Progress on molecular biomarkers and classification of malignant gliomas

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Abstract Gliomas are the most common primary intracranial tumors in adults. Anaplastic gliomas (WHO grade III) and glioblastomas (WHO grade IV) represent the major groups of malignant gliomas in the brain. Several diagnostic, predictive, and prognostic biomarkers for malignant gliomas have been reported over the last few decades, and these markers have made great contributions to the accuracy of diagnosis, therapeutic decision making, and prognosis of patients. However, heterogeneity in patient outcomes may still be observed, which highlights the insufficiency of a classification system based purely on histopathology. Great efforts have been made to incorporate new information about the molecular landscape of gliomas into novel classifications that may potentially guide treatment. In this review, we summarize three distinctive biomarkers, three most commonly altered pathways, and three classifications based on microarray data in malignant gliomas.

Keywords malignant glioma; molecular biomarker; IDH1; MGMT; molecular classification

Introduction

Gliomas are the most common primary intracranial tumors in adults. In 2007, the World Health Organization (WHO) classified gliomas into astrocytomas, oligodendrogliomas, ependymomas, and others, based on morphology [1]. Apart from the most common pediatric glioma, pilocytic astrocytoma (WHO grade I), which is relatively well demarcated from the surrounding tissue and can thus be resected, most gliomas are diffused [2]. Diffuse gliomas are categorized into low-grade gliomas (LGGs, WHO grade II) and high-grade gliomas (HGGs, WHO grades III and IV), depending on their rate of growth. Anaplastic astrocytomas (WHO grade III) and glioblastomas (WHO grade IV) represent the major groups of malignant gliomas in the brain. The most malignant of the HGGs is glioblastoma multiforme (GBM). Primary GBMs (pGBMs) arise de novo in older patients and have a short duration of clinical symptoms [3], whereas secondary GBMs (sGBMs) develop from preceding grade II or III gliomas, which feature longer durations of symptoms and frequently affect patients younger than 40 years [4]. Allowing for individual variability, the survival of patients with glioblastoma has improved from an average of 10 months to 14 months after diagnosis over the past 5 years as a result of improvements in the standard of care [5]. On rare occasions, patients with GBM may survive for over 3 years. Several clinical and histopathological elements have been associated with a better prognosis for GBM, including younger age, good performance status, gross total resection, adjuvant treatments, giant-cell subtype, and oligodendroglial differentiation [6,7]. Heterogeneity in patient outcomes highlights the insufficiency of a classification system based purely on histopathology, which provides diagnostic information about the group as whole but limited information about individual patients. In the era of developing targeted therapies, a classification based on histopathology cannot provide sufficient insight to allow patient stratification. Great efforts have therefore been made to incorporate new information about the molecular landscape of gliomas into novel classifications that may potentially guide treatment. In addition, many biomarkers associated with patient outcomes and sensitivity to certain therapies (so-called prognostic and predictive factors) have been reported in recent decades by screening of high throughput microarray data followed by in vivo, in vitro, and clinical studies; such markers are likely to continue to be identified with further improvements in
screening technology. Considering that a large number of reports on biomarkers and classifications of gliomas are available, we screened the most common and important ones and discuss them below.

**Molecular biomarkers associated with malignant gliomas**

**Isocitrate dehydrogenase (IDH) 1/2 gene mutation**

IDH catalyzes the oxidative carboxylation of isocitrate to α-ketoglutarate, resulting in the reduction of NADP to NADPH [8]. IDH 1 and 2 function in the cytoplasm and mitochondria, respectively, representing one of the most significant recent discoveries in the field of GBM. Recent findings demonstrate that IDH1 gene mutation is associated with younger patients and secondary GBMs and has better outcomes [9]. Subsequent studies have found that IDH1 mutation occurs in 60% to 90% of all WHO grade II and grade III diffused gliomas and sGBMs [10–14] but rarely in pGBMs and pilocytic astrocytomas [10]. IDH2 gene mutations are found in 5% of all gliomas [15]. IDH1/2 mutations have not been found in histologically tumor-like tissue, such as gliosis, adverse radiotherapy reactions, virus infection, infarction, or demyelination, thus improving the diagnostic accuracy of biopsies [16,17]. NADPH, which can prevent cells from oxidative stress, decreases after IDH mutation [10,18], while α-ketoglutarate, which can degrade the tumor-growth and angiogenesis promoter hypoxia-inducible factor (HIF)-1α, increases [19]. Heterozygotic IDH1/2 mutation enhances the activity of enzymes catalyzing the production of hydroxyglutarate, which may be associated with tumor formation [20,21]. Thus, IDH1/2 mutation is considered a diagnostic and prognostic marker and is one of the most exciting findings in glioma research.

**Loss of heterozygosity (LOH) in chromosome 1p/19q**

LOHs in the short arm of chromosome 1 (1p) and long arm of chromosome 19 (19q) are commonly found in oligodendrogliomas [22]. Although tumor suppressive genes have not been found on 1p and 19q, a recent exome-sequencing study of oligodendrogliomas revealed inactivating mutations of the CIC gene on 19q and the FUBP1 gene on 1p in a substantial fraction of oligodendroglialomas [23], providing important insights into the pathogenesis, diagnosis, prognosis, and treatment of these tumors. LOH in 1p/19q can be found in 90% of all oligodendroglialomas (WHO grade II), 60% of all anaplastic oligodendroglialomas (WHO grade III), 30% to 50% of all oligoastrocytomas, and less than 10% of all diffuse astrocytomas, including GBM [22]. There is a strong relationship between LOH of 1p/19q and oligodendrogial differentiation but this loss is not detected in all oligodendroglialomas; thus, the 1p/19q status cannot be inferred on the basis of histology [24]. Previous studies have confirmed the prognostic and predictive values of LOH in 1p/19q in relation to first-line chemotherapies [25–28].

To some extent, as a diagnostic, predictive, and prognostic marker, LOH in 1p/19q can shed more light on gliomas with oligo components.

**O-6-Methylguanine-DNA methyltransferase (MGMT)**

MGMT is a DNA repair enzyme that can remove alkyl groups from the O6 position of guanine, a function that underlies the development of resistance to alkylating agent therapy in some patients [29]. Methylation of cytosines in the MGMT promoter CG-dinucleotide-rich sites can silence its expression relative to normal tissue, promoting reactions with alkylating agents [30,31]. MGMT promoter methylation can be found in all grades of gliomas and has been identified as an independent prognostic factor in anaplastic gliomas and GBMs, including aged GBM patients, in some [25,31–34], but not all studies [35]. Some researchers have found that the methylation status varies during disease progression and is a prognostic factor in primary but not secondary tumors [36]. MGMT promoter methylation has been reported to have predictive value in GBM patients treated with temozolomide [30,37] but not in those with anaplastic gliomas [25,38].

**Three most commonly altered pathways in malignant gliomas**

Previous studies have identified the three most commonly altered pathways in GBMs as the receptor tyrosine kinase (RTK)/RAS/phosphoinositide 3-kinase (PI3K) (88%), p53 (87%), and retinoblastoma protein (RB) (77%) pathways [39].

Numerous growth factors are involved in the RTK/RAS/PI3K pathway, and abnormal activation of this signaling pathway may result from amplification or mutation of growth factor receptor genes, which may either be driven by activating downstream pathways or by loss or mutation of tumor suppressor genes.

Epidermal growth factor receptor (EGFR) is the most commonly altered factor in the aforementioned pathway [40,41]; it promotes cell proliferation by activating downstream mitogen-activated protein kinase and PI3K-Akt pathways [42]. EGFR gene amplification or mutation is found in

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**Table 1** Summary of diagnostic, prognostic, and predictive values of three distinct markers

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Diagnostic</th>
<th>Prognostic</th>
<th>Predictive</th>
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<tbody>
<tr>
<td>IDH1 mutation</td>
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<td></td>
<td>✓</td>
</tr>
<tr>
<td>MGMT promoter</td>
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<td>✓</td>
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<tr>
<td>methylation</td>
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<tr>
<td>LOH of 1p/19q</td>
<td>✓</td>
<td>✓</td>
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