., Gerhard L. and Nahser H. (1987) Familial glioma: occurrence within the "familial cancer syndrome" and systemic malformations. *J. Neurol.* **234**, 220–232.

Wang A., Liu Z., Li G. and Zhang L. (2011) Expression and significance of P53 protein and MDM-2 protein in human gliomas. *Chin. Med. J.* **124**, 2530–2533.

Weary P. E., Gorlin R. J., Gentry W. C., Comer J. E. and Greer K. E. (1972) Multiple hamartoma syndrome (Cowden's disease). *Arch. Dermatol.* **106**, 682–690.

Wechsler D. S., Shelly C. A., Petroff C. A. and Dang C. V. (1997) MXI1, a putative tumor suppressor gene, suppresses growth of human glioblastoma cells. *Cancer Res.* **57**, 4905–4912.

Wu J. K., Ye Z. and Darras B. T. (1993) Frequency of p53 tumor suppressor gene mutations in human primary brain tumors. *Neurosurgery* **33**, 824–831.

Wu W., Kemp B. L., Proctor M. L., Gazdar A. F., Minna J. D., Hong W. K. and Mao L. (1999) Expression of DMBT1, a candidate tumor suppressor gene, is frequently lost in lung cancer. *Can. Res.* **59**, 1846–1851.

Wu L., Cai C., Wang X., Liu M., Li X. and Tang H. (2011) MicroRNA-142-3p, a new regulator of RAC1, suppresses the migration and invasion of hepatocellular carcinoma cells. *FEBS Lett.* **585**, 1322–1330.

Yadav A. K., Renfrow J. J., Scholtens D. M. *et al.* (2009) Monosomy of chromosome 10 associated with dysregulation of epidermal growth factor signaling in glioblastomas. *JAMA* **302**, 276–289.

Yang T. Q., Lu X. J., Wu T. F. *et al.* (2014) MicroRNA-16 inhibits glioma cell growth and invasion through suppression of BCL2 and the nuclear factor-κB1/MMP9 signaling pathway. *Cancer Sci.* **105**, 265–271.

Yao C. J., Han T. Y., Shih P. H., Yi T. Y., Lai I. C., Chang K. H., Lai T. Y., Chang C. L. and Lai G. M. (2014) Elimination of cancer stem-like side population in human glioblastoma cells accompanied with stemness gene suppression by Korean herbal recipe MSC500. *Integr. Cancer Ther.* **13**, 541–554.

Zhu Y., Guignard F., Zhao D., Liu L., Burns D. K., Mason R. P., Messing A. and Parada L. F. (2005) Early inactivation of p53 tumor suppressor gene cooperating with NF1 loss induces malignant astrocytoma. *Cancer Cell* **8**, 119–130.

Zhu X., Li Y., Shen H., Li H., Long L., Hui L. and Xu W. (2013) miR-137 inhibits the proliferation of lung cancer cells by targeting Cdc42 and Cdk6. *FEBS Lett.* **587**, 73–81.