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Review Article

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Molecular Biology and Cellular Signaling Pathways in Glioblastoma

Nikolaos Andreas Chrysanthakopoulos[1], Panagiotis Andreas Chrysanthakopoulos[2]

[1]Dental Surgeon (DDSc), Department of Pathological Anatomy, University of Athens, Athens, Greece.

[2]Colonel-Neurosurgeon (MD), Director of Neurosurgery Clinic, 'NIMTS', Military Hospital, Athens, Greece.

Corresponding Author: Nikolaos Andreas Chrysanthakopoulos, Dental Surgeon (DDSc), Oncologist, Resident in Maxillofacial and Oral Surgery, 401 General Military Hospital of Athens, Athens, Greece, **Tel:** +30-2610-225288; **Email:** nikolaos_c@hotmail.com

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ABSTRACT

Glioblastoma, also known as glioblastoma multiforme (GBM) or diffuse astrocytoma, WHO grade IV is the most aggressive and frequent primary brain cancer characterized by extremely poor prognosis despite developments in molecular Biology and genetics and new anti-neoplasmatic treatments and shows a great morphological and genetical heterogeneity.

Cancer pathogenesis characterized by the accumulations of molecular abnormalities and abnormalities in cellular signaling pathways that can lead to the known hallmarks of cancer:sustaining proliferative signaling due to mutations in proto-oncogenes, evading growth suppressors due to mutations affecting the tumor suppressor genes, enabling replicative immortality due to telomerase activation, resisting cell death due to up-regulation of anti-apoptotic or down regulation of pre-apoptotic molecules, inducing angiogenesis, activating tissue invasion and metastasis. GBM's molecular biology and pathogenesis are still complicated and in several aspects remain still unknown. It is characterized by rapid infiltrating growth, and microvascular proliferation and/or by expressing tissue necrosis. Its development could be as a primary tumor or as a secondary due to a malignant transformation that can arise from a lower grade brain tumor and/or with the isocitrate dehydrogenase (IDH) gene mutation. Previous and recent researches have recorded approximately 20 mutated genes that are implicated in GBM pathogenesis that are promoted by genomic instability and alternative pathways.

KEYWORDS

Glioblastoma; Gliomas; Signaling Pathways; Genomic.

INTRODUCTION

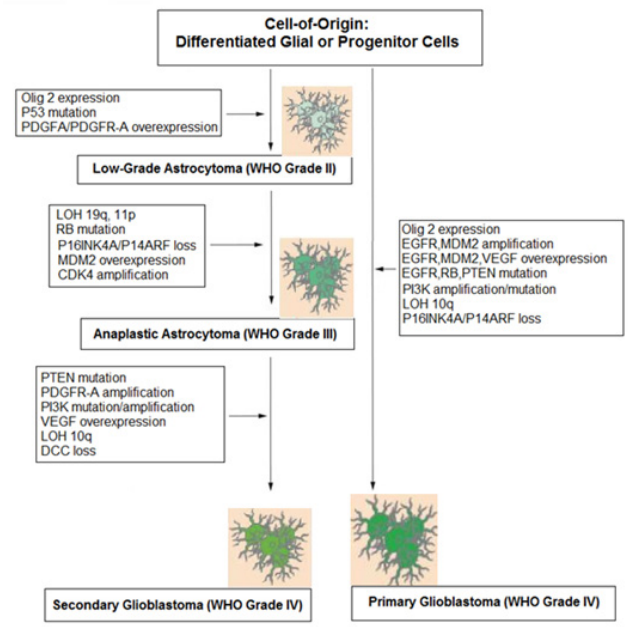
Glioblastoma, also known as glioblastoma multiform (GBM) or diffuse astrocytoma, WHO grade IV is the most aggressive and frequent primary brain cancer characterized by extremely poor prognosis shows a great morphological and genetical heterogeneity. GBM can be presented as a primary or as a secondary tumor as a result of a malignant transformation from a lower grade brain tumor and/or with mutation in the gene of isocitrate dehydrogenase (IDH) [1, 2].

GBMs are considered as the most common malignant brain tumors, its frequency varies between 12.0%-15.0% of all intracranial tumors, and 50.0% to 60.0% of astrocytic tumors with an annual incidence of 5.26 /100,000 population or 17,000 new diagnoses per year [3], are more common tumors in the 8th decade of life the primary type mainly, whereas the secondary affects younger ages. GBM prognosis is extremely poor as the five-year survival is only 5.0%. Patients usually survive for 12 to 15 months after the final diagnosis [4].

According to the gene expression profile GBMs can be classified into several histopathological types such as Classical, Proneural, Neural and Mesenchymal. The main gene mutations that have been recorded in GBMs are heterozygosity loss (LOH) on chromosome 10q and amplification of the epidermal growth factor receptor (EGFR). Two models have been sug-

gested to explain the possible pathogenetic mechanisms of the tumor, the vascular occlusion model and the tumor stem cell model. The tumors that are considered to originate from glial cell include grades I, pleomorphic xanthoastrocytomas, pilocytic astrocytomas, subependyma l giant cell astrocytomas, grade II oligodendrogliomas and astrocytomas, grade III anaplastic oligodendro gliomas, anaplastic oligoastrocytomas, anaplastic astrocytomas, anaplastic ependymomas and grade IV GBM [5]. (Table 1).

Table 1: Glioblastoma sub-types with the main genomic features.



GBM is an extremely invasive and proliferative tumor with highly abnormal vascularization, displays resistant to the common chemotherapy and radiotherapy and in general is difficult to be completely removed surgically [6].

Two molecular types have been determined, the primary GBM or de novo and the secondary that can arise due to a malignant transformation from a lower grade brain tumor and/or with the isocitrate dehydrogenase (IDH) gene mutation [7,8]. (Tables 1, 2).

Genome expression researches have been recorded several molecular and genetic abnormalities, such as Phosphatase and Tensin Homolog (PTEN) loss [9], gene amplifications at chromosome 7, deletions at chromosome 10, EGFR amplification/mutations and deletion in the locus INK4a/ ARF [10], whereas mesenchymal GBM is characterized by a very high mutation/deletion rate of Neurofibromatosis type 1(NF1), PTEN mutations, high levels of CHI3L1 and MET expression, genes involved in the Tumor Necrosis Factor (TNF) and Nuclear Factor of κ-light Polypeptide Gene Enhancer in B-cells (NFKB1) signaling pathways [11].

Proneural GBM is characterized by abnormalities, mutations mainly, of Platelet Derived Growth Factor Receptor A (PDGFRA), p53 mutations, carries the glioma CpG island methylator phenotype (GCIMP), that often is linked to isocitrate dehydrogenase (IDH)1 and 2 mutations and is characterized by common gene expression elements with secondary GBMs and

Table 2: The main molecular abnormalities in Glioblastoma according to its sub-type.

	Classical GBM	Proneural GBM	Neural GBM	Mesenchymal GBM
Gene/Signal Pathway/ Alteration	-CDKN2A(p14/p16)/RB/Homozygote Deletion	-PDGFRA/PDGF/Overexpression, Mutation	-NEFL/-/Expression	-PTEN/-/Mutation
	-EGFR/EGF,TNF-α/Overexpression, Mutations	- IDH1/-/Mutation	-GABRA1/ GABA/-/	-NF1/AKT/Deletion and/or Mutation
	-NESTIN/-/Overexpression	-PIK3CA,PIK3R1/AKT/Mutation	-SLC12A5/-/-/	
	-NOTCH3,JAG1,LENG/NOTCH/-	-P53/P53/Mutation		-CH31L1, MET/-/ Expression
	SMO,GAS1,GLI2/SHH/-	-CDKN!A(P21)/Low expression		
		-DCX,DLL#,ACSL1,TCF4/SOX/Overexpression		
		-OLIG2/-/-/		
		-NKX2-2/-/-/		

lower grade gliomas [12]. Research of GCIMP-negative tumors showed that was contained tumors with the glioma-GCIMP phenotype that are usually IDH wild-type [13].

Proneural GBM possible has more molecular and genetic aberrants that still remain uknown [10, 11].

Isocitrate Dehydrogenase (IDH) gene mutations and GBM pathogenesis

Isocitrate dehydrogenase (IDH) is a cytoplasmic enzyme in tricarboxylic acid (TCA) cycle that catalyzes isocitric acid and leads to the formation of α-ketoglutaric acid, whereas reduces coenzyme II nicotinamide adenine dinucleotide phosphate (NADPH) by oxidative decarboxylation and displays three isoforms 1,2 and 3 [14,15] .

Mutations of IDH gene result in the formation of 2-hydroxyglutaric acid from α-ketoglutaric acid. That abnormal pathway inhibits the α-ketoglutaric acid-dependent enzymes, and leads to function abnormalities of those such as epigenetic changes in a number of genes. One of those epigenetic changes is hypermethylation at a great number of genes that can lead to aberrant gene expression and inactivation of tumor suppressor's genes, molecular abnormalities that can cause GBM development [15, 16].

The most common mutations concern IDH1 isoform, whereas mutations in that enzyme consist an initiating event in gliomas pathogenesis and can separate primary from secondary GBM, however 5,0% of primary and 80,0% of secondary GBMs have such a mutation [15].

The most frequently mutation in diffuse gliomas, more than 90,0% concerns IDH1 gene and only 10,0% concerns IDH2 gene, whereas IDH3 mutations have not been found out yet [17].

The differentiation between "IDH1 mutant" and "IDH1 wild type" is important feature that is related to brain tumors, as IDH1 mutations are mainly R132H (90.0%), despite the fact that other substitutions at location R132 have also been recorded [18].

Mutations in the IDH2 gene are common finding in acute myeloid leukemia and rarely occur in glioma. In addition, mutations in IDH genes have also been found in cholangiocarcinomas and cartilaginous tumors [19].

Such mutations have been observed in 60.0%-80.0% of astrocytomas Grade II and III, oligo dendrogliomas, and oligoastrocytomas, whereas 5.0%-6.0% of primary GBMs dissemble IDH1mutations, the majority of secondary GBMs carry that mutation [15,19,20].

A better prognosis in any case of glioma grade is associated with the presence of IDH mutations [16, 17, 21].

Receptor Tyrosine Kinase (RTKs) molecular abnormalities and the specific role of Epidermal Growth Factor Receptor (EGFR) in GBM pathogenesis

Receptor tyrosine kinases (RTKs) consist elements of the wide family of protein tyrosine Kinases, encompassing the receptor tyrosine kinase proteins which contain a transmembrane domain, as well as the non-receptor tyrosine kinases that do not contain transmembrane domains [22]. RTKs are the high-affinity cell surface receptors for a great number of growth factors, cytokines, and hormones. In human genome have been found out 90 unique tyrosine kinase genes, however 58 of them encode for receptor tyrosine kinase proteins [23]. They consist dominant regulators of normal cellular signaling pathways, however play a critical role in the development and progression of many types of cancer [24].

Mutations in RTKs can result to activation of a series of signaling pathways and cascades that have numerous effects on genes and proteins expression [25].

In gliomas RTKs show molecular abnormalities, such as gene amplification in a wide spectrum of RTKs, such as EGFR (60.0%-70.0%), PDGFRA (12.0%-15.0%), and MET (5.0%) [26].

It has been mentioned previously that the EGFRvIII variant, that is present in up to 20.0% of GBM [50], is heterogeneously expressed across EGFRvIII-positive tumors [27], suggesting that its crucial contribution to gliomagenesis is inhibited by paracrine mechanisms [27,28]. It is possible that RTKs contribute to lead mitogenic cellular signaling pathways in GBM [29].

GBM cell lines after analyzing showed a co-activation of three or more RTKs. In addition, experimental trials showed variable co-expression of activated RTKs among individual cells derived from a single primary GBM. Therefore, in a single GBM exists a complicated RTK activation despite the fact that the etiology for the mentioned co-activation still remains activation despite the fact that the etiology for the mentioned co-activation still remains unknown. Researches that were focused on the structural genomics level and clonal heterogeneity in GBM cases revealed that approximately 13,0 % of GBMs that showed amplifications of EGFR, PDGFRA, or MET concealed large copy number gains in the mentioned genes [30,31].

The EGFR, known as ErbB-1, is a member of a family of closely related proteins. EGFR belongs to the family of receptors with tyrosine kinase activity (RTKs), known as HER/ErbB family and consists of 4 known receptors: EGFR or HER1-4/ErbB1-4. The EGFR gene, located on chromosome 7p12, encodes for

a transmembrane tyrosine kinase receptor. Its activation by appropriate ligand results in the activation of the receptor's intracellular tyrosine kinase domain which

undergoes autophosphorylation and is able to trigger a cascade of intracellular events that promote cell proliferation and migration [32].

EGFR gene amplification has been observed in 40,0-50,0% of the classical GBM type [33] and 63,0-75,0% of GBM cases transfer EGFR gene rearrangements that lead to tumors characterized by wild-type EGFR and mutated EGFR [34].

A splice variant that is responsible for a EGFR mutant form has been observed in 20,0-50,0% of GMB-induced by EGFR gene amplification , whereas in anaplastic astrocytomas, the incidence of EGFR amplification is 17,0% . The presence of EGFR gene amplification in GBM cases is associated with poor clinical prognosis [35]. However, in contrast to EGFR mutants in lung cancer, treatment with EGFR tyrosine kinase inhibitors (TKIs) appears to be less successful in GBM compared with lung cancer [36, 37].

Increased expression of other receptor tyrosine kinases (RTK) such as PDGFRA and Vascular Endothelial Growth Factor (VEGFR) contribute to growth of GBM through the activation of RAS/ERK or phosphatidylinositide-3 kinase (PI3K)/AKT-dependent signaling pathways [35].

Cells that carry EGFR amplification usually show different types of EGFR mutations, such as EGFRvIII rearrangement, that is due to deletion of exons 2-7 in EGFR mRNA and leads to an in-frame deletion of 267 amino acids in the extracellular domain of EGFR and it results to be unable to bind ligand [38]. EGFRvIII rearrangement decreases kinase degradation and over-activates the downstream targets of signaling pathways. In GBM patients, EGFRvIII mutation indicates poor prognosis [39].

Recent investigations have shown that EGFR wild type is necessary for the oncogenic effect of EGFRvIII. Dimerization of EGFRvIII is required for its activation and EGFRvIII may homo- or heterodimerize with EGFR. As a matter of fact exists a feed-forward loop as EGFRvIII is activated in case wild type EGFR is co-expressed. Heparin-binding epidermal growth factor (HBEGF) activates EGFR wild type and this activation induced by EGFRvIII [40].

EGFRvIII increased activation results to create an increased transactivation of several RTK families such as EphA2 and Met that may have possible involvement in EGFRvIII oncogenesis [41]. Recently, it has been found out in individual GBM cells an EGFR-EGFRvIII-STAT3 signaling axis that co-amplify EGFR and EGFRvIII. It has also been shown that exists a co-operation between EGFR and EGFRvIII in case of in vivo transformation and EGF treatment of cells that express EGFR and EGFRvIII could lead to phosphorylation of both kinases. It is clear that EGFR promotes in a single direction EGFRvIII signaling in GBM cells. EGFR-catalyzed phosphorylation of EGFRvIII has as a result its transportation into the nucleus and an increased production of a complex between EGFRvIII and STAT3. The last observation suggest that the mentioned kinases increase and continue for a long time STAT3 activity in the nucleus.Therefore is possible that increased EGFR levels even in the absence of EGFRvIII could unsettle that function, whereas targeting EGFR in combination with STAT3 signaling may be a treatment direction for EGFRvIII-positive GBM patients [42].

It has been shown the presence of multiple EGFR variants in a single GBM tumor focusing on the intratumoral heterogeneity of GBM that could be attributed to the plasticity of EGFR amplicons [43].

EGFRvII is produced by deletion of exons 2-7 of the EGFR gene and can be appeared in 9.0% of GBM cases that are focally amplified. EGFRvII's constitutive expression can lead to AKT downstream activation signaling, according to that of EGFRvIII, but without increased activation of ERK. There has been a possibility EGFRvII may activate an alternative signaling pathway such as STAT3 and set a more direct way to induce alterations in transcription. It seems that EGFRvII is able to increase EGFR Tyrosine Kinase Inhibitors' (TKIs) sensitivity [43, 44].

In 90.0% of GBMs cases PI3K molecular signaling pathway is hyperactivated due to molecular aberrants such as activating mutation or EGFR amplification and PTEN gene loss [45]. PI3K signaling pathway regulates anti-apoptotic mechanisms and promotes tumor growth and survival, including through sterol regulatory element binding protein 1 (SREBP-1)-dependent lipogenesis [46].

Promoter methylation of MGMT (O6-methyl guanine-DNA methyltransferase) and GBM

O6- methyl guanine-DNA methyltransferase (MGMT) is a protein that is encoded by the MGMT gene that is located on chromosome 10q26 and is crucial for genome stability. It repairs the naturally occurring mutagenic DNA damages and prevents mismatch and errors during DNA replication and transcription. Consequently, loss of MGMT increases the oncogenesis risk after exposure to alkylating agents. MGMT is transferred into the nucleus in case of DNA damage, it binds to O6-methyl-guanine and demethylates the alkylating agent after interaction with it [47].

Epigenetic events, as genes methylation can lead to inactiva-

tion of tumor suppressor genes, DNA repair genes, and pro-apoptotic genes, abnormalities that can induce carcinogenesis [48, 49].Approximately 50.0 % of MGMT promoter methylation have been observed in the secondary GBMs, and mainly in elder patients [50].

MGMT promoter methylation status is considered as a survival predictive biomarker especially in elderly GBM patients, whereas in younger ones the pro-neural GBM type that characterized by hypermethylation of CpG sites is associated with better prognosis, as is well known that epigenetic mechanisms also have prognostic significance in GBM patients [37].

Telomerase Reverse Transcriptase Gene (hTERT) genetic mutations and GBM

Telomerase consists a ribonucleoprotein enzyme complex that maintains and prolongs chromosome ends- telomeres of the eukaryotic chromosomes using one native RNA molecule as a template and thus is able to extend the number of cell divisions [51]. It acts as a RNA dependent-DNA- polymerase that can compensate for the loss of those DNA sequences by producing telomeric replicates in cells that still have the ability to be divided. A catalytic subunit,telomerase reverse transcriptase (hTERT) with the telomerase RNA component (TERC) comprises the most important unit of the telomerase complex [52].

Mutations in the hTERT have been observed in about 75.0% of GBM cases. Despite the fact that hTERT mutation status itself cannot be a predictive or prognostic factor for GBM treatment results, it is possible that the positive prognosis attributed to MGMT promoter methylation in GBM patients may depend on simultaneous hTERT promoter mutation [53, 54].

RB1 mutation and deletion in GBM

The retinoblastoma protein pRb encoded by RB1 gene that is located on chromosome 13, consists a tumor suppressor protein that is associated with abnormalities in several types of cancers. Its main function is to prevent excessive cell growth by inhibiting cell cycle progression until a cell is ready to divide. At that point of the cell cycle, pRb is phosphorylated, becomes inactive and allows cell cycle progression as binding and repressing E2F transcriptional targets. It is also a recruiter of several chromatin remodeling enzymes such as methylases and acetylases. The CDKN2A/p16-CDK4/6-RB pathway characterized by molecular abnormalities in GBM patients [55]. Those abnormalities play a critical role in gliomagenesis or umor progression from lower-grade astrocytomas [56]. CDK4 and CDK6 phosphorylate RB1, that induces the release of the transcription factor E2F, thus facilitating the transition of the cell cycle from the G1 to S phase and this process is negatively regulated by the p16 protein which binds and inhibits CDK4/6 unction.Consequently, expression abnormalities of p16, CDK4, CDK6, or RB1 can lead to cell cycle dysregulation [57]. It has been shown that this pathway is altered in 80% of primary GBMs and the most common genetic abnormality concerns CDKN2A gene mutation or deletion, CDK4 amplification, and RB1 mutation or deletion. Rb promoter methylation is another epigenetic alteration that has been shown in 14,0% of primary GBM and 43,0% of secondary ones [58].

Genetic Mutations of Phosphatase and Tensin Homolog (PTEN) and GBM

PTEN consists a protein that, is encoded by the PTEN gene located on chromosome 10q23 and acts as a tumor suppressor gene through the action of its phosphatase protein product, that is involved in the cell cycle regulation, preventing cells proliferation and division. Mutations of this gene can lead in the development of several types of cancer [59, 60].

The protein encoded by PTEN gene is a phosphatidylinositol-3, 4, 5-trisphosphate 3-phosphatase (PIP3). It contains a tensin-like domain and a catalytic domain similar to that of the dual specificity protein tyrosine phosphatases and dephosphorylates phosphoinositide substrates. Thus, negatively regulates intracellular levels of phosphatidylinositol-3, 4, 5-trisphosphate in cells and acts as a tumor suppressor by negatively regulating Akt/PKB signaling pathway. PTEN is also able to inhibit cell invasion, cell adherence to the surrounding matrix and vascularization, whereas in case of excessive cell differentiation, it has the ability to regulate cell cycle and induce apoptosis. Consequently contributes to inhibition of tumor growth [60].

Approximately 86.0% of GBM patients have lost PTEN gene expression and show molecular abnormalities in receptor tyrosine kinase/phosphoinositide 3-kinase (RTK/PI3K) signaling pathway that it regulates cell survival, cell proliferation, adhesion, cell mobility and differentiation. Patients that suffered from primary GBM display PTEN point mutation in 26,0%-34,0% ,whereas in anaplastic astrocytomas patients the PTEN mutation rate is approximately 18,0%. It is important to mention that GBM patients with PTEN mutation have poor prognosis [61].

Mutation and deletion of Neurofibromatosis type 1 (NF1) gene and GBM

NF1 gene is located on chromosome 17q11.2 and encodes for the neurofibromatosis protein, acts as a potential tumor suppressor , regulates negatively the Ras oncogene and consists a mechanistic target of rapamycin (mTOR) signaling pathways in astrocytes. In GBM patients is observed inactivation of that

gene (type 1) due to excessive degradation by the ubiquitin-proteasom pathway, whereas it's genetic loss consists the second reason that is able to lead to excessive cell proliferation and oncogenesis [62].

NF1 loss leads to increased activity in crucial pro-tumorigenic signaling pathways, particularly the Mitogen-Activated Protein Kinase (MAPK) pathway. NF1 patients are predisposed to several types of tumors affecting the central and peripheral nervous system such as pilocytic astrocytoma whereas adults patients, may develop gliomas of all types and grades [63]. A retrospective study of NF1-associated gliomas showed that 27.0% were diffusely infiltrating astrocytomas, and 22.0% were high grade gliomas, such as anaplastic astrocytomas and GBMs [64]. Another study that was based on mice was found that NF1 and Tp53 co-inactivation led to GBM development and was characterized by high penetration [65, 66].

Mutations are more common in mesenchymal type of GBM [67], whereas experimental trials in mice showed that NF1 deletion could lead to an excessive astrocytes proliferation and migration as a result of mTOR transactivation that is mediated by the Ras oncogenic signaling pathway. Mutations or deletions of that gene, lead to regulation of STAT3 signaling pathway, that consist potential down-stream target genes, by the mechanistic Target Of Rapamycin Complex 1(mTORC1) and Ras-related C3 botulinum toxin substrate 1 (Rac1) and enhance cyclin D1 levels that are responsible for an excessive cell proliferation [68].

In astrocytes of genetically engineered mice models double hit of NF1gene can lead in vivo and in vitro to cell proliferation, however it is not adequate to induce GBM [69], whereas in case of homozygous NF1 deletions (NF1-/-), astrocytes need heterogeneity to induce GBMs [70].

NF-κB signalling in GBM

The nuclear factor NF-kB is a transcription factor that is activated by the EGFR signaling pathway and is involved in the evasion of apoptosis (programmed cell death). It is also activated by inflammatory cytokines (TNF-α, IL-1β, IFN-γ) and bacterial products (LPS), consists an important effector of the inflammatory response as regulates normal immune response, shows anti-apoptotic action by interaction with Bcl-2 and Bcl-XI factors and is associated with chronic nflammation and carcinogenesis of the respiratory tract, etc. and maybe the key that allows preneoplasmatic and malignant cells to escape from apoptosis [71].

Its abnormal constitutive activation has been observed in GBM [72], whereas the encoding nuclear factor of κ-light polypeptide gene enhancer in B-cells inhibitor-A (NKFBIA) is a NF-kB inhibitor that abolish signaling in the NF-κB and EGFR pathways and plays a crucial role as a suppressor in GBM cases. Deletion of the nuclear factor NFKBIA has an effect that is similar to amplification of EGFR in the pathogenesis of GBM. A two-gene model that was based on NFKBIA expression and MGMT expression was strongly associated with the clinical course of the disease [73].

The role of Programmed Cell Death Protein 4 (PDCD4) protein in GBM

Programmed Cell Death Protein 4 (PDCD4) is a nuclear/cytoplasmic protein that encoded by the PDCD4 gene that consists a tumor suppressor gene, inhibits translation by interacting with translation initiation factor eIF4A and inhibits its RNA helicase activity that has been involved in the development of several types of cancer. In the nucleus, PDCD4 affects the transcription of specific genes by modulating the activity of several transcription factors [74, 75].

PDCD4 interacts with nuclear factor NF-kB in GBM cases. To be more specific, PDCD4 interacts with p65 and inhibits NF-kB nuclear localization and consequently, inhibits NF-κB transcriptional activation [76].

PDCD4 protein regulates Matrix Metalloproteinase-9 (MMP-9) and VEGF that are NF-kB target genes and are overexpressed in GBM tissues [76,77].

Astrocyte Elevated Gene-1 protein (AEG-1) expression and GBM

Astrocyte elevated gene-1 protein (AEG-1) is a protein that is encoded by the MTD gene [78]. AEG-1 acts as an oncogene in several malignant tumors such as elanoma, malignant glioma, breast cancer and hepatocellular carcinoma. It is highly expressed in those cancers contributes to their development and progression, induced by c -Myc oncogene and plays a crucial role in independent proliferation of cancer cells [79]. AEG-1 plays a critical role in tumorigenesis in several organs as already has reported, and consists a Ras target and activates many oncogenic cellular signaling pathways such as MAPK/ERK, PI3K-AKT, NFκB and Wnt, that regulate cellular functions including invasion, cell proliferation, angiogenesis, metastasis and chemoresistance [80,81].

AEG-1 was firstly identified as an human immunodeficiency virus (HIV-1) and tumor necrosis factor A(TNF-A)-inducible transcript in primary human fetal astrocytes and showed a significant interest in the field of cancer as its expression was found to be increased in subsets of breast cancer, GBM and melanoma cells, whereas plays a central role in Ha-ras-mediated oncogenesis through PI3K/Akt signaling pathway, pro-

motes the transformation of immortalized melanocytes and is overexpressed in more than 90,0 % of brain tumors [82]. In addition, AEG-1 also ctivates the VEGF promoter in malignant glioma cells [83].

As already has been reported AEG-1 expression is increased in several types of cancers, whereas its overexpression protects primary and transformed human and mice cells from serum starvation-induced apoptosis due the activation of PI3K/Akt signaling pathway. Those observations suggest, that AEG-1 may function as an oncogene [83].

Its expression was also elevated in adult astrocytes transformed by SV40-T antigen, hTERT, and oncogenic Ha-ras that displayed an aggressive glioma-like phenotype [84].

Regarding the relationship between AEG-1 and the Excitatory Amino Acid Transporter 2 (EAAT2) that consists one of the major glutamate transporters expressed predominantly in astroglial cells, a strong negative association between expression of AEG-1 and the EAAT2 has been reported . EAAT2 suppression is responsible for a reduction of uptake of glutamate by glial cells, and leads to induction of necrosis of neuronal cell that contributes to glioma-induced neurodegeneration. In addition, AEG-1 promotes gliomagenesis, particularly based on the main characteristics of glioma that are tumor growth and invasion [85].

AXL receptor tyrosine kinase overexpression and GBM

Tyrosine-protein kinase receptor is an enzyme that in humans is encoded by the AXL gene [86]. It has been proposed that AXL facilitates immune escape and drug-resistance by cancer cells, functions that can lead to aggressive and metastatic cancers [87].

It normal function is associated with signals transduction from the extracellular matrix into the cytoplasm by binding growth factors like vitamin K-dependent protein growth-arrest-specific gene 6 (GAS6), whereas is also involved in the stimulation of cell proliferation and survival [88] as activates downstream signaling pathways that include PI3K-AKT-mTOR, MEK/ERK, F-kB, and JAK/STAT [89].

AXL overexpression in astrocytoma/glioblastoma has been reported according to recent studies [90,91] and especially its overexpression in astrocytoma cell invasion and migration [91], however the functional influences of AXL expression in astrocytoma that are associated with signaling, cell survival, and cell proliferation still remain unclear. In addition, it has not been confirmed a role for the Mer RTK in astrocytoma, whereas it has been recorded an abnormal expression of Mer and AXL RTKs in astrocytoma cell lines and primary patient samples, and the role of AXL in cell survival, proliferation, and migration. Mer and AXL receptor tyrosine kinases are expressed at abnormally elevated levels in a wide spectrum of cancers, and those receptors are able to activate crucial anti-apoptotic signaling pathways that can promote oncogenesis. Inhibition of either Mer or AXL RTK expression can lead to extremely different phenotype compared with the parental astrocytoma cells, with enhanced apoptosis and apoptotic signaling, decreased cell proliferation and growth, and higher sensitivity to chemotherapeutic agents [92].

TP53 promoter methylation and mutations in GBM

The TP53 gene encodes for a protein that is involved in the cell cycle, response to DNA damage, cell differentiation, and cell death, and is responsible for genomic stability [93]. Mutations of the TP53 gene often cause changes in the functions of the protein and lead to its inactivation and accumulation of mutated protein in the nuclei of tumor cells [94].

The TP53 mutation have been observed in about 30.0% of cases of primary GBM and in 65.0%-90,0% of cases of secondary GB, and especially 59,0% in low-grade astrocytoma and 53,0% in anaplastic astrocytoma, finding that indices that TP53 mutation occurs early in tumorigenesis [95].

TP53 point mutations are equally concern the 5-8 exons (hotspot mutations) in cases of primary GBM, whereas in secondary GB most frequent point mutation are distributed at codon 248 and 273 (exon 7 and 8), and in CpG sites (methylation region) [96].

The abnormal function of the mutated TP53 can lead not only in mutations, but can causes abnormalities in cellular signaling pathway s that are involved genes such as MDM2, MDM4, or CDKN2A/p14ARF, that binds to MDM2 and inhibits MDM2-mediated TP53 degradation. It has been recorded that in 87.0% of GBMs were recorded molecular abnormalities that concern the TP53/MDM2/CDKN2A signaling pathway [58].

Proneural type of GBM that characterized by high expression of oligodendrocytic genes was carried the majority of TP53 mutations and TP53 heterozygosity loss 54.0% [97]. In primary GBM, has been found an association between EGFR amplification and absence of TP53 mutation as is considered mutually exclusive [96].

MGMT promoter methylation is associated with GBM pathogenesis, as already has been reported, however that alteration was linked to the presence of G: C to A: T transition mutations in TP53 in many types of cancer, including GBM [98].

Tripartite Motif (TRIM) proteins and GBM

Tripartite motif (TRIM) proteins are members of the E3 ubiq-

uitin ligases family that contain a TRIM encompassing RING finger domain, one or two zinc-binding B-box domains and coiled coil domains and are encoded by the TRIM3 gene that is located on chromosome 11p15.5 [99]. TRIM proteins are responsible for cellular functions as regulate cell proliferation, apoptosis and transcriptional regulation [100].

TRIM3 was firstly identified and determined as a brain-enriched RING finger protein [99]. 25% of GBMs and lower-grade gliomas showed TRIM3 loss caused by its deletion or DNA methylation. TRIM3 deletion is highly associated with the GBM proneural transcriptional type that is enriched for genes that regulate neural development and proliferation. In the same investigation was suggested that TRIM3 regulates cell proliferation and differentiation through the Musashi/Numb/Notch/Hedgehog signaling pathway, as well as c-Myc, and its loss increases the glioma stem-cell population by disrupting asymmetric cell division and cellular differentiation [101].

Loss of Heterozygosity (LOH) as additional genetic alteration that contributes to GBM pathogenesis

LOH on chromosome 10 consists the most frequent genetic alteration in GBMs, and occurs in 80% of cases, however rarely occurs in low-grade astrocytomas and it accounts for 40% of the anaplastic astrocytomas. It has been shown that the majority of GBMs have lost an entire copy of chromosome 10. Partial LOH GBMs show three common deletion on10p14-pter [102], 10q23-24 [103] and 10q25-qter [102].

LOH 10 has been observed in 60%-100% of GBMs with EGFR amplification [104] and in 40%- 80% of GBMs with a p53 mutation [104] and this finding leads to the suggestion that LOH 10 is implicated in primary and secondary GBMs' pathogenesis, whereas secondary GBMs with LOH 10 do not have loss of chromosome 10p but are characterized by partial or complete loss of chromosome 10q.

LOH on 22q is a common alteration in 11-39% of gliomas, uncommon in low-grade astrocytomas, but is more frequently found in anaplastic astrocytomas and GBMs. That alteration occurs more frequently in the advanced stage of several types cancers and it suggests a link between 22q LOH and tumor progression [105].

LOH on chromosome 19q has been recorded in 70% of oligodendrogliomas, and in 50% of oligoastrocytomas, in15% of diffuse low-grade astrocytomas, in nearly 45% of anaplastic astrocytomas, and 25% of unselected GBMs , finding that could be attributed to the fact that a significant percentage of unselected GBMs does not develop through LOH 19q [106,107].

It was also found that approximately 29% of primary GBMs, tumors from an initial resection and 40% of recurrent GBMs, tumors from a non-initial surgical resection characterized by LOH on chromosome19q.That alteration is frequently implicated in the progression from low-grade astrocytomas to secondary GBMs, but is not typically involved in the development of primary GBMs. Even though no evidence exists, the higher frequency of LOH 19q in the previous study could be suggested that in the pathway that leads to secondary GBMs, LOH 19q consists an alteration that takes place after LOH on chromosome 10 [107]. LOH on chromosome 10q25-qter is associated with obtainment of GBM phenotype, but LOH on chromosome 19 was observed in only 1 of 5 cases with foci showing a sudden histological transition from low-grade or anaplastic astrocytoma to GBM [107].

LOH on chromosome 1p has been detected in nearly 10% of low-grade astrocytomas, in 20% of anaplastic astrocytomas, and 10% of GBMs [107-109]. On that chromosome have been detected genes that are involved in cancer pathogenesis, such as p73 [110] at 1p36.33, E2F2 [111], TR2 [112], TNFR2 [113], DR3 [114], and DR 5 [115] at 1p36, and RAD54 [116] and p18 (INK4C) [117] at 1p32. Loss of the 1p36 locus has been recorded in oligodendrogliomas (70%) and oligoastrocytomas (50%) [107,118].

Oligodendrogliomas with LOH on 1p often show concurrent LOH on 19q [118,119], finding that leads to a suggestion of a cooperation between those genetic alterations. In the previous study on GBMs, there was no significant association between LOH on chromosomes 1p and 19 [118]. LOH on chromosome13q has been recorded in almost 20% of low-grade astrocytomas [55,120], 25% of anaplastic astrocytomas [55,120], and 35% of GBMs [55,120,121].The Retinoblastoma gene (RB) is located at 13q14.2 [122] and the breast cancer susceptibility locus 2 (BRCA2) on 13q12.1 [123,124]. Only in 10% of GBMs [55, 120,125] have been recorded mutations that concern the RB gene, finding that suggests the presence of other tumor suppressor gene on this chromosome.

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