Glioma Biology and Molecular Markers

Adam L. Cohen and Howard Colman

Abstract The tumors classified as gliomas include a wide variety of histologies including the more common (astrocytoma, glioblastoma), as well as the less common histologies (oligodendroglioma, mixed oligoastrocytoma, pilocytic astrocytoma). Recent efforts at comprehensive genetic characterization of various primary brain tumor types have identified a number of common alterations and pathways common to multiple tumor types. Common pathways in glioma biology include growth factor receptor tyrosine kinases and their downstream signaling via the MAP kinase cascade or PI3K signaling, loss of apoptosis through p53, cell cycle regulation, angiogenesis via VEGF signaling, and invasion. However, in addition to these common general pathway alterations, a number of specific alterations have been identified in particular tumor types, and a number of these have direct therapeutic implications. These include mutations or fusions in the BRAF gene seen in pilocytic astrocytomas (and gangliogliomas). In oligodendrogliomas, mutations in IDH1 and codeletion of chromosomes 1p and 19q are associated with improved survival with upfront use of combined chemotherapy and radiation, and these tumors also have unique mutations of CIC and FUBP1 genes. Low grade gliomas are increasingly seen to be divided into two groups based on IDH mutation status, with astrocytomas developing through IDH mutation followed by p53 mutation, while poor prognosis low grade gliomas and primary glioblastomas (GBMs) are characterized by EGFR amplification, loss of PTEN, and loss of cyclin-dependent kinase inhibitors. GBMs can be further characterized based on gene expression and gene methylation patterns into three or four distinct subgroups. Prognostic markers in diffuse gliomas include IDH mutation, 1p/19q codeletion, and MGMT methylation, and MGMT is also a predictive marker in elderly patients with glioblastoma treated with temozolomide monotherapy.

Keywords Astrocytoma · Glioblastoma · Oligodendroglioma · Pilocytic astrocytoma · IDH1 · EGFR · BRAF · 1p/19q codeletion · MGMT methylation

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Contents

1 Introduction

Gliomas are the most common primary brain tumor in adults, affecting about 20,000 people in the US each year [14]. Pathologically, gliomas are divided into astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas based on histopathologic appearance. Most gliomas are astrocytic (82 %), followed by unspecified gliomas (7 %), oligodendroglial tumors (6 %), and mixed oligoastrocytomas (3 %) [14]. However, it is now understood that these histologies include a heterogeneous group of tumors with distinct molecular ontology and biology. Molecular classification has allowed for the identification of prognostic and predictive markers for some types of gliomas, and molecular subclasses are becoming increasingly important in the clinical classification and treatment of gliomas.

2 Histology

The 2007 World Health Organization classification recognizes three types and four grades of gliomas based on their microscopic appearance [45]. Grade 1, or pilocytic, astrocytomas are noninvasive tumors found primarily in children. Diffuse gliomas include astrocytomas, oligodendrogliomas. Grade 4 astrocytomas are called glioblastomas (GBMs). While some gliomas are mixed and have areas consistent with more than one type of histology, some investigators hypothesize that the different tumor types arise from different cells of origin and specific molecular alterations. Oligodendrogliomas probably arise from oligodendroglial precursor cells [44, 54, 72]. Radial glial cells have been proposed to be the cell of origin of ependymomas [74]. The cell of origin of astrocytomas has been proposed to be reactive astrocytes of the subventricular zone (for *NF1* and *PDGF*-driven astrocytomas), neural progenitor cells of the frontal lobe (for IDH-mutant astrocytomas), and neural stem cells/progenitor cells in the subventricular zone [1, 22, 41].

3 Important Pathways in Glioma Biology

3.1 RTK/RAS/PI(3K), P53, Rb

Publications from the Cancer Genome Atlas (TCGA) effort showed that more than three quarters of GBMs have alterations, including deletions, amplifications, or mutations, in three pathways: growth factor downstream signaling, particularly through the phosphatidyl inosital-3-kinase (PI3K) pathway, apoptosis regulation via p53 signaling, and cell cycle regulation via cyclin-dependant kinases and retinoblastoma 1 signaling [75]. Alterations in growth factor receptor/PI3K/MAPK signaling can include amplification of the epidermal growth factor receptor (*EGFR/erbB1*), platelet derived growth factor receptor (*PDGFR*), or *MET* genes or mutation in *EGFR* or the *HER2/erbB2* receptor gene. Mutations in *EGFR*, particularly the EGFRvIII variant in which most of the extracellular domain is deleted, occur in 25–30 % of GBM [29, 76]. Downstream signaling from growth factor receptors can be activated by loss or mutation in the neurofibromatosis 1 gene (*NF1*), mutations in *KRAS*, mutations in *PIK3CA* (the gene for *PI3K*), and deletion or loss of heterozygosity of *PTEN,* the inhibitor of PI3K [75]. Although about one-third of GBM can have mutation or deletion of *TP53*, loss of p53 function can also be obtained through amplification of *MDM2* or *MDM4* [8]. Lastly, cell cycle regulation is disrupted through mutation or deletion of the cell cycle inhibitors *CDKN2A*, *CDKN2B*, and *CDKN2C* as well as less frequent amplifications in cyclins and cyclin-dependent kinases or actual loss of the *RB1* gene.Translocations and fusion proteins may play an important role in activation of growth factor signaling. About 4 % of GBMs have fusions of *EGFR* with *SEPT14*, which activates STAT3 signaling, and another 2 % have fusions of *EGFR* with *PSPH,* which regulates neural stem cell proliferation [17, 49]. In addition, approximately 3 % of GBM have translocations causing a fusion between the fibroblast growth factor receptor genes, *FGFR1* or *FGFR3,* and the transforming acidic coiled-coil containing protein genes, *TACC1* or*TACC3* [67]. There is in vitro and in vivo evidence that tumors with these fusions can be inhibited with appropriate tyrosine kinase inhibitors, but whether they are prognostic or predictive in people is not yet known.

3.2 IDH Mutation

In 2008, a multigroup collaboration using whole exome sequencing identified a common point mutation in the metabolic gene *IDH1* in 12 % of glioblastoma samples [53]. Further studies found that this mutation is present in ~80 % of grade 2–3 gliomas and secondary GBM [2, 7, 26, 37, 62, 84, 88]. Mutations in *IDH2* have also been identified in gliomas, although they are much less common and are mutually exclusive with mutations in *IDH1* [26, 69, 88]. All mutations identified to date have been a single amino acid missense mutation in *IDH1* at arginine 132 (R132) or the analogous residue in *IDH2* (R172).

Although initial reports suggested that the mutant IDH functions in a dominate-negative fashion by heterodimerizing to wild-type *IDH1* and impairing its activity [89, 92, 93], more recent in vitro studies have shown that the mutated *IDH1* protein acquires the ability to convert α-ketoglutarate (α-KG) to R(-)-2-hydroxyglutarate (2-HG) [13, 32]. These findings led to the hypothesis that mutant *IDH* is an oncogene and 2-HG is an "oncometabolite" [18].

New evidence suggests that by antagonizing α-KG, 2-HG competitively inhibits the activity of many α-KG-dependent dioxygenases, including but not limited to histone demethylases (e.g., collagen prolyl-4-hydroxylase, prolyl hydroxylases, and the ten-eleven translocation (TET) family of DNA hydroxylases) [16, 63, 87]. Profiling of GBM from the TCGA demonstrated an association between IDH mutation and increased promoter methylation (G-CIMP) [50], which generally results in transcriptional silencing of the associated genes [35]. Two recent independent studies demonstrated that the G-CIMP phenotype was not correlated with IDH mutation but that IDH mutation alone is actually the cause of the G-CIMP hypermethylation phenotype in diffuse gliomas [11, 40].

3.3 Hypoxia, Pseudohypoxia, and Angiogenesis

Gliomas often exist in hypoxic or pseudohypoxic conditions. The extreme example of hypoxia is pseudopallisading necrosis in GBM, when the tumor outgrows its own blood supply. Hypoxia causes the upregulation of hypoxia inducible factor (*HIF1a*), and *HIF1a* can induce new vessel formation and stem cell survival processes. *HIF1a* is overexpressed in gliomas, particularly high grade gliomas [43]. *HIF1a* degradation via the ubiquitin-proteosome system is also inhibited by alterations in prolyl hydroxylases driven by 2-hydroxyglutarate produced by mutant IDH. Thus, IDH mutation can result in a situation in which HIF1a protein levels are high (consistent with hypoxia) while oxygen tension is normal. This situation has been called "pseudohypoxia" and may be a major driver of biology in these tumors along with other consequences of altered proline hydroxylation.

Blood vessel formation in gliomas often takes the form of angiogenesis, driven by vascular endothelial growth factor (*VEGF*). *VEGF* is overexpressed in brain tumors, with increasing expression corresponding to increased grade [10, 56, 57]. Angiogenesis can also be supported by *CXCR4* signaling [90]. Alternatively, gliomas can coopt normal vessels, a process often mediated by angiopoietin signaling, or new vessels can be formed from bone marrow derived endothelial cells, in a process termed vasculogenesis [46, 60]. Glioma cells may even be able to transform into malignant endothelial cells [66]. It has been proposed that blockade of angiogenesis, particularly inhibition of *VEGF* signaling, may lead to increased glioma invasiveness, although this hypothesis remains controversial [38].

Invasion into normal brain is one of the hallmarks of diffuse gliomas and is one of the features making them incurable by surgery alone. Gliomas migrate along the secondary structures of Scherer, such as white matter tracks, neuronal tracks,

vasculature, or subpial spaces [64]. Glioma migrations is facilitated by secretion of a variety of proteases, including matrix metalloproteases (MMPs), membrane type matrix metalloproteases (MT-MMPs), and adamalysins (ADAMS) [48]. Expression and secretion of these proteases can be regulated by TGF-beta and NF-κB.

4 Oligodendrogliomas

Oligodendrogliomas can be grade 2 (low grade) or grade 3 (anaplastic) [45]. There are no grade 4 oligodendrogliomas. One of the earliest steps in the development of oligodendrogliomas is mutation in isocitrate dehydrogenase 1 (*IDH1*) or 2 (*IDH2*) [84]. Mutation in *IDH1* or *IDH2* is followed by an unbalanced translocation resulting in loss of the p-arm of chromosome 1 and the q-arm of chromosome 19 [39, 59]. This translocation inactivates one copy of the Capicua transcriptional repressor (CIC) gene and the FUSE binding protein 1(*FUBP1*) gene [5]. Oligodendrogliomas then can develop a mutation in the other copy of these genes. Such mutations occur in 52 % of grade 2 oligodendrogliomas and 84 % of anaplastic (grade 3) oligodendrogliomas [31]. Whether these alterations are sufficient for oligodendroglioma development has not been established. The events involved in the transformation of grade 2–3 oligodendrogliomas have also not been established.

Codeletion of 1p and 19q is also a prognostic marker among all gliomas and among oligodendrogliomas, regardless of grade [91]. Indeed, mixed oligoastrocytomas with 1p/19q deletion have prognosis similar to oligodendrogliomas, while those without 1p/19q deletion have worse prognosis, similar to astrocytomas [30]. Moreover, 1p/19q codeletion is also a predictive marker among anaplastic oligodendrogliomas. Two randomized trials showed improved survival with the addition of chemotherapy to radiation for people with newly diagnosed anaplastic oligodendrogliomas whose tumors had 1p/19q codeletion but not for people whose tumors did not have this codeletion [9, 77]. Therefore, codeletion of 1p/19q, which can be detected by fluorescent in situ hybridization, is a clinically useful biomarker for oligodendrogliomas.

5 Astrocytoma Histopathologic and Molecular Classification

Grade 1, or pilocytic, astrocytomas are non-infiltrating neoplasms that occur mostly in children and adolescents but can occur in adults as well [45]. Pilocytic astrocytomas lack many of the mutations found in the diffuse gliomas. However, nearly all pilocytic astrocytomas have alterations in the *BRAF* oncogene leading to its activation, primarily by fusion with the *KIAA1549* gene [33]. Other mechanisms of RAF pathway activation include fusion of *SRGAP3* and *RAF1*, *BRAFV600E*

mutation, in-frame insertion in the *BRAF* gene, or fusion of *BRA*F with *FAM131B* [12, 33, 34]. Activation of *BRAF* in neural progenitor cells is sufficient to cause pilocytic astrocytomas in mice and to transform human neural stem cells [21, 58]. How to target these alterations remains an area of study.

Diffuse gliomas can be categorized according to grade: low grade (grade II), anaplastic (grade III), and glioblastoma (GBM, grade IV). Traditionally, GBMs have been classified as primary or secondary on the basis of clinical presentation [65]. Secondary GBMs display evidence of progression from a lower grade tumor, whereas primary GBMs present as grade 4 at diagnosis. Secondary GBMs are predominantly found in younger patients (median age of ~45 years compared with median age of ~60 years for primary GBM) and tend to occur less frequently than primary GBMs, making up ~5 % of total GBMs [51]. Secondary GBMs are more likely to have mutation in IDH1 or IDH2. Despite the differences in their ontology, these high grade tumors are histopathologically indistinguishable [51].

In the 1990s, this clinical classification began to be correlated to molecular biology with the observation that amplification of the epidermal growth factor receptor (EGFR) gene and mutation or loss of heterozygosity of the TP53 gene was mutually exclusive, with the former being seen in primary glioblastoma and the latter being seen in secondary glioblastoma and lower grade gliomas [80, 83]. More recently, large-scale efforts have been made to identify the major genetic and epigenetic alterations and to define important molecular subtypes in GBM and lower grade gliomas [55, 79].

Gene expression patterns have been used by multiple groups to classify adult high grade gliomas into 3–4 groups [55, 71, 79]. The Cancer Genome Atlas (TCGA) identified four subgroups of GBM based on gene expression patterns, which were called Proneural, Neural, Mesenchymal, and Classical [79]. Individual gene expression subtypes were associated with specific genetic and epigenetic alterations. For example, proneural GBMs are enriched for the G-CIMP phenotype, *IDH* mutations, *PDGFRA* amplifications, and *CDK4* amplifications. Classical GBMs are enriched for *EGFR* mutations, particularly the EGFRvIII variant. Mesenchymal GBMs are more likely to have *MET* amplification and *NF1* mutation or loss and display increased angiogenesis, hypoxia, inflammatory infiltrates and inflammatory signaling pathways, including *NF-κB, STAT3, TGF-β* [3, 6, 55, 79] Secondary GBMs are virtually always Proneural, while primary GBM can be any of the subtypes. Most primary GBMs have *EGFR* amplification and deletion of the *PTEN* gene [8].

6 Prognostic and Predictive Markers in Astrocytomas

The two strongest prognostic factors in astrocytomas are *IDH* mutation status and grade [25, 88]. Indeed, prognosis for *IDH*-mutant GBMs is better in some series than that for *IDH*-wild-type grade 3 astrocytomas. The prognostic importance of *IDH* mutation is independent of other known prognostic factors, including age, and

MGMT methylation status [62]. However, it remains to be determined whether *IDH* mutation is a prognostic factor only or whether it is predictive of outcome to specific treatments or mechanistically related to treatment response. Small retrospective series have suggested that the response rate to alkylating chemotherapy is also higher in *IDH*-mutated grade 2 tumors than in wild-type tumors and that progression-free survival after radiation or alkylating chemotherapy is higher for people with *IDH*-mutated tumors than for people with wild-type tumors [28, 36, 68]. In the German Glioma Group retrospective study, *IDH* mutation influenced survival only in those patients who received radiation or chemotherapy immediately after surgery [24]. *IDH* mutation does not predict progression-free survival for temozolomide treatment in low grade astrocytomas that had previously received radiation [73]. *IDH* mutation may also predict the benefit of complete resection in high grade gliomas [4]. However, their retrospective nature and lack of control groups limits the conclusions that can be drawn from these studies.

MGMT, the gene encoding the DNA repair enzyme O6-methylguanine-DNA methyltransferase, is methylated in 30–40 % of GBMs and 80 % of *IDH*-mutated low grade gliomas [19, 27, 42]. The presence of methylated *MGMT* is prognostic in all grades of glioma, including both oligodendroglial and astrocytic histologies [42, 61, 70, 78]. Given the strong association between G-CIMP phenotype and *MGMT* methylation, the prognostic significance of each of these independently cannot be assessed. It is also not clear whether the observation that *MGMT* methylation is more significant than expression level measured by RNA or protein is due to biology or to technical artifacts of the assays used.

MGMT was originally studied because of its role in repairing damage from alkylating agents such as the nitrosoureas or temozolomide. However, it remains controversial whether *MGMT* methylation is predictive of benefit from temozolomide. In the long-term follow-up of EORTC 26981-22981/NCIC CE3, *MGMT* methylation was prognostic in both the radiation alone and radiation plus temozolomide groups. Moreover, there was a statistically significant improvement in survival with the addition of temozolomide in both the *MGMT* methylated and unmethylated groups with similar hazard ratio, although the absolute benefit was much smaller in the unmethylated group [70]. In the elderly population, two trials (NOA-08 and the Nordic trial) have suggested that people with GBM with *MGMT* methylation have improved survival with temozolomide monotherapy compared to radiation, while the opposite is true for elderly people with GBM with unmethylated *MGMT* [47, 85]. The role of *MGMT* or other potential biomarkers other than *IDH* in grade 2 or 3 astrocytomas remains uncertain.

7 Ependymomas

Ependymomas have been subtyped based on both location (supratentorial, infratentorial, or spinal cord) or by gene expression pattern. Common genetic alterations in ependymomas include *NF2* mutation or loss, *HER2/erbB2* and *erbB4*

amplification, and *RASSF1A* and *HIC1* methylation [15, 20, 23, 81]. Two groups have used gene expression to identify two types of ependymoma, one characterized by growth factor receptor signaling and the other by large chromosomal rearrangements along with altered metabolism and cytoskeleton pathways [82, 86]. Most recently, a fusion gene involving c11orf95 and *relA*, the active component of NF-κB, was found to be a driver alteration in supratentorial ependymoma [52]. The high frequency observed of this fusion in the supratentorial ependymomas suggest that this is both a key driver of biology in this tumor subtype and may also be a potential target for specific drug development. Prognostic markers for ependymoma are not well established.

8 Conclusion

Gliomas include multiple distinct histopathologic types of tumors under the current WHO classification. Recent findings regarding some of the key driving alterations in some tumor types elucidate both the distinct biologies that define different histopathologies, and identify distinct molecular subtypes within single histopathologies. There appear to be at least three key molecular ontology pathways to the development of diffuse glioma. One pathway starts with *IDH* mutation followed by *TP53* mutation and results in astrocytic lineage tumors. These gliomas start as grade 2 astrocytomas, have the G-CIMP phenotype, and presumably then acquire other genetic alterations that result in progression to higher grade tumors. Another pathway starts with *IDH* mutation followed by loss of 1p/19q, which is associated with mutation in the *CIC* gene or the *FUBP1* gene. These alterations result in development of grade 2 oligodendrogliomas, which can then acquire other genetic alterations to become anaplastic oligodendrogliomas. The third pathway includes those gliomas that are wild-type for *IDH*. These gliomas appear to rapidly acquire multiple complex genetic alterations, including amplification or mutation of *EGFR*, and loss of the *PTEN* gene, and become GBMs very early in their development. *IDH*, 1p/19q codeletion, and *MGMT* are validated prognostic and probably predictive markers as well.

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