REVIEW

Advances in glioma biomolecular subtyping

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ABSTRACT

The evolution of glioma biomarkers has advanced during the last decade based on innovative genomic technologies, illustrated by interactions between specific genetic alterations and based on diagnoses formulated by both histological and biomolecular evidence. Recent guidelines have provided a more practical scheme for classifying intracranial glial-cell tumors using both morphological and genetic methods. In this review we characterize several classic gliomas biomarkers and their associations with clinical significance according to the 2016 WHO Classification of Central Nervous System Tumors to summarize their biomolecular evolvement in gliomas. (Am J Transl Med 2017. 1(4):212-218).

Keywords: glioma, biomolecular markers, IDH, 1p/19q, TERT.

INTRODUCTION

The biomolecular era arrived after the revolutionary adaption of the 2016 World Health Organization Classification of Tumors of the Central Nervous System included for the first time both histology and molecular parameters to these guidelines (Louis et al., 2016). By using of both phenotype and genotype, diagnoses have become more objective and correlated to clinical relevance (Louis et al., 2014). In combination with this newest classification, this review emphasizes the correlations between biomarkers and adjuvant therapeutic management.

CLASSIC GLIOMA BIOMARKERS

Chromosome 1p/19q co-deletion

The co-existence of 1p and 19q deletions has been determined as a prognostic factor for gliomas, with an approximate prevalence of 70–80% in oligodendrogliomas, belonging to a subgroup with prolonged survival (Jenkins et al., 2006; Lin et al., 2014). This 1p/19q co-deletion has also been correlated with the incidence of ATRX loss (Wiestler et al., 2013). Research has also demonstrated that anaplastic oligodendroglioma patients have benefited greatly from chemotherapy (Cairncross et al., 2013; van den Bent et al., 2013a; Schiff, 2017). According to a report from the European Organisation for Research and Treatment of Cancer (EORTC), their clinical trial consisted of 368 anaplastic oligodendroglioma patients who were randomly assigned to either a radiation alone group or to a radiation plus chemotherapy group (PCV for six cycles). Those patients with combined 1p/19q deletions showed better sensitivity to chemotherapy and superior outcomes. Similar results were reported not only for anaplastic oligodendrogliomas but also for anaplastic oligo-astrocytomas (Cairncross et al., 2013), strongly suggesting that adjuvant management using radiation plus PCV should be considered first in the 1p/19q co-deleted subgroup.

For the subset of patients with 1p/19q non-co-deleted anaplastic gliomas, the concurrent treatment with the adjuvant temozolomide might be a promising solution, as recent interim results of the CATION trial (van den Bent et al., 2017) revealed that 5-year overall survival increased (55.9% with versus 44.1% without temozolomide) as did progression free survival (42.8 months with versus 19.0 months without temozolomide). This novel approach may represent the new standard of care for patients with 1p/19q non-co-deleted anaplastic gliomas, but further follow-up research will be required.

O6-Methylguananine-DNA methyltransferase (MGMT)

The alkylating agent temozolomide remains the best and most reliable regimen for gliomas (Stupp et al., 2005). MGMT is a protein that may rapidly reverse the alkylation at the O6 position of guanine that produces drug resistance to alkylating medicines (Pegg et al., 1995). The methylation status of the MGMT promoter has been considered the most promising predictor of alkylating-drug sensitivity in glioblastoma for decades (Esteller et al., 2000; Gerson, 2004; Weller et al., 2010), even for glioblastomas in children (Donson et al., 2007; Schlosser et al., 2010) and in elderly patients (>65 years old) (Malmstrom et al., 2012; Wick et al., 2012).

The methylation status of the MGMT promoter has also been found to predict the responsiveness to PCV chemotherapy in anaplastic gliomas (van den Bent et al., 2013b), not only revealing representative chemosensitivity, but also reflecting the molecular glioma biotype (Weller et al., 2010).

Isocitrate dehydrogenase (IDH)

IDH mutations have been shown to be the earliest aberrations occurring during the development of gliomas (Suzuki et al., 2015). Recurrent mutations in isocitrate dehydrogenase 1 (IDH1), arginine to histidine switching at amino acid 132, were discovered in 12% of glioblastoma tumor samples, occurred in younger patients, and were associated with increased survival (Parsons et al., 2008). Further research demonstrated a 70% incidence of IDH 1 mutations across WHO grade II to grade IV gliomas, and also demonstrated a similar genomic switching at position 172 (designated IDH 2) that occurred in <1% of gliomas (Watanabe et al., 2009; Yan et al., 2009; Hartmann et al., 2010). Other reports found that the IDH 1 mutation had a crucial role in both oncogenesis and in established gliomas with the CpG island methylator phenotype (G-CIMP)

by remodeling the methylome (Turcan et al., 2012), and by blocking cell differentiation by modulating additional αKG-dependent enzymes (Lu et al., 2012).

Evidence has emerged that clinical and remedial distinctions can be made between IDH mutation-type and IDH wild-type gliomas (Miller et al., 2017). Radiologically, IDH-mutation gliomas can be distinguished from IDH wild-types by enhanced patterns (contrast enhancement on MR scans) that are usually specific to IDH-mutated tumors in high-grade or recurrent subgroups (Beiko et al., 2014; Qi et al., 2014). The combination sequences of DWI, DSC-PWI, and conventional MR imaging could identify IDH-mutated gliomas as entities with hypoperfusion because of a more intact blood-brain barrier (Xing et al., 2017). Notably, IDH-mutation gliomas tended to be located in the frontal lobes anatomically rather than elsewhere in the brain (Lai et al., 2011; Qi et al., 2014).

It is well known that IDH mutations have been associated with increased survival compared to IDH wild-type gliomas (Yan et al., 2009). Moreover, IDH-mutated astrocytic gliomas have been prognostically demonstrated to benefit from maximal resections (Beiko et al., 2014), leading to a more individualized genotype strategy for surgery.

Human Telomerase Reverse Transcriptase (hTERT)

Point mutations in the Human Telomerase Reverse Transcriptase (TERT) promoter region frequently occur in primary glioblastomas (Killela et al., 2013; Walsh et al., 2014) and have worse outcomes compared to gliomas without these mutations (Lotsch et al., 2013). Furthermore, the combination of IDH mutations, 1p/19q co-deletions, and TERT-promoter mutations have been strongly correlated with corresponding outcomes (Labussiere et al., 2014; Cancer Genome Atlas Research et al., 2015; Eckel-Passow et al., 2015).

Integration of molecular biomarkers

The integration of the three most frequent biomarkers (1p/19q, IDH, and TERT-promoter mutations) has categorized gliomas into five principal groups (Eckel-Passow et al., 2015). This classification was based on either three positive mutations in both TERT and IDH, mutations in IDH alone, mutations in TERT alone, and a triple-negative classification, distributed among all of the histological types of gliomas. These phenotypes were then assessed by patient age at diagnosis and patient survival. Of the five subgroups, the triple-negative and the TERT-promoter only mutation groups were associated with the worst rates of survival.

Another astonishing study of integrative genotyping in diffuse low-grade gliomas revealed the interactions of several genomic mutations using RNA, DNA copy number, and DNA methylation platforms. It revealed that IDH mutants and non 1p/19q co-deletion astrocytomas commonly carried collateral mutations causing TP53 and ATRX inactivations (Cancer Genome Atlas Research et al., 2015). In contrast, the genomic variations and clinical behaviors among the majority of gliomas without IDH mutations and primary glioblastomas were very similar. Notably, the low-grade glioma subtype carrying both IDH mutations and 1p/19q co-deletions showed the most favorable prognoses.

Nearly 40% of IDH wild-type glioblastomas carried MGMT-promoter methylations (Wick et al., 2014).

GENETIC ADVANCES IN GLIOMA DIAGNOSIS

The *three-layer* concept for diffuse-glioma diagnosis, using histological typing (layer 1), histological tumor grading (layer 2), and molecular testing results (layer 3) to determine a final integrated diagnosis, was substituted for traditional morphological pathology methods in the 2016 World Health Organization Classification of Tumors of the Central Nervous System 2016 WHO CNS tumor classification (Louis et al., 2016; Reifenberger et al., 2017).

According to this classification, IDH mutations are the primary biomarkers, followed by histology and tumor grading, the status of 1p/19q co-deletions and H3-K27M mutations status, and then aberrations such as ATRX, BRAF V600E, and TERT-promoter mutations used to redefine diffuse gliomas into their diverse subgroups. Diffuse astrocytomas can therefore be classified as IDH-mutant astrocytomas, WHO grade II-IV; IDH-mutant and 1p/19q-codeletion oligodendroglial tumors, WHO grade II-III; IDH wild-type glioblastoma, WHO grade IV; and H3-K27M-mutant diffuse midline diffuse gliomas, WHO grade IV.

Although improvements in molecular diagnosis were rapidly evolving, therapeutic procedures lagged (Weller et al., 2015). For example, the benefits of bevacizumab, a monoclonal antibody that suppresses angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A), were limited in glioblastoma (Chinot et al., 2014; Fine, 2014), and the latest trial of lomustine plus bevacizumab resulted in no survival advantage for patients with progressive glioblastoma (Wick et al., 2017).

CONCLUSION

Since the adoption of molecular parameters into the 2016 World Health Organization Classification of Tumors of the Central Nervous System, there has been a clinical diagnostic transformation with improved objectiveness and precision. However, only more clinical trials based on these newly published guidelines will produce more sophisticated and personalized management of patients with glioma.

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