Research progress of glioma-related molecular markers

Lai Xiong†, Xiao Qi Xie‡, Wei Ming Li§, Xin Wu, Yong Luo, Ping Ai, Feng Wang*, Deng Bing Wu*, Yuan Zhao Liu, Jing Bo Kang, Ruoyu Wang, Bao Lin Qu, Xian Feng Li, Jun Jie Wang

1Department of Medical Oncology, Cancer Center, West China Hospital, West China Medical School, Sichuan University, Sichuan, P.R. China
2Department of Critical Care Medicine, West China Hospital, Sichuan University, Sichuan, P.R. China
3Precision medicine center, West China Hospital, Sichuan University, Sichuan, P.R. China
4Cancer Hospital, Ansteel Group Hospital, Anshan, Liao Ning, P.R. China
5Department of Radiotherapy, Beijing Hospital, Beijing, P.R. China
6Department of Radiotherapy, The Sixth Medical Center of PLA General Hospital, Beijing, P.R. China
7Department of Medical Oncology, Affiliated Zhongshan Hospital of Dalian University, Dalian China
8Department of Radiotherapy, Chinese PLA General Hospital, Beijing, P.R. China
9Department of Radiotherapy, First Hospital of Shanxi Medical University, Taiyuan, Shanxi, P.R. China
10Department of Radiation Oncology Cancer Center Peking University 3rd Hospital, P.R. China

† Authors contributed equally

* Corresponding authors: Wei Ming Li*, Feng Wang*, Deng Bing Wu*

E-Mail: wangfeng5024@126.com (Feng Wang)
Abstract:

Glioma is a primary brain tumor with a high incidence and a poor prognosis. Although it is treated by surgery, radiotherapy and other methods, the prognosis of patients is still not satisfactory. With the continuous development of medical technology, more and more Many biological molecular markers are recognized. The combined deletion of 1p / 19q is considered to be a characteristic molecular marker and independent prognostic factor in oligodendro glioma, and it can also be used as an important indicator to evaluate the sensitivity of chemotherapy. MGMT promoter methylated glioma patients are often more sensitive to chemotherapy drugs. IDH1 mutations occur widely in different types of gliomas such as oligodendroglioma and diffuse astrocytoma and suggest a good prognosis. The most common type of EGFR mutation is EGFRv III, which can enhance tumorigenicity, proliferation, migration and invasiveness of tumor cells. Positive EGFRv III in tumor tissues indicates a poor prognosis. CAR-targeting EGFRv III T-cell adoptive immunotherapy for glioblastoma multiforme has become a research hotspot. VEGF can promote angiogenesis in gliomas, and its expression is related to the pathological grade of gliomas. TERT activation Mutations can enhance telomerase activity and lead to unlimited proliferation of tumor cells. The mutation rate of BRAF is higher in low-grade gliomas such as hairy cell astrocytoma and children's gliomas. ATRX gene mutation, TP53 gene mutation, ppENK activation Methylation of the daughter is also of diagnostic significance for the precise pathological typing of gliomas. In addition, some miRNAs and Inc RNAs have become a hot topic in the field of glioma molecular markers. With more and more of these molecules With the study of markers, we are continuously moving towards the precise diagnosis of glioma, individualized treatment and improvement of prognosis.

Keywords: glioma, prognosis, molecular markers

Foreword:

Glioma is one of the common primary tumors in the skull [1], with a high incidence and recurrence rate and a poor prognosis. It is difficult to completely remove the operation, and the survival time is short, which poses a greater threat to human health. World Health Tissue gliomas are divided into four grades, grades i and ii are low-grade gliomas, grades iii and iv
are high-grade gliomas, of which high-grade gliomas are more invasive and the patient's The prognosis is poor [2]. At present, the treatment of glioma is mainly surgery or surgery plus chemoradiation. Postoperative patients have a high recurrence rate and a limited survival time, which has caused patients with certain physical, psychological, and economic factors. Therefore, the diagnosis and treatment of glioma is still a big problem. With the continuous expansion and deepening of clinical research and science and technology, biological markers and molecular pathological typing can diagnose and treat a variety of diseases. Provide assistance. Early diagnosis, evaluation of prognosis, and treatment options for gliomas combined with molecular markers based on histology have become a major advance in the diagnosis and treatment of gliomas. Exploring effective early diagnosis and accurate prognosis of gliomas Evaluation indicators provide patients with personalized treatment means and improve the survival rate of patients has important clinical implications. In this review, we collect the relevant article reviews the progress at home and abroad for glioma prognostic molecular markers set forth.

1. Joint deletion of 1p / 19q chromosome

1p / 19q combined deletion (loss of heterozygosity (LOH)) refers to an unbalanced translocation on the chromosome (1; 19) (q10; p10). The incidence of 1p / 19q combined deletion in oligodendrocyte tumors is 80% ~ 95%, about 40% to 60% in oligodendroblastoma [3]. At present, the combined deletion of 1p / 19q is considered to be a characteristic molecular marker [4] in oligodendroglioma. The detection of 1p / 19q combined deletion has diagnostic significance for the classification and pathological classification of gliomas.

Studies have confirmed that the prognosis of oligodendroglioma patients with 1p / 19q combined deletion is often better, with a median survival of approximately 2 times that of non-deleted patients [5], and the sensitivity of these patients to chemotherapy drugs is relatively Patients who are not missing are higher [6]. A 2012 European Cancer Therapeutic Research Organization (EORTC) and Radiation Therapy Oncology Group (RTOG) study showed that patients with anaplastic oligodendroglioma with 1p19q combined deletion undergo concurrent chemotherapy during radiation Can extend the overall survival of patients [7,8]. Some scholars have shown that 1p / 19q combined deletion can be used as an independent prognostic factor [9] for oligodendroglioma. Therefore, 1p / 19q combined deletion can be used as oligodendrocyte Plasma cell tumors are an important indicator for
assessing chemotherapy sensitivity and prognosis, but their prognosis and clinical significance in other types of gliomas need more research to explore.

2. MGMT promoter methylation

O6-methylguanine-DNA-methyltransferase (MGMT) is a DNA repair enzyme that has been studied extensively and is widely present in living organisms, with a molecular weight of 22KDa, which can repair DNA damage caused by alkylating agents, leading to patients Resistance to temozolomide (TMZ) and nitrosourea chemotherapeutics [10]. These chemotherapeutics can induce tumor cell DNA damage, form DNA cross-links and block DNA replication to inhibit tumor development. Can inhibit tumor cell DNA cross-linking to affect the effect of chemotherapy. Therefore, this DNA repair enzyme affects the development of glioma and chemotherapy resistance. MGMT gene is located on chromosome 10q26, and abnormal methylation of this gene will cause MGMT The protein expression is reduced, which inhibits the development of tumors. MGMT promoter methylation has been found in WHO grade II-IV gliomas, which is considered to be a molecular marker for judging the prognosis of glioma and predicting the effectiveness of treatment. One [11]. Studies have shown that radiotherapy combined with temozolomide chemotherapy can increase the overall survival of elderly glioblastoma patients compared with radiotherapy alone [12]. A prospective cohort study of high levels of MGMT promoter unmethylation Brain glueThe prognosis of tumor patients and methylated patients after temozolomide chemotherapy was found, and the average total survival time of the two groups was 1.8 and 10.6 months [13]. One included 11 MGMT states and glioblastoma. In the meta-analysis of the survival correlation study of WHOIV patients, genetic testing confirmed the methylation status of MGMT promoter in all patients. It was found that patients with glioblastoma methylated by MGMT promoter had lower OS and PFS than non-methylated patients. Both were prolonged [14]. In another meta-analysis, compared with patients with MGMT promoter unmethylated glioblastoma, OS in methylated patients was prolonged, but there was no significant difference in PFS between the two groups [15]. Gene testing for MGMT promoter methylation in at least glioblastoma patients has clinical significance in judging prognosis and selecting treatment options.
3. Isocitrate dehydrogenase (IDH)

Isocitrate dehydrogenase (IDH) catalyzes the oxidative decarboxylation of isocitrate into α-ketoglutarate (α-KG) during the tricarboxylic acid cycle of the cell. At present, IDH1, IDH2, and IDH3 isozymes. IDH1 and IDH2 belong to nicotinamide adenine dinucleotide phosphate acid (NADP +)-dependent homodimer, both of which mainly catalyze in the tricarboxylic acid cycle. IDH1 is present in the cytoplasm and peroxisomes, and plays an antioxidant role to protect cells from damage. IDH2 and IDH3 are present in mitochondria, IDH3 is nicotinamide adenine dinucleotide (reduced nicotinamide adenine dinucleotide (NAD +)-dependent heterotetramerase, mainly provides energy for mitochondrial sugar metabolism, and the reaction process catalyzed by it is irreversible, and IDH1, IDH2 catalyzed reaction process is reversible. Closely related to gliomas are also IDH1 and IDH2, and IDH3 mutations are currently not found in gliomas, probably because IDH3 has a limited role in the progression of gliomas.

The relationship between the mutation of isocitrate dehydrogenase and the development, prognosis and treatment of glioma has been the focus of current research. IDH1 mutations occur widely in oligodendroglioma, diffuse astrocytoma, anaplastic star Glioblastoma, anaplastic oligodendroglioma, anaplastic ganglioglioma, secondary glioblastoma and other types of gliomas, but in primary glioblastoma The mutation rate in cell tumors is at a low level of only 5%. At the same time, the literature shows that IDH1 mutations can also occur in other different types of tumors such as melanoma, acute myeloid leukemia, cholangiomas, and chondroma. In gliomas, the mutation of IDH1 is mainly due to the conversion of arginine to histidine at position 132. The mutation of IDH2 is located at position 172, which is related to the occurrence of oligodendrocyte glioma It is currently found that IDH1 and IDH2 are less mutated at the same time, which may be different due to the mutual exclusion of the occurrence mechanism. The mutation frequency of IDH1 in glioma is higher than that of IDH2. The IDH1 mutation rate is higher in young patients than in older patients. Higher. IDH1 mutations and their accompanying mutationsGlioma histological types may also have some relevance. Often accompanied by co-chromosome deletion 1p19q when oligodendroglioma IDH1 mutation, but astrocytoma IDH1 mutations are mainly associated with TP53 mutations.

IDH1 mutations are closely related to the prognosis of glioma patients. Patients with IDH mutations often have a better prognosis than tumor patients without mutations. Studies have shown that IDH1 mutations combined with 1p19q combined deletion of glioma patients are
effective in chemotherapy Better than other types\textsuperscript{[24]}. Currently there are more and more studies on glioma IDH mutations. Now IDH mutations can not only help distinguish different pathological categories or lineages of gliomas, but IDH mutation status may become in the future. One of the foundations for the separation of different subtypes of gliomas provides a more reliable basis for the subdivision of glioma pathological types and the selection of precise and accurate treatment options.

4. Epidermal Growth Factor Receptor (EGFR)

Epidermal growth factor receptor, as a member of the Erb B receptor family, affects cell proliferation and growth through the activation of the PI3K-Akt pathway\textsuperscript{[25]}. The Erb B receptor family includes the epidermal growth factor receptor, HER2, Erb B3 and Erb B4, they are composed of extracellular ligand binding part, transmembrane intracellular and extracellular information transmission part, intracellular activation part and downstream ligands. The downstream subsequent reactions are closely related to cell division and proliferation and migration invasion. It has been confirmed that it is mutated or over-expressed in tumors. The most common type of EGFR mutation is epidermal growth factor receptor type III (EGFRvIII). Many studies have found that EGFRvIII is used in lung cancer, kidney Cell cancer, breast cancer, ovarian cancer and other human tumors are expressed\textsuperscript{[26-28]}. The mutation site is the extracellular ligand binding site. It is mainly due to the second to seventh exons of the 26 exons Deletion of 801 base pairs caused by deletion of deletions, and the deletion end is connected by a new glycine codon, so that EGFRvIII deletes 267 amino acids in the extracellular region bound to the ligand, and a glycine residueFusion group replaces the extracellular region of 6 to 273 amino acids at the fusion site and forms EGFRvIII\textsuperscript{[29]}. Because it lacks the extracellular ligand binding region and cannot bind to the ligand, the receptor does not require ligand-dependent activation of tyrosine Kinases can induce autologous phosphorylation to activate multiple downstream signaling pathways, including multiple signaling pathways such as mitogen-activated protein kinases, which cause cascades, which affect tumor cell proliferation and inhibit apoptosis, and EGFRvIII also enhances tumors. Cells are tumorigenic, proliferative, migratory, and invasive\textsuperscript{[30]}. Unlike wild-type EGFR, which is mainly located on the cell membrane, EGFRvIII is mainly present in the cytoplasm, which suggests that the two have different transport, signal transduction, and degradation pathways.
EGFRvIII is only expressed in tumor tissues, and its high expression is closely related to the tumorigenesis and development of patients and the patient's prognosis. The relationship between EGFRvIII and common recurrent glioblastoma multiforme glioblastoma is widely studied. Glioma-like tumors are rich in blood vessels and show invasive growth. More than half of EGFR overexpressing patients with glioblastoma (Glioblastoma, GBM) are positive for EGFRvIII, and often accompanied by PTEN deletion, which suggests that EGFRvIII Overexpression may lead to invasive loss of PTEN function. This type of patients has a poor prognosis and a short survival time. Even after surgery, radiotherapy and chemotherapy, the median survival time is still short. With tumor-related science such as molecular biology With the continuous improvement of gliomas treated by single surgery, it has gradually been replaced by multi-modal comprehensive treatments such as radiochemotherapy and molecular targeted therapy. Recently, people have paid attention to the individualized treatment of molecular targeted drugs because of its high Specificity and low side effects. Therefore, finding molecular targets related to glioblastoma multiforme is of great significance for the treatment of this type of glioma.Glioblastoma has a high EGFRvIII expression rate, about 30% -40%, and EGFRvIII is only expressed in tumor tissues, so it is a very ideal target for glioblastoma multiforme \[31\].Researches continue to explore the immunotherapy of glioblastoma targeting EGFRv III, including dendritic cell vaccines, peptide vaccines, monoclonal antibodies, and Chimeric antigen receptor (CAR) T-cell adoptive cells. Immunotherapy. Adoptive CAR-T cell adoptive immunotherapy for EGFRvIII as a target for the treatment of glioblastoma multiforme has become a research hotspot. T cells express genetically modified CAR to produce tumor targeting and killing activity. T cells that are more able to interfere with the tumor's immunosuppressive microenvironment. This in vitro genetic modification to enhance the targeting and lethality of T lymphocytes is the advantage of adoptive immunotherapy over active immunity \[32\]. These advantages make CAR-T cell immunotherapy can eliminate the immune tolerance of tumor patients to traditional treatment. A team of studies has confirmed that CAR-T cells targeting EGFRvIII in malignant mice with immune functionThe tumor model can survive for a long time in vivo and the recurrence rate of mouse EGFRvIII-positive glioma is greatly reduced \[33\]. This CAR-T cell adoptive immunotherapy has the effect of effectively inhibiting tumor growth and reducing the related mortality of patients with glioblastoma. Great application prospects. In addition, Rindopepimut, a peptide vaccine approved by the US FDA, can induce EGFRvIII-specific cellular and humoral immunity. Studies have also confirmed that dendritic cell vaccines can induce EGFRvIII-specific cellular immunity and inhibit tumors ( \[34\] . With the continuous
research progress of the EGFRvIII signaling pathway, the immunotherapy as a target is undoubtedly a future direction for the treatment of malignant gliomas.

5. **Vascular endothelial growth factor (VEGF)**

VEGF belongs to one of the members of the platelet-derived factor family. It is a biologically active glycoprotein with a relative molecular weight of 34 to 46 kD. It is a major regulator of angiogenesis. The VEGF family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor (PIGF), of which VEGF-A is the main regulator of angiogenesis, and VEGF-C and VEGF-D are related to lymphangiogenesis VEGF combines with specific receptors on vascular endothelial cells to affect the migration, proliferation, survival and permeability of endothelial cells (EC), thereby promoting angiogenesis and development and vascular permeability. After specific binding, the downstream intracellular kinase is activated, and the vascular endothelial cell signaling is completed through the cascade reaction, which enhances the cell mitotic proliferation ability, and at the same time the vascular endothelial cell migration and deformation ability is also improved and effectively improves vascular permeability. The microvessel angiogenesis constitutes a new tumor blood supply network.[35] VEGF has been reported in many malignant tumors such as esophageal cancer, breast cancer, liver cancer, lung cancer and colon cancer..VEGF variety of malignancies as prognostic biomarker and a potential therapeutic target.

Due to the hypoxia caused by the rapid proliferation of malignant glioma cells, this can promote the release of VEGF by tumor cells and promote angiogenesis in gliomas. Some scholars have found that the expression of VEGF is related to the pathological grade of gliomas. It is helpful for the diagnosis of glioma, and the combined detection of VEGF with Ki-67 and MRI can also improve the accuracy of judging the malignancy of glioma and effectively assess the prognosis of patients.[36] Now the main clinical VEGF inhibitors include Bevacizumab, Vatalanib, Vandetanib, etc.

6. **TERT promoter mutation**

The telomerase reverse transcriptase (TERT) gene is located at the end of the short arm of chromosome 5 5p15.33. The gene encodes TERT, which is an important part of telomerase. It is important for protecting the integrity of chromosomes and promoting tumor cells.
Continuous proliferation has important regulatory effects. Therefore, it has a certain effect on the occurrence and development of malignant tumors. TERT promoter mutations (TERT promoter mutations) are mainly cytosine (C) mutations at the 250 and 228 sites on the promoter. It is thymine (T), which results in the up-regulation of TERT mRNA expression, which enhances telomerase activity and leads to unlimited proliferation of tumor cells [37]. Some studies have shown that in astrocytoma, oligodendrocyte glioma, and glioblastoma, the highest mutation rate in cell tumors indicates that TERT promoter mutations are related to the risk of gliomas [38]. In addition, TERT promoter mutations occur mainly in patients with high-grade gliomas, and compared with wild-type patients, the mutant type shows a shorter postoperative survival time of the patient [39] indicates that the TRET promoter mutation is correlated with the prognosis of high-grade glioma patients. Studies have found that the TERT promoter mutation in glioma blastomaIDH gene mutations are significantly negatively correlated with EGFR amplification [40]. However, other scholars have found that in patients with primary glioblastoma, mutants of the TERT promoter and TERT promoter There is no significant difference in survival of wild-type patients [41]. Therefore, whether the TERT promoter can be used as one of the prognostic indicators in glioma is still controversial, and further research is needed to explore its important role.

7. Braf gene mutation

The V-RAF murine sarcoma viral oncogene homolog B1 (V-RAF murine sarcoma viral oncogene homologue B1, BRAF) gene is located on the long arm q34 of chromosome 7, and is a member of the RAF gene family. It is mainly found in testis and nerve tissues. In it, its serine / threonine-specific kinase encodes an important part of the Ras / Raf / Mek / Erk signaling pathway that regulates cell growth, proliferation, and apoptosis. Melanoma, bile duct cancer, ovarian cancer, colorectal cancer, and Mutations in the BRAF gene can be found in tumors such as thyroid papillary carcinoma. The BR600 gene V600E mutation is a mutation of thymine (T) to adenine (A) at the 1799 base site, which causes valine at the site to mutate to the valley Amino acid [42] The mutation of BRAF gene changes the activity of BRAF, and the abnormal activation of MEK-ERK signaling pathway leads to the proliferation of cells and induce tumors.

Some research results show that low-grade gliomas such as hairy-cell astrocytoma and children with glioma have a higher mutation rate of braf, and inhibitors of the braf v600e
mutation have a certain effect on treatment [43]. It has been found in pediatric neurocytic glioma, pleomorphic xanthocytoma astrocytoma, diffuse astrocytoma, and anaplastic astrocytoma. Some scholars believe that braf v600e mutation and epithelioid glioblastoma. The clinical grade of cell tumors is closely related, which can make it develop from a low level to a high level, indicating that the braf v600e mutation can be used as one of the indicators to predict the potential risk of tumor malignancy [44].

At present, the treatment of tumor patients with BRAF V600E mutations is mainly using simple BRAF inhibitors or inhibitors combined with radiation therapy. BRAF V600E inhibitors can reduce MPAK activity, inhibit the cell cycle, and promote apoptosis to inhibit tumor development. Some scholars Studies of patients with melanoma with BRAF V600E mutations have shown that BRAF V600E inhibitors can effectively prolong patient survival and improve their quality of life [45]. Therefore, BRAF V600E inhibitors may provide new directions for glioma drug treatment research. However, in Drug resistance and adverse reactions during the application of inhibitors or combined radiotherapy in the treatment of gliomas are a major obstacle to its clinical application. Patients with glioma who received radiotherapy combined with BRAF V600E inhibitor Vemurafenib were found to cause inhibition Agent-associated dermatitis, and even radiation-associated pneumonia and proctitis [46]. Therefore, how to use the inhibitor to avoid related adverse reactions will be one of the research topics in the future.

8. ATRX gene mutation

α-thalassemia / mental retardation syndrome X-linked (ATRX) gene is located on the long arm q21.1 of the X chromosome, and its encoded ATRX protein serves as an important part of various cellular pathways One is that it plays an important regulatory role in many aspects such as DNA replication, damage repair, and gene transcription regulation. Compared to adult high-grade gliomas, ATRX gene mutations occur in younger low-grade gliomas. More common in patients with tumors [47], and in IDH-mutated astrocytomas and anaplastic astrogliomas, IDH-mutated glioblastomas, ATRX gene mutations often coexist with TP53 gene mutations [48]. The coexistence of ATRX gene mutation and IDH gene mutation indicates that the pathological type of glioma may be astrocytoma or secondary glioblastoma derived from it, which also indicates that ATRX gene mutation is important for judging glioblastoma. The pathological typing of tumors has certain diagnostic significance. In terms of prognosis,
mutations in the ATRX gene in patients with low-grade glioma with IDH gene mutations but no 1p19q combined deletion often suggest patients with a longer overall survival (OS). Progression-free survival (PFS) \(^{49}\). In the future remains to be more research is needed to explore the role of development ATRX gene mutations in gliomas.

9. **TP53 gene mutation**

Tumor suppressor P53 (TP53) gene is located on the short arm p13.1 of chromosome 17, which is one of the tumor suppressor genes. The encoded P53 protein can mediate the cell's response to DNA damage, stabilize the genome, and regulate Cell cycle and inducing apoptosis \(^{50}\). Mutation of TP53 gene will cause the tumor suppressive effect of the encoded protein to be lost, which will help tumorigenesis and development. TP53 gene mutation has a certain degree of auxiliary diagnostic value. Mutated primary glioblastoma and oligodendroglioma are rare, but they are low-grade in giant cell glioblastoma, IDH-mutated secondary glioblastoma, and precursors Or anaplastic astrocytoma patients are more common \(^{51}\). Generally speaking, the presence of TP53 gene mutation, ATRX gene mutation, and IDH gene mutation at the same time suggest grade II, grade III astrocytoma or IDH mutation Diagnosis of type glioblastoma.

Some studies have found that tp53 gene mutation is a factor of poor independent prognosis of grade oligodendroglioma and astrocytoma. Compared with the wild type, its mutation is positive, which indicates that patients have shorter overall survival and progression-free survival and tumors. Malignant progress \(^{52}\). In addition, there are literatures that confirm that the tp53 gene mutation is not related to the prognosis of glioblastoma \(^{53}\). Therefore, the tp53 gene mutation has a certain degree of clinical significance in judging the prognosis of glioma.

10. **Methylation of the ppENK promoter**

Preproenkephalin (ppENK) is localized on chromosome 8q23-24 and exists in the central and peripheral nervous system. It is currently found in gliomas, papillary myxomas in the pancreatic duct, papillary myxomas in the pancreatic duct, and pancreatic ductal epithelial tumors. Methylation of the ppENK promoter has been found. ppENK is a precursor of opioid growth factors, which can inhibit tumor growth and differentiation, and participate in cell regeneration, growth and development, wound healing and angiogenesis. ppENK methylation
Correlation with glioma pathological typing, ppENK methylation occurs most frequently in astrocytomas and oligodendroglioma.

11. miRNAs

MicroRNAs (miRNAs) are small non-coding RNAs with a length of 19 to 24 nucleotides. They are mainly divided into two categories: oncogenes and tumor suppressor genes. The role of miRNAs includes regulating transcription and translation and participating in cell proliferation, Apoptosis and differentiation process. Abnormally expressed miRNAs can cause uncontrolled expression of downstream genes and induce tumors. Detection and study of differential expression of miRNA in glioma tissues is helpful for pathological grading and prognosis of high-grade glioma patients. Differentially expressed miRNAs have been found in a variety of tumors, and Wu et al. detected that expression in serum samples from patients with miR-210 glioblastoma that can mediate tumor angiogenesis was found to be approximately normal 8 times.

Studies have found four gene molecular markers in low-grade gliomas, including miR-10b, miR-15b-3p, miR-590-3p, and miR-196a. Some scholars have found that the higher the WHO classification, the higher the expression levels of miR-525-5p, miR-524-5p, miR-586, miR-619, miR-433 and miR-301a, and the poorer the prognosis of patients with WHO grade III gliomas. Positive correlation. Srinivasan et al. identified and verified molecular markers of 10 miRNAs in GBM, of which 7 miRNAs include miR-31, miR-222, miR-148a, miR-221, miR-146b, miR-200b, miR-193a are classified as dangerous oncogenes, and the other three miRNAs (miR-20a, miR-106a, miR-17-5p are protective miRNAs. Another one analyzes low-grade glial In the study of differentially expressed miRNAs in tumors and normal tissues, a total of 591 miRNAs were found to be differentially expressed. Further regression and survival analysis revealed that miR-10b-5p and miR-15b-5p can predict the pathological grade of patients and be in low-grade tumors. It is closely related to the patient's OS. Some scholars have detected the expression of miRNA-182 in serum samples of HGG patients and found that the expression can reflect the testPatient's pathological grade and prognosis. This detection of molecular markers of peripheral blood genes can greatly assist in the early diagnosis, disease management and clinical prognosis of tumors. It is believed that certain gliomas in peripheral blood circulation Potential diagnostic and prognostic biomarkers and therapeutic target miRNAs will be one of the future research hotspots.
12. Inc RNAs

Long non-coding RNA (Inc RNA) is over 200 nucleotides long and has no ability to encode proteins. Although Inc RNAs cannot encode proteins, they can regulate gene transcription and expression and affect translation, cell differentiation, nuclear plasma transport, cell cycle and other physiological processes.[62] In recent years it has been found in glioma, liver cancer, gastric cancer, kidney cancer, colorectal cancer, liver cancer, gastric cancer, kidney cancer, colorectal cancer, etc. A variety of tumors play a non-negligible biological regulatory function. Abnormal expression of Inc RNAs can affect the progression and recurrence of gliomas. HOTAIR (HOX transcript antisense RNA) is one of the more studied Inc RNAs. Some studies have found that it is related to the poor prognosis of patients with various malignancies including glioma[63]. In glioma, the expression of HOTAIR is related to the pathological grade of glioma, and the higher the glioma pathological grade, the higher the expression level[64]. However, the specific mechanism of HOTAIR to regulate gene expression in glioma cells needs more research.

Differential expression of Lnc RNAs between tumors and normal brain tissues can help clinical diagnosis and prognosis of glioma patients. Some scholars have found that multiple Lnc RNAs in oligodendrocyte gliomas and astrocytes Differential expression of glioma[65], which suggests that specific Lnc RNAs can be used as a basis for distinguishing oligodendrocyte gliomas from astroglomas. In addition, Zhang[66] et al. Screened from TCGA (The Cancer Genome Atlas) According to the data of patients with glioblastoma in the database, it is concluded that the six Lnc RNAs of MIAT, GAS5, KIAA0495, PART1, MGC21881, and PAR5 are closely related to the patient's OS and are independent risk factors for the patient's prognosis. In addition, it can regulate Lnc RNA function. The small interfering RNA (si RNA) of molecular targeted therapeutic drugs is gradually being actively researched. The close relationship between the differential expression of Lnc RNA and the prognosis of glioma makes Lnc RNA a hot spot in the field of glioma pathological molecular markers. This also provides another direction for thinking about diagnostic and prognostic markers for glioma research and new targets for treatment.

Conclusion and Outlook

The detection and typing of circulating tumor cells is an important method to monitor the early metastasis, treatment response and prognosis of head and neck tumors. A number of
studies have shown that positive circulating tumor cells indicate a worse treatment response and prognosis. A number of clinical trials with longer follow-up are ongoing. With the continuous development of detection technology, further identification of specific subpopulations of circulating tumor cells that play an important role in tumor invasion and metastasis in future research is one of the keys. In order to fully identify the circulation Polyclonal subpopulations of tumor cells, to avoid incomplete separation caused by tumor cell progression, and multi-marker labeling are particularly important. In addition, the establishment of standardized detection protocols will also help to unify research methods between different institutions, resulting in more uniform Accurate research conclusions.

Acknowledgements

This project is funded by the research and data on the evaluation method of stereotactic radiotherapy equipment (Subject No. : 2017YFC0113701).

Research and development of tumor real-time monitoring molecular diagnostic products based on liquid biopsy -- a major science and technology project of guangdong province 2019B020232003

Dalian municipal Science and technology innovation projects (2018 j12sn063) : a new method for the detection optical flow control chip peripheral blood tumor cells research Science and technology innovation project of Dalian City (No: 2018 j12sn063)

Liaoning provincial key research and development plan project name: construction project no. 2018225050 fat stem cell storage and application platform no. 2018020143-301

Project name of natural science foundation of liaoning province: basic research on the regulation effect of gegenqinlian decoction based on 16S rRNA gene on intestinal flora of mice with radioactive enteritis project no. 20180550798;Contract no. : 2018011225-301

Nature foundation guidance program PhD initiation fund project name: the relationship between fluoxetine in inhibiting astrocytoma growth and TRPC1 research project no. : 20180551182 contract no. 2018011575-301
References


Science Translational Medicine, 2015, 7(275):275ra22-275ra22.


47


