Review

Most frequent molecular and immunohistochemical markers present in selected types of brain tumors

Romana Richterová[1,2], Jana Jurečeková[1], Andrea Evinová[1], Branislav Kolarovszki[2], Martin Benčo[2], Július De Riggo[2], Juraj Šutovský[2], Silvia Mahmood[1], Peter Račay[1] and Dušan Dobrota[1]

[1] *Department of Medical Biochemistry, Comenius University Bratislava, Jessenius Faculty of Medicine, Malá hora 4, Martin, Slovak Republic*

[2] *Department of Neurosurgery, Comenius University Bratislava, Jessenius Faculty of Medicine, University Hospital Martin, Kollárova 2, Martin, Slovak Republic*

Abstract. Tumors of brain tissue and meninges create a heterogeneous group with various biological behavior, therapy management and differing prognosis. Some of these do not require treatment, some can be cured by surgery and some are rapidly fatal despite treatment. Despite huge progress in tumor research, innovations in diagnostic tools and therapy, prognosis remains, in case of malignant tumor types, very serious. There has been an increased understanding of molecular abnormalities occurring in primary brain tumors. Genome-wide analyses of tumors have improved the knowledge in tumor biology. The aim of the research is to explain the oncogenesis features thus leading to the use of new therapeutic modalities in order to prolong survival rate of patients and at the same time providing satisfactory life quality. This article offers a short review of the basic genetic alterations present with some histological types of brain tumors.

Key words: Brain tumors — Glioma — Meningioma — Genetic alteration

Abbreviations: CDK, cyclin dependent kinase; CNS, central nervous system; DCC, deleted in colorectal cancer gene; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; GFAP, glial fibrillary acidic protein; IDH, isocitrate dehydrogenase genes; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; IGFR, insulin-like growth factor receptor; LOH, loss of heterozygosity; MDM2, murine double minute-2; MGMT, O^6-methylguanine-DNA methyltransferase; NF2, neurofibromatosis type 2; PCNSL, primary central nervous system lymphoma; PDGF, platelet-derivated growth factor; PTEN, phosphatase and tensin homology; RB1, retinoblastoma gene; SHH, sonic hedgehog pathway; STAT6, signal transducer and activator of transcription; TGF-α, transforming growth factor α; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; WNT, Wingless pathway.

Introduction

Intracranial tumors considerably contribute to morbidity and mortality in patients. These consist of cells whose differentiation and cell division spin out of control. Their etiology is multifactorial. The tumors take their origin as a result of an accumulation of various genetic alterations which allow the cells to escape physiological regulatory mechanisms and their destruction by the immune system cells (Wrensch et al. 2002). Despite a huge amount of potential risk factors for tumorigenesis, only 3 of them had been verified: some hereditary syndromes (neurofibromatosis type 1 and 2, Turcot, Li-Fraumeni, Cowden syndrome, etc), radiation exposure (including therapeutic exposition) and severe immunosupression are confirmed as a risk factor of brain lymphomas. But these identified factors are responsible only for a small amount of tumors (Fisher et al. 2007; Bondy

Correspondence to: Romana Richterová, Department of Neurosurgery, University Hospital Martin, Kollárova 2, 036 01 Martin, Slovak Republic
E-mail: romana.richterova@gmail.com

et al. 2008). Many risk factors remain unclear in the onset of oncogenesis. Recent research indicates that the immune system plays a role in both the development of and host defence against brain tumors (Albesiano et al. 2010; Charles et al. 2011). It is believed that among the molecular and immunological factor, also diet, environmental and personal exposition might play an important role in the etiopathogenesis of tumor development (Wrensch et al. 2002; Bondy et al. 2008; Curran and Bertics 2012).

Molecular biological features of selected brain tumor types

Cells might be deviated from normal cell cycle (proliferation, differentiation, cell death) by two types of genes – oncogenes and tumor suppressor genes. These genes spark oncogenesis by accumulating genetic lesions. Oncogenes, when activated, can cause cells to escape apoptosis and thus further proliferate themselves. The most common forms of genetic alteration in these genes are the amplification of genetic material and an activating mutation. It is dominant, as mutation of one allele is sufficient to express the function of the oncogene.

On the other hand, tumor suppressor genes and their protein products cause inhibition of cell growth. The most common genetic alterations in these genes are deletions (loss of genetic material) or inactivating (inhibitory) mutations. Mutant forms of tumor suppressor genes are recessive. Mutations on both alleles are required to abolish its function.

Table 1. Primary brain tumors in adults and their distribution according to histological classification (modified from CBTRUS 2000–2004)

Histological type	%
Meningioma	33.00
Glioblastoma	18.30
Tumors of cranial nerves	8.60
Pituitarytumors	8.00
Hematological neoplasms	2.80
Anaplastic astrocytoma	2.60
Astrocytoma	2.20
Oligodendroglioma	1.90
Not specified malignant glioma	1.60
Ependymoma	1.20
Neuronal/glial tumor	0.80
Pilocytic astrocytoma	0.60
Craniopharyngeoma	0.50
PNET/medulloblastoma	0.40
Germ cell tumors	0.20
Others	17.30

Brain metastases are the most frequent tumors in intracranial localisation. The most frequent malignant primary brain tumors in adults are gliomas and primary central nervous system (CNS) lymphomas, most frequent benign tumors are meningiomas and pituitary adenomas (Table 1), (Wrensch et al. 2002; Louis et al. 2007; CBTRUS 2008).
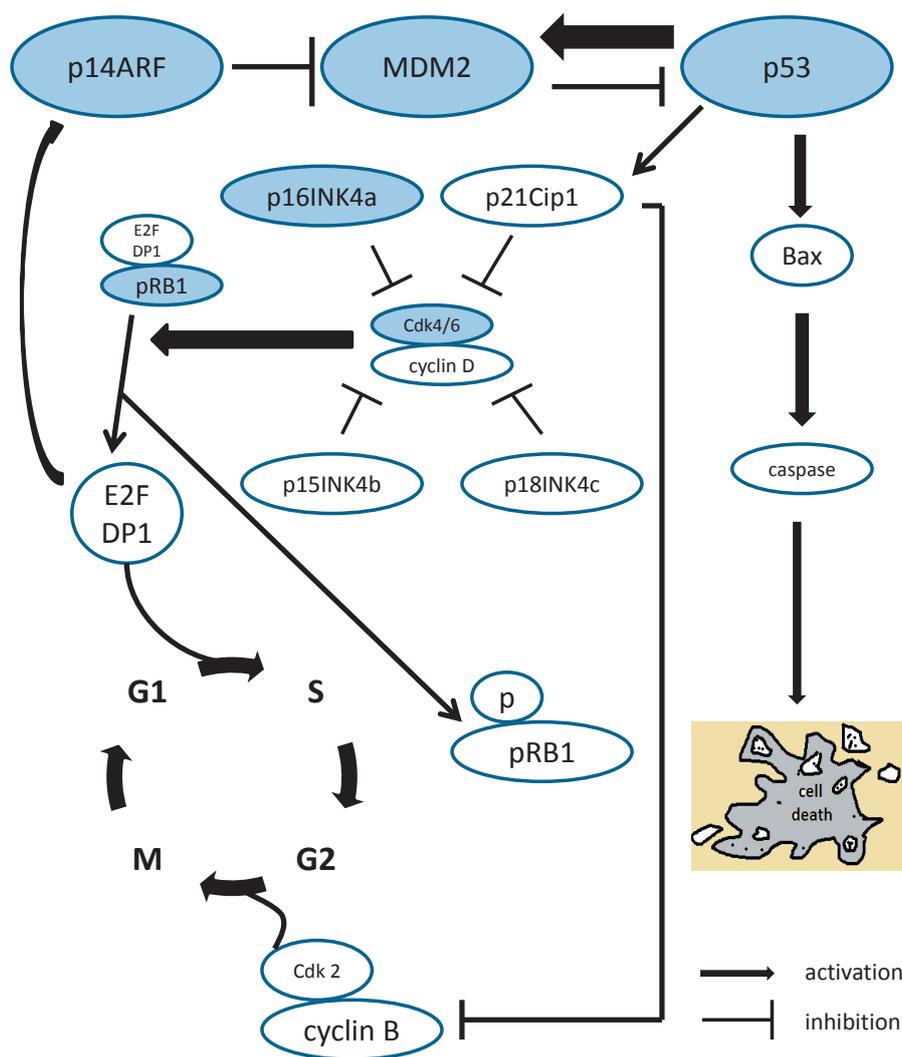
Gliomas

Gliomas are the most common type of primary brain tumors (about 70–80%), (Louis et al. 2007; Ricard et al. 2012). Gliomas can originate from neural stem cells, progenitor cells (Persson et al. 2010), or de-differentiated mature neural cells that transformed into cancer stem cells (Stiles and Rowitch 2008; Ricard et al. 2012). It is suggested that gliomas may arise from neuroepithelial stem cells (NEPs); some glioblastomas may rise from oligodendrocyte-type 2 astrocytes. NEP is a growth precursor for all cell types in the brain and spinal cord and possess the capacity for survival, self-renewal and uncontrolled cell division. Its growth is regulated by the epidermal growth factor (EGF) or fibroblast growth factor (FGF), (Nupponen and Joensuu 2006; Kozler et al. 2007).

Mutations of tumor suppressor genes lead to loss of function and overexpression of oncogenes occurring in oncogenesis. Various molecular abnormalities occur in gliomagenesis (Figure 1). The most frequently altered genes are: *TP53, MDM2, CDKN1A, CDKN1B, CDKN2A, CDKN2B, p14^{ARF}, CDK4, CDK6, RB1* (the retinoblastoma gene) and more.

The TP53 gene is localized on 17p13.1. The product of this gene is the tumor suppressor protein p53. *TP53* is a critical tumor suppressor that restricts proliferation and cell growth following stress. This protein is known for its ability to induce cell cycle arrest, cell reaction to DNA damage, apoptosis, senescence, autophagy, cell differentiation and neovascularisation and cell death (Vousden and Prives 2009; Hede et al. 2011). Because of the crucial role of p53 as a tumor suppressor, *TP53* is one of the most frequently mutated genes in human cancer cells (Iacob and Dinca 2009). The p53 and RB cell cycle and cell death signaling pathway is shown on Figure 1. Adult malignant astrocytoma was one of the first tumors shown to have frequent *TP53* mutations (Nigro et al. 1989; Iacob and Dinca 2009). The dysfunction of *TP53* disrupts the p14ARF pathway, delaying the process of apoptosis and further promoting genomic instability (Krakstad and Chekenya 2010). The most common positions of alterations are codons 175, 248 and 273 contributing substantially to the overall high incidence of alterations in p53's DNA-binding domain. Polymorphisms in codon 72 have been associated with susceptibility to human cancer. A possible association has

Figure 1. The tumor suppressor protein p53 and RB cell cycle and cell death signaling pathway. Alterations in this pathway cause inability of cells to undergo apoptosis and they proliferate. Proteins marked with full colour are most frequently altered in astrocytomas. MDM2, mdm2 TP53 binding protein homologue; RB, retinoblastoma.

been found between *TP53* Arg72Pro polymorphisms and susceptibility to brain tumors, particularly in high-grade astrocytomas (Parhar et al. 2005). Another study has failed to confirm this observation (Zhang et al. 2012). Loss of an allele on chromosome 17p and mutation of *TP53* occur in one-third of all astrocytomas, but the mutation of *TP53* is the most important in the formation of astrocytomas grade II (Hede et al. 2011; Wang et al. 2011). It also plays a role in their progression to secondary glioblastoma (shows a previous history of progression from lower-grade astrocytoma), but on the contrary, it is relatively rare (cca 10%) in primary glioblastoma (Furnari et al. 2007; Ohgaki and Kleihues 2007) and pilocytic grade I astrocytoma (Hede et al. 2011). This fact helped to establish two different genetic pathways that lead to glioblastoma formation – primary and secondary glioblastoma (Ohgaki and Kleihues 2007; Hede et al. 2011). Protein p53 was shown to be a prognostic marker (Levidou et al. 2010). Recently, novel functions of p53 in

stem cells have been found, these including suppression of pluripotency and inhibition of stem cell self-renewal (Zhao and Xu 2010).

MDM2 (murine double minute-2) is an oncogene located on chromosome 12q14.3-q15. The protein product of this gene is E3 ubiquitine ligase, it negatively regulates p53 and suppresses cell cycle arrest or apoptosis and also promotes cell survival and growth (Thomasova et al. 2012). MDM2 protein suppresses p53´s transcriptional activity and targets p53 for proteasomal degradation (Wade et al. 2010). Amplification and overexpression of *MDM2* excludes *TP53* from having an effect on the cell cycle. Amplification of this gene is present in 10% of glioblastoma without a *TP53* mutation (Hede et al. 2011). Overexpression of MDM2 plays an important role in glioma tumorigenesis, but does not seem to be involved in glioma progression (Wang et al. 2011). MDM2 is strongly expressed in many malignancies with wild type p53 as an alternate mechanism to disrupt the p53

pathway in early cancer development (Eischen and Lozano 2009; Hede et al. 2011).

CDKN1A gene is located on chromosome 6p. The product of this gene is protein p21 whose transcription is regulated by the level of protein p53. Protein p21 is a member of the kinase inhibitor protein (KIP) family. It has a negative effect on the function of cyclin E/CDK2 (cyclin dependent kinase) and cyclin A/CDK2 complexes and activates cyclin D/CDK complexes. This protein has a huge effect on controlling cell proliferation by regulating binding to different CDK complexes (He et al. 2006). All exogenous effects that cause *TP53* mediated cell cycle arrest or apoptosis induce transcription of protein p21. Amplification of this gene is frequent in all glial tumors (Walker et al. 2011).

CDKN1B gene is localized on chromosome 12p13.1-p12. The product of this gene is protein p27. This protein is also a member of the KIP family and has opposite effects on the function of different CDK complexes. It inhibits the function of cyclin E/CDK2 and cyclin A/CDK2 complexes and it seems to activate cyclin D/CDK complexes (He et al. 2006). Frequent binding of p27 to cyclin D/CDK complexes was found in proliferating cells. On the other hand, in G_1-arrested cells p27 was found in complexes with cyclin E/CDK2. The crucial role for cell cycle progression seems to depend on the competition for binding of p27 between cyclin D/CDKs and cyclin E/CDK2 complexes. High expression of p27 is present in diffuse astrocytoma (grade II), low expression is seen in malignant gliomas and some carcinomas, and very low expression in anaplastic astrocytomas and glioblastoma (Yue et al. 2012).

CDKN2A and CDKN2B genes are located on chromosome 9p21. Their products are proteins p16 and p15 acting as inhibitors of CDK (mainly CDK4 and CDK6), (Liu et al. 2010). Proteins p16 and p15 inhibit the phosphorylation of RB1 protein by binding to cyclin D and thus preventing its interaction with CDK4 and CDK6. Mutations of these genes are connected with a higher risk of glioma development (Shete et al 2009; Wrensch et al 2009). Homozygous deletion in *CDKN2A,* results in suppression of RB1 protein function via elevated CDK4/6 activity, and is detectable in almost 50% of gliomas and also the loss of expression has been linked to poor prognosis (Simon et al. 2006, 2010; Goldhoff et al. 2012). Polymorphisms in *CDKN2A/CDKN2B* genes are not connected with tumor grade and prognosis (Simon et al. 2010). Regulation of p16/ p14^{ARF} is important for sensitivity to ionizing radiation, the only environmental factor strongly connected with gliomagenesis (Liu et al. 2010).

Gene p14^{ARF} is also located on locus 9p21. Its product protein p14^{ARF} inhibits degradation of p53 mediated by *MDM2*. Upregulation of *p14^{ARF}* increases p53 level which in turn increases the sensitivity of p53 pathway and induces cell cycle arrest and apoptosis (Liu et al. 2010). Germline mutations of p14^{ARF} have been reported to cause

melanoma-astrocytoma syndrome (Randerson-Moor et al. 2001).

Both *CDK4 gene* (localized on chromosome 12q14) and *CDK6 gene* (7q21-22) products CDK4, CDK6 proteins have a catalytic kinase activity. They produce complexes with cyclin D and are inhibited by proteins p15 and p16. *CDK6*, an oncogene, is required for proliferation and viability of tumor tissue (Wiedemeyer et al. 2010). Overexpression of all CDK proteins can inhibit function of p15 and p16 (inhibitors of CDK), (Malumbres and Barbacid 2009). Amplification of *CDK4* and *CDK6* is present in 15% of high-grade gliomas (Wiedemeyer et al. 2010).

The retinoblastoma gene (RB1) is located on chromosome 13q14.2. Its product is the RB1 protein which is the final point of kinase activities of CDK4/CDK6-cyclin D complexes. RB protein controls entry into the cell cycle, it acts as gatekeeper to S-phase entry. This protein is normally not phosphorylated and it is associated with the transcription factor E2F. RB with E2F acts as a silencing complex and restricts access to transcription factors. Phosphorylation of RB1 protein leads to the release of transcription factor E2F. Such altered conformation allows access to cdk2 during S-phase which produces additional phosphorylation and further inhibiting E2F binding (Goldhoff et al. 2012). This disruption of RB/E2F allows transcription of crucial genes required for cell cycle entry. Aberrations of *RB* pathway are common in glioblastoma and play a critical role in gliomagenesis and tumor progression for lower-grade astrocytomas (Chow et al. 2011). These alterations are present in 80% of all primary glioblastoma (The cancer genome atlas 2008). Alteration of this gene is present in one-third of high-grade astrocytomas. Mutated *RB1* has the same effect as the amplification of *CDK4/CDK6* or mutation of *CDKN2A/CDKN2B*, nevertheless these genetic alterations are never present together. This information demonstrates that oncogenesis of grade III and grade IV astrocytomas proceeds by only one of these alternative genetic pathways. Alterations in *RB1* expression have been associated with increased tumor proliferation and decreased survival (Kim et al. 2011). *RB1* may have a more direct correlation with prognosis in lower-grade (II, III) astrocytomas than in glioblastoma (Kim et al. 2011). The RB pathway is nearly universally inactivated in human cancers, including glioblastoma (Wiedemeyer et al. 2010).

Deleted in colorectal cancer gene (DCC) is located on chromosome 18q21.3 and its product is the DCC protein. This transmembranous protein is expressed in high quantities in the nervous system. Products of this gene create part of the receptor for netrin 1. Netrins play important roles in direct cell and axon migration during neural development (Rajasekharan and Kennedy 2009). These proteins are also expressed in adult tissues, although their function is not yet

known. DCC induce apoptosis and cell cycle arrest in G_2 point and it is also required for chemoattraction to netrin-1 slowing the rate of spontaneous cell migration (Jarjour et al. 2011). An anti-oncogenic function had been suggested for DCC, although netrin signaling disruption contributing to tumorigenesis is still poorly understood (Jarjour et al. 2011). Immunohistochemical examinations demonstrate that the expression of DCC decreases in many malignancies, including the most high-grade gliomas and also during progression from low-grade astrocytomas to glioblastoma. This shows that *DCC* is connected with the formation of secondary glioblastoma, but not with the formation of primary glioblastoma (Kozler et al. 2007; Jarjour et al. 2011).

Phosphatase and tensin homology PTEN (also called MMAC1, TEP-1) is a tumor suppressor gene on chromosome 10q23.3. The product of this gene is a lipid phosphatase that counteracts the effect of PI3K signaling, thereby negatively controlling the activation of this pathway (Figure 2). This gene is mutationally or transcriptionally inactivated in many tumor types, including astrocytomas (Bleeker et al. 2009). Germinal *PTEN* mutations were seen in some autosomal hereditary diseases, such as Cowden disease, Bannayan-Zonana syndrome, etc. Monosomy of chromosome 10 is frequently seen in glioblastoma, but rarely in low-grade astrocytoma. Loss of function of this tumor supressor gene is present in both, primary and secondary glioblastoma (Hede et al. 2011). *PTEN* is mutated or lost in 60–70% of high-grade glioma (Dey et al. 2008) and is associated with poor prognosis (Walker et al. 2011). After the exposure to ionizing radiation, PTEN acts as a critical determinant of cell fate between senescence and apoptosis (Lee et al. 2011).

Paternally expressed gene 3 (PEG3) is located on 19.chromosome. *PEG3* is an imprinted gene that is expressed mainly during embryogenesis and in adult ovary, testis, muscle and brain (Jiang et al. 2010). The low gene expression was confirmed in glioblastoma and its high expression was observed in oligodendrogliomas. Results show that abnormal regulation of *PEG3* induces formation of some gliomas and also plays an important role in tumorigenesis (Otsuka et al. 2009).

Growth factors also play an important role in oncogenesis as mutations of these factors are frequently present in gliomas.

Epidermal growth factor (EGF) gene is located on chromosome 4q25. EGF binds to EGFR inducing a dimerisation of one or several members of the EGFR family (ErbB 1-4), activating several thyrosine kinases and other downstream signal molecules promoting transcription in the cell nucleus (Sjöström et al. 2010). In a small study including only 42 patients, poor survival of glioblastoma patients with functional polymorphism 61 A/G located in the EGF promoter was observed (Bhowmick et al. 2004). But 2 other studies

with a bigger group of patients failed to replicate the initial observation (Costa et al. 2007; Vauleon et al. 2007).

Epidermal growth factor receptor (EGFR) gene is located on chromosome 7p12. EGFR is a transmembranous receptor responsible for communication with its extracellular ligands (EGF and TGF-α (transforming growth factor α)) and for transmission of their signalisation within the cell. *EGFR* is the most frequently amplified gene in astrocytomas (approximately one-third of glioblastoma cases, less seen in anaplastic astrocytomas). *EGFR* is closely connected with tumor proliferation, metastasis, apoptosis, angiogenesis, and sensitivity to therapy and drug resistance (De Luca et al. 2008). Mutations in the *EGFR* gene are associated with early relapses and poor prognosis (Hu et al. 2013). Expression of *EGFR* is higher in high-grade and poorly-differentiated gliomas and together with amplification of *EGFR* is correlated with tumor progression (Hoelzinger et al. 2005; De Luca et al. 2008; Hofer and Lassman 2010; Hu et al. 2013). More than 50% of glioblastomas have a mutation of *EGFR* which can exist in 3 variations: *EGFRvIII*, *δEGFR* and *de2-7EGFR* (deletion, loss of exons 2-7 of mRNA strand). The δEGFR promotes tumorigenesis of glioblastoma cells in vivo by increasing cellular proliferation (Narita et al. 2002), decreasing cellular apoptosis (Puputti et al. 2006) and promoting tumor cell invasion (Lal et al. 2002). Amplification and specific mutation of *EGFR* (*de2-7EGFR*) is typical for primary glioblastoma. Primary glioblastoma with this mutation simultaneously have monosomy of chromosome 10. Amplification in glioblastoma is present also without homozygote deletion or mutation of *PTEN* (simultaneously present in 20% of primary glioblastoma), but in most cases it is associated with *CDKN2A* deletion (Kozler et al. 2007). It has been suggested that alteration of *EGFR* alone is not enough to cause tumorigenesis but another alteration in protein RB1 pathway is necessary to cause tumor formation (Figure 2).

Platelet-derived growth factor (PDGF) exists as five types of dimers consisting of 4 types of polypeptides, each encoded by a different gene – A, B, C and D. PDGFA (gene *PDGFA*, localized on 7p22), PDGFB (gene *PDGFB*, localized on 22q13.1), PDGFC (gene *PDGFC*, localized on 4q32), and PDGFD (gene *PDGFD*, localized on 8q11). There are only 2 receptors: PDGFR-α (gene *PDGFRA* on chromosome 4q11-q13) and PDGFR-β (gene *PDGFRB* on chromosome 5q31-q32). Overexpression of PDGF and PDGFR are frequently present in astrocytoma (mainly glioblastoma) and medulloblastoma, but amplification is rare (Furnari et al. 2007). Deletion of 17p is often connected with PDGFR-α overexpression (Kozler et al. 2007). PDGFR pathway aberrations are mainly associated with secondary glioblastoma (Puputti et al. 2006) (Figure 2).

Insulin-like growth factor (IGF) plays a role in the regulation of tumor cell biology. The IGF system is comprised
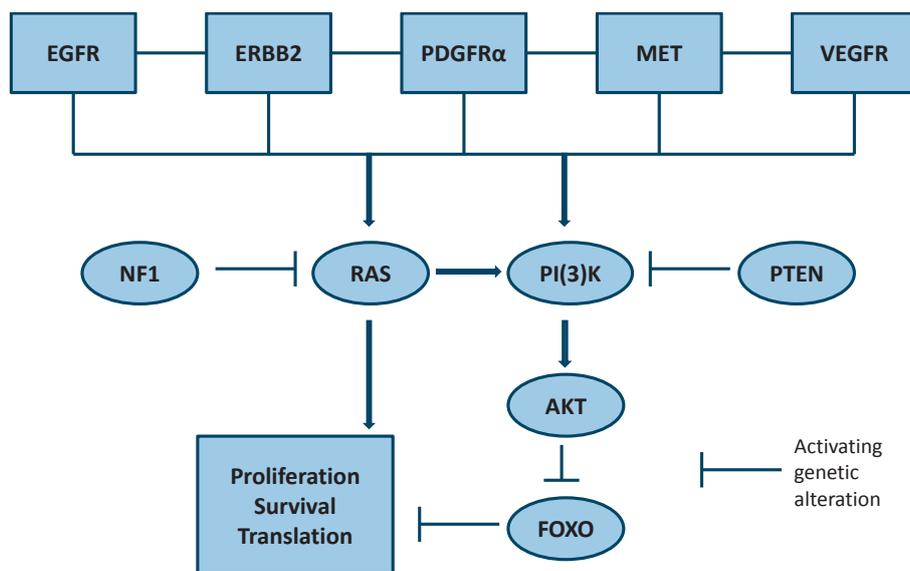
Figure 2. Frequent genetic alteration in RTK/RAS/PI(3)K pathway. Most frequently altered genes are PTEN, NF1 and EGFR genes. AKT, protein kinase B; EGFR, epidermal growth factor receptor; ERBB2, receptor tyrosine-protein kinase erbB-2; FOXO, forkhead box proteins; MET, hepatocyte growth factor receptor; NF1, neurofibromatosis type 1; PDGFRα, platelet-derived growth factor receptor α; PI3K, phosphoinositol 3 kinase; PTEN, phosphatase and tensin homology; RAS, protein superfamily of small GTPases; RTK, receptor tyrosine kinase;VEGFR, vascular endothelial growth factor receptor.

of two ligands: IGF1 (gene located on 12q23.2) and IGF2 (somatomedin A, located on 11p15.5) and its receptors: IGF1R (gene located on 15q26.3) and IGF2R (6q26), six binding proteins (IGFBP 1-6) and various IGFBP-related peptides. IGF1 is a major physiological mediator of growth hormone and has a strong influence on cell proliferation and differentiation. It also inhibits apoptosis by blocking the initiation of the apoptotic pathway. Its receptor IGF1R is involved in malignant transformation processes. IGFBPs modulate interactions between IGF and IGFR. IGFBP3 (located 7p13-p12) which acts as an apoptotic agent, inhibits IGF1 activity and has growth promoting effects (Lön et al. 2008). *IGF1*, *IGF2* and *IGF1R* genes have been reported to be amplified in glioma as well as in other cancers (Furstenberger and Senn 2002; Renehan et al. 2004; Russo et al. 2005). Polymorphism of *IGF1R* indicates a possible association with glioma risk (low-grade). No connection between *IGF* polymorphisms and glioblastoma risk has been found (Lön et al. 2008).

Regarding other growth factors and their receptors, astrocytoma genesis is also associated with the overexpression of FGF, (*aFGF* – chromosome 5q31.3-q33.2, *bFGF* – chromosome 4q27-q25) and vascular endothelial growth factor – VEGF (receptor 1 – chromosome 13q12, receptor 4 – chromosome 5q33-qter). Level of expression of *VEGF* is directly correlated with the occurrence of bleeding into the tumor. Although *EGFR* and *VEGFR* are heavily activated in glioblastoma, agents targeting these showed disappointing results in clinical trials (Brown et al. 2008; Norden et al. 2008).

From other types of genes connected with gliomagenesis, the most frequently observed alterations are: *glutathione*

S-transferases genes, *isocitrate dehydrogenases genes* and epigenetic changes of *methylguanin O-methyltransferase gene*.

Glutathion S-transferases (GST) genes: GSTP1 (location 11q13), *GSTM1* (1p13.3), *GSTT1* (22q11.23), *GSTO1* (10q25.1). GSTs are phase II biotransformation enzymes that function on the detoxification of a wide range of exogenous agents including carcinogens. They are responsible for glutathion conjugation of alkylators and scavenging of free radicals generated by radiation (Kilburn et al. 2010). *GST*s provide enzymatic and non-enzymatic functions and are involved in many important cellular processes, such as: stress response, cell proliferation, apoptosis, oncogenesis, tumor progression and drug resistance (Lo and Ali-Osman 2007). Genetic variations in these genes are important in determining the response to carcinogens. *GST* polymorphisms may result in altered or absent enzyme activity and have been associated with survival rate in cancer patients. Results of recent studies suggested a relationship between brain tumor incidence with *GSTM1* null genotype but not with *GSTT1* or *GSTP1* gene variants (Pinarbasi et al. 2005). Other studies observed no association between *GST* and the related enzyme polymorphisms and adult brain tumor risk (Schwartzbaum et al. 2007). Another study has shown a longer survival in patients with *GSTP1* and *GSTM1* polymorphisms in patients with grade III gliomas. These patients also had an increased risk of adverse events resulting from chemotherapy that primarily comprised nitrosourea alkylating agents (Okcu et al. 2004). *GST*s also determine drug resistance and response of cancer patients to therapy (Lo and Ali-Osman 2007).

Isocitrate dehydrogenase genes IDH1 (located 2q33.3) and *IDH2* (located 15q26.1). IDHs (IDH1, IDH2 and IDH3) are

enzymes involved in the citric acid cycle that catalyze the oxidative decarboxylation of isocitrate to a α-ketoglutarate while reducing $NADP^+$ to NADPH (NAD^+ to NADH in the case of IDH3). A critical structure of IDH1 in the enzymatic interaction with the substrate isocitrate is the arginine 132 (R132), an identical role played by R172 in IDH2. The mutations of these genes are missense substitutions which lead to reduction of enzymatic activity of the encoded protein (Yan et al 2009; Pusch et al. 2011). Mutations of R132 result in a greater than 80% enzyme activity reduction compared with the wild type (Zhao et al. 2009). *IDH* genes were found to have mutations mainly in tumors that have evolved from low-grade gliomas (secondary glioblastoma), (Ichimura et al. 2009; Jha et al. 2011; Toedt et al. 2011), on the other hand, they are rare in primary glioblastoma (7%) and pediatric glioblastoma (11%), (Kim and Liau 2012). The *IDH* mutations are found across different molecular and histologic brain tumors subtypes (diffuse astrocytoma, oligodendroglioma, secondary glioblastoma, etc.) suggesting that there are early genetic alterations in tumorigenesis and they occur early in the development of a glioma from the stem cell that can give rise to both astrocytes and oligodendrocytes (Yan et al. 2009). Within the group of *IDH1* or *IDH2* mutated anaplastic astrocytomas and glioblastomas, 80% of this tumors also had mutations of *TP53*, but only 3% had alterations in *PTEN, EGFR, CDKN2A* or *CDKN2B*. On the contrary, anaplastic astrocytomas and glioblastomas with wild type *IDH* genes had a few *TP53* mutations (18%) and more frequent alterations of *PTEN, EGFR, CDKN2A* or *CDKN2B* (74%), (Parsons et al. 2008; Ichimura et al. 2009; Yan et al. 2009). This fact indicates that *IDH* mutations occur more likely in secondary glioblastomas. One study identified the mutations that affected amino acid 132 of *IDH1* in more than 70% of WHO grade II, III astrocytomas, oligodendrogliomas and secondary glioblastomas (Yan et al. 2009). Tumors without *IDH1* mutations often had mutations affecting the analogous amino acid (R172) of the *IDH2* gene. Tumors with such mutations have distinctive genetic and clinical characteristics and these particular patients had a better outcome than those with wild-type *IDH* genes. This makes mutation of *IDH1* a novel prognostic factor in gliomas (Balss et al. 2008; Parson et al. 2008; Weller et al. 2009; Yan et al. 2009). On the other hand, a study conducted by Parson et al. found *IDH1* mutations in approximately 12% of glioblastoma (Parson et al. 2008). Explanation for this finding could be that the authors did not divide primary from secondary glioblastoma in there study. Within the group of primary glioblastomas, *IDH1* mutations are rare and create a prognostically favorable subgroup (Weller et al. 2009).

The MGMT gene codes for a protein with alkyltransferase activity – O^6-methylguanine-DNA methyltransferase (MGMT), a DNA-repair enzyme, which causes tumor resistance to alkylating and methylating agents (e. g. temozolo-

mide). Activity of this enzyme is regulated by a promoter. Methylation of this promoter area of *MGMT* results in its inactivation. Weller et al. found *MGMT* promoter methylation in 44% of glioblastoma patients. Prolongation of progression-free survival was observed in patients treated with temozolomide, but not in patients receiving radiotherapy alone as their first-line treatment (Weller et al. 2009). Another author states that methylation of *MGMT* promoter in tumor tissue is associated with longer survival regardless of the therapy method used (Hegi et al. 2005). *MGMT* promoter hypermethylation is associated with prolonged progression-free survival and overall survival in patients with glioblastoma treated with alkylating agents (e.g. temozolomide), (Hegi et al. 2005; Herrlinger et al. 2006; Glas et al. 2009). Methylation status of the *MGMT* promoter is clinically the most relevant molecular parameter (Weller et al. 2009) and has been used as a biomarker to predict the sensitivity of gliomas to DNA alkylating chemotherapeutics (Von Deimling et al. 2011). Expression of MGMT is not associated with tumor grade (Hu et al. 2013).

According to WHO classification of brain tumors there are four main types of gliomas: astrocytomas, oligodendrogliomas, mixed oligoastrocytomas and ependymomas (Louis et al. 2007).

Astrocytoma

According to WHO classification (Luis et al. 2007) in order of increasing anaplasia, types of astrocytomas usually include: pilocytic astrocytoma (grade I), diffuse astrocytoma (grade II), anaplastic astrocytoma (grade III) and glioblastoma (grade IV). Low grade astrocytomas can progress to higher malignancy grade, leading to the formation of secondary glioblastoma, as opposed to the frequent primary glioblastomas (Ricard et al. 2012). High-grade astrocytomas are grade III and grade IV astrocytomas.

Diffuse infiltrative astrocytomas are tumors of astrocyte origin. Except pilocytic astrocytoma which has different behavior and is demarcated, other astrocytic tumors grow unbounded (Ricard et al. 2012). Astrocytomas spread along tracts in the white matter, then the tumor cells infiltrate cerebrospinal fluid and vessels between duplications of the meningeal layers. Healthy cells are unable to move in the white matter. Astrocytoma cells interact with the elements of structural proteins of the extracellular matrix to further promote their invasiveness. This way of spreading of tumor cells is induced by the activation of receptors and growth factors – integrins and proteins – DCC (deleted in colorectal cancer), hyaluron receptors CD44, RHAMM (receptor for hyaluronan mediated motility), BEHAB (brain enriched hyaluronan binding), ontogenetic protein SPARC (secreted protein, acidic and rich in cysteine), receptors of PDGF, TGF-α, EGFR and bFGF (Kim C. et al. 2011; Sciaccaluga

et al. 2013; Viapiano et al. 2008). Interaction of the extra-cellular matrix proteins with activated growth factors and their receptors happen as a result of genetic alteration (mutation, deletion, overexpression or amplification). Border of the tumor plays the crucial role in invasion. There is also a localized migration by an activating protein – tenascin (Mustafa et al. 2012).

Formation and progression of tumor is always accompanied by angiogenesis. Tumor cells in an increased proliferative state need a greater oxygen supply in order to grow (Gil-Gil et al. 2013). Angiogenic switch is triggered by hypoxia and starts with the up-regulation of vascular endothelial growth factor – VEGF (Mustafa et al. 2012). Microvascular proliferation and increase of vascularity in malignant gliomas is caused not only by increased angiogenesis, but also by remodelation of vessel wall and by activation of endothelial precursor cells with tha capacity to form de novo blood vessels – vasculogenesis (Li Calzi et al. 2010). Angiogenesis is mediated by the release of proangiogenic factors (e.g. VEGF, bFGF, angiopoietins 1–4), by endothelial, stromal and tumor cells, by the binding of these factors to their corresponding thyrosine kinase receptors such as: VEGF receptor (VEGFR-1, VEGFR-2 and VEGF-3), Tie-1, Tie-2, PDGFR-β, c-met and integrins (Tchaicha et al. 2011; Mustafa et al. 2012; Fagiani and Christofori 2013). These receptors are up-regulated on the surface of the tumor vessels and the tumor itself generates ligands for these receptors (Kozler et al. 2007). VEGF plays the most important role for angiogenesis in the tumor, providing increased vascular permeability and lymphangiogenesis (Gil-Gil et al. 2013). It also increases permeability of the blood-brain barrier and participates in the formation of brain edema. VEGF is also produced by tumor cells and the amount of VEGF produced depends on the grade of the tumor – a higher VEGF production was observed in association with higher grade tumors (Saharinen et al. 2011). VEGF in conjunction with angiopoietin 2, promotes neovascularisation. Tie-2 receptor triggers capillary remodelling. In case of tumor progression there is increased expression of this receptor by endothelial cells (Fagiani and Christofori 2013). Angiopoietin 4 promotes tumor angiogenesis and glioblastoma progression (Brunckhorst et al. 2010). Another receptor involved in capillary remodelling is PDGFR-β (Tchaicha et al. 2011).

Apoptosis as programmed cell death is important for the regulation of cell population and the balance between proliferation and cell growth on one side and cell death on the other side (Lockshin and Zakeri 2007). It plays a key role in central nervous system development, immune regulation, brain tumor development and also degenerative diseases (Mellai and Schiffer 2007). Resistance to apoptosis contributes to carcinogenesis and tumor progression. Since most of the current anticancer therapy regimes primarily act by activation of cell death pathways, including apoptosis, in

cancer cells this adaptive stress response promotes the development of acquired resistance (Fulda 2010). Temozolomide, frequently used in glioma chemotherapy, induces apoptosis and autophagy in glioma cells. Necrosis is only marginally induced (Knizhnik et al. 2013). The same stimulus can elicit both, necrosis and apoptosis, depending on the intensity of the initial insult and on preservation or loss of energy production in the cell (Mellai and Schiffer 2007). The apoptosis pathway plays a role on proteins, such as: p53, p21, Bcl-2, Bax, caspases etc. Other than expected, apoptosis was demonstrated in gliomas, with an increasing frequency from low grade to glioblastoma and was related to shorter survival. However, apoptotis index did not predict recurrence in astrocytomas (Mellai and Schiffer 2007). Inability to undergo apoptosis as a consequence of p53 inactivation might play a role in brain tumor development. Tumor cells escaping apoptosis have damaged DNA leading to an accumulation of mutations and, therefore, tumor progression (Krakstad and Chekenya 2010).

Low-grade astrocytomas often show loss of heterozygozity (LOH) of 22q and gain of chromosome 7 and amplification of 8q (Reifenberger and Collins 2004). Cca 40% of high-grade astrocytomas show deletion on chromosome 19q. In 20–30% of gliomas there is a LOH on chromosome 22q. It is suggested that some unknown tumor suppressor, which plays a role in the early stages of astrocytoma genesis, is localized on this chromosome (Kozler et al. 2007). Progression from low-grade to anaplastic astrocytoma and formation of secondary glioblastoma is connected with deletions on chromosomes 6, 9p, 11p, 17p, 13q, rarely with an amplification of 12q (Kozler et al. 2007; Walker et al. 2011). On the other hand, LOH on 10p, 10q is common in primary glioblastoma (Walker et al. 2011) (Figure 3).

Oligodendroglioma

Oligodendrogliomas originate from differentiated oligodendrocytes (oligodendroglial cells) or in immature glial precursor cells. Besides glioblastoma and astrocytomas, oligodendrogliomas represent the third most frequently encountered type of glial tumors and constitute 2.5% of all primary brain tumors (Ohgaki 2009). According to the WHO grading there are two forms of oligodendrogliomas – oligodendroglioma (grade II) and anaplastic oligodendroglioma (grade III), (Engelhard et al. 2003; Louis et al. 2007). Unlike other brain tumors, oligodendrogliomas very rarely metastasize to other locations, such as lung, liver, bone and cervical lymph nodes (Volavsek et al. 2009).

Genetic alterations of oligodendrogliomas are different from astrocytomas alterations. No specific immunohistochemical markers for these tumors exist. The most common genetic alteration in this type of tumor is a deletion at chromosomal loci 1p and 19q. LOH of 19q is found in 50–80%
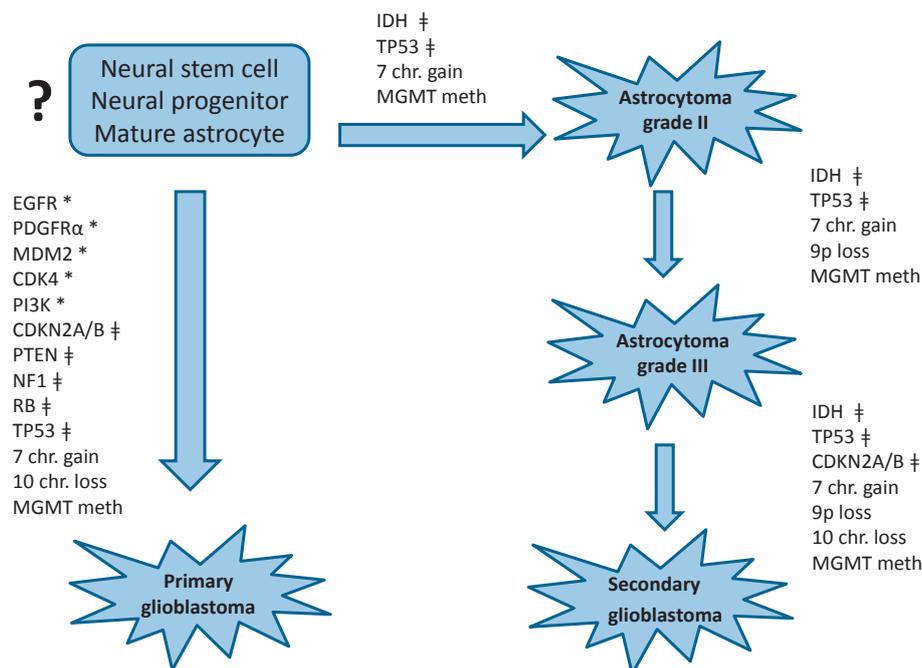
Figure 3. Gene and genomic regions involved in the biology of astrocytomas and primary and secondary glioblastoma. CDK4, cyclin dependent kinase 4; CDKN2A/B, cyclin dependent kinase inhibitor 2A/B; EGFR, epidermal growth factor receptor; IDH, isocitrate dehydrogenase; MDM2, mdm2 TP53 binding protein homologue; MGMT, O6-methylguanin DNA methyltransferase; meth, methylation; NF1, neurofibromin 1; PDGFR α, platelet derived growth factor receptor α; PI3K, pphosphoinositide 3 kinase; PTEN, phosphatase and tensin homologue; RB, retinoblastoma; TP53, tumor suppresor protein 53; * gain of function through amplification or mutation; ‡ homozygous deletion or mutation.

of oligodendrogliomas, LOH of 1p in cca 70% (Van den Bent 2004). Tumors with LOH on 1p also have LOH on 19q, what exert to their synergetic effect. A combined loss of 1p and 19q identifies a group of good tumor prognosis (Giannini et al. 2008; Velnar et al. 2009). Moreover, other studies showed more favourable survival in patients with tumors with combined loss of 1p and 19q also when treated with radiotherapy only (Van den Bent et al. 2006; Cairncross et al. 2006; Kouwenhoven et al. 2009). Pediatric oligodendrogioma only rarely exhibit chromosomal abnormalities (Stupp and Hegi 2007).

Only a small amount of tumors have mutations or deletions in the *CDKN2C* gene on 1p32. The *TP53* mutation is present only in 10–15% of these tumors. This mutation occurs in tumors without 1p and 19q loss. These tumors are histologically anaplastic or mixed oligoastrocytomas and they express poor chemosensitivity (Ducray et al. 2008). Patients with TP53 mutations (and intact 1p 19q chromosomes) have only 33% efficacy rate with chemotherapy treatment. On the other hand, 100% response rate was observed in patients with 1p 19q codeletion and intact TP53 (Mueller et al. 2002).

Tumor cells are under influence of growth factors and the expression of their receptors. The most important receptors are EGFR and PDGF/PDGFR (Riemenschneider et al. 2004). VEGF and its receptors play an important role in angiogenesis. Overexpression of EGFR was observed in 50% of oligodendrogliomas, overexpression of other growth factors is less frequent (Stupp and Hegi 2007).

Anaplastic oligodendrogliomas may evolve from a low-grade oligodendroglioma, becoming more anaplastic over time, or present de novo. They have the same genetic alterations as grade II (deletion on 1p and 19q) and also deletions on chromosomes 9 and 10, which accompany malignant progression also in other astrocytic tumors (Stupp and Hegi 2007). In 25% of cases of anaplastic oligodendrogliomas, a homozygous deletion on *CDKN2A* has been observed. Mutation of PTEN (frequently present in astrocytomas) is very rare. Multiple deletions are seen also on other chromosomes, for example 4, 6, 11, 15 and 18. Anaplastic oligodendrogliomas with deletion on chromosomes 10 and 9 and with amplification on chromosome 7 usually do not have typical deletions on 1p and 19q (Stupp and Hegi 2007). An average amount of chromosomes with lesions are higher in grade III then in grade II and this confirms the hypothesis that malignant transformation is connected with growing amount of genetic alterations (Mueller et al. 2002; Kozler et al. 2007).

Oligoastrocytomas, although classified separately, are heterogenous tumors with molecular features similar to oligodendrogliomas or astrocytomas. Some oligoastrocytomas show LOH on 1p and LOH on 19q - thus genetically resembling oligodendrogliomas, whereas 30% show mutations in the *TP53* gene or LOH on 17p suggesting a relation to astrocytomas. Significantly, LOH on 1p and LOH on 19q are inversely associated with *TP53* mutation (Mueller et al. 2002). Amplification of *EGFR* is more frequent in oligoastrocytomas than in oligodendrogliomas. Tumors with this amplification have overal survival similar to patients with glioblastoma (Kouwenhoven et al. 2009) (Figure 4).
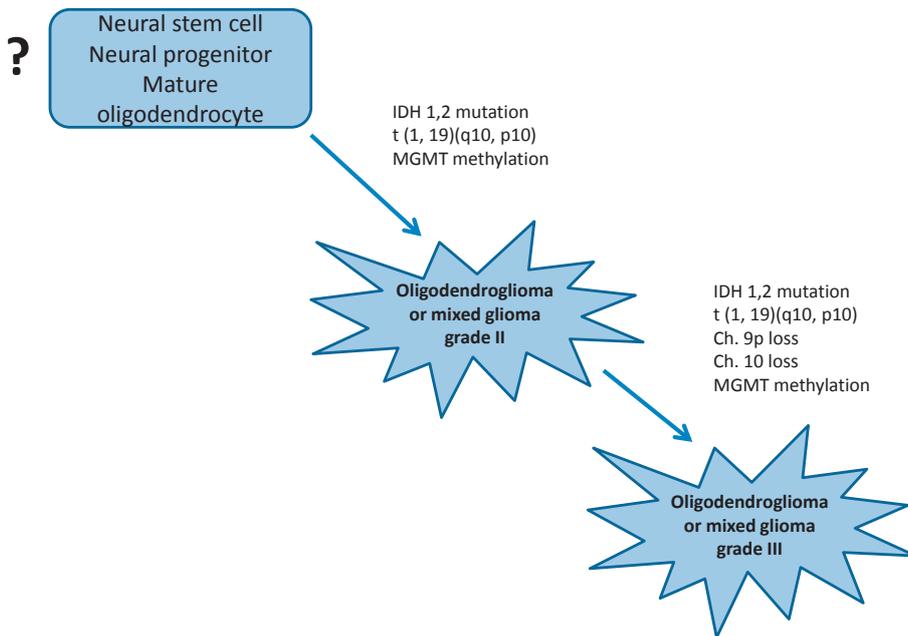
Figure 4. Gene and genomic regions involved in the biology of oligodendrogliomas and mixed gliomas (oligoastrocytomas). IDH, isocitrate dehydrogenase; MGMT, O6-methylguanin DNA methyltransferase.

Ependymoma

Ependymoma is the third most common pediatric brain tumor (Kilday et al. 2009). Ependymomas grow from ependymal cells which cover the internal layer of cerebrospinal fluid pathways (Yao et al. 2011). Most of the ependymomas in children occur intracranially, whereas adult cases predominantly occur within the spinal cord (Kilday et al. 2009). There are four known forms of ependymoma: subependymoma (grade I), myxopapillary ependymoma, ependymoma (grade II) and anaplastic ependymoma (grade III) (Kozler et al. 2007; Louis et al. 2007).

Immunohistochemical diagnosis relies on immunoreactivity to glial fibrillary acidic protein (GFAP), protein S-100 and to vimentin.

The only known hereditary form of ependymoma is part of neurofibromatosis type 2 (NF2). The *NF2* gene is located on 22q, which is often lost in ependymomas in spinal localization. However, most of these tumors in intracranial localization do not have alterations of this chromosome (Buccoliero et al. 2010). There have also been reported cases of ependymoma in patients with Li-Fraumeni syndrome, Turcot syndrome (Mullins et al. 1998) and multiple endocrine neoplasia type 1 syndrome (Al-Salameh et al. 2010). Furthermore, there are a few families with increased ependymoma incidence without any currently known familial cancer syndromes (Dimopoulos et al. 2006).

The most frequently observed chromosomal anomalies in pediatric ependymomas include loss of chromosomes 1p, 2, 3, 6/6q, 9p, 13q, 17, and 22, as well as gains of 1q, 5, 7, 8, 9,

11, 18, and 20 (Kilday et al. 2009). In 50% of ependymoma cases a deletion is present on chromosome 17 (Kozler et al. 2007). In adult ependymomas, chromosomes 6, 10, 13q, 14q, 16, and 22/22q are frequently lost whereas chromosomes 2, 5, 7, 9, 12, 18, and X are gained, with gains of 7 and 9 and loss of 22q being the most frequently observed, though with each occurring in only 30% of cases or less (Kilday et al. 2009).

The most frequently observed aberration in pediatric intracranial ependymomas is the gain of chromosome 1q (over 20%). According to the literature, this genetic aberration is preferentially associated with tumors in the posterior fossa location and with anaplastic histological features. It is also a significant predictor of tumor aggressiveness and poor patient outcome (Kilday et al. 2009; Yao et al. 2011).

Homozygous deletion at *CDKN2A* locus is characteristic for anaplastic supratentorial tumors (Korshunov et al. 2010). This deletion is (together with young age at diagnosis and gain of 1q) one of the most reliable indicators of unfavorable outcome. In contrast, gains of chromosomes 9, 15q, and 18 and loss of chromosome 6 are features indicating excellent chance of survival. Deletion of *CDKN2A* occurrs in >90% of supratentorial ependymomas but is rare in tumors from other parts of the CNS (Korshunov et al. 2010; Yao et al. 2011).

Meningioma

Meningiomas are thought to be formed from arachnoidal cap cells in the meningeal coverings (Louis et al. 2007). They are mostly benign, slowly growing tumors which represent

up to 34% of primary brain tumors (CBTRUS 2008). According to WHO grading, there are 3 types of meningiomas: meningioma (grade I), atypical meningioma (grade II) and anaplastic meningioma (grade III), (Louis et al. 2007). Another classification is made according to their localization and histopathological features. Despite mostly being of histologically benign character they often invade brain tissue which explains a high amount of tumor recurrence. Risk factor for meningioma recurrence include histopathological malignancy grade, subtotal resection, young age, specific subtypes, brain infiltration and high proliferative rate (Torp et al. 2005; Backer-Grøndahl et al. 2012). Tumors with higher Ki-67 (proliferation index) and proliferating cell nuclear antigen (PCNA) are more likely to invade brain tissue independent of grade of the tumor. Recurrence rate after 5-years is 5% in grade I, 40% in grade II and 80% in grade III meningioma (Riemenschneider et al. 2006). Anaplastic (malignant) meningioma rarely metastases extracranialy (to lungs, liver and bones), it's just in 0.17% of cases (Choy et al. 2011).

Immunoreactivity for epithelial membranous antigen (EMA) – lower in atypical and anaplastic forms, for vimentin, for carcinoembryonic antigene (CEA) and for cytokeratin (both in secretory meningiomas) was observed in most of the meningiomas (Perry et al. 2004).

The most common genetic abnormality found in these tumors is monosomy 22. About 50% of all meningiomas have loss of allele on 22q, a region encoding the *NF2* gene. Gene *NF2* plays an important role in pathogenesis of autosomal dominant neurofibromatosis type 2, in which meningiomas, schwannomas and other nervous system tumors are often present (Choy et al. 2011). Nearly all NF2-associated tumors and 54–78% of sporadic meningiomas have deletions in this region (Ragel and Jensen 2005).

DAL-1 gene (differentially expressed in adenocarcinoma of the lung 1) is located at 18p11.3 and encodes protein 4.1B – a regulator of proliferation and apoptosis (Choy et al. 2011). This protein has been implicated as a potential tumor suppressor in meningiomas (Gerber et al. 2006). LOH of 4.1B/DAL-1 was reported in 60% of sporadic meningiomas (Gutmann et al. 2001), however, other studies showed a lower frequency (Nunes et al. 2005).

Telomerase is a reverse transcriptase that rebuilds the lost telomere repeat sequences and thus elongates chromosomes. Its activity is regulated during the development and growth of the human body (is found in fetal tissues, adult germ cells) and has a very low, almost undetectable activity in adult somatic cells (Choy et al. 2011). This enzyme is often reactivated in malignancies to sustain chromosomal integrity during aggressive growth. Its activity in grade I meningiomas is low (3–21%). However, 58–92% of atypical and 100% of anaplastic meningiomas demonstrate telomerase activity (Laurendeau et al. 2010). Telomerase activity is associated with higher recurrence rate and greater malignancy in meningiomas, and it may serve as a potential prognostic marker (Laurendeau et al. 2010; Choy et al. 2011).

Atypical and anaplastic tumors generally display more complex karyotypes associated with aggressive behavior (Yew et al. 2013). Atypical forms of meningioma have often deletions on chromosomes: 1p, 6q, 9q, 10q, 14q, 17p and 18q. The same alteration plus deletion on chromosomes 6q, 9p, 10 and 14q are present in anaplastic forms. Deletions of 1p are the second most common chromosomal aberrations in higher grade meningiomas. It is also identified with a higher recurrence rate. Gene amplifications were identified in atypical and anaplastic meningiomas on chromosomes 1q, 9q, 12q, 15q, 17q and 20q (Liu et al. 2005; Riemenschneider et al. 2006; Marwin and Perry 2010; Yew et al. 2013). Malignant progression is associated with a stepwise cumulative acquisition of chromosomal gains and losses (Choy et al. 2011; Yew et al. 2013). Increased CpG island hypermethylation, as an epigenetic alteration, has also been associated with malignant meningioma progression (Liu et al. 2005).

Various growth factors have been investigated in meningiomas. PDGF and its receptor PDGFR-β are overexpressed in these tumors. Meningiomas also show overexpression of EGFR, which is not detectable in normal human meningeal tissue. EGFR ligands – TGF-α and EGF also contribute to the activation of EGFR (Perry et al. 2004; Choy et al. 2011). Increased expression of TGF-α is associated with more aggressive tumor growth. Meningiomas also express TGF-β and its receptors (Wen et al. 2010).

VEGF and endotelin 1 (ET-1) play an important role in angiogenesis of meningiomas. VEGF-A and VEGFR-1 receptor have function in tumor neovascularisation and peritumoral edema. VEGF express 84% and VEGFR 67% of meningiomas (Ragel and Jensen 2010). It has been already proven that after total resection the secretion of VEGF-A from microscopic residues of tumor can cause neovascularisation and tumor recurrence (Yamasaki et al. 2000). Increased EGF and PDGF can induce VEGF expression (Ragel and Jensen 2010).

Medulloblastoma

Medulloblastoma is a malignant embryonic tumor with invasive growth. It appears in the cerebellum and is most often seen in children. It accounts for about 20% of all CNS tumors in children (Dhall 2009). At the time of diagnosis one-third of the patients have already present metastases in cerebrospinal fluid pathways.

The crucial factors for diagnosis of medulloblastoma are the immunohistochemical evidence of synaptophysin (marker of neuronal differentiation, not present in gliomas and mesenchymal tumors), intermediate filament proteins

(IFP), mainly nestrin, vimentin and GFAP, neuron-specific IFP, retinal S-antigen, rhodopsin, NCAM (neural cell adhesion molecule – reflects the degree of differentiation), NGF (nerve growth factor) and its receptors Trk A, B and C (Takei et al. 2007). High values of proliferation index Ki-67 (over 20%) are connected with a worse prognosis (Meurer et al. 2008). Expression of survivin correlates with poor clinical outcome and might be a predictive factor for the recurrence or presence of metastasis (Abdel-Aziz et al. 2013).

Gene-based research has already identified most common pathways connected with medulloblastoma: sonic hedgehog pathway (SHH), Wingless pathway (WNT) and NOTCH pathway (Northcott et al. 2011; Parsons et al 2011). Tight regulation of these cascades is essential for normal brain development. On the other hand, its dysregulation may cause tumorigenesis (Li et al. 2013). Recently, 4 molecular subgroups of medulloblastomas have been identified: SHH, WNT, Group 3 and Group 4 (Robinson et al. 2012; Taylor et al. 2012; Li et al. 2013). Each of these subgroups has distinct molecular profiling and genomic defects, histological type, progenitors, clinical parameters, and patient outcomes (Gibson et al. 2010; Robinson et al. 2012).

SHH subgroup comprises about 25–30% of medulloblastomas with the high frequency of desmoplastic histology (Robinson et al. 2012; Li et al. 2013). The majority of SHH are found in infants under 3 years of age or in adults upwards of 16 years. Prognosis is good in infants and intermediate in adults. Regulators and target genes of SHH pathway (patched – *PTCH,* smoothened – *SMO,* suppressor of fused gene – *SUFU, MYC, CCND1,CCND2* genes) are overexpressed in the SHH subgroup. The most frequent chromosomal abnormality in SHH is the loss of 9q (21–47%), (Northcott et al. 2011; Pugh et al. 2012), followed by gain of 3q and 9p and loss of 10q, 20p and 21p (Northcott et al. 2012). Some tumors within this subgroup harbor amplifications and loss of genes associated also with p53 and PI3K pathway (Northcott et al. 2012; Li et al. 2013). These tumors also contain *MLL2* (mixed lineage leukemia gene 2), *MLL3, TP53* and *PTEN* mutations (Parsons et al. 2011).

WNT subgroup (10–15% of all meduloblastomas) is characterized by classic histology (Kool et al. 2012), age above 3 years, good prognosis and infrequent metastasis (Li et al. 2013). Genetic analyses have shown the enrichment of genes of WNT signaling pathway (adenomatous polyposis coli – *APC, CTNN1, AXIN1, MYC, JUN, FRA, AXIN2, SMARCA4, CREBBP, MED13, CCND1* genes), *CTNNB1* mutation, *DDX3X* mutations and loss of chromosome 6 (Kool et al. 2012; Northcott et al. 2012; Pugh et al. 2012; Robinson et al. 2012; Min et al. 2013). Loss of chromosome 6 is associated with 88% of WNT tumors (Schwalbe et al. 2011).

Subgroup 3 and 4 display mostly classical histology, occur mostly in children and have poor (group 3) and intermediate (group 4) prognosis (Northcott et al. 2011; Li et al. 2013). Both subgroups have higher expression of genes involved in photoreceptor differentiation, high level of medulloblastoma oncogenes OTX2 and FOXG1B (Northcott et al. 2011; Robinson et al. 2012). Subgroup 3 shows alterations of genes involved in cell cycle, protein biosynthesis, glutamate receptor signaling and p38 mitogen-activated protein kinase (MMAPK) pathway, subgroup 4 has most often alterations of genes of neuronal differentiation and development, cytoskeleton organization and biogenesis and vesicle mediated transport (Northcott et al. 2011; Li et al. 2013). The most common structural abnormality is iso-chromosome 17q (I17q). I17q has breakpoint in proximal part of 17p resulting in dicentric chromosome with deletion on 17p. Higher incidence of I17q was observed in subgroup 4 (Northcott et al. 2011; Min et al. 2013). Other aberrations include gain of 7 and 18q and loss of 8 and 11p. *MYC* and *MYCN* amplification, common in subgroup 3 (15%), is very rarely observed in subgroup 4 (Kool et al. 2012; Robinson et al. 2012; Li et al. 2013).

Abnormalities of chromosome 1 (for example trisomy of 1q), loss of 10q, 11, trisomy of chromosome 7 are other possible genetic alterations. Hypermethylation of *HIC1* promotor was found in 80% of medulloblastoma cases (Waha et al. 2003).

Malignant lymphoma

Primary central nervous system lymphoma (PCNSL) is an uncommon extranodal non-Hodgkin lymphoma that accounts for 2.7% of all malignant brain tumors. It needs to be distinguished from secondary lymphomas that primarily grow in other localizations than in the central nervous system. Incidence of primary brain lymphoma has dramatically arisen in the last 3 decades. Known risk factors for development of PCNSL are AIDS (acquired immune deficiency syndrome), iatrogenic immune suppression for transplant procedures, congenital immune deficiency syndromes (e. g. ataxia-teleangiectasia, Wiskott-Aldrich syndrome) and autoimmune conditions (e. g. rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis etc.), (Bhagavathi and Wilson 2008).

Primary brain lymphomas are mostly composed of diffuse large B-cells (T-cell lymphomas and primary Hodgkin lymphomas are extremely rare) and in general have poorer prognosis than metastatic lymphomas. The immunohistochemical analyses show expression of CD45, CD20 (β-cell marker found in large atypical cells), CD10, CD79a and CD3 (T-cell marker found in small benign admixed cells) markers, GFAP positivity, most of PCNSL also monoclonal superficial and cytoplasmic immunoglobulins (most often the combination IgM/κ). Most of these tumors are BCL2

(B-cell lymphoma), BCL6 and MUM-1 positive (Camilleri-Broet et al. 2005; Lin et al. 2006). Interleukin-4 and STAT6 (signal transducer and activator of transcription) are involved in the pathogenesis of PCNSL; STAT6 is associated with tumor progression and a shortened survival (Rubenstein et al. 2006). Deletions are very often found on 6q (cca 50%), 6p, 17p and 18p, amplifications on chromosome 1q, 7q, 12 and 18q. Translocations have been also found (1;14, 6;14, 13;18 and 14;21). Homozygous deletion and promoter hypermethylation of *CDKN2A* is frequent (Bhagavathi and Wilson 2008), mutations of *TP53* are extremely rare (Rubenstein et al. 2006).

Some cytokines and chemokines act as growth factors for tumor cells, inhibitors of apoptosis, attractors of immune cells, facilitators of invasion, promoters of angiogenesis and tumor-stromal cells interactions mediators (Sasayama et al. 2012).

Interleukin-10 (IL-10), produced by Th2-cells, monocytes and macrophages is known as growth and differentiation factor for B-cells and induces higher secretion of immunoglobulins (Mosser and Zhang 2008). IL-10 increases BCL2 expression and protects malignant cells for apoptosis. Elevated level of IL-10 in cerebro-spinal fluid is highly associated with the occurrence of PCNSL, shorter progression-free survival and overall survival (Sasayama et al. 2012).

CXCL12 and CXCL13 are known as homing factors for B-cells, production of CXCL13 in CNS is higher in patients with PCNSL and decreases with response to therapy (Fischer et al. 2009).

The favourable prognostic factors include a single, well-circumscribed intracranial lesion, the absence of meningeal or periventricular tumor, the absence of immunodeficiency, and age younger than 60 years (Bhagavathi and Wilson 2008).

Most common prognostic factors connected with brain tumors

When interpreting molecular biological and other factors, it is necessary to distinguish whether the factor is etiological or prognostic. Molecular markers influencing the prognosis are shown in Table 2.

Astrocytic tumors exhibit various genetic alterations. Mutation of *TP53* is very common in astrocytomas and is most important in the formation of astrocytomas grade II (Hede et al. 2011; Wang et al. 2011). It is also connected with their progression to secondary glioblastoma (Ohgaki and Kleihues 2007; Furnari et al. 2007). p53 was shown to be a prognostic marker (Levidou et al. 2010). Homozygous deletion (but not polymorphisms) in *CDKN2A* and loss of expression has been linked to poor prognosis in patients (Simon et al. 2010; Goldhoff et al. 2012).

Alterations of the *RB* pathway play a critical role in gliomagenesis, tumor progression from lower-grade astrocytomas (Chow et al. 2011), has been associated with increased tumor proliferation and decreased survival (Kim et al. 2011). *RB1* has a more direct correlation with prognosis in lower-grade (II, III) astrocytomas than glioblastoma (Kim et al. 2011).

PTEN is mutated or lost in 60–70% of high-grade glioma (Dey et al. 2008) and is associated with poor prognosis (Walker et al. 2011).

Progression from low-grade to anaplastic astrocytoma and formation of secondary glioblastoma is connected with a deletion on chromosomes 6, 9p, 11p, 17p, 13q, rarely with an amplification of 12q (Walker et al. 2011), decreased expression of DCC (Jarjour et al. 2011), mutation of *TP53* (Ohgaki and Kleihues 2007; Furnari et al. 2007), amplification of *EGFR* (Hu et al. 2013), increased expression of Tie-2 receptor by endothelial cell (Fagiani and Christofori 2013)

Table 2. Molecular markers modifying survival in primary brain tumors

Tumor type	Better survival	Shortened survival
Astrocytoma	p27 expression, DCC expression	VEGF, Tie-2 receptor, CDKN2A deletion, RB pathway alterations, 6, 9p, 11p, 17p, 13q deletions
Glioblastoma	IDH mutations	EGFR, PTEN mutation, Ki-67, expression of cathepsin B, Angiopoietin 4, p53 dysfunction
Oligodendroglioma	loss of chromosome 1p and 19q	CDKN2A, CDKN2C deletions, p53 dysfunction, 9, 10 deletions
Oligoastrocytoma	–	EGFR
Ependymoma	9, 15q, 18 gain, 6 deletion	1q gain, CDKN2A deletion
Meningioma	telomerase activity	1p, 6q, 9p, 10 and 14q deletions, TGF-α expression
Medulloblastoma	TrkC mRNA, SHH, Wnt subgroup	subgroup 3, 4, Ki-67, survivin
Lymphoma	–	STAT 6, higher IL-10 in CSF

CDK, cyclin dependent kinase; CSF, cerebro-spinal fluid; DCC, deleted in colorectal cancer gene; EGFR, epidermal growth factor receptor; IDH, isocitrate dehydrogenase genes; PTEN, phosphatase and tensin homology; RB, retinoblastoma gene; SHH, sonic hedgehog pathway; STAT6, signal transducer and activator of transcription; VEGF, vascular endothelial growth factor receptor; Wnt, Wingless pathway.

and increased expression of angiopoietin 4 (Brunckhorst et al. 2010), and others.

Mutations in the *EGFR* gene are associated with early relapses and poor prognosis (Hu et al. 2013). Expression of *EGFR* is higher in high-grade and poorly-differentiated gliomas and together with amplification of *EGFR* is correlated with tumor progression (Hoelzinger et al. 2005; De Luca et al. 2008; Hofer and Lassman 2010; Hu et al. 2013).

Within the group of primary glioblastomas, *IDH1* mutations are rare and create a prognostically favorable subgroup (Weller et al. 2009).

MGMT promoter hypermethylation is associated with prolonged progression-free survival and overall survival in patients with glioblastoma treated with alkylating agents (Hegi et al. 2005; Herrlinger et al. 2006; Glas et al. 2009). Methylation status of the *MGMT* promoter is clinically the most relevant molecular parameter (Weller et al. 2009) and has been used as a biomarker to predict the sensitivity of gliomas to DNA alkylating chemotherapeutics (Von Deimling et al. 2011).

Within the group of *oligodendrogliomas*, tumors with a combined loss of 1p and 19q create a group of good prognosis tumors (Giannini et al. 2008; Velnar et al. 2009), in patients treated with radiotherapy plus chemotherapy, also when treated with radiotherapy only (Cairncross et al. 2006; Van den Bent et al. 2006; Kouwenhoven et al. 2009; Weller et al. 2009).

Deletions on chromosomes 9 and 10 accompany malignant progression to anaplastic oligodendrogliomas (Stupp and Hegi 2007).

A *CDKN2C* deletion is present in anaplastic or mixed oligoastrocytomas. Tumors with such a deletion express poor chemosensitivity (Ducray et al. 2008). Patients with *TP53* mutations (and intact 1p 19q chromosomes) have low efficacy rate of the chemotherapy treatment, thus having the worse prognosis. On the other hand, 100% response rate was observed in patients with 1p 19q codeletion and intact *TP53* (Mueller et al. 2002).

Amplification of *EGFR* is more frequent in oligoastrocytomas and is connected with the worse overal survival (Kouwenhoven et al. 2009).

The most frequently observed aberration in pediatric intracranial *ependymomas* is the gain of chromosome 1q (over 20%), what is a significant predictor of tumor aggressiveness and poor patient outcome (Kilday et al. 2009; Yao et al. 2011).

In ependymomas, homozygous deletion at *CDKN2A* is a predictor of unfavorable outcome (Korshunov et al. 2010). In contrast, gains of chromosomes 9, 15q, and 18 and loss of chromosome 6 are features indicating excellent chance of survival.

Telomerase activity in *meningioma* is associated with a higher recurrence rate and greater malignancy, and it may serve as a potential prognostic marker (Laurendeau et al. 2010; Choy et al. 2011).

Deletions of 1p are very common in higher grade meningiomas and it is also identified with a higher recurrence rate. Gene amplifications were identified in atypical and anaplastic meningiomas on chromosomes 1q, 9q, 12q, 15q, 17q and 20q (Liu et al. 2005; Riemenschneider et al. 2006; Marwin and Perry 2010; Yew et al. 2013). Increased CpG island hypermethylation, as an epigenetic alteration, has also been associated with malignant meningioma progression (Liu et al. 2005). Increased expression of TGF-α is associated with more aggressive tumor growth (Yew et al. 2013).

In *medulloblastomas*, high values (over 20%) of expression of Ki-67 (factor of cell proliferation, which reflects degree of malignancy) are connected with a worse prognosis (Meurer et al. 2008). Expression of survivin correlates with poor clinical outcome and might be a predictive factor for recurrence or presence of metastasis (Abdel-Aziz et al. 2013).

Within the group of *lymphomas*, STAT6 is associated with tumor progression and a shortened survival (Rubenstein et al. 2006). An elevated level of IL-10 in cerebro-spinal fluid (CSF) is highly associated with the occurrence of PCNSL, shorter progression-free survival and overall survival (Sasayama et al. 2012). Production of CXCL13 in CNS is higher in patients with PCNSL and decreases with response to therapy (Fischer et al. 2009).

The favourable prognostic factors for lymphoma include a single, well-circumscribed intracranial lesion, the absence of meningeal or periventricular tumor, the absence of immunodeficiency, and age younger than 60 years (Bhagavathi and Wilson 2008).

Established prognostic factors for brain tumors, like age at the time of diagnosis, pathological grading, extend of surgery and Karnofsky performance score insufficiently predict the outcome in most instances. That is the reason why there is a need for more precise prognostic factors.

Conclusion

Recently there has been much progress in brain tumor research, although therapy remains limited. A lot of numerous chromosomal, genetic and epigenetic aberrations occur at random frequency in gliomas. However, the clinical value of most glioma-associated molecular aberrations in terms of their significance as diagnostic, prognostic or predictive molecular markers has remained unclear (Weller et al. 2009).

Morphologically indistinguishable tumors can be differentiated into molecular subtypes that might be eventually be used for identifying potential therapy targets and for determining prognosis.

Effectiveness of brain tumor therapy is limited by the poor ability of therapy agents to cross the blood-brain barrier (Dai et al. 2003). Identification of molecular characteristics of brain tumor gives opportunity for the targeted molecular therapy, for example EGFR inhibitors, PDGFR inhibitors, farnesyltransferase inhibitor, mammalian target of rapamycin, VEGFR inhibitors and other inhibitors of angiogenesis (Wen and Kesari 2004). Other forms of promising therapeutic methods are gene therapy and immunotherapy. These approaches remain at an early stage of development. Ultimately, truly effective therapies will result from the use of combination of treatment modalities.

Tumors with the same histological appearance often display variable clinical behavior. Recently, molecular subgroups with various prognosis and therapy response have been identified. This is the reason why it is imperative to probe deeper into the molecular genetic basis in search of reliable prognostic markers and therapeutic targets. A better understanding of the brain tumor biology is necessary in order to reveal ways of improving therapy and prolong sufficient life quality of patients with brain tumors.

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