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REVIEW

MicroRNAs as Biomarkers of Brain Tumor

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Abstract: Brain tumors have been deadly cancers for years, and in most cases they are difficult to diagnose in their early stages. For this reason, researchers need to develop low-cost, sensitive methods for examining cancer biomarkers. Such biomarkers include microRNA. MicroRNA expression in various body fluids shows a high correlation with cancer. A number of studies have demonstrated changes in microRNA expression in cerebrospinal fluid and blood samples from patients with brain tumors. New biomarkers such as microRNAs may help diagnose brain tumors at the very beginning of the disease, enabling early treatment and increasing the chances of survival. This review describes the diagnostic role of microRNAs and the prospects for their use as biomarkers in patients with brain tumors.

Keywords: microRNAs, brain tumor

Introduction

Tumors of the central nervous system (CNS) are very malignant tumors in humans, accounting for approximately 1.35% of all malignant tumors and approximately 3% of cancer-related deaths. CNS tumors include both primary tumors originating from the inside CNS, as well as secondary tumors that arise as a result of the spread of metastases. The main types of primary brain tumors (approximately one third of all tumors) are gliomas, and include astrocytomas, glioblastomas, oligodendrogliomas and ependymomas. Secondary brain tumors most often originate from lung, breast and melanoma tumors. Despite progress in therapeutic methods, the prognosis for patients with CNS tumors is poor.[1] Detecting a brain tumor at an early stage of development significantly increases the chance of successful treatment. Therefore, it is necessary to develop simple, sensitive, fast, and relatively cheap analytical methods for its detection. In addition to the imaging methods used, biochemical tests involving the examination and quantitative measurement of biomarkers may be useful. Biomarkers are substances that occur physiologically in cells or fluids of the human body, and their quantitative abnormalities occur in patients with cancer or pre-cancer. In recent years, research has focused on microRNA as a biomarker for brain tumors. The interest in microRNAs in cancer diagnostics is the result of their biological nature and high concentrations found in biological fluids; enabling easy detection and preventing sample processing complications.[2] MicroRNAs are a class of small non-coding RNAs (<25 bp) that are involved in the degradation or blocking of target microRNA at the post-transcriptional level. MicroRNA genes are transcribed at an early stage as primary microRNAs (pri-microRNA). The pri-microRNA is then cleaved into a microRNA precursor (pre-microRNA) before being released from the nucleus. After reaching the cytoplasm, the pre-microRNA is cleaved into mature microRNA. To perform their regulatory roles, mature microRNAs attach to the RNA-induced silencing complex, which consists of Argonaute and other proteins.[3] MicroRNAs play an important role in the stability and intercellular relationship of both healthy and malignant cells. There are three routes of microRNA secretion: passive release from damaged cells due to apoptosis or necrosis; active release facilitated by extracellular vesicles and active release via an RNA binding protein-dependent pathway (miRNA-Ago2 complex). MicroRNAs can also be secreted independently of vesicles. Nearly 90% of cell-free microRNAs are present in a non-vesicular state, specifically associated with Ago24 proteins.[4]

The role of microRNAs in cancer development and progression is to modulate the processes of growth, differentiation and apoptosis. Numerous studies show that microRNA dysregulation is involved in cancer initiation, invasion and

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metastasis.[5–7] They are frequently deregulated in cancer and have shown great potential as tissue-based markers for cancer classification and prognosis including gliomas. They are often deregulated during cancer development and have great potential as tissue markers for classifying and prognosticating cancer, including gliomas. MiRNAs are found in extracellular body fluids such as serum and plasma. It has also been shown that the level of secreted microRNA in blood and other body fluids significantly correlates with cancer progression, therapeutic response and patient survival. Thus, microRNAs show great potential as powerful and noninvasive brain tumor biomarkers.

This review provides current knowledge about the role of microRNAs in the pathogenesis of brain tumor as well as the potential use of microRNAs as diagnostic biomarkers for brain tumors.

MicroRNAs in Oncogenesis

MicroRNAs regulate numerous of processes occurring in the human body including cells proliferation. Moreover, cell growth, tumor invasion, tumor metastasis, immune response, angiogenesis, apoptosis - all these processes are dependent on microRNAs. Therefore, dysregulation of microRNA expression represents a significant function in cancer initiation and progression. MicroRNAs are closely related to cancer due to changes in microRNA target binding sites and the mechanism of microRNA processing in cancer cells. The reasons for the extensive differences in microRNA gene expression between normal and malignant cells may be attributed to the location of these genes in regions of the genome associated with cancer, epigenetic mechanisms, and changes in the microRNA processing apparatus. They can stop cancer from growing; and also constitute oncogenes. Thus, changes in a small subset or a single microRNA can modify a number of cellular processes leading to tumorigenesis.[8] MicroRNA chains alter gene expression by binding to appropriate regions at 30 untranslated target sites of messenger RNAs. This interaction reduces protein synthesis by hindering the translation process or causing the breakdown of a specific mRNA. It is estimated that microRNAs directly influence the regulation of approximately 60% of human genes. Moreover, some microRNAs can bind to several microRNA targets, sometimes involving the same signaling pathway. On the other hand, specific microRNAs modify many different microRNA binding sites within 30 untranslated regions, adding a layer of regulatory complexity.[9] It has been demonstrates that micro-RNAs hyporegulated in glioblastomas directly affect the oncogenes c-Met, Notch, Bmi-1, epidermal growth factor receptor, tyrosine kinase receptor, and also genes responsible for cell cycle control. Hyporegulation of microRNA-205 is considered an independent factor in the assessment of mortality among patients with gliomas, which can be used as an important prognostic indicator for patients with gliomas of higher (III–IV) grade of malignancy. Activation of microRNA-497 expression in glioma cells led to a decrease in the expression of the vascular endothelial growth factor (VEGF) and the density of blood vessels, thereby being a negative regulator of angiogenesis. This micro-RNA acts as a favorable prognostic factor. It was found that the evolutionarily conserved RNA-binding protein LIN28, which has the ability to block the maturation of microRNA precursors from the let-7 family, is overexpressed in patients with glioblastoma multiforme with a poor prognosis. The decrease in LIN28 expression in U251 glioma cell culture leads to inhibition of the cell cycle in the G1 phase, slowing down of proliferation and activation of apoptosis.[10] MicroRNAs are very precise tuners of the expression of many genes in response to abnormal cellular signals. It has been widely demonstrated that in low-grade glioma tissues, compared to the surrounding brain cells, there are bidirectional trends: with a decrease in the level of oncosuppressor expression, eg miRNA-137, an increase in parameters is observed in microRNA-9. In the case of other oncogenic factors, there is a correlation between their expression in cancer cells and the stages of gliomas.[11] Low- and well-differentiated gliomas are characterized by an anti-apoptotic activation mechanism and a signaling pathway that increases the survival of their cells. Sippl et al examined changes in the expression of microRNA-21, microRNA-24, and microRNA-26a in tumor samples from 10 over 100 patients with glioblastoma multiforme and approximately 10 samples of non-tumor brain tissue from controls. They found that microRNA-21 and microRNA-26a were highly overexpressed in the glioma multiforme sample. Furthermore, high level of microRNA-24 expression tended to contribute to the long-term overall survival patient with glioma; but with significantly microRNA-26a expression, prolonged progression-free survival was obvious.[12] MicroRNA-21 has one of the highest expressions in human tissues; and its expression is further increased in glioblastoma t cells. It shows an approximately 5–15-fold increase in the expression in glioblastoma cells compared to the norm. MicroRNA-21 stimulates oncogenesis in glioma cells by inhibiting tumor suppressor genes HNRPK, TOPORS,

TGFBR2/3JMY, TIMP3, RECK, DAXX, PDCD4.[13] Moreover, low levels of its expression are weakly associated with increased survival, according to Cancer Genome Atlas. Suppression of microRNA-21 causes, together with low EGFR expression, cell cycle arrest in the G1/S phase and ultimately suppression of tumor growth. Depending on the expression level of certain microRNAs, gliomas of various degrees of malignancy differ not only from the peritumoral tissue, but also from each other. In some cases, glioblastoma multiforme can be distinguished from oligodendroglioma.[14] Although, most microRNAs are produced in cells themselves, many microRNAs, termed cell-free microRNAs, have been detected in many body fluids, eg blood or cerebrospinal fluid. Expression pattern of cell-free microRNAs is subject to significant changes (abnormality or disorder) in different human diseases, including brain cancer. These microRNAs exhibit nuclease insensitivity, making them potential candidates as attractive biomarkers for diagnostics, prognosis, and monitoring of treatment response.[5]

Other factors also play a role in the pathogenesis of brain tumors. For example macrophage migration inhibitory factor is now emerging as a prospective anti-angiogenic therapy in brain tumor as high levels of this factor have recently been linked to tumor recurrence and poor survival. It has been demonstrated that the tumor microenvironment, which promotes vasculogenic structure, releases hypoxia-induced macrophage migration inhibitory factor, and that its expression is correlated with that of vascular endothelial growth factor.[15] Another factor may be RAB 42 - a member of the mammalian Rab family small GTPases. Single gene analysis of RAB42 showed that RAB42 is an independent prognostic factor of adverse prognostic. RAB42 expression is associated with multiple clinical features. Furthermore, indicated that RAB42 promoted the proliferation, migration and invasion of brain tumor and the pro-oncogenic mechanism of RAB42 is associated with the activation of vascular endothelial growth factor signaling pathways.[16]

MicroRNAs as Biomarkers of Brain Tumor

A key factor influencing the appropriate approach to the treatment of primary or metastatic brain tumors is the precise determination of the type of tumor. In the use of molecular parameters to classify CNS tumors, individual cell-free microRNAs that have prognostic significance as markers may represent a key element in the development of neurosurgeons' intervention strategies, enabling the choice of real-time intraoperative monitoring and enabling clinical trials. In recent years, microRNA expression in glioblastoma has been extensively studied. Numerous studies have demonstrates that certain microRNAs are correlated with the diagnosis and prognosis of glioblastomas. Among other things, microRNA-301a is strongly expressed in glioblastoma blood exosomes and may be a good diagnostic and predictive indicator in the course of glioma.[17] Regarding microRNA-21, it was the first microRNA recognized in association with cancer, and its positive expression was confirmed in various types of cancers, with firmly associated oncogenic properties.[18] It influences different cellular processes, cellular processes, from tumor formation to cell apoptosis. Moreover, its association with cancer treatment resistance is established. In the case of meningioma, the presence of microRNA-21 was found especially in stage III and IV tumors.[19] Although Aran et al detected microRNA-21 expression in the plasma of patients with brain tumor, found no noticeable discrepancies compared to material taken from control group. This lack of differentiation can be explained mainly by the gentleness of tumors.[20] Recently, Turk et al showed a significant statistical difference in microRNA-17 expression between glial cancers and the healthy with higher microRNA-17 level observed in tissue tumors. Likewise, in metastatic cases, microRNA-17 expression was statistically higher compared to the control group. The increased level of this microRNA in secondary brain tumor foci is confirmed by research evidence indicating the impact on axon-myelin remodeling and functional recovery after stroke. These findings indicate that microRNA-17 may be a useful biomarker for differentiating glial tumors and brain metastases from normal brain tissue.[21] In the brain, microRNA-17 has been found to influence neuronal development by regulating the expansion of neural stem cells and their transition to intermediate progenitor cells. Furthermore, microRNA-17 has been associated with the regulation of oligodendroglial cell number, highlighting its importance in maintaining central nervous system homeostasis. MicroRNA-17 has neuroprotective effects, as evidenced by the participation of this microRNA in the protection of neonatal rats against ischemic brain damage.[22] Although, other research studies have shown its involvement in stimulating cell growth and chemoresistance, suggesting its oncogenic nature.[2] Further studies should elucidate the mechanisms of microRNA-17's influence on the oncogenesis of brain cancers and brain metastases, taking into account the effects of other microRNAs. In recent years, several microRNAs have been associated with glial

tumorigenesis. The study by Li and coworkers demonstrated that astrocyte-upregulated gene-1 (AEG1) serves as a target of microRNA-542 to promote glioma proliferation and invasion.[23] Zhi et al analyzed patient serum and found that increased level of microRNA-106a-5p, microRNA-20a-5p, microRNA-181b-5p correlated with the stage of cancer advancement, and microRNA-106a-5p, microRNA-19a-3p, and microRNA-181b - 5p is associated with a poor prognosis.[24] Moreover, Zhao and coworkers isolated microRNA from blood and reported that microRNA-182, microRNA-222-3p, microRNA-20a-5p, microRNA-145-5p and microRNA-106a-5p correlated with poor patient outcomes.[25] MicroRNA-15b will inhibit cell cycle progression and cell proliferation, making it a potential prognostic biomarker for glioblastoma. The presence of microRNA-15b was also noted to be the opposite correlates with worsening histopathology of glioblastoma and different other glioblastomas and consequently, overall survival of glioma patients containing less microRNA-15b.[26] Another microRNA with similar suppressive effects is microRNA137. The microRNA-137 promoter was found to be hypermethylated in tumor samples, which is hypothesized to negatively regulate the target gene, GLIPR-1.[27] Expression of several other microRNAs in glioblastoma, including microRNA-181d, microRNA-127, microRNA-648, and microRNA-643, was found to modulate temozolomide resistance by silencing MGMT promoters. The results of these in vitro and in vivo studies were confirmed by microarray and PCR validation, and the activity of such microRNA was examined for its effects on MGMT expression at different levels, either genetic or proteomic. However, despite the confirmed silencing capabilities, microRNA production was found to be decreased in the setting of worsening glioblastoma symptoms, accompanied by a greater level of immunity to temozolomide. The adversarial correlation of different described microRNAs with chemotherapy resistance mechanisms, although not fully understood, may provide more information on the research that should be conducted using microRNAs as a strong regulator of genes such as MGMT, worsening the course. Tang et al examined the expression of microRNA-185 in the blood of glioma patients and found that the expression of microRNA-185 in the plasma of glioma patients was significantly increased compared to benign tumor lesions in the brain. Moreover, the expression level of microRNA-185 in glioblastoma patients returned to normal levels after surgery and chemotherapy. Therefore, it can be concluded that the expression of microRNA-185 is associated with the progression of glioblastoma and may constitute a potential biomarker in the diagnosis of glioblastomas.[28] Literature data indicate that microRNA-221 may have oncogenic properties and correlates with cell proliferation and migration. It was found that due to the oncogenic effect of increased expression level of microRNA-221, the increase in the level of this microRNA plays a very important role in cell cycle deregulation in high-grade gliomas. Additionally, increasing the level of microRNA-221 is associated with poor prognosis not only in glioma, but also in pancreatic adenocarcinoma and papillary thyroid cancer.[29] Wang et al showed a significant increase in the expression of microRNA-214 in the blood of patients with grade I and II malignant glioblastomas compared to the healthy people. Moreover, patients suffering from stage I gliostomas showed more clearly increase in microRNA-214 expression than appropriate stage II patients. Moreover, a receiver operating characteristic analysis was performed to evaluate the diagnostic performance of this microRNA, showing a very large area under the curve (AUC) 0.885 in patients with grade I or -II malignant glioblastomas compared to the healthy. Researchers found that increased expression of microRNA −214 in glioblastoma was resulted in a worse course of the disease. Moreover, microRNA-214 may be an independent prognostic factor for overall survival in glioblastomas, especially in more severe tumors (II° glioblastomas.[30] Studies conducted on patients with various grades of glioma showed that the expression of microRNA-29 in the blood was significantly lower than in the control group, showing low sensitivity and specificity in the diagnosis of low-grade glioblastomas but a high diagnostic value for gliomas with a high degree of malignancy. Therefore, it is widely believed that microRNA-29 is of great importance in the diagnosis of high-grade gliomas.[31] This is confirmed by the research of Liu and coworkers who investigated the expression of microRNA-29 in the blood of 120 glioma patients and 120 healthy individuals of the same sex and age. MicroRNA-29b levels were found to be decreased in glioma patients, while VEGFA expression was increased. Additionally, investigators used ROC curves to estimate the diagnostic utility of microRNA-29b and VEGFA in patients with glioblastomas. The AUC was 0.913 and 0.752, respectively.[32] Sippl et al showed strong overexpression of microRNA-181d in cancer cells and blood of patients with glioma multiforme compared to the healthy subjects. Even though most prognostic and predictive biomarkers gliomas are currently examined in surgically resected tumor samples AUC values suggest that the two groups can be distinguished by analyzing of microRNA-181d expression. Additionally, the researchers showed that the Cancer Genome Atlas analysis

showed eight potential proteins targets regulated by microRNA-181d.[33] In recent years, a comprehensive serum microRNA signature has been reported in a very large group of patients with malignant glioblastoma. Specifically, microRNA-340, microRNA-576-5p and microRNA-626 showed significantly overexpression, while microRNA7-5p, microRNA-320, let-7 g-5p demonstrated marked low expression in glioma patients.[34] Moreover, microRNA-125b, a component of the let-7c cluster commonly considered to be a very good biomarker of different human tumors, has also been characterized as a potential marker of glioma. Furthermore, it appears that microRNA-125b may play a dual function depending on the cell type: it can be both an oncomicroRNA and a tumor suppressor microRNA, acting on tumor suppressor genes or oncogenes, respectively. MicroRNA-125b acts on numerous genes involved in the p53 pathway and inhibits apoptosis in cancer tissues, however, it may negatively affect the expression of proteins regulating cell proliferation, suggesting an oncosuppressive role.[35] Moreover, Wu et al investigated the predictive value of blood microRNA-29 in screening for high-grade glioma.[31]

Recently, scientists have turned their attention on microRNA as a biomarker for brain tumors. According to Scopus, microRNAs have attracted a lot of interest in the area of brain cancer research over the years. The number of articles describing microRNAs as a biomarker of CNS tumors is constantly increasing, which indicates a great interest in microRNA analysis (Table 1).[36]

MicroRNAs Detection Methods

There is a urgent need to create simple, fast, sensitive and cheap analytical methods for detecting cancer biomarkers, including microRNAs. Conventional methods used to quantify and identify microRNAs are DNA microarray, real-time quantitative polymerase chain reaction (RT-qPCR), deep sequencing, and Northern blot techniques.[37] In general, they are characterized by high specificity and good sensitivity, however, the methods are complex and require advanced technology, using expensive equipment and materials, trained personnel to perform the test, and are time-consuming. Therefore, more effective and cheaper new techniques for the diagnosis and therapy of cancer, including brain tumors, are still being sought. Recently, a variety of methods have been developed to provide high sensitivity and specificity while being easy to operate, based on different direct detection technologies eg localized surface plasm on resonance, photoelectrochemical and electrochemical biosensors which are popular because they are miniaturized and their mass

Table 1 Clinical Application of Selected microRNAs in Brain Tumors

MicroRNA	Expression	Source	Significance
MicroRNA-21	Up-regulation	Plasma/CSF	Diagnosis; Prognosis; Response to treatment
MicroRNA-182	Up-regulation	Plasma	Prognosis
MicroRNA-221	Up-regulation	Plasma	Diagnosis; Prognosis
MicroRNA-15a/b	Up-regulation	Plasma/CSF	Diagnosis; Prognosis
MicroRNA-7-5p	Down-regulation	Plasma	Diagnosis; Response to treatment
MicroRNA-20a-5p	Up-regulation	Plasma	Diagnosis; Prognosis
MicroRNA-106a-5p	Up-regulation	Plasma/CSF	Prognosis; Response to treatment
MicroRNA-125b	Down-regulation	Plasma/CSF	Diagnosis; Response to treatment
MicroRNA-19a-3p	Up-regulation	CSF	Diagnosis
MicroRNA-137	Down-regulation	Plasma	Prognosis
MicroRNA-626	Up-regulation	Serum	Diagnosis
MicroRNA-26a	Up-regulation	Serum	Prognosis
MicroRNA-24	Up-regulation	Serum	Prognosis
MicroRNA-17	Up-regulation	Serum	Diagnosis; Prognosis
MicroRNA-181b-5p	Up-regulation	Plasma/CSF	Diagnosis; Prognosis
MicroRNA-222-3p	Up-regulation	Serum	Prognosis
MicroRNA-20a-5p	Up-regulation	Serum	Prognosis
MicroRNA-320	Down-regulation	Plasma	Diagnosis
MicroRNA-643	Up-regulation	Plasma/CSF	Prognosis; Response to treatment
MicroRNA-129b	Up-regulation	Plasma	Diagnosis; Prognosis

production does not require high costs. They can be modified with a range of recognition elements that are widely used as versatile tools for developing nucleic acid (E-DNA)-based sensors. Moreover, such biosensors have demonstrated reliable results thanks to a comprehensive approach based on modern nanomaterials, bioorganic polymers, electroactive molecules or catalysts.[38] Recently, electrochemical microRNA biosensors have been investigated from various perspectives. Therefore, various strategies based on the use of multifunctional nanomaterials in biosensors have been described. For example, Chen et al focused on the use of oligonucleotides and nanomaterials in the amplification process for microRNA detection.[37] Moreover, Mujica et al described electrochemical biosensors using different combinations of oligonucleotide strategies.[39] Besides, Mohammadi et al analyzed different amplification strategies using enzymes, nanomaterials and oligonucleotides for microRNA analysis and their various possible combinations.[40] MicroRNA electrochemical biosensor systems that use RedOx biomarkers in their operation seem to be of the greatest importance. The above assumptions are based on microRNA sensors with an electroactively labeled DNA probe sequence, or the use of a catalyst that generates RedOx particles, or a system with a RedOx DNA intercalating agent, or the use of a free RedOx tracer, and finally other RedOx label-free detection methods. In fields of electrochemical biosensors, other methods can also be used to detect miRNAs as cancer biomarkers, including guanine oxidation, electrode surface RedOx current, and labeled microRNA. The last method requires labeled microRNA, which is a difficult step in applying the biosensor to real samples. Sabahi et al recently described a labeled microRNA biosensor for the quantification of microRNA-21. This was achieved by using cadmium ions (Cd2+), which are connected to the phosphate group of microRNA as a result of an electrostatic reaction. The labeled microRNA then hybridize with a capture probe immobilized on a fluorine-doped tin oxide electrode/SWCNT/dendritic gold nanostructures until Au-thiol interaction.[41] It can be concluded that electrochemical biosensors are an effective and practical approach to the analysis of microRNAs in clinical practice, characterized by high sensitivity. However, the problem of analyzing microRNAs in a real sample with respect to the RedOx intercalating agent and the free RedOx indicator cannot be ignored. However, methodological advances in sequencing techniques used for microRNA detection have significantly improved the identification of expression changes of individual microRNAs.

Methods often used to detect microRNAs are methods based on quantitative reverse transcription polymerase chain reaction (RT-qPCR), stem-and-loop RT-qPCR, poly(A) tail RT-qPCR, and miQPCR. The combination of reverse transcription (RT) and quantitative PCR, or RT-qPCR, is currently the most convenient and practical way to detect precursor and mature miRNAs due to its greater sensitivity, ease and less time-consuming than methods such as cloning, northern hybridization, microarray analysis and deep sequencing. The stem-loop amplification technique detected high- and medium-abundance microRNAs. The poly(A)-tailing method detected both abundant and rare miRNAs, but failed to detect hairpin microRNAs. Only a few microRNAs were detected by miQPCR. It is suggested that a combination of PCR methods should be used to reliably quantify microRNA Droplet digital PCR (ddPCR) can also play a pivotal role in detecting low allele frequency mutations within solid tumors.[42]

A promising non-invasive diagnostic and monitoring method that can potentially help in the diagnosis of CNS tumors is liquid biopsy. It enables rapid, precise and real-time detection of cancer, prognosis and monitoring of treatment of CNS cancers. This approach may also reveal the heterogeneity of these tumors and will likely replace tissue biopsy in the future. The key components of liquid biopsy mainly include circulating tumor cells (CTCs), circulating tumor nucleic acids (ctDNA, miRNA) and exosomes, and samples can be obtained from the cerebrospinal fluid, plasma and serum of patients with CNS tumors.[43]

Future Prospects and Conclusion

Molecular testing of cancer is of great interest due to its clinical value in the diagnosis, prognosis and treatment of patients. For this reason, it is very necessary to find useful molecular markers that would help clinicians optimize the treatment of patients with brain tumors. Despite many years of research aimed at discovering effective biomarkers for detecting and predicting the course of brain tumors, only a few have yielded promising results. It has been shown that such molecular biomarkers include microRNAs. The tissue specificity of microRNAs suggests that microRNAs are involved in the carcinogenesis. MicroRNA levels change with angiogenesis, apoptosis, autophagy, inflammation and tumorigenesis as well as are closely associated with brain tumors. Extensive evidence suggests that microRNAs may

mediate the occurrence and progression of CNS tumors through microRNA sponging, transcriptional regulation, and protein interactions.[44] The large differences in microRNA gene expression between cancer's and healthy tissues may be due to the location of these genes in sites of the cancer-related genome, epigenetic pathways, and disorders in the microRNA processing apparatus. Because microRNAs are very stable and commonly expressed in different body fluids or tissues, they may play role of diagnostic and prognostic biomarkers. Further research should be conducted to investigate microRNAs that play a role in the development of brain tumors. Some biomarkers show correlations with other biomarkers. These microRNAs can be used in combination with classical biological diagnostic markers for clinical complementary screening of early-stage CNS tumors. Of the decades-long studies aimed at developing a sensitive and specific biomarker for the diagnosis of brain tumors, only a few have yielded satisfactory results. Classical molecular markers and microRNAs were then used as therapeutic targets to develop therapies that would ultimately help cure brain tumors. Biomarker discovery is indeed a very difficult task, but with advances in genomics and proteomics, more and more biomarkers are being discovered, leading to the development of fully functional, accessible brain tumor therapies. Therefore, the search for effective CSF tumor biomarkers must be performed by looking at the complex molecular pathways of the disease as a whole. Some researchers suggest that a single serum microRNA as a biomarker for detecting low-grade brain tumor is not sensitive and specific, but has some importance in the diagnosis of high-grade tumor.[11] A combination of microRNAs can be used. Sensitivity, specificity, and AUC of single miRNAs and miRNA panels were 0.83, 0.85, 0.90; vs 0.90, 0.95, 0.97, respectively. Compared with Asians, miRNAs have a higher overall diagnostic accuracy in Caucasians, with sensitivity of 0.84 versus 0.87, specificity of 0.84 versus 0.96, and AUC of 0.91 versus 0.96, respectively.[45]

The extensive experience accumulated so far in determining the microRNA expression using various methods in the diagnosis of brain tumors has many advantages. It has a relatively high specificity which provides an opportunity to precisely monitor the effectiveness therapeutic procedures, as well as the possibility of its use in early cancer diagnosis, provided that appropriate microRNAs panels are selected. However, there are some obstacles that limit the use of microRNAs in clinical diagnostics. These include low sensitivity, lack of characteristic tumor-specific sequences, lack of standardization, and the need for comparison with normal references.[45] Moreover, many studies were conducted on small cohorts of patients with various histological structures of CNS tumors. Additionally, CNS tumors are heterogeneous tumors, which makes the interpretation of the results difficult obtained and the selection of microRNAs as diagnostic markers.[43] For this purpose, an important process is the standardization of methods for assessing microRNA expression levels and selecting appropriate reference genes. In order to obtain true data, it is recommended to conduct large-scale prospective studies to determine the involvement of microRNAs in the oncogenesis of CNS tumors and to confirm their effectiveness as biomarkers in cancer diagnosis. As more and more CNS cancer-associated and histologically diverse microRNAs are detected, the elucidation of the complex biomolecular regulatory pathways of brain tumors and the application of microRNAs-based CNS tumor detection and therapy will have better prospects.[4]

Our review indicated that microRNAs could be potential diagnostic biomarkers for brain tumors. Additionally panels of multiple microRNAs could discriminate patients with brain tumors more accurately than a single microRNA. However large sized studies should be conducted to confirm the clinical value of microRNAs in brain tumors diagnostic.

Abbreviations

AEG1, astrocyte-upregulated gene-1; AUC, Area Under Curve; CNS, central nervous system; CTCs, circulating tumor cells; ctDNAs, circulating tumor nucleic acids; ddPCR, droplet digital PCR; pre-microRNA, microRNA precursor; pri-microRNA, primary microRNA; RT-PCR, reverse-transcription polymerase chain reaction; VEGF, vascular endothelial growth factor.

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Disclosure

The authors report no conflicts of interest in this work.

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