

Review Article

Genetic alterations and signaling pathways in the evolution of gliomas

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(Received July 08, 2009/Revised August 03, 2009/Accepted August 03, 2009)

Gliomas are the most common primary brain tumors. They account for more than 70% of all neoplasms of the central nervous system and vary considerably in morphology, location, genetic alterations, and response to therapy. Most frequent and malignant are glioblastomas. The vast majority (>90%) develops rapidly after a short clinical history and without evidence of a less malignant precursor lesion (primary or *de novo* glioblastoma). Secondary glioblastomas develop more slowly through progression from low-grade or anaplastic astrocytoma. These glioblastoma subtypes constitute distinct disease entities that affect patients of different age, develop through distinct genetic pathways, show different RNA and protein expression profiles, and may differ in their response to radio- and chemotherapy. Recently, isocitrate dehydrogenase 1 (*IDH1*) mutations have been identified as a very early and frequent genetic alteration in the pathway to secondary glioblastomas as well as that in oligodendroglial tumors, providing the first evidence that low-grade astrocytomas and oligodendrogliomas may share common cells of origin. In contrast, primary glioblastomas very rarely contain *IDH1* mutations, suggesting that primary and secondary glioblastomas may originate from different progenitor cells, despite the fact that they are histologically largely indistinguishable. In this review, we summarize the current status of genetic alterations and signaling pathways operative in the evolution of astrocytic and oligodendroglial tumors. (Cancer Sci 2009)

Our understanding of biology and genetics of gliomas has greatly improved during the past two decades, but unfortunately, this has not yet led to an effective therapy. Treatment with cytostatic agents and radiotherapy still dominates first-line adjuvant therapy but targeted intervention is now increasingly being tested, particularly with inhibitors of neo-angiogenesis and growth factor receptors. At the same time, large scale sequencing of the glioblastoma genome has led to the discovery of novel genetic alterations and signaling pathways which may add additional targets for novel interventions.^(1,2) This review summarizes genetic alterations operative in the development of astrocytic and oligodendroglial gliomas, with an updated model of signaling pathways and the role of glial precursor cell lineages.

Definition of Glioma Types

Gliomas are the most common primary brain tumors, accounting for more than 70% of all primary central nervous system (CNS) neoplasms. The most frequent and most malignant gliomas are glioblastomas (World Health Organization [WHO] grade IV).⁽³⁻⁵⁾

Primary and secondary glioblastoma. The majority of glioblastomas (>90%) develop very rapidly in elderly patients

(mean, 62 years) after a short clinical history, without clinical or histological evidence of a pre-existing, less malignant precursor lesion (primary or *de novo* glioblastoma). Two-thirds of patients with primary glioblastoma have a clinical history of <3 months.⁽⁴⁾ Secondary glioblastomas are less frequent (<10%), affect younger patients (mean age at diagnosis, 45 years), and develop more slowly through progression from low-grade diffuse astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III). In a population-based study, the mean time of progression from low-grade glioma to glioblastoma was 5.3 years and from anaplastic astrocytoma to glioblastoma 1.4 years.⁽⁵⁾ Although histologically largely indistinguishable, primary and secondary glioblastomas develop through different genetic pathways.^(4,6)

Low-grade diffuse astrocytoma (WHO grade II) is a well-differentiated and slow-growing tumor, but shows a consistent tendency to diffusely infiltrate surrounding brain structures. Therefore, tumors tend to recur after surgical resection and this is often associated with progression to more malignant histologic types, that is anaplastic astrocytoma (WHO grade III) and eventually secondary glioblastoma (WHO grade IV).^(3,5)

Oligodendroglioma (WHO grade II) is a well-differentiated, slowly growing, diffusely infiltrating tumor in adults, typically located in the cerebral hemispheres and composed predominantly of cells morphologically resembling oligodendroglia.⁽³⁾ Anaplastic oligodendroglioma (WHO grade III) is an oligodendroglioma with focal or diffuse histological features of malignancy and a less favorable prognosis.⁽³⁾

Oligoastrocytoma (WHO grade II) is composed of a conspicuous mixture of two distinct neoplastic cell types morphologically resembling the tumor cells in oligodendrogliomas and low-grade astrocytomas.⁽³⁾ Anaplastic oligoastrocytoma (WHO grade III) is an oligoastrocytoma with a histological feature of malignancy. With respect to gene status and survival, oligoastrocytomas are intermediate between low-grade diffuse astrocytomas and oligodendrogliomas.^(3,7)

EGFR/RAS/NF1/PTEN/PI3K Pathway

Growth receptors (e.g. EGFR, PDGFRA) become activated through the binding of their respective ligands (e.g. EGF, TGF- α , PDGF) to their extracellular domain, which results in recruitment of phosphatidylinositol 3-kinase (PI3K) to the cell membrane. The PI3K complex is composed of a catalytically active protein p110 α (encoded by *PIK3CA*) and a regulatory protein p85 α (encoded by *PIK3RI*). PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP₂) to the respective 3-phosphate (PIP₃) which activates downstream effector molecules such as AKT (protein kinase B) and mTOR, the mammalian target of

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rapamycin. This results in cell proliferation and increased cell survival by blocking apoptosis. PTEN inhibits the PIP₃ signal,⁽⁸⁾ thereby inhibiting cell proliferation (Fig. 1a). The *NF1* tumor suppressor gene encodes neurofibromin that functions primarily as a RAS negative regulator, and also plays a role in adenylate cyclase and AKT–mTOR mediated pathways (Fig. 1a).⁽⁹⁾

EGFR amplification occurs in approximately 40% of primary glioblastomas, but is very rare in secondary glioblastomas.^(4,10,11) All primary glioblastomas with *EGFR* amplification showed *EGFR* overexpression, while 70–90% of those with *EGFR* overexpression had gene amplification.^(12,13) *EGFR* amplification is often associated with deletion mutants, *EGFRvIII* (deletion of exons 2–7) being the most frequent type. *EGFRvIII* shows constitutive activation of the receptor, and failure to attenuate signaling by receptor down-regulation, and exerts mitogenic effects.⁽¹⁴⁾

The *PTEN* gene is mutated in 15–40% of primary glioblastomas, but rare in secondary glioblastomas.^(4,12,15) *PIK3CA* mutations and amplification are rare (5% and 13%) in both primary and secondary glioblastomas.⁽¹⁶⁾ About two-thirds (63%) of primary glioblastomas and one-third of secondary glioblastomas showed alterations in at least one of *EGFR*, *PTEN*, or *PIK3CA* genes.⁽¹⁶⁾ The Cancer Genome Atlas (TCGA) pilot project identified additional genetic alterations in (mostly primary) glioblastomas, that is *NF1* mutations/homozygous deletions (18%) and *PIK3R1* mutations (10%), with overall frequency of alterations in the *EGFR/RAS/NF1/PTEN/PIK* pathway in 88% of glioblastomas.⁽¹⁾ Increased mRNA expression of PDGFR has been observed in astrocytic tumors of all grades, but gene amplification was only detected in a small subset of glioblastomas.⁽¹⁷⁾

About 50% of both oligodendrogliomas and anaplastic oligodendrogliomas show *EGFR* overexpression at the mRNA and protein levels.⁽¹⁸⁾ PDGF A and B, as well as their corresponding receptors (PDGFR- α and PDGFR- β) are co-expressed in most oligodendrogliomas.⁽¹⁹⁾ In contrast, *EGFR* amplification, *PTEN* mutations, and *PIK3CA* mutations may be observed in only a small fraction of anaplastic oligodendrogliomas.⁽³⁾

TP53/MDM2/MDM4/p14^{ARF} Pathway

The *TP53* gene encodes a protein that plays a role in several cellular processes, including the cell cycle, response of cells to DNA damage, cell death, and cell differentiation.⁽²⁰⁾ Following DNA damage, TP53 is activated and induces transcription of genes such as p21^{Waf1/Cip1}.^(21,22) MDM2 is induced by wild-type TP53,^(23,24) which binds to mutant and wild-type TP53, thereby inhibiting the ability of wild-type TP53 to activate transcription.^(25,26) The p14^{ARF} binds to MDM2 and inhibits MDM2-mediated TP53 degradation and transactivational silencing.^(22,27) MDM4 (also called MDMX) also regulates TP53 activity.⁽²⁸⁾ p14^{ARF} is negatively regulated by TP53 (Fig. 1a).⁽²²⁾ Thus, loss of normal TP53 function may result from alterations in TP53, MDM2, MDM4, or p14^{ARF}.

TP53 mutations are significantly more frequent in secondary glioblastomas than in primary glioblastomas (65% vs 28%).^(4,5) Of the *TP53* mutations in secondary glioblastomas, 57% were in hot-spot codons 248 and 273, while in primary glioblastomas, mutations were more evenly distributed. G:C → A:T mutations at CpG sites were significantly more frequent in secondary than primary glioblastomas, suggesting that the acquisition of *TP53*

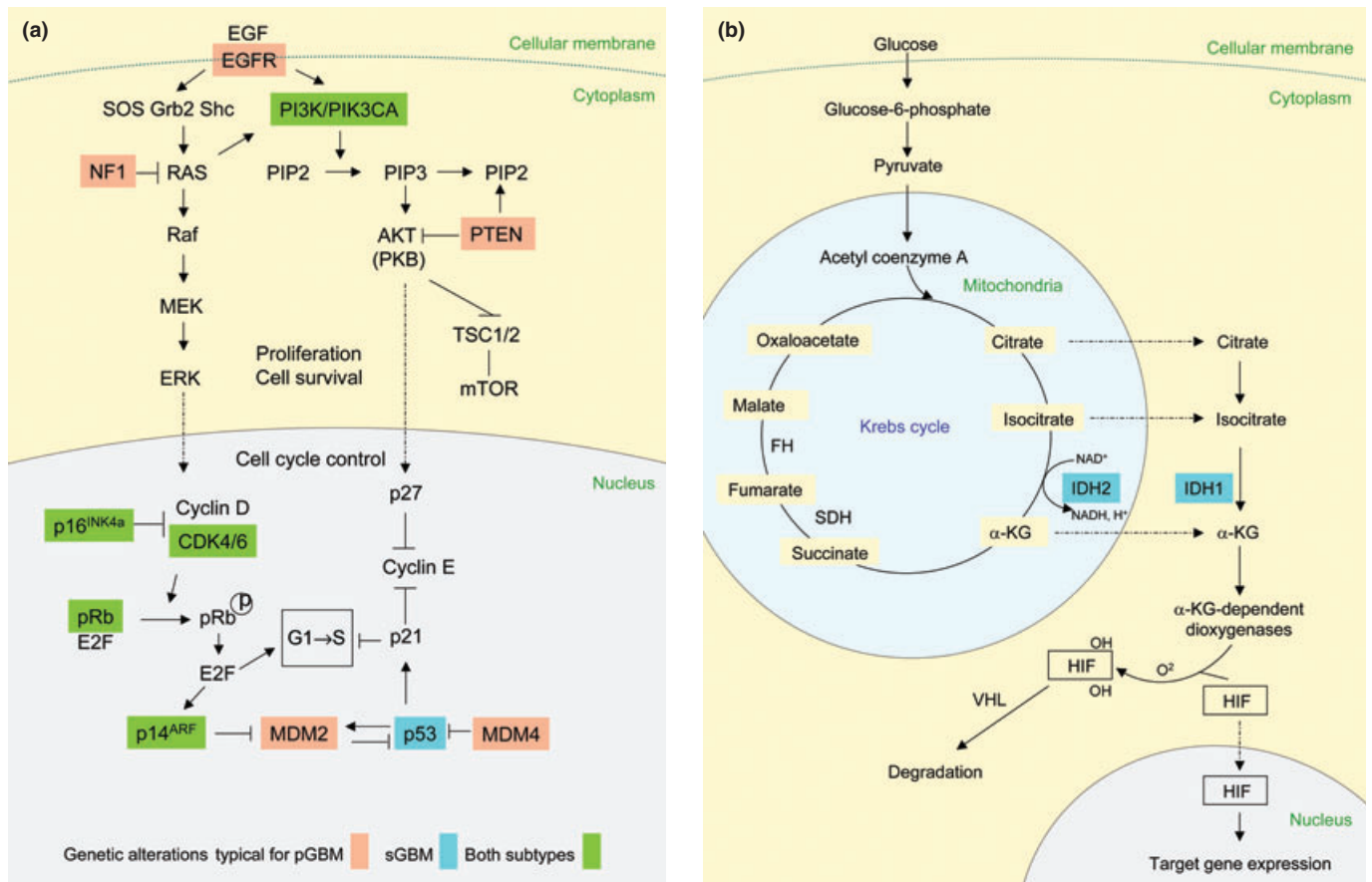


Fig. 1. Major signaling pathways involved in the pathogenesis of glioblastomas. pGBM, primary glioblastoma; sGBM, secondary glioblastoma; α -KG, α -ketoglutarate; FH, fumarase; SDH, succinate dehydrogenase; HIF-1, hypoxia-inducible factor-1; VHL, Von Hippel-Lindau.

mutations in these glioblastoma subtypes may occur through different mechanisms.⁽⁴⁾ Promoter methylation of *p14^{ARF}* is frequent in secondary glioblastomas, and the analysis of multiple biopsies from the same patients revealed *p14^{ARF}* methylation already in one-third of low-grade astrocytomas.⁽²⁹⁾ Loss of *p14^{ARF}* expression due to homozygous deletion or promoter methylation is frequent in primary glioblastomas (50%).⁽²⁹⁾ *MDM2* amplification is not frequent (<15%);⁽²⁹⁾ it occurs exclusively in primary glioblastomas that lack a *TP53* mutation.^(30,31)

At least one alteration in the *TP53/MDM2/p14^{ARF}* pathway (*TP53* mutations, *p14^{ARF}* homozygous deletion, *p14^{ARF}* promoter methylation, *MDM2* amplification) was observed in approximately 50% of primary glioblastomas, and in >70% of secondary glioblastomas.⁽³²⁾ There was a significant inverse correlation between *MDM2* amplification and *TP53* mutation and between *p14^{ARF}* alterations and *TP53* mutations.⁽³²⁾ The recent TCGA pilot project (mostly primary glioblastomas) showed that the overall frequency of genetic alterations in the *TP53/MDM2/MDM4/p14^{ARF}* pathway in glioblastomas was 87%, through *TP53* mutations or homozygous deletion (35%), *MDM2* amplification (14%), *MDM4* amplification (7%), or *p14^{ARF}* homozygous deletion or mutation (49%).⁽¹⁾

Approximately 20% of oligodendrogliomas showed *p14^{ARF}* promoter methylation,⁽³³⁾ and *p14^{ARF}* homozygous deletion or promoter methylation were observed in 40% of anaplastic oligodendrogliomas.⁽³³⁾ The overall frequencies of alterations in the *TP53/MDM2/p14^{ARF}* pathway were 21% in oligodendrogliomas and 50% in anaplastic oligodendrogliomas.⁽³³⁾

p16^{INK4a}/CDK4/RB1 Pathway

The RB1 protein controls the progression through G₁ into the S-phase of the cell cycle. The CDK4/cyclin D1 complex phosphorylates the RB1 protein, thereby inducing release of the E2F transcript factor that activates genes involved in the G₁ → S transition.⁽²¹⁾ p16^{INK4a} binds to CDK4, inhibits the CDK4/cyclin D1 complex, and thus inhibits the G₁ → S transition (Fig. 1a).⁽²¹⁾ Therefore, loss of normal RB1 function may result from altered expression of any of the *p16^{INK4a}*, *CDK4*, or *RB1* genes.

Homozygous deletion of the *p16^{INK4a}* gene, *CDK4* amplification, and loss of RB1 were largely mutually exclusive; the overall frequency of these alterations was 50% in primary

glioblastomas and approximately 40% in secondary glioblastomas.⁽³⁴⁾ The recent TCGA pilot project (mostly primary glioblastomas) showed that the overall frequency of genetic alterations in the RB1 signaling pathway was 78%, through *p16^{INK4a}* homozygous deletion or mutations (52%), *p15^{INK4b}* homozygous deletion (47%), *p18^{INK4c}* homozygous deletion (2%), *CDK4* amplification (18%), cyclin D₂ (*CCND2*) amplification (2%), *CDK6* amplification (1%), *RB1* mutation or homozygous deletion (11%).⁽¹⁾

Alterations in the *p16^{INK4a}/CDK4/RB1* pathway were rare (4%) in oligodendrogliomas, but frequent (65%) in anaplastic oligodendrogliomas.⁽³³⁾

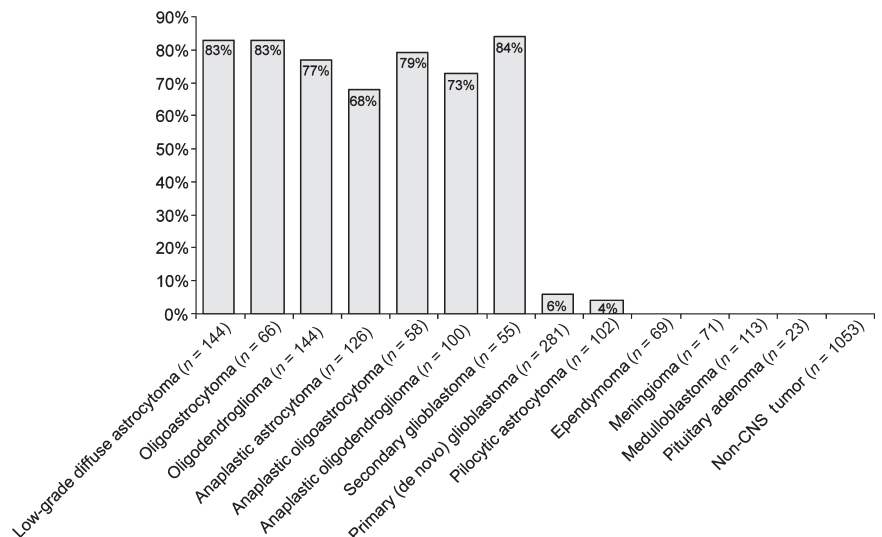
IDH1

The *IDH1* gene at 2q33 encodes isocitrate dehydrogenase 1 (IDH1),⁽³⁵⁾ which catalyzes the oxidative carboxylation of isocitrate to α-ketoglutarate, resulting in the production of NADPH in the citric acid (Krebs) cycle (Fig. 1b).^(36,37) In contrast to other mitochondria IDH forms, IDH1 is present in the cytosol. *IDH1* mutations decrease the enzyme activities *in vitro*.⁽³⁸⁾ Heterozygous *IDH1* mutations impair the enzyme's affinity for its substrate and dominantly inhibit wild-type IDH1 activity through the formation of catalytically inactive heterodimers.⁽³⁹⁾ Forced expression of mutant IDH1 in cultured cells reduced formation of the enzyme product, α-ketoglutarate (α-KG), and increased the levels of hypoxia-inducible factor subunit HIF-1α, a transcription factor that facilitates tumor growth (Fig. 1b).⁽³⁹⁾

IDH1 mutations were first identified in an analysis of 20 661 protein-coding genes in glioblastomas.⁽²⁾ Subsequent studies demonstrated that *IDH1* mutations are very frequent (>80%) in low-grade astrocytomas, anaplastic astrocytomas, secondary glioblastomas, oligodendrogliomas, anaplastic oligodendrogliomas, oligoastrocytomas, and anaplastic oligoastrocytomas.^(38,40,41) In contrast, *IDH1* mutations appear to be rare (<5%) or absent in pilocytic astrocytomas and primary glioblastomas,^(38,40,41) and absent in ependymomas and other CNS tumors, as well as in tumors outside of the nervous system (Fig. 2).^(38,40-42)

The majority (>60%) of low-grade astrocytomas have *TP53* mutations plus *IDH1* mutations,⁽⁴¹⁾ while the majority of oligodendrogliomas typically show *IDH1* mutations plus 1p/19q loss (>60%). *IDH1* mutations are therefore the first and only genetic alterations that are frequent among diffuse astrocytomas,

Fig. 2. *IDH1* mutations are frequent genetic alterations in astrocytomas and oligodendrogliomas, very rare in other tumors of the nervous system, and virtually absent in tumors outside the central nervous system (CNS). Data on CNS tumors are combined from Balss *et al.*,⁽⁴⁰⁾ Watanabe *et al.*,⁽⁴¹⁾ and Yan *et al.*;⁽³⁸⁾ data on other tumors including cancers of the bladder, breast, stomach, colorectal, lung, thyroid, ovary, and prostate; lymphoma and leukemia; and melanoma, are combined from Yan *et al.*⁽³⁸⁾ and Bleeker *et al.*⁽⁴²⁾



oligodendrogliomas, and oligoastrocytomas, suggesting that these gliomas may share the same cell of origin (Fig. 3). The histological criteria for the diagnosis of low-grade astrocytomas, oligodendrogliomas, and, in particular, oligoastrocytomas are highly subjective. Since the majority of these low-grade gliomas are now genetically characterized by the presence of an *IDH1* mutation plus *TP53* mutation or of an *IDH1* mutation plus 1p/19q loss, the molecular classification of low-grade diffuse gliomas may eventually replace the histological classification.

Loss of Heterozygosity (LOH)

The most frequent genetic alteration in primary glioblastomas (up to 80%) is LOH on chromosome 10, often with loss of an entire allele (10p and 10q).^(4,43–46) There are at least three commonly deleted loci, that is 10p14-15, 10q23-24 (*PTEN*), and 10q25-pter, suggesting the presence of several tumor suppressor genes that may play roles in their pathogenesis.^(43–45,47) LOH 10q is also frequent in secondary glioblastomas (up to 70%),^(4,46) although it is usually partial; LOH at 10q25-qter was associated with histologically-recognized progression from low-grade or anaplastic astrocytoma to a highly anaplastic glioblastoma phenotype. LOH 10p is very rare in secondary glioblastomas.⁽⁴⁶⁾ LOH 10q has been reported in 35–60% of anaplastic astrocytomas.^(45,48) LOH 10q is infrequent occurring in only approximately 10% of anaplastic oligodendrogliomas.⁽⁴⁹⁾

LOH 13q has been detected in 12% of primary and in 38% of secondary glioblastomas and typically includes the *RBI* locus.⁽⁵⁰⁾ LOH 6q occurs in approximately one-third of anaplastic astrocytomas.⁽⁵¹⁾ The chromosomal region at 9p23-24.1 is frequently deleted in glioblastomas. It encodes the *PTPRD* gene, a receptor protein tyrosine phosphatase with tumor suppressor function that is also mutated in a small subset (6%) of glioblastomas and frequently (37%) inactivated by promoter methylation.^(52,53)

LOH 22q is frequent in primary glioblastomas (41%) and in secondary glioblastomas (82%).⁽⁵⁴⁾ Characterization of the 22q deletions in primary glioblastomas identified two minimally deleted regions at 22q12.3-13.2 and 22q13.31.⁽⁵⁴⁾ The small (957 kb) deletion was identified in 22 of 23 secondary glioblastomas, a region in which the tissue inhibitor of metalloproteinases-3 (*TIMP-3*) is located.⁽⁵⁴⁾ LOH on 22q has been reported at a frequency of 20–30% in both low-grade and anaplastic astrocytomas.⁽³⁾

Loss of 1p and 19q

Oligodendrogliomas and anaplastic oligodendrogliomas typically show concurrent deletion of chromosomes 1p and 19q (up to 80%), and this is associated with increased chemosensitivity to treatment with PCV (procarbazine, CCNU, and vincristine) and a more favorable clinical outcome.^(55–58) In most cases, the entire 1p/19q arms are involved.^(57,59–61) Jenkins *et al.*⁽⁵⁸⁾ showed that combined deletion of chromosomes 1p and 19q is due to unbalanced translocation between chromosomes 1 and 19 [t(1;19)(q10;p10)]. The prevalence of this translocation suggests that the combined loss of two or more genes on 1p and 19q are required for the development of the majority of oligodendrogliomas.⁽⁵⁸⁾ Molecular cytogenetic deletion mapping studies have suggested that the minimal regions of deletion and, by implication, the putative candidate genes reside within 1p36 and 19q13.3.^(57,61,62) Isolated deletions of 19q are also common in astrocytic and oligodendroglial tumors.^(61,63,64) Isolated deletions of 1p are rare in gliomas and are associated with a poorer prognosis.^(57,65)

LOH 1p is rare in both primary (12%) and secondary glioblastomas (15%),⁽⁵⁰⁾ but is associated with longer patient survival.⁽⁶⁶⁾ LOH 19q (common deletion at 19q13.3) has been found to be frequent in secondary glioblastomas (54%) but rare in primary glioblastomas (6%).⁽⁵⁰⁾

cDNA and Protein Expression Profiles

Although usually histologically indistinguishable, primary and secondary glioblastomas show significantly different mRNA and protein expression profiles, reflecting their significant difference in genetic alterations.⁽⁶⁾ Genes typically expressed in primary glioblastomas include Fas,⁽⁶⁷⁾ VEGF,⁽⁶⁸⁾ and VEGF fms-related tyrosine kinase 1, which are likely a reflection of the presence of large ischemic necroses in primary glioblastomas.⁽⁶⁷⁾ Insulin-like growth factor binding protein-2 (IGFBP-2), a modulator of the action of insulin-like growth factors, is also typically expressed at a high level in primary glioblastoma.⁽⁶⁹⁾ Primary glioblastomas also preferentially express genes typical of a stromal response, suggesting the importance of extracellular signaling.⁽⁷⁰⁾ AEBP1, up-regulated >4-fold in the majority of primary glioblastomas compared to secondary glioblastomas, is a transcriptional repressor, and has been shown to interact with PTEN and inhibit its function.⁽⁷¹⁾ Proteins expressed uniquely in primary glioblastomas include tenascin-X precursor, enolase 1, centrosome-associated protein 350, and EGFR. A significant variation in cDNA expression profiles was observed among different primary glioblastomas, probably reflecting their genetic heterogeneity.⁽⁶⁹⁾

ASCL1 is overexpressed in 86% of low-grade astrocytomas and 88% of secondary glioblastomas, which is accompanied by inhibition of Notch signaling.⁽⁷²⁾ Other proteins typically expressed in secondary glioblastomas include ERCC6, DUOX2, HNRPA3, WNT-11 protein precursor, cadherin-related tumor suppressor homolog precursor, and ADAMTS-19.⁽⁷³⁾ Quantification of the cytokines in the supernatant of 30 tissue-correspondent glioma cultures revealed a high expression level of PDGF-AB in secondary glioblastomas.⁽⁶⁸⁾ The extent of variation of cDNA expression profiles among low-grade astrocytomas was much less than that among glioblastomas, suggesting that low-grade astrocytomas are genetically more homogeneous.^(69,74)

Response to Chemotherapy

In most centers, first-line adjuvant therapy for glioblastomas consists of treatment with the alkylating agent temozolomide (TMZ) and concurrent radiotherapy.^(75,76) *O*⁶-Methylguanine-

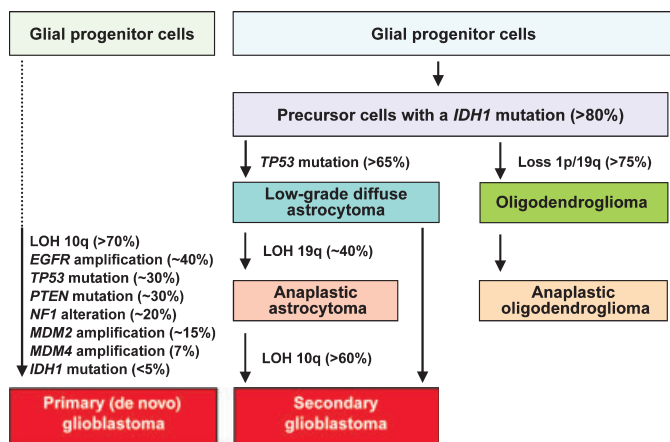


Fig. 3. Proposed genetic pathways to astrocytic and oligodendroglial gliomas.

DNA methyltransferase (MGMT) is a repair protein that specifically removes promutagenic alkyl groups from *O*⁶-methylguanine,⁽⁷⁷⁾ a promutagenic DNA adduct that causes G:C → A:T mutations during DNA replication.^(78,79) Loss or reduction of MGMT activity due to promoter methylation is frequent (40–57%) in glioblastomas,^(80–82) and MGMT methylation is associated with response to chemotherapy and longer survival among glioblastoma patients treated with TMZ.^(80,83,84)

Chemotherapy-induced Genetic Alterations

Some genetic alterations appear to be associated with chemotherapy. Mutations and loss of expression of the *MSH6* mismatch repair gene have been observed in a small subset of glioblastomas treated with TMZ, but not in untreated glioblastomas.⁽⁸⁵⁾ *MSH6* mutations were significantly associated with a hypermutator glioblastoma phenotype.^(75,85) In the recent TCGA study, seven hypermutated tumors were observed; all were from patients previously treated with TMZ or CCNU. Six of the seven hypermutated glioblastomas harbored mutations in at least one of the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, or *PMS2*, as compared with only one sample among 84 non-hypermutated cases.⁽¹⁾

Brain Tumor Stem Cells

Most genetic analyses in brain tumors were carried out on the bulk tumor mass. The cancer stem cell hypothesis postulates that only a small fraction of tumor cells have the capacity for self-renewal and tumor initiation. These brain tumor stem cells differ from the majority of tumor cells in gene expression⁽⁸⁶⁾ and biological behavior, including proliferation, spread, and sensitivity to chemo- and radiotherapy.^(87,88)

CD133 (prominin) has been used as a putative stem cell marker in normal and malignant brain tissues. Brain tumor cells

expressing CD133 appear to possess a capacity for proliferation, self-renewal, and differentiation.⁽⁸⁹⁾ Only the CD133+ brain tumor fraction contained cells that were capable of tumor initiation in NOD-SCID mouse brains,⁽⁹⁰⁾ although this observation was not confirmed in another study.⁽⁹¹⁾ CD133+ expression in glioblastoma cells was associated with their resistance to radiotherapy and chemotherapy.^(87,88) CD133+ and CD133– glioblastoma-derived cancer stem cells showed differential growth characteristics and molecular profiles.⁽⁸⁶⁾ One study showed that the relative content of CD133+ cells was significantly higher in primary than in secondary glioblastomas, and that CD133+ expression was associated with neurosphere formation only in primary glioblastomas,⁽⁸⁶⁾ reinforcing the view that the origin and cancer stem cells in primary and secondary glioblastomas may be different. Alternatively, CD133 may not be the only brain stem cell marker. Griguer *et al.*⁽⁹²⁾ reported evidence that CD133 expression may be reversibly up-regulated by hypoxia or by mitochondrial dysfunction through pharmacological inhibition of the electron transport chain.

Outlook

During the past decade, much progress has been made in our understanding of the origin, biology, and genetics of gliomas. Regrettably, this has only led to moderate improvements in clinical outcome. Therapeutic targeting of pathways operative in malignant astrocytomas, for example the EGFR/RAS/NF1/PTEN/PI3K pathway, has had limited success so far, and in most centers, the first-line therapy for glioblastoma is still a cytotoxic agent (TMZ) and radiotherapy. However, we anticipate that the genome-wide sequencing of gliomas will lead to the identification of additional signaling pathways and novel targets for therapy. Eventually, extensive genetic profiling of gliomas will become a laboratory routine, constituting for an important further step towards personalized treatment.

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