Review

MicroRNAs As Biomarkers of Brain Tumors

Jelski Wojciech * and Barbara Mroczko

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MicroRNAs as Biomarkers of Brain Tumors

Wojciech Jelski [1,*] and Barbara Mroczko [1,2]

[1] Department of Biochemical Diagnostics, Medical University, Bialystok, Poland
[2] Department of Neurodegeneration Diagnostics, Medical University, Bialystok, Poland
* Correspondence: wjelski@umb.edu.pl; Tel.: +48-85-746-8587; Fax: +48-85-746-8585

Abstract: Brain tumors still remain a deadly cancer that, in most cases, is difficult to diagnose at an earlier stage. Therefore, it is necessary to develop rapid, sensitive methods for detecting cancer biomarkers. Such a biomarker may be a microRNA which expression level in body fluids is strongly correlated with cancer. Numerous studies have demonstrated changes in the expression of microRNAs in cerebrospinal fluid and blood samples collected from patients with brain tumors. These new biomarkers have the potential to help diagnose brain cancers at an early stage, avoiding the most invasive procedures. This review discusses the functional role of microRNAs and the prospects for their use as diagnostic biomarkers in patients with brain tumors.

Keywords: microRNAs; brain tumor

1. Introduction

One of the most malignant tumors in humans is a tumor of the central nervous system (CNS), accounting for over 1.35% of all malignant tumors and approximately 3% of cancer 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. The most common cancers that metastasize to the brain include lung, breast, and melanoma 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 inexpensive analytical tools for its detection. In addition to the imaging methods used, biochemical tests based on the detection and quantification of biomarkers may be useful. Biomarkers are substances that occur naturally in the tissues or fluids of the human body and are present in abnormal amounts in patients with cancer or pre-cancerous conditions. In recent years, research has focused on microRNA (miRNA) as a biomarker for brain tumors. The interest in miRNAs in cancer diagnostics is related to their biochemical nature and their large amounts in biological fluids; allowing for easy detection, avoiding 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 mcroRNA at the post-transcriptional level. MicroRNAs play an important role in the homeostasis and intercellular communication of both healthy and malignant cells. 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 metastasis [3]. 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..

2. The Role of microRNAs in Oncogenesis

MicroRNAs regulate a number of processes occurring in the human body including cell proliferation. Moreover, cell growth, tumor invasion, tumor metastasis, angiogenesis, apoptosis and

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immune response - all these processes are dependent on microRNAs (Figure 1). Therefore, dysregulation of microRNA expression plays an important role in initiation and progression of cancer. 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 act as tumor growth suppressors; and also as oncogenes. Thus, changes in a small subset or a single microRNA can modify a number of cellular processes leading to tumorigenesis [4]. MicroRNAs chains influence gene activity by attaching to appropriate sites within 30 untranslated regions of messenger RNA targets. This interaction reduces protein synthesis by hindering the translation process or promoting degradation of the target mRNA. It is estimated that 60% of human genes are directly regulated by microRNA. Moreover, some microRNAs can bind to more than one mRNA target, sometimes in the context of the same signaling pathway. Conversely, specific mRNAs can modify many different miRNA binding regions within their 30 untranslated regions, adding layers of regulatory complexity [5]. 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 tissue, there are two-way trends: with a decrease in expression oncosuppressor levels, e.g. miRNA-137, an increase in these parameters is observed in miRNA-9. In the case of other oncogenic factors, there is a correlation between the level of their expression in tumor tissues and the degree of malignancy of gliomas [6]. Low- and high-grade gliomas are characterized by activation anti-apoptotic mechanisms and signaling pathways that increase 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 significantly overexpressed in the glioblastoma multiforme sample. Furthermore, high levels of micoRNA-24 expression tended to contribute to the long-term overall survival of glioblastoma patients; but with high microRNA-26a expression levels, prolonged progression-free survival was obvious [7]. MicroRNA-21 has one of the highest expressions in human cells; and its expression level is further increased in glioma tissues. It shows an approximately 5-15-fold increase in the expression level in glioma tissues compared to the norm. The oncogenic effect of microRNA-21 in glioma cells occurs by suppressing the expression of tumor suppressor genes, such as HNRPK, TOPORS, TAp63, TGFBR2/3 JMY, TIMP3, RECK, TP53BP2, DAXX, PDCD4 [8]. Moreover, low levels of its expression are weakly associated with increased survival, according to the Cancer Genome Atlas (TCGA). Inhibition of microRNA-21 leads, together with a decrease in EGFR expression, to cell cycle arrest in the G1/S phase and ultimately to inhibition of tumor growth.

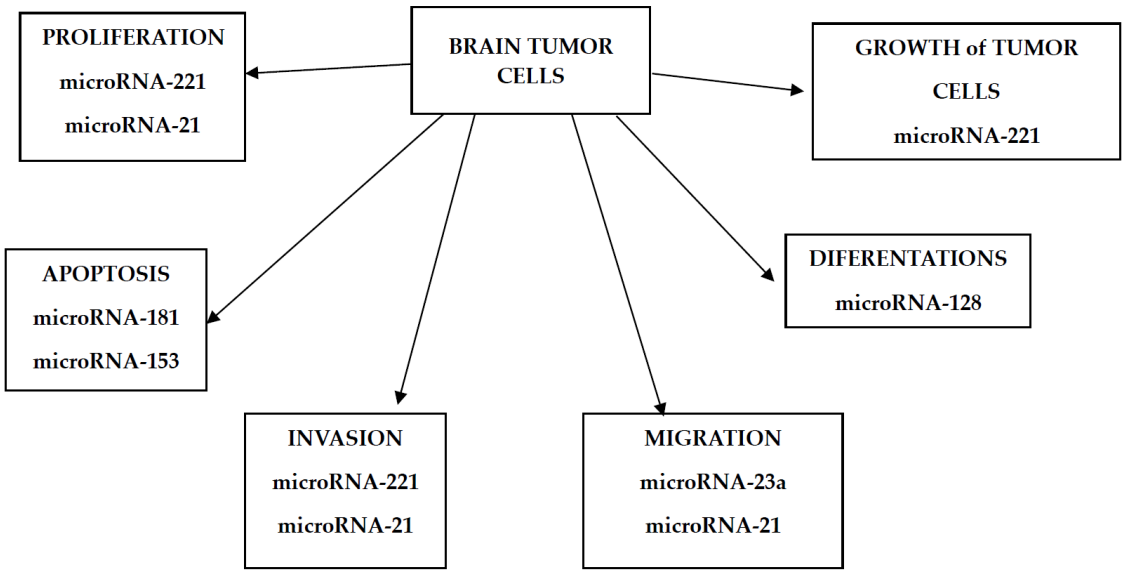

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Figure 1. Role of microRNAs in brain tumor cells.

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. For example, in some cases, glioblastoma multiforme can be distinguished from oligodendroglioma [9]. Although, most microRNAs are produced in cells themselves, many microRNAs, termed cell-free miRNAs, have been identified in various body fluids, such as blood or cerebrospinal fluid. The expression pattern of cell-free microRNAs is subject to significant changes (deviations or disruptions) in various human diseases, including brain tumors. These microRNAs exhibit nuclease resistance, which makes them potential candidates as attractive biomarkers for diagnosis, prognosis and monitoring of therapeutic responses [10].

3. microRNAs as Biomarkers of Brain Tumors

A key factor shaping the approach to the treatment of patients with primary or metastatic brain tumors is the precise determination of the type of tumor. In the use of molecular parameters to classify CNS tumors, distinct cell-free microRNAs that have prognostic significance as biomarkers may play a key role in the development of surgical intervention strategies, enabling real-time intraoperative monitoring choices and facilitating participation in clinical research activities. In recent years, microRNA expression in glioma has been extensively studied. Many studies have shown that certain microRNAs are correlated with the diagnosis and prognosis of gliomas. Among other things, microRNA-301a is highly expressed in glioma serum exosomes and may be a good diagnostic and prognostic indicator in the course of glioma [11]. Regarding microRNA-21, it was the initial miRNA identified in association with cancer and its positive expression was documented in various types of cancers, with strongly associated oncogenic properties [12]. It influences various cellular processes, from tumor initiation to cell death. Moreover, its association with cancer treatment resistance is established. In the case of meningiomas, microRNA-21 was detected especially in more advanced cancer cases [13]. Although Arar et al detected microRNA-21 expression in the plasma of meningioma patients, found no noticeable discrepancies compared to samples obtained from healthy people. This lack of distinction can be explained mainly by the benign nature of meningiomas [14]. Recently, Turk et al. showed a significant statistical difference in microRNA-17 expression levels between glial tumors and the control group with higher microRNA-17 expression observed in glial tumors. Similarly, in metastatic cases, microRNA-17 expression was statistically higher compared to the control group. Increased expression of microRNA-17 in brain metastases is supported by research evidence indicating its involvement in axon-myelin remodeling and functional recovery after stroke. These findings suggest that microRNA-17 may be a potential biomarker for differentiating glial tumors and brain metastases from normal brain tissue [15]. 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 also has neuroprotective effects, as evidenced by its role in protecting neonatal rats against ischemic-hypoxic brain damage [16]. Although, other studies have demonstrated its role in promoting cell growth and chemoresistance, suggesting its oncogenic nature [17]. Further studies should elucidate the mechanisms of microRNA-17's influence on the development and progression of brain tumors and brain metastases, taking into account the influence of other microRNAs. In recent years, several microRNAs have been associated with glial tumorigenesis. For example, the study by Li et al. demonstrated that astrocyte-upregulated gene-1 (AEG1) serves as a target of microRNA-542 to promote glioblastoma proliferation and invasion [18]. Zhi et al. analyzed patient serum and found that increased expression of microRNA-106a-5p, microRNA-20a-5p, and 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 [19]. AMoreover, Zhao et al. isolated microRNA from patients' serum and reported that microRNA-182, microRNA-222-3p, microRNA-20a-5p, microRNA-145-5p and microRNA-106a-5p correlated

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with poor patient outcomes [20]. 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 various other gliomas and, consequently, overall survival of patients with glioma containing less microRNA-15b [21]. 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 [22]. 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 consistent with validation by microarray and PCR analysis, 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 higher degree of resistance to temozolomide. The adversarial correlation of various 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 potent regulator of genes such as MGMT that worsen prognosis. Tang et al. studied the expression of microRNA-185 in the blood of patients with glioma and benign forms of brain tumors (pituitary adenoma, meningioma, and acoustic neuroma) and found that the expression of microRNA-185 in the plasma of patients with glioma was significantly increased, while when in the case of the remaining benign there were no obvious changes in the brain tumors. 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 [23]. 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 [24]. Wang et al. showed a significant increase in the expression level of microRNA-214 in the blood of patients with grade I and II malignant gliomas compared to the control group. However, patients suffering from stage I gliomas showed a more pronounced increase in microRNA-214 expression than their stage II counterparts. Furthermore, a receiver operating characteristic analysis was performed to evaluate the diagnostic performance of this microRNA, showing an exceptionally high area under the curve (AUC) of 0.885 in patients with grade I and -II malignant gliomas compared to the control group. The researchers also found that increased expression of microRNA -214 in glioma patients was associated with a worse prognosis. Moreover, microRNA-214 may be an independent prognostic predictor of overall survival in gliomas, especially in more severe tumors (grade II gliomas) [25]. 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 lower sensitivity and specificity for the diagnosis of low-grade gliomas but a high diagnostic value (AUC = 0.91) 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 [26]. This is confirmed by the research of Liu et al. who investigated the expression and significance 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 evaluate the diagnostic value of microRNA-29b and VEGFA in patients with gliomas. The AUC was 0.913 and 0.752, respectively [27]. Sippl et al. showed strong overexpression of microRNA-181d in cancer cells and blood of patients with glioblastoma multiforme compared to the control group. Even though most prognostic and predictive biomarkers for gliomas are currently developed using tumor samples obtained during surgical interventions AUC values indicate that the two groups can be distinguished

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by analysis of microRNA-181d expression. Additionally, the authors showed that the Cancer Genome Atlas analysis showed 8 potential protein targets regulated by microRNA-181d [28]. In recent years, a comprehensive serum microRNA signature has been reported in a large cohort of malignant glioma patients. In particular, seven blood microRNAs (microRNA-15b, microRNA-133a, microRNA-23a, microRNA-197, miR-150, microRNA-497 and microRNA-548b-5p), whose concentrations were significantly reduced in the serum of patients with malignant astrocytoma in compared with healthy people [29]. Additionally, serum microRNAs with different expression were found in patients with glioblastoma compared to the control group. Specifically, microRNA-340, microRNA-576-5p and microRNA-626 showed significantly overexpression, while microRNA7-5p, microRNA-320, let-7 g-5p showed significantly low expression in glioma patients [30]. Moreover, microRNA-125b, a member of the let-7c cluster widely considered to be a very good biomarker of various human cancers, has also been described as a potential biomarker of glioma. Furthermore, it appears that microRNA-125b may have a dual role depending on the cell type: it can act as both an oncomicroRNA and a tumor suppressor microRNA, targeting tumor suppressor genes or oncogenes, respectively. On the one hand, microRNA-125b targets many genes involved in the p53 pathway and induces apoptosis blockade in cancer cells, on the other hand, it may negatively affect the expression of proteins involved in the regulation of cell proliferation, suggesting an oncosuppressive role [31]. Moreover, Wu J et al. investigated the predictive value of serum microRNA-29 in screening for high-grade glioma [32].

In recent years, researchers have focused 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 related to the detection of microRNAs as a biomarker of CNS tumors is constantly increasing, which indicates a great interest in microRNA analysis (Table 1).

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-128	Down-regulation	Plasma/CSF	Diagnosis; Response to treatment;
microRNA-20a	Up-regulation	Plasma	Diagnosis; Prognosis;
microRNA-106a	Up-regulation	Plasma/CSF	Prognosis; Response to treatment;
microRNA-125b	Down-regulation	Plasma/CSF	Diagnosis; Response to treatment;
microRNA-19	Up-regulation	CSF	Diagnosis;
microRNA-137	Down-regulation	Plasma	Prognosis;
microRNA-92a	Up-regulation	CSF	Diagnosis;
microRNA-100	Down-regulation	Serum	Prognosis;
microRNA-210	Up-regulation	Serum	Prognosis;
microRNA-205	Up-regulation	Plasma	Diagnosis; Prognosis;
microRNA-223	Up-regulation	Plasma/CSF	Diagnosis; Prognosis;
microRNA-124	Up-regulation	Plasma	Prognosis;
microRNA-185	Up-regulation	Serum	Prognosis;
microRNA-497	Down-regulation	Plasma	Diagnosis;
microRNA-16	Down-regulation	Plasma/CSF	Prognosis; Response to treatment
microRNA-122	Down-regulation	Plasma	Diagnosis; Prognosis;

4. microRNAs Detection Methods

It is necessary to develop simple, fast, sensitive, and inexpensive analytical tools 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 [33]. In general, they are characterized by high specificity

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and good sensitivity, but the methods are complex and require a high level of technology, which requires expensive equipment and materials, qualified personnel to perform the test, and is 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 various direct detection methods such as localized surface plasmon resonance, photoelectrochemical and electrochemical biosensors. Electrochemical biosensors are popular because they are miniaturized and their mass production does not require high costs. They can be modified with a range of recognition elements and are widely used as versatile devices for the development of nucleic acid (E-DNA)-based biosensors. Moreover, such biosensors have demonstrated reliable results thanks to a comprehensive approach based on modern materials and nanomaterials, natural bioorganic polymers, electroactive molecules and catalysts [34]. 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 [33]. Moreover, Muijca et al. described electrochemical biosensors using various combinations of oligonucleotide strategies [35]. Besides, Mohammadi et al. reviewed different amplification strategies based on enzymes, nanomaterials and oligonucleotides for microRNA analysis and their various possible combinations. [36]. MicroRNA electrochemical biosensing systems based on the RedOx marker seem to be of the greatest importance. These approaches are based on microRNA biosensors 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 the field 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 [37].

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, technological advances in sequencing methods used in microRNA discovery have dramatically improved the identification of expression changes of individual microRNAs.

5. 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. Therefore, it is important 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 the diagnosis and prognosis of brain tumors, only a few have yielded promising results. It has been shown that such molecular biomarkers include microRNAs. The temporal and tissue specificity of microRNAs suggests that microRNAs are involved in the process of 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 [38]. The large differences in microRNA gene expression between malignant and normal cells may be due to the location of these genes in regions of the genome associated with cancer, epigenetic mechanisms, and changes in the microRNA processing apparatus. Because microRNAs are very stable and widely

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expressed in various body fluids and tissues, they can be used as diagnostic and prognostic biomarkers. Further research is needed to investigate microRNAs associated with brain tumors. Some biomarkers show correlations with other biomarkers. These microRNAs can be used in combination with traditional biological diagnostic indicators for clinical complementary screening of early-stage brain tumors. Some researchers suggest that a single plasma microRNA as a biomarker in the diagnosis of low-grade brain tumor is not sensitive and specific, but has some importance in the diagnosis of high-grade tumor [5].

The extensive experience accumulated so far in determining the level of microRNA expression using various methods in the diagnosis of brain tumors has many advantages. It is characterized by relatively high specificity and provides an opportunity to precisely monitor the effectiveness of therapy and even the possibility of using it for 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 [39]. Moreover, many studies were conducted on small groups of patients with different histological structures of brain tumors. Additionally, brain tumors are heterogeneous tumors, which complicates the interpretation of the results obtained and the selection of microRNAs as diagnostic markers [40]. For this purpose, an important process is the standardization of methods for determining microRNA expression levels and selecting optimal reference genes. In order to obtain reliable data, large-scale prospective studies are recommended to determine the involvement of microRNAs in the oncogenesis of CNS tumors and to confirm their effectiveness as biomarkers in diagnosis. As more and more brain tumor-associated and structurally diverse microRNAs are detected, the elucidation of the complex molecular regulatory mechanisms of brain tumors and the application of microRNAs-based brain tumor diagnosis and treatment will have better prospects [41].

Biomarker discovery is indeed a very difficult task, but with advances in proteomics and genomics strategies, more and more biomarkers are being discovered and tested in order to create fully functional brain tumor diagnostics.

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