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Progress in the study of markers related to glioma prognosis

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Abstract. – OBJECTIVE: In the era of precision medicine, molecular and genetic biomarkers act as the key indicators for glioma patients' recurrence and prognosis.

MATERIALS AND METHODS: We summarize the biomarkers of glioma prognosis from molecular level, gene level and microRNA level.

RESULTS: In molecular biomarkers, cyclinD1 high expression/P16 low expression, MIF high expression and VEGF high expression were all related to glioma patients' poor prognosis; in genetic biomarkers, MGMT promoter methylation absence, IDH1 wild type, HIF-α high expression, Chromosome 1p/19q non-deletion and TERT promoter mutation were associated with poor prognosis for glioma; in microRNA biomarkers, miR-524-5p, miR-586, miR-433, miR-619, miR-548d-5p, miR-525-5p, miR-301a, miR-210, miR-10b-5p, miR-15b-5p and miRNA-182 high expression, miR-124, miR-128, miR-146b and miR-218 low expression were commonly seen in glioma poor prognosis patients.

CONCLUSIONS: With the continuous development of science and technology, the diagnosis of glioma will tend to the gene and molecular level. Finding specific markers is helpful for the early diagnosis and accurate prognosis of glioma, which provides the possibility for individualized treatment.

Key Words:
Glioma, Prognosis, Markers.

Introduction

Glioma is the most common malignant tumor of the central nervous system[1]. According to tumors' features of cellular atypia, cell proliferation, angiogenesis, and necrosis, the World Health Organization (WHO) further distinguished malignant grades (I to IV) for glioma[2]. The recommended therapy for high grade glioma (HGG) patients is combined therapy with surgery, radiotherapy and chemotherapy, but most patients' survival time is still short[3,4]. Early diagnosis and accurate prognosis assessment of glioma are important clinical problems to be solved.

In recent years, some biomarkers and therapeutic methods of glioma have been continuously discovered and updated[5-7]. The application of non-invasive biomarkers enables the stratification assessment and personalized treatment of glioma, which also significantly improved the prognosis of HGG patients. In this review, we briefly summary the current research progress on markers related to glioma's prognosis.

Clinical Indicators Related to Glioma's Prognosis

Clinically relevant physiological and pathological indicators can predict the survival time

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of HGG patients to some extent. WHO classifies gliomas as I-IV, grade I and II belong to low-grade glioma (LGG), and the average survival time of LGG patients is 2 to 4 years; grades III and IV belong to high-grade glioma (HGG), HGG patients' the average survival time is about 1 to 2 years, while many grade IV patients' survival time often less than 1 year[8]. A study[9] of 605 HGG patients found that the 1-year overall survival rate of patients younger than 40 years of age was significantly higher than those older than 40 years of age. Patients with no convulsions before surgery had an average survival time of 15.11 months, while patients with convulsions had an average survival time of 25 months[9]. The Karnofsky Performance Scale (KPS) is essential for predicting survival in HGG patients. In the HGG patients with a preoperative KPS score higher than 70, the median survival time was 17.08 months, while the HGG patients with a preoperative KPS score below 70 had a median survival time of only 13.5 months[10].

The microblood vessel countation (MVC) count can reflect the growth, invasion and migration of the tumor. In HGG, microvascular proliferation is significantly increased, and permeability is also increased to varying degrees. Therefore, microvascular density, maturity and permeability can be used as indicators of tumor prognosis. Intraoperative contrast enhanced ultrasound (CEUS), conventional magnetic resonance imaging (MRI) and Dynamic contrast-enhancement magnetic resonance imaging (DCE-MRI) are both imaging techniques that reflect tissue hemodynamics. Conventional MRI could be used to assess microvascular permeability in HGG patients by analyzing the proportion of immature microvessels[11]. HGG is characterized by rapid growth of tumor microvessels, incomplete vascular wall and significant edema around the tumor. These characters could be captured by real-time intraoperative CEUS, contrast agent can be rapidly filled in the tumor, and the imaging intensity is significantly increased in the tumor area, which can be in sharp contrast with the surrounding normal blood vessels. CEUS's quantitative analysis of imaging intensity can indirectly reflect the malignant degree of glioma. It contributes to glioma grading, accurate localization, it improves surgical resection rate, as well as prognosis and it also has extremely important clinical reference value. However, CEUS cannot accurately measure tumor volume and is also influenced by operator skill and experience[12]. Although with the development of three-dimensional ultrasound imaging technology, the above problems have been solved to some extent[13]. But there is still no uniform standard for CEUS on glioma's grading and diagnosis.

DCE-MRI has been shown to be more accurate in responding to microvascular density and histopathological grading and it has also been widely used to evaluate the prognosis of a variety of malignancies. Allarakha et al[14] found that DCE-MRI can improve the accuracy of tumor area recognition in breast cancer patients. However, the visual evaluation is greatly influenced by the doctors' subjective consciousness, and its repeatability is poor. In the past decade, computer-assisted diagnosis (CAD) has been widely used in the diagnosis and prognosis of diseases. Combining DCE-MRI with CAD system automated quantitative technology can make objective and digital quantitative analysis of tumor lesion range and microvessel density, reduce misdiagnosis rate and improve the accuracy of diagnosis and prognosis. However, there are few reports on the application of CAD system automated quantitative technology to the diagnosis of glioma in the field of DCE-MRI imaging, and further research is needed.

Molecular Biomarkers

In recent years, biomarkers at the molecular level have been gradually accepted as indicators of glioma development and prognosis. The ideal molecular biomarker needs to be highly sensitive and specific, thus it should be closely related to the pathogenesis of the disease. The current research shows that the occurrence and development of glioma is a complex and multi-step process, glioma cell cycle abnormality and cell proliferation are the main mechanism[15]. Cyclin-dependent kinase inhibitor D1(cyclinD1) and cell cycle-dependent kinases (CDKs) are key factors in regulating the cell cycle. CyclinD1 is a positive regulator of cell cycle progression[16]. P16 also known as CDKN2, inhibits cell proliferation by inhibiting CDK4 and CDK6 kinase activity, P16 is a typical cell cycle negative regulator[17]. Zhao et al[18] found the expression of CyclinD1 and P16 in HGG patients' tumor tissues and precancerous tissues. CyclinD1's expression in tissues was positively correlated with pathological grade, cyclinD1 expression was highest in glioma grade IV patients. CDKN2 was negatively correlated with tumor grade. Finally, researchers concluded that CyclinD1 and p16 may be independent biomarkers for judging the clinical prognosis of glioma[18]. Combined detection of

CyclinD1+/P16- expression may predict the poor survival of glioma[18]. Macrophage migration inhibitory factor (MIF) is an important multifunctional cytokine released and activated by macrophages, T cells and pituitary glands. MIF can control the cell cycle inhibitor P27 and tumor suppressor P53 by inhibiting the JUN-activated domain-binding protein (JAB1), thereby controlling tumor cell proliferation[19]. MIF also increases the expression of erythropoietin (EPO) in glioma cells and promotes proliferation and angiogenesis. Wang et al found that high expression of MIF was closely associated with postoperative recurrence and prognosis in HGG patients, they considered MIF could be used as an independent predictor of prognosis in HGG patients[20].

Vascular endothelial growth factor (VEGF) can directly or indirectly participate in the invasion and angiogenesis of malignant tumors. It is the prognostic biomarker and potential therapeutic target for many malignant tumors. Yuan et al[21] found that the expression of VEGF is related to the glioma's pathological grade, and VEGF can be used as a biomarker for glioma's diagnosis, combined detection with Ki-67, VEGF and nuclear magnetic resonance can not only accurately determine the degree of glioma malignancy, but also effectively evaluate patients' prognosis. Another important mechanism for the development of glioma is that glioma cells can escape from immune surveillance through a variety of mechanisms. Detecting the patient's immunity helps to improve the predictive accuracy of the patient's prognosis[22]. Guan et al[23] found that SLC9A1 can mediate PD-1/PD-L1 signaling pathway involved in glioma cells' immune escape by activating $CD3^+$T and $CD8^+$ T lymphocytes. The prognostic value of $CD3^+$T and $CD8^+$ T lymphocytes for colon cancer has also been confirmed[23,24]. Changes in the patient's blood $CD3^+$ T and $CD8^+$ T lymphocytes can also reflect the degree of disease. PD-L1 and receptor PD-1 work together to maintain the body's immune homeostasis and participate in tumor cell immune escape. By blocking PD1/PD-L1 could effectively prevent tumor immune escape. The prospect of PD-1/PD-L1 in glioma's treatment and prognosis evaluation is promising.

Gene Biomarkers

MGMT promoter methylation and glioma

DNA methylation is an extra-genetic modification which is catalyzed by DNA methylase. Abnormal methylation plays an important role in the tumors' development. O6-Methylguanine-DNA -methyltransferase (MGMT) is a DNA repair enzyme which is found in almost all organisms. It is also the most studied methylase. MGMT protects chromosome damage and plays an important role in tumor development, drug resistance and radiotherapy resistance. It was found that the increase of methylation status and down-regulation of MGMT can significantly increase the cancerization of glioma cells.

O6 guanine complexes removed from DNA are closely related to preventing DNA mutation damage[25]. Alkylating agents are mainly used to treat tumors by inducing tumor cells' DNA damage, forming DNA cross-linking, and blocking DNA replication. MGMT can prevent the formation of DNA cross-linking, then reducing the cytotoxicity of alkylating agents and affecting the effects of chemotherapy. Hegi et al[26] considered glioblastoma patients with methylated MGMT promoter benefited by temozolomide (Temodal®, Temodar®, Merck & Co, White House Station, NJ, USA), while those who did not have a methylated MGMT promoter did not have such benefit. However, Mur et al[27] found that MGMT methylation was extensively heterogeneous in HGG patients. MGMT methylation was only associated with prognosis in patients over 65 years of age. MGMT methylation is an important indicator to judge whether patients need to receive chemotherapy and it may need to be combined with other biomarkers in the prognosis of glioma.

IDHI mutant and glioma

Isocitrate dehydrogenase 1 (IDH1) is mainly localized in cytosol and requires NADP+(nicotinamide adenine dinucleotide phosphate) as an electron and hydrogen acceptor. Parsons et al[28] firstly sequenced 20661 protein-coding genes of 22 glioma samples and found that 12% of patients with glioblastoma multiforme (GBM) had repeated mutation in the IDH1 active site, and IDH1 mutation occurred mostly in young and secondary GBM. Subsequently, Carli et al[29] found IDH1 mutant in more than 70% of WHO grade II and III astrocytomas and oligodendrogliomas, patients with IDH1 mutant had a better outcome than those with wild-type IDH genes. Sonoda et al[30] show that IDH1 mutation occurs frequently in anaplastic oligodendroglioma, secondary glioblastoma, oligodendroglioma, anaplastic astrocytoma, anaplastic ganglion tumor and ganglion glioma, the mutation rate is 75%, 67%, 67%, 62%, 60% and38%, but in primary glioblastoma the mu-

tation rate is lower, only 5%. Lv et al[31] indicate that IDH1 mutant is tissue-specific and it plays a unique role in the development of high-grade gliomas.

Bleeker et al[32] suggest IDH1 mutation may also correlate with the benefit from VEGF(R)- *vs*. EGFR-targeted therapy at the time of recurrence in glioma patients.

Li et al[33] found mutation of the IDH1gene increases glioma chemosensitivity. IDH1 gene mutation disrupts the stability of the active center of IDH1, reducing the binding capacity of the active center to isocitrate, and their binding products are key kinases of the enzymatic reaction, which inhibit the cycle of the tricarboxylic acid.

Thus, it also reduces the production of α-ketoglutarate (α-KG) and further reduces the produced α-KG to 2-hydroxyglutarate (2HG)[34]. On the one hand, α-KG is closely related to the formation and stability of hypoxia-inducible factor α (HIF-α)[35]. HIF-α plays an important role in the development of tumors[36]. Liu et al[37] found that HIF-α is associated with glioma's pathological grade. In glioma patients with high HIF-α expression, the higher pathological grade, the worse the prognosis. On the other hand, a large accumulation of 2HG affects the activity of DNA demethylase, leading to tumorigenesis[38]. Bralten et al[39] reported that supplementation of exogenous α-KG can reverse the occurrence and development of glioma, which also provide new ideas for the development of glioma treatment.

Chromosome 1p/19q deletion and oligodendroglioma

The chromosome 1p/19q deletion was first discovered in oligodendrogliomas[40], and subsequent studies have shown that 1p/19q deletion occurs mainly in low-grade oligodendrogliomas[41]. 1p/19q deletion rate in WHO II grade oligodendroglioma patients is about 70%, and in WHO grade III oligodendroglioma patients is about 15%[42]. 1p/19q deletion's incidence rate is lower in astrocytoma and glioblastoma, approximately about 12% and 3%[43]. Odia et al[44] found that in glioma the 1p/19q deletion was secondary to the IDH1 mutation. The 1p/19q assay may help identify glioma sources and pathological grades.

Co-deletion of chromosome 1p/19q increased survival in patients with low-grade gliomas and oligodendrogliomas, these patients' median survival time was twice more than the 1p/19q non-deletion patients[45]. At the same time, 1p/19q deletion increased the sensitivity of chemotherapeutic drugs[46]. According to the National Comprehensive Cancer Center Network (NCCN) guidelines, the standard treatment for oligodendroglioma patients with 1p/19q deletion was surgical resection combined with chemotherapy alone[47]. Eckel-Passow et al[48] believe that the combination of 1p/19q mutation and TERT promoter mutation, IDH mutation and pathological indicators can accurately reflect the prognosis, and they didn't consider 1p/19q deletion as an independent prognostic factor for glioma.

TERT promoter mutation in glioma

Human telomerase reverse transcriptase (hTERT) is located on chromosome 5p15.33 and is a major component of telomerase. Telomerase can protect chromosome integrity and as an important regulator for cell immortality, it could promote the tumor cells' continuous proliferation[49].

Zhou et al[50] the TERT promoter mutation is significantly associated with the risk of glioma, with the highest mutation rate in glioblastoma, astrocytoma, and oligodendroglioma. TERT promoter mutation is also associated with races. The highest incidence of TERT mutation was found in Caucasian HGG patients. TERT promoter mutation mainly occurs in patients with HGG at grades III and IV, the survival time of the mutant patients was significantly shorter than that of the wild type[51].

MicroRNA and glioma

MiRNAs bind to the characteristic 3'UTR region of mRNA and are involved in cell proliferation, apoptosis, and differentiation by regulating transcription and translation. Abnormal miRNAs can cause the expression of downstream oncogenes and tumor suppressor genes to be out of control, leading to the occurrence or deterioration of tumors. The results of glioma tissue showed that some miRNAs increased or decreased significantly in glioma tissues, and the expression of miRNA in glioma tissues was studied in-depth, which was helpful for pathological grade and prognosis evaluation of HGG patients[52]. MiR-524-5p, miR-586, miR-433, miR-619, miR-548d-5p, miR-525-5p and miR-301a are expressed in different pathological grades of gliomas, and their expression was positively correlated with poor prognosis in HGG glioma patients[53]. With the increasing researches on miRNA, more miRNA related to the prognosis in the patients with glioma had also been discovered. In glioblastoma patients' serum samples, the expression of miR-210 was approximately 7 times higher than healthy controls[54]. MiR-210 mediates the development of glioma mainly by enhancing the self-renewal capacity of mesenchymal stem cells and participating in angiogenesis[55].

Studies have found that miR-124, miR-128, miR-146b and miR-218 are under expressed in glioma tissues. It is found that downregulation of the above miRNAs can promote glioma cell proliferation and inhibit apoptosis *in vitro*. The mechanism may be related to activation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)[56]. TRAIL is a member of the TNF family that binds to the death receptors DR4 and DR5, activates the caspase signaling pathway, and induces rapid and massive apoptosis in cells, thereby killing tumors. Xiao et al[57] found 591 miRNAs differentially expressed between LGG and normal tissues, and screened out two miRNAs (miR-10b-5p and miR-15b-5p) related to pathological grades by regression analysis. It was found that miR-10b-5p and miR-15b-5p are closely related to the overall survival time of patients in low-grade tumors and can be used as an independent biomarker. Lu et al[58] found a method based on gold nanoparticle fluorescence quenching technology to detect the tumor level and prognosis of HGG patients by detecting the expression level of miRNA-182 in human blood. These studies indicate that some of the miRNAs in the blood circulation may be potential diagnostic and prognostic biomarkers for gliomas.

With the continuous development of science and technology, the diagnosis of glioma will tend to be at the genetic and molecular levels. Finding specific molecular markers contributes to the early diagnosis and accurate prognosis of gliomas, providing the possibility of personalized treatment.

Discussion

Glioma is a heterogeneous, recrudescent central nervous system tumor with a very poor prognosis. At present, the treatment of glioma is mainly based on surgery combined with radiotherapy and chemotherapy, but the patient's postoperative survival time is still short, the treatment effect is limited, which caused the patient has a great burden on the physiological, psychological and economic. Therefore, the diagnosis and treatment of glioma have been the most challenging subject in neurosurgery. Prognostic predictors help patients' disease grading and accurate prognosis evaluation, providing the possibility for personalized treatment. Traditional prognosis indicators rely mainly on clinical pathological grades, but gliomas have unique growth and biological characteristics. The intracranial structure is complex, and the high grades gliomas are invasive. it is extremely difficult to define the boundary with surrounding normal tissues, which seriously affects the therapeutic effect of glioma. With the widespread use of imaging and computer technology in the clinic, the therapeutic effect and prognosis accuracy have been further improved, new markers help us to be more aware of the potential and complex interrelations of glioma. In recent years, glioma molecular biomarkers and gene biomarkers have also been gradually discovered and recognized. In this review, we summarized the biomarkers of glioma prognosis from molecular level, gene level and microRNA level, specific markers were shown in Table I.

Table I. The summary of makers related to glioma prognosis.

Markers	Poor prognosis of glioma
Clinical	WHO grade IIII-IV
	age>40
	Convulsions
	KPS>70
Molecular biomarkers	CyclinD1 high expression/P16 low expression
	MIF high expression
	VEGF high expression
Gene biomarkers	MGMT promoter methylation absence
	IDH1 wild type
	HIF-α high expression
	Chromosome 1p/19q non-deletion
	TERT promoter mutation
MicroRNA	miR-524-5p, miR-586, miR-433, miR-619, miR-548d-5p, miR-525-5p and miR-301a high expression
	miR-210 high expression
	miR-124, miR-128, miR-146b and miR-218 low expression
	miR-10b-5p and miR-15b-5p high expression
	miRNA-182 high expression

Conclusions

The future diagnosis and prognosis of glioma is the "integration" diagnosis of pathological grade, molecular markers and gene markers. We believe that with the development of more basic and clinical research, pathogenesis of glioma will gradually be clarified, prognosis prediction and treatment selection would be individualized and precise.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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