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Mini review

Progress in the application of molecular biomarkers in gliomas

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ABSTRACT

Gliomas are a common adult central nervous system tumor, and glioblastoma (GBM), which has a poor prognosis, is the most lethal of all gliomas. The overall survival of GBM patients is only 12–14 months after diagnosis. With progress in the precision of personal medication, therapeutic options for various tumors have become gradually dependent on the molecular profiles of patients. GBM is one of the tumors in which treatment response relies largely on the molecular characteristics of the tumor. Therefore, awareness of the genetic background of each patient will help decision-making regarding the best treatment strategy to use. In this review, a novel molecular classification of gliomas based on recent findings of their genetic characteristics is introduced. Representative molecular markers, such as *IDH1* mutation, *1p19q* co-deletion, MGMT promoter methylation and *EGFRvIII* amplification, are described. Furthermore, the development of non-coding RNAs and omics studies of GBM are briefly discussed. Finally, a novel concept for non-invasive detection that could facilitate both diagnosis and treatment monitoring is presented. There is no doubt that the use of molecular profiling by biomarkers will indeed improve the overall survival and quality of life of GBM patients.

1. Introduction

Gliomas are the most common primary central nervous system tumors, accounting for nearly half of all brain tumors. Gliomas are divided into ependymoma, astrocytoma, oligodendroglioma, brainstem glioma, optic nerve glioma and mixed gliomas depending on predominant cell type. Based on pathological phenotypes according to WHO guidelines, gliomas are further categorized into four grades (I to IV), where grade I and II reflect low-grade gliomas, and grade III and IV (glioblastoma, GBM) reflect high-grade gliomas. Nearly 60% of high-grade gliomas are GBMs, and the incidence rate for these tumors is approximately 3 per 100,000 [1]. GBM is the most frequent type of malignant glioma in adults, accounting for 17% of all intracranial tumors [2]. The current standard strategy for GBM treatment is surgery followed by concurrent ionizing radiation and chemotherapy. However, due to extensive invasion and rapid proliferation, the survival of GBM patients is only approximately one year (12–14 months), and the 5-year survival rate is only 9.8% at best [3]. For grade II and III gliomas, the prognosis is much better but remains poor, at 2 years and 2–5 years, respectively [4].

2. The molecular classification of GBM

The WHO grades gliomas from I to IV according to pathologic criteria, whereas the newly emerging molecular classification is based on data from The Cancer Genome Atlas (TCGA). As the first cancer type studied by TCGA, GBM is divided 'molecularly' into Proneural, Neural, Classical, and Mesenchymal subtypes based on the gene expression profile of four gene sets [5,6]. Proneural GBMs exhibit alterations in *alpha-type platelet-derived growth factor receptor*, point mutations in *isocitrate dehydrogenase (IDH)*, overexpression and activation of the phosphatidylinositol 3-kinase pathway, and inhibition of the translation repressor 4EBP1 [6,7]. The Classical subtype exhibits chromosome 7 amplification and chromosome 10 loss accompanied by *EGFR* amplification/mutation, downregulation of proapoptotic proteins and mitogen-activated

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protein kinase (MAPK), and slightly increased Notch1 and Notch3 levels [6,7]. A predominantly hemizygous deletion of the region at 17q11.2 occurs in Mesenchymal subtypes, which also exhibit enhanced endothelial markers, inflammation markers, an activated MAPK pathway, and decreased mTOR pathway signaling [6,7]. The Neural subtype typically expresses neuronal markers, such as neurofilament light polypeptide, gamma-aminobutyric acid A receptor-alpha 1, synaptotagmin I, and solute carrier family 12-member 5 [6].

The glioma-CpG island methylator phenotype (G-CIMP) is a novel molecular characteristic used in the classification of gliomas. Noushmehr et al. [8] identified G-CIMP in 272 GBMs that exhibited concerted hypermethylation at a large number of loci in the TCGA database. These data were validated in another set of GBMs and low-grade gliomas, where G-CIMP tumors were found to be more prevalent among lower-grade gliomas, suggesting that they belong to the Proneural subtype. G-CIMP tumors share pathway features with the Proneural subtype, accompanied by decreased in Cox-2, IGFBP2, and Annexin 1. Patients with G-CIMP tumors are younger at the time of diagnosis and experience significantly improved outcomes [8]. Brennan et al. [7] confirmed that the G-CIMP phenotype contributes to an improved prognosis in patients with Proneural GBMs by affecting downstream target genes. Molecular changes indicate that most non-G-CIMP mesenchymal GBMs evolved from a Proneural precursor [9].

Turcan et al. [10] demonstrated that the mutation of *IDH1* is sufficient to establish the G-CIMP subtype through methylome remodeling. The authors further tested whether the extensive DNA methylation observed in G-CIMP tumors contributes to the dedifferentiation of glioma cells by treating *IDH1* mutant glioma-initiating cells with a DNA methyltransferase (DNMT) inhibitor. The data suggests that targeting pathological DNA methylation can reverse the hypermethylation status induced by mutation of *IDH1*, block the differentiation of glioma-initiating cells and potentiate tumor control [11]. These findings emphasize the importance of the role of DNA methylation in glioma development and treatment.

3. Biomarkers based on genetic changes

3.1. IDH mutation

IDH is one of the key factors in metabolism that catalyzes the oxidative decarboxylation of isocitrate and produces α-ketoglutarate and CO_2. IDH1 and IDH2 catalyze the same reaction outside the context of citric acid cycle and use $NADP^+$ as a cofactor. Mutations in *IDH* genes (*IDH1* and *IDH2*) are observed in over 70% of low-grade gliomas and a portion of GBMs [10,12,13]. The most frequent *IDH1* mutation (over 95%) occurs at arginine 132 (R132H). The wild-type IDH1 converts isocitrate to α-ketoglutarate (a potential oncometabolite), whereas the mutant IDH1 results in a neomorphic enzymatic function and catalyzes α-ketoglutarate into 2-hydroxyglutarate, which is an oncometabolite that has been associated with genomic hypertension, genetic instability and malignant transformation. *IDH1* mutation is one of the most common and earliest genetic alterations in gliomas and is one of the most effective diagnostic and predictive markers used for glioma patients. Jose et al. [13] investigated the TCGA data and found that the level of pyruvate carboxylase was higher in human gliomas containing an *IDH1* mutation than in those that were wild-type. Fractional flux, which depends on the activity of pyruvate carboxylase, is therefore increased in cells with an *IDH1* mutation. Morteza et al. [14] demonstrated that mutated IDH1-R132H affects phosphoethanolamine and glycerophosphocholine and subsequently alters phospholipid metabolism in glioma.

Forced expression of mutant IDH1 in human astrocytes leads to methylome changes that mimic the pattern observed in G-CIMP-positive low-grade gliomas. Duncan et al. [15] concluded that mutation of *IDH1* is the molecular basis for the G-CIMP phenotype, which highlights the importance of epigenetics in carcinogenesis and in devising therapeutic strategies. Using cluster analysis, Shinawu et al. [16] identified a G-CIMP-positive phenotype in long-term surviving glioma patients and found that it was tightly associated with *IDH1* mutation status. Schumacher et al. [17] found that $CD4^+$ Th1 cells and antibodies spontaneously occurred in patients with IDH1-R132H gliomas and that they specifically recognized IDH1-R132H. This peptide vaccine exhibits an effective mutation-specific antitumor immune response.

3.2. 1p19q co-deletion

Previous studies have demonstrated that loss of genetic information on chromosome *1p* and *19q* occurs frequently in gliomas. Allelic loss in *1p* has been found in gliomas with a major oligodendroglial component: grade II oligodendrogliomas (6/6), grade III anaplastic oligodendrogliomas (5/6), and grade II to III mixed oligoastrocytomas (2/3) [18]. The incidence of allelic loss in *19q* is particularly high in oligodendroglial tumors (81%) and mixed gliomas (31%). More than 75% of tumors with allelic deletion in *19q* also exhibited a loss of heterozygosity in loci in *1p* [19]. Patients with a *1p19q* co-deletion have longer overall survival with radiotherapy [20]. A perspective study revealed that patients with an *1p19q* co-deletion exhibit two-fold longer survival times when treated with radiotherapy combined with PCV (procarbazine, lomustine and vincristine) than those treated with radiotherapy alone [21].

Evidence indicates that *1p19q* co-deletion serves not only as a favorable prognosis factor but also as a predictor for chemosensitivity. Currently, the *1p19q* co-deletion is used in prognosis and treatment response evaluations in combination with other markers for gliomas. Co-deletion of *1p19q* and *MGMT* promoter methylation are independent positive prognostic markers due to the increased sensitivity of tumor cells to radiation and chemotherapy. Furthermore, *1p19q* co-deletion is strongly correlated with *IDH* mutation because tumors with a *1p19q* deletion also exhibit *IDH* mutations. Patient survival is substantially increased when a patient exhibits combined *IDH* mutation, *MGMT* promoter methylation and *1p19q* co-deletion [22,23].

3.3. O^6-methylguanine DNA-methyltransferase (MGMT) promoter hypermethylation

MGMT is a DNA repair enzyme that can directly remove the alkyl group from the O^6-atom of guanine when induced by alkylating agents, such as temozolomide, thereby decreasing tumor cell responsiveness to chemotherapeutic agents. The *MGMT* promoter is frequently methylated in gliomas, which subsequently leads to the loss of MGMT activity [7,24]. Clinical studies have previously demonstrated that *MGMT* promoter methylation is a positive prognostic marker that renders tumors more sensitive to radiation [20]. Substantial evidence indicates that the methylation level of *MGMT* is a positive predictive marker for the responsiveness of newly diagnosed gliomas to alkylation agents [25–27]. Another two prospective randomized phase III trials reported that the promoter methylation status of *MGMT* plays a predictive role in elderly patients who receive temozolomide treatment [28,29]. However, the *MGMT* promoter methylation level is not the only independent predictive marker for temozolomide treatment.