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Non-coding RNAs as Genetic Biomarkers for the Diagnosis, Prognosis, Radiosensitivity, and Histopathologic Grade of Meningioma

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Abstract

Meningioma is considered the most common primary benign brain tumor. It originates from the arachnoid cells of the leptomeninges surrounding the brain. The mainstay treatment of meningiomas is microsurgical resection. Meningioma prognosis depends on tumor grade, location, and patient age. Recently, using non-coding RNA as a prognostic and diagnostic biomarker for many tumors became a trend. Herein, we demonstrate the importance of non-coding RNAs, including microRNAs and lncRNAs in meningioma and their potential role in meningioma's early diagnosis, prognosis, histological grade, and radiosensitivity. In this review, many microRNAs were found to be upregulated in radioresistant meningioma cells such as microRNA-221, microRNA-222, microRNA-4286, microRNA-4695-5p, microRNA-6732-5p, microRNA-6855-5p, microRNA-7977, microRNA-6765-3p, and microRNA-6787-5p. Moreover, there are many microRNAs downregulated in radioresistant meningioma cells such as microRNA-1275, microRNA-30c-1-3p, microRNA-4449, microRNA-4539, microRNA-4684-3p, microRNA-6129, and microRNA-6891-5p. Also, we highlight the possible use of non-coding RNAs as serum non-invasive biomarkers and their potential role as therapeutic targets to treat high-grade meningiomas. Recent studies show that microRNA-497, microRNA-195, microRNA-18a, microRNA-197, and microRNA-224 are downregulated in the serum of patients with meningiomas. Additionally, microRNA-106a-5p, microRNA-219-5p, microRNA-375, and microRNA-409-3p are found to be upregulated in the serum of patients with meningioma. We also found that there are many deregulated microRNAs in meningioma cells that can be used as potential biomarkers for meningioma diagnosis, prognosis, and histopathologic grade, such as microRNA-17-5p, microRNA-199a, microRNA-190a, microRNA-186-5p, microRNA155-5p, microRNA-22-3p, microRNA-24-3p, microRNA-26-5p, microRNA-27a-3p, microRNA-27b-3p, microRNA-96-5p, microRNA-146a-5p, microRNA-29c-3p, microRNA-219-5p, microRNA-335, microRNA-200a, microRNA-21, microRNA-107, microRNA-224, microRNA-195, microRNA-34a-3p, and microRNA-let-7d. Of interest, we found fewer studies discussing deregulated long non-coding RNAs (lncRNAs) in meningioma cells. LncRNAs work as competitive endogenous RNA (ceRNA) by binding to oncogenic or anti-oncogenic microRNAs. We found that lncRNA- NUP210, lncRNA-SPIRE2, lncRNA-SLC7A1, lncRNA-DMTN, lncRNA-LINC00702, and lncRNA-LINC00460 are upregulated in meningioma cells. In contrast, lncRNA-MALAT1 was found to be downregulated in meningioma cells.

Introduction And Background

Meningioma is considered the most common primary benign brain tumor. It originates from the arachnoid cells of the leptomeninges surrounding the brain [1]. The mainstay treatment of meningiomas is microsurgical resection. The meningioma prognosis depends on tumor grade, location, and patient's age [1-4]. Chemotherapy and hormonal treatment have bad results in treating meningioma, despite meningiomas' expression of hormonal receptors; subsequently, patients having recurrence after surgical resection and radiotherapy have very limited options for treatment [2,5-8]. As a result, searching for other potential therapies for meningioma should be encouraged by studying the role of non-coding RNAs on tumor differentiation, growth, and proliferation.

According to the WHO classification, meningiomas are classified into three grades: classic (WHO-I), atypical (WHO-II), and malignant (WHO-III) [9]. If a meningioma meets three out of the following five histologic features, it is considered atypical meningioma. These features include small cells with a high nuclear: cytoplasmic ratio, prominent nucleoli, spontaneous necrosis, loss of whorling or fascicular architecture, and hypercellularity [10]. Less than 20% of meningioma cases are considered WHO-II or WHO-III and have aggressive behavior, high recurrence rate, and higher morbidity and mortality rates [2,4,9-11].

Recently, using non-coding RNA as a prognostic and diagnostic biomarker for many tumors became a trend [12]. Herein, we demonstrate the importance of non-coding RNAs' expression in meningiomas and their potential role in meningioma's early diagnosis. In contrast to the small part of our genome that is transcribed into messenger RNAs (mRNAs) to produce protein, most of our genome is transcribed into non-

coding RNAs (ncRNA) that are not translated into proteins. Also, ncRNAs were considered to have unknown and less important roles than the protein-encoding genes [12]. Despite this, ncRNAs have been shown to have an important role in regulating gene expression, and cell differentiation [13]. NcRNAs having greater than 200 nucleotides (nt) are called long non-coding RNA (lncRNA) while those having 200 nt or less are considered small ncRNAs [12].

MicroRNAs are considered a type of small ncRNAs that regulates gene expression by binding to mRNAs [14]. It can bind to oncogenic or anti-oncogenic mRNAs; as a result, microRNAs may be able to suppress or induce tumor growth and proliferation [15]. In a large study containing 110 patients, Zhi et al. examined the expression of 200 microRNAs in meningioma cells and found that twelve microRNAs are significantly upregulated in meningioma cells and act as oncogenic factors [16]. These microRNAs include microRNA-17-5p, microRNA-199a, microRNA-190a, microRNA-186-5p, microRNA-155-5p, microRNA-22-3p, microRNA-24-3p, microRNA- 26b-5p, microRNA-27a-3p, microRNA-27b-3p, microRNA-96-5p, and microRNA-146a-5p [16]. They also found that microRNA-29c-3p and microRNA-219-5p are significantly downregulated in meningioma cells [16]. In this review, we focus on microRNAs that are significantly upregulated or downregulated in meningioma cells and are associated with meningioma cells' proliferation, growth, and migration.

LncRNAs can suppress or induce tumor growth and proliferation through many mechanisms. First, it can attach to the promoters of many tumor suppressor genes, enabling lncRNAs to silence those genes through its epigenetic modifications [12,17]. Second, it can bind to microRNAs and act as a competing endogenous RNA (ceRNA); as a result, it can alter microRNAs' binding to protein-coding mRNAs [18]. Herein, we discuss dysregulated microRNAs and lncRNAs associated with meningioma growth, proliferation, and malignancy transformation.

Review

MicroRNA-335 as a potential therapeutic target in meningioma and a possible biomarker of meningioma diagnosis

MicroRNA-335 is found to have a protective role in some tumors such as breast cancer metastasis, and malignant astrocytoma [19,20]. In contrast to the anti-oncogenic role of microRNA-335 in these tumors, Shi et al. found that microRNA-335 has an oncogenic effect in meningioma [11]. They showed that the inhibition of microRNA-335 induces cell arrest and suppresses cell proliferation. They suggested that this happened due to microRNA-335 ability to decrease the expression of the tumor-suppressing human retinoblastoma 1 (Rb1) protein. Moreover, they found that overexpression of microRNA-335 induces cell growth and proliferation [11]. This suggests the possibility of using microRNA-335 as a therapeutic target in meningioma treatment.

MicroRNA-200a as a potential therapeutic target in meningioma and a possible biomarker of meningioma prognosis

Senol et al. found that microRNA-200a inhibits meningioma cells' growth and migration by decreasing the expression of the non-muscle heavy chain IIB (NMHCIIB) protein by targeting its mRNA [21]. They also found that on microRNA-200a overexpression, cells from malignant meningiomas (WHO-III) showed a significant decrease in migration [21]. Of interest, overexpression of microRNA-200a has been found to decrease the migration of tumor cells such as breast epithelial cells, and nasopharyngeal carcinoma [22,23]. This shows the potential role of microRNA-200a as a therapeutic target to decrease the aggressiveness of malignant meningiomas. Further, it shows the possibility of using microRNA-200a as a biomarker for meningioma's aggressiveness.

MicroRNA-21 and microRNA-107 as potential biomarkers associated with changes in the histopathologic grades

Katar et al. found that increased expression of microRNA-21 and decreased expression of microRNA-107 are significantly associated with higher histopathologic grades [24]. Of interest, overexpression of microRNA-21 is associated with grade 3 and 4 gliomas, compared to grade 1 gliomas and normal brain tissues [25-27]. Barnabo et al. and Shi et al. found that there is a positive correlation between glioma grade and microRNA-21 expression [25,27]. Furthermore, Teplyuk et al. found that increased expression of microRNA-21 is associated with more advanced disease in glioblastoma multiforme (GBM) and metastatic brain tumors [26]. Regarding microRNA-107, Song et al. found that microRNA-107 expression is negatively correlated with renal cell carcinoma's stage and size [28]. They also showed that decreased expression of microRNA-107 is associated with the incidence of metastasis [28]. Li et al. suggested that by targeting CKD8 in meningioma cells, microRNA-107 inhibits migration and proliferation [29].

MicroRNA-224 as a potential biomarker associated with changes in the histopathologic grades and a possible biomarker for meningioma diagnosis

Wang et al. found that there is a higher microRNA-224 expression in meningioma cells compared to normal cells [30]. They also found that microRNA-224 expression is positively correlated with the histopathologic grade [30]. They suggested that microRNA-224 induces meningioma's growth and proliferation by targeting the early growth response 2 (ERG2) protein's expression, which is a contributor to the apoptosis process [30]. Interestingly, microRNA-224 has been reported to be positively correlated to poor prognosis and aggressive behavior in many tumors such as liver, gastric, lung, and prostate cancers [31-33].

MicroRNAs as potential therapies inducing radiosensitivity of meningioma cells and possible biomarkers for radioresistance

Ionizing radiation's therapeutic effect is achieved by its ability to cause DNA damage, which induces several repair signaling cascades [34]. Subsequently, it leads to P53 protein phosphorylation [34,35]. Phosphorylated P53 induces the expression of various genes including the Phosphatase and Tensin Homolog (PTEN) gene. As a result, it induces cell arrest and apoptosis [34-36]. This shows that the PTEN protein has an antioncogenic effect, and its expression can be induced by ionizing radiation.

In contrast to the previously discussed antioncogenic effect of ionizing radiation, ionizing radiation can induce epithelial-mesenchymal transition (EMT) and cancer cells' invasive and migratory properties [37-40]. As a result, ionizing radiation can induce meningioma cells' invasiveness, recurrence, or malignant transformation. This paradoxical effect of ionizing radiation encourages more research to find potential radiosensitive-inducing agents. In meningioma cells, Zhang et al. found that decreasing microRNA-221 and microRNA-222 expression can enhance the apoptosis-inducing effect of ionizing radiation by increasing PTEN levels [41].

Regarding other tumors, recent studies show the effect of co-suppression of both microRNA-221 and microRNA-222 expression on inducing radiosensitivity [42,43]. Zhang et al. found that decreased expression of microRNA-221 and microRNA-222 induces radiosensitivity in gastric cancer and GBM cells by increasing the expression of the PTEN gene [42,43]. Furthermore, Khoshinani et al. showed that microRNA-222 regulates radiosensitivity by targeting PTEN in colorectal cancer cells [44]. Similarly, Xue et al. found that anti-microRNA-221 induces radiosensitivity in colorectal cancer cells by regulating the expression of the PTEN protein [45].

In a retrospective study, Zhang et al. compared both radiosensitive patients versus radioresistant patients. There was no significant difference in gender, age, peritumoral edema, Ki-67 index, tumor size, and tumor location between these two groups [46]. They found that in patients with radio-resistance, there are seven significantly upregulated microRNAs (microRNA-4286, microRNA-4695-5p, microRNA6732-5p, microRNA6855-5p, microRNA7977, microRNA-6765-3p, microRNA 6787-5p) and seven downregulated microRNAs (microRNA-1275, microRNA-30c-1-3p, microRNA4449, microRNA-4539, microRNA-4684-3p, microRNA-6129, microRNA-6891-5p) [46]. All microRNAs associated with increased radiosensitivity or radioresistance are summarized in Table *1*. This highlights the possibility of using ncRNAs as a potential therapeutic target to increase meningioma cells' responsiveness to radiotherapy.

MicroRNA	Expression in radioresistant cells	Reference
MicroRNA-221	Upregulated	[41]
MicroRNA-222	Upregulated	[41]
MicroRNA-4286	Upregulated	[46]
MicroRNA-4695-5p	Upregulated	[46]
MicroRNA-6732-5p	Upregulated	[46]
MicroRNA-6855-5p	Upregulated	[46]
MicroRNA-7977	Upregulated	[46]
MicroRNA-6765-3p	Upregulated	[46]
MicroRNA-6787-5p	Upregulated	[46]
MicroRNA-1275	Downregulated	[46]
MicroRNA-30c-1-3p	Downregulated	[46]
MicroRNA4449	Downregulated	[46]
MicroRNA-4539	Downregulated	[46]
MicroRNA-4684-3p	Downregulated	[46]
MicroRNA-6129	Downregulated	[46]
MicroRNA-6891-5p	Downregulated	[46]

TABLE 1: MicroRNAs expression in radio-resistant meningioma cells

MicroRNA-195 as a malignant meningioma suppressor and a potential biomarker for meningioma histopathologic grade

Song et al. found that increased expression of microRNA-195 significantly decreased meningioma cells' proliferation, invasion, and migration by targeting fatty acid synthase (FASN), which is found to be upregulated in high-grade meningioma compared to grade 1 meningioma cells [47]. This shows the possibility of using microRNA-195 as a biomarker for meningioma's histopathologic grade. Of interest, microRNA-195 is found to be downregulated in many tumors such as non-small-cell lung cancer, and hepatocellular carcinoma [48,49]. Also, Mao et al. reported that osteosarcoma cell migration and invasion are suppressed by microRNA-195 [50].

Song et al. also found that there are many lncRNAs, such as NUP210, SPIRE2, SLC7A1, and DMTN, act as ceRNAs by sponging microRNA-195 and preventing it from binding to mRNA [47]. As a result, these lncRNAs are considered oncogenic by increasing FASN expression by targeting microRNA-195 [47].

MicroRNAs as serum non-invasive biomarkers for meningiomas

Tang et al. examined the levels of serum microRNA-185 in patients with meningiomas, gliomas, acoustic neuroma, and pituitary adenoma [51]. They found that the plasma level of microRNA-185 is only significantly changed in gliomas [51]. Another failed trial to find serum biomarkers for meningioma is reported by Wang et al. [52]. They found that serum microRNA-21, microRNA-128, and microRNA-342-3p are insignificantly altered in meningiomas [52]. Fortunately, Negroni et al. found that in patients with high-grade meningiomas, serum levels of microRNA-497 and microRNA-195 are lower than in those who do not have meningiomas [53]. This demonstrates the potential use of microRNA-497 and microRNA-195 as serum biomarkers for high-grade meningioma. Furthermore, Li et al. found that serum and cerebrospinal fluid (CSF) levels of microRNA-18a are significantly lower in patients with invasive meningioma than in healthy subjects [54]. They also found that only CSF levels of microRNA-18a are significantly lower in invasive meningioma than in patients with non-invasive meningioma [54].

In another study, Zhi et al. found that in patients with meningioma, microRNA-106a-5p, microRNA-219-5p, microRNA-375, and microRNA-409-3p are increased in the serum [55]. In contrast to this, they found that serum levels of microRNA-197 and microRNA-224 decreased in those patients [55]. This highlights the possibility of microRNAs as serum biomarkers for meningiomas. Of interest, the effect of inhibition of one

of the microRNAs reported by Zhi et al. is studied by Hu et al. [56]. They found that inhibition of microRNA-197 in meningioma cells by Quercetin induces apoptosis and inhibits proliferation [56]. Quercetin's effect on meningioma cells' proliferation was reported in a previous study by Piantelli et al. [57]. However, the molecular mechanism was unknown. MicroRNAs that are considered potential serum non-invasive biomarkers for meningioma are summarized in Table 2. More clinical studies are encouraged to study the correlation between the serum levels of different ncRNAs and menenigeoma's diagnosis, prognosis, histopathologic grade, and radiosensitivity.

MicroRNA	Expression	Reference
MicroRNA-497	Downregulated	[53]
MicroRNA-195	Downregulated	[53]
MicroRNA-18a	Downregulated	[54]
MicroRNA-106a-5p	Upregulated	[55]
MicroRNA-219-5p	Upregulated	[55]
MicroRNA-375	Upregulated	[55]
MicroRNA-409-3p	Upregulated	[55]
MicroRNA-197	Downregulated	[55]
MicroRNA-224	Downregulated	[55]

TABLE 2: Serum microRNAs expression in meningioma patients

MicroRNA-34a-3p as a potential biomarker for meningioma diagnosis

Ludwig et al. found that microRNA-34a-3p is lower in grade II meningiomas compared to grade I meningiomas. They also suggested using microRNA-34a-3p as a biomarker that can differentiate higher-grade meningiomas [58]. In another study, Werner et al. found that microRNA-34a-3p inhibits apoptosis, proliferation, and invasiveness by targeting SMAD4, FRAT1, and BCL2 [59]. SMAD4 has an antioncogenic effect in the early stages of tumor development; however, it has an oncogenic effect in the late stages by stimulating angiogenesis and EMT [60]. Lower levels of microRNA-34a-3p increase SMAD4 expression and induce meningiomas' growth, invasiveness, and proliferation.

BCL2 has an antiapoptotic role. High levels of BCL2 are associated with increased recurrence in patients with benign meningioma. Moreover, in patients with atypical meningioma, BCL2 is found to be associated with a shorter time to recurrence [61,62]. Lower levels of microRNA-34a-3p increase BCL2 expression and induce meningiomas' growth, invasiveness, and proliferation. Similarly, lower levels of microRNA-34a-3p increase FRAT1 expression and induce meningioma proliferation and invasiveness [59].

MicroRNA-let-7d as a potential biomarker for meningioma proliferation and invasion

MicroRNA-let-7d downregulation is found to be associated with poor survival in head and neck squamous cell carcinomas [63]. Furthermore, in another study by Su et al., they found that microRNA-let-7d can suppress growth and metastasis in renal cell carcinoma [64]. In meningioma cells, Li et al. found that high levels of microRNA-let-7d suppress proliferation, and stimulate apoptosis by targeting Astrocyte Elevated Gene-1 (AEG-1) [65]. AEG-1 is an oncogenic protein. Its inhibition induces apoptosis in prostate cancer and retinoblastoma [65,66]. In contrast, AEG-1 overexpression leads to cervical cancer progression [67]. Similarly, AEG-1 is overexpressed in meningioma cells [65]. All microRNAs mentioned in this review and associated with meningioma growth, proliferation, and invasion are summarized in Table 3.

MicroRNA	Expression in meningioma	References
MicroRNA-17-5p	Upregulated	[16]
MicroRNA-199a	Upregulated	[16]
MicroRNA-190a	Upregulated	[16]
MicroRNA-186-5p	Upregulated	[16]
MicroRNA155-5p	Upregulated	[16]
MicroRNA-22-3p	Upregulated	[16]
MicroRNA-24-3p	Upregulated	[16]
MicroRNA-26-5p	Upregulated	[16]
MicroRNA-27a-3p	Upregulated	[16]
MicroRNA-27b-3p	Upregulated	[16]
MicroRNA-96-5p	Upregulated	[16]
MicroRNA-146a-5p	Upregulated	[16]
MicroRNA-29c-3p	Downregulated	[16]
MicroRNA-219-5p	Downregulated	[16]
MicroRNA-335	Upregulated	[11]
MicroRNA-200a	Downregulated	[21]
MicroRNA-21	Upregulated	[24]
MicroRNA-107	Downregulated	[24]
MicroRNA-224	Upregulated	[30]
MicroRNA-195	Downregulated	[47]
MicroRNA-34a-3p	Downregulated	[58]
MicroRNA-let-7d	Downregulated	[65]

TABLE 3: MicroRNAs associated with meningioma growth, proliferation, and invasion

lncRNAs as biomarkers for meningioma diagnosis, prognosis, and histopathologic grade

In contrast to microRNAs, fewer lncRNAs associated with meningioma progression, growth, and invasion are studied. These lncRNAs act as a molecular sponge or ceRNA by binding to microRNAs. As a result, it can decrease or increase oncogenic or antioncogenic proteins [18]. Song et al. also found that there are many lncRNAs, such as NUP210, SPIRE2, SLC7A1, and DMTN, act as ceRNAs by sponging microRNA-195 and preventing it from binding to mRNA [47]. As a result, these lncRNAs are considered oncogenic by increasing FASN expression by targeting microRNA-195 [47].

Li et al. found that in malignant meningioma, lncRNA-LINC00702 upregulates ZEB1 by binding to microRNA-4652-3p [68]. Furthermore, Xing et al. found that lncRNA-LINC00460 induces meningioma metastasis and progression by binding to microRNA-539/MMP-9 [69]. Also, lncRNA-MALAT1 is found to act as a ceRNA by targeting microRNA-145, which is considered an oncogenic microRNA. Subsequently, lncRNA-MALAT1 overexpression can lead to reduced meningioma invasiveness [70]. All lncRNAs mentioned in this review and associated with meningioma growth, proliferation, and invasion are summarized in Table 4.

LncRNA	Expression in meningioma	Reference
LncRNA- NUP210	Upregulated	[47]
LncRNA-SPIRE2	Upregulated	[47]
LncRNA-SLC7A1	Upregulated	[47]
LncRNA-DMTN	Upregulated	[47]
lncRNA-LINC00702	Upregulated	[68]
lncRNA-LINC00460	Upregulated	[69]
lncRNA-MALAT1	Downregulated	[70]

TABLE 4: lncRNAs expression in meningioma cells

Conclusions

Non-coding RNAs, including microRNAs and lncRNAs, are potential biomarkers for meningioma diagnosis, prognosis, aggressiveness, histopathologic grade, and radiosensitivity. More clinical studies with large samples are encouraged to examine serum, biopsy, and CSF levels of these non-coding RNAs' sensitivity and specificity.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Marosi C, Hassler M, Roessler K, Reni M, Sant M, Mazza E, Vecht C: Meningioma. Crit Rev Oncol Hematol. 2008, 67:153-71. 10.1016/j.critrevonc.2008.01.010
2. Montoure AJ; Eraky AM; Martinez del Campo E; Bovi J; Connelly J; Zwagerman NT: Incidence of surgery after gamma knife radiosurgery for parasagittal and parafalcine meningiomas is higher than meningiomas in other locations: a 10-year institutional analysis and review of the literature. J Clin Images Med Case Rep. 2022, 3:10.52768/2766-7820/2099
3. Lim P, Eraky AM, Coss D, Zwagerman N: Intraosseous meningioma along the left petrous bone: a rare cause of trigeminal neuralgia. Cureus. 2022, 14:e32414. 10.7759/cureus.32414
4. Nakamura M, Roser F, Michel J, Jacobs C, Samii M: The natural history of incidental meningiomas. Neurosurgery. 2003, 53:62-70; discussion 70-1. 10.1227/01.neu.0000068730.76856.58
5. Adegbite AB, Khan MI, Paine KW, Tan LK: The recurrence of intracranial meningiomas after surgical treatment. J Neurosurg. 1983, 58:51-6. 10.3171/jns.1983.58.1.0051
6. Adeberg S, Hartmann C, Welzel T, et al.: Long-term outcome after radiotherapy in patients with atypical and malignant meningiomas—clinical results in 85 patients treated in a single institution leading to optimized guidelines for early radiation therapy. Int J Radiat Oncol Biol Phys. 2012, 83:859-64. 10.1016/j.ijrobp.2011.08.010
7. Stupp R, Mason WP, van den Bent MJ, et al.: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005, 352:987-96. 10.1056/NEJMoa043330
8. Amirjamshidi A, Mehrazin M, Abbassioun K: Meningiomas of the central nervous system occurring below the age of 17: report of 24 cases not associated with neurofibromatosis and review of literature. Childs Nerv Syst. 2000, 16:406-16. 10.1007/s003819900205
9. Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM: Meningioma grading: an analysis of histologic parameters. Am J Surg Pathol. 1997, 21:1455-65. 10.1097/00000478-199712000-00008
10. Louis DN, Perry A, Reifenberger G, et al.: The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016, 131:803-20. 10.1007/s00401-016-1545-1
11. Shi L, Jiang D, Sun G, et al.: miR-335 promotes cell proliferation by directly targeting Rb1 in meningiomas. J Neurooncol. 2012, 110:155-62. 10.1007/s11060-012-0951-z
12. Eraky AM, Keles A, Goodman SL, Baskaya MK: Serum long non-coding RNAs as potential noninvasive biomarkers for glioblastoma diagnosis, prognosis, and chemoresistance. J Integr Neurosci. 2022, 21:111. 10.31083/j.jin2104111
13. Kapranov P, Cheng J, Dike S, et al.: RNA maps reveal new RNA classes and a possible function for pervasive transcription. Science. 2007, 316:1484-8. 10.1126/science.1138341

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14. Sreekumar R, Sayan BS, Mirnezami AH, Sayan AE: MicroRNA control of invasion and metastasis pathways . Front Genet. 2011, 2:58. 10.3389/fgene.2011.00058

15. Chen CZ: MicroRNAs as oncogenes and tumor suppressors . N Engl J Med. 2005, 353:1768-71. 10.1056/NEJMp058190

16. Zhi F, Zhou G, Wang S, et al.: A microRNA expression signature predicts meningioma recurrence . Int J Cancer. 2013, 132:128-36. 10.1002/ijc.27658

17. Tsai MC, Manor O, Wan Y, et al.: Long noncoding RNA as modular scaffold of histone modification complexes. Science. 2010, 329:689-93. 10.1126/science.1192002

18. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP: A ceRNA hypothesis: the Rosetta stone of a hidden RNA language?. Cell. 2011, 146:353-8. 10.1016/j.cell.2011.07.014

19. Tavazoie SF, Alarcón C, Oskarsson T, et al.: Endogenous human microRNAs that suppress breast cancer metastasis. Nature. 2008, 451:147-52. 10.1038/nature06487

20. Shu M, Zheng X, Wu S, et al.: Targeting oncogenic miR-335 inhibits growth and invasion of malignant astrocytoma cells. Mol Cancer. 2011, 10:59. 10.1186/1476-4598-10-59

21. Senol O, Schaaij-Visser TB, Erkan EP, et al.: miR-200a-mediated suppression of non-muscle heavy chain IIb inhibits meningioma cell migration and tumor growth in vivo. Oncogene. 2015, 34:1790-8. 10.1038/onc.2014.120

22. Xia H, Ng SS, Jiang S, et al.: miR-200a-mediated downregulation of ZEB2 and CTNNB1 differentially inhibits nasopharyngeal carcinoma cell growth, migration and invasion. Biochem Biophys Res Commun. 2010, 391:535-41. 10.1016/j.bbrc.2009.11.093

23. Ahmad A, Aboukameel A, Kong D, et al.: Phosphoglucose isomerase/autocrine motility factor mediates epithelial-mesenchymal transition regulated by miR-200 in breast cancer cells. Cancer Res. 2011, 71:3400-9. 10.1158/0008-5472.CAN-10-0965

24. Katar S, Baran O, Evran S, et al.: Expression of miRNA-21, miRNA-107, miRNA-137 and miRNA-29b in meningioma. Clin Neurol Neurosurg. 2017, 156:66-70. 10.1016/j.clineuro.2017.03.016

25. Shi R, Wang PY, Li XY, et al.: Exosomal levels of miRNA-21 from cerebrospinal fluids associated with poor prognosis and tumor recurrence of glioma patients. Oncotarget. 2015, 6:26971-81. 10.18632/oncotarget.4699

26. Teplyuk NM, Mollenhauer B, Gabriely G, et al.: MicroRNAs in cerebrospinal fluid identify glioblastoma and metastatic brain cancers and reflect disease activity. Neuro Oncol. 2012, 14:689-700. 10.1093/neuonc/nos074

27. Barbano R, Palumbo O, Pasculli B, et al.: A miRNA signature for defining aggressive phenotype and prognosis in gliomas. PLoS One. 2014, 9:e108950. 10.1371/journal.pone.0108950

28. Song N, Ma X, Li H, Zhang Y, Wang X, Zhou P, Zhang X: microRNA-107 functions as a candidate tumor suppressor gene in renal clear cell carcinoma involving multiple genes. Urol Oncol. 2015, 33:205.e1-11. 10.1016/j.urolonc.2015.02.003

29. Li XY, Luo QF, Wei CK, Li DF, Li J, Fang L: MiRNA-107 inhibits proliferation and migration by targeting CDK8 in breast cancer. Int J Clin Exp Med. 2014, 7:32-40.

30. Wang M, Deng X, Ying Q, Jin T, Li M, Liang C: MicroRNA-224 targets ERG2 and contributes to malignant progressions of meningioma. Biochem Biophys Res Commun. 2015, 460:354-61. 10.1016/j.bbrc.2015.03.038

31. Liu M, Liu J, Wang L, et al.: Association of serum microRNA expression in hepatocellular carcinomas treated with transarterial chemoembolization and patient survival. PLoS One. 2014, 9:e109347. 10.1371/journal.pone.0109347

32. Unoki M, Nakamura Y: EGR2 induces apoptosis in various cancer cell lines by direct transactivation of BNIP3L and BAK. Oncogene. 2003, 22:2172-85. 10.1038/sj.onc.1206222

33. Wan Y, Zeng ZC, Xi M, et al.: Dysregulated microRNA-224/apelin axis associated with aggressive progression and poor prognosis in patients with prostate cancer. Hum Pathol. 2015, 46:295-303. 10.1016/j.humpath.2014.10.027

34. Santivasi WL, Xia F: Ionizing radiation-induced DNA damage, response, and repair . Antioxid Redox Signal. 2014, 21:251-9. 10.1089/ars.2013.5668

35. Ou YH, Chung PH, Sun TP, Shieh SY: p53 C-terminal phosphorylation by CHK1 and CHK2 participates in the regulation of DNA-damage-induced C-terminal acetylation. Mol Biol Cell. 2005, 16:1684-95. 10.1091/mbc.e04-08-0689

36. Shieh SY, Ahn J, Tamai K, Taya Y, Prives C: The human homologs of checkpoint kinases Chk1 and Cds1 (Chk2) phosphorylate p53 at multiple DNA damage-inducible sites. Genes Dev. 2000, 14:289-300.

37. Puisieux A, Brabletz T, Caramel J: Oncogenic roles of EMT-inducing transcription factors . Nat Cell Biol. 2014, 16:488-94. 10.1038/ncb2976

38. Lee SY, Jeong EK, Ju MK, et al.: Induction of metastasis, cancer stem cell phenotype, and oncogenic metabolism in cancer cells by ionizing radiation. Mol Cancer. 2017, 16:10. 10.1186/s12943-016-0577-4

39. Zhang Q, Jia GJ, Zhang GB, et al.: A logistic regression model for detecting the presence of malignant progression in atypical meningiomas. World Neurosurg. 2019, 126:e392-401. 10.1016/j.wneu.2019.02.062

40. Wang Y, Shi J, Chai K, Ying X, Zhou BP: The role of Snail in EMT and tumorigenesis . Curr Cancer Drug Targets. 2013, 13:963-72. 10.2174/15680096113136660102

41. Zhang Q, Song LR, Huo XL, et al.: MicroRNA-221/222 inhibits the radiation-induced invasiveness and promotes the radiosensitivity of malignant meningioma cells. Front Oncol. 2020, 10:1441. 10.3389/fonc.2020.01441

42. Chun-Zhi Z, Lei H, An-Ling Z, et al.: MicroRNA-221 and microRNA-222 regulate gastric carcinoma cell proliferation and radioresistance by targeting PTEN. BMC Cancer. 2010, 10:367. 10.1186/1471-2407-10-367

43. Zhang C, Kang C, You Y, et al.: Co-suppression of miR-221/222 cluster suppresses human glioma cell growth by targeting p27kip1 in vitro and in vivo. Int J Oncol. 2009, 34:1653-60. 10.3892/ijo_00000296

44. Khoshinani HM, Afshar S, Pashaki AS, et al.: Involvement of miR-155/FOXO3a and miR-222/PTEN in acquired radioresistance of colorectal cancer cell line. Jpn J Radiol. 2017, 35:664-72. 10.1007/s11604-017-0679-y

45. Xue Q, Sun K, Deng HJ, Lei ST, Dong JQ, Li GX: Anti-miRNA-221 sensitizes human colorectal carcinoma

cells to radiation by upregulating PTEN. World J Gastroenterol. 2013, 19:9307-17. 10.3748/wjg.v19.i48.9307

46. Zhang X, Zhang G, Huang H, Li H, Lin S, Wang Y: Differentially expressed microRNAs in radioresistant and radiosensitive atypical meningioma: a clinical study in Chinese patients. Front Oncol. 2020, 10:501. 10.3389/fonc.2020.00501

47. Song LR, Li D, Weng JC, Li CB, Wang L, Wu Z, Zhang JT: MicroRNA-195 functions as a tumor suppressor by directly targeting fatty acid synthase in malignant meningioma. World Neurosurg. 2020, 136:e355-64. 10.1016/j.wneu.2019.12.182

48. Wang M, Zhang J, Tong L, Ma X, Qiu X: MiR-195 is a key negative regulator of hepatocellular carcinoma metastasis by targeting FGF2 and VEGFA. Int J Clin Exp Pathol. 2015, 8:14110-20.

49. Zheng J, Xu T, Chen F, Zhang Y: MiRNA-195-5p functions as a tumor suppressor and a predictive of poor prognosis in non-small cell lung cancer by directly targeting CIAPIN1. Pathol Oncol Res. 2019, 25:1181-90. 10.1007/s12253-018-0552-z

50. Mao JH, Zhou RP, Peng AF, Liu ZL, Huang SH, Long XH, Shu Y: microRNA-195 suppresses osteosarcoma cell invasion and migration in vitro by targeting FASN. Oncol Lett. 2012, 4:1125-9. 10.3892/ol.2012.863

51. Tang H, Liu Q, Liu X, Ye F, Xie X, Xie X, Wu M: Plasma miR-185 as a predictive biomarker for prognosis of malignant glioma. J Cancer Res Ther. 2015, 11:630-4. 10.4103/0973-1482.146121

52. Wang Q, Li P, Li A, Jiang W, Wang H, Wang J, Xie K: Plasma specific miRNAs as predictive biomarkers for diagnosis and prognosis of glioma. J Exp Clin Cancer Res. 2012, 31:97. 10.1186/1756-9966-31-97

53. Negroni C, Hilton DA, Ercolano E, Adams CL, Kurian KM, Baiz D, Hanemann CO: GATA-4, a potential novel therapeutic target for high-grade meningioma, regulates miR-497, a potential novel circulating biomarker for high-grade meningioma. EBioMedicine. 2020, 59:102941. 10.1016/j.ebiom.2020.102941

54. Li P, Gao Y, Li F, et al.: MicroRNA-18a regulates invasive meningiomas via hypoxia-inducible factor-1α. Exp Ther Med. 2015, 10:1165-70. 10.3892/etm.2015.2630

55. Zhi F, Shao N, Li B, et al.: A serum 6-miRNA panel as a novel non-invasive biomarker for meningioma . Sci Rep. 2016, 6:32067. 10.1038/srep32067

56. Hu SA, Cheng J, Zhao WH, Zhao HY: Quercetin induces apoptosis in meningioma cells through the miR-197/IGFBP5 cascade. Environ Toxicol Pharmacol. 2020, 80:103439. 10.1016/j.etap.2020.103439

57. Piantelli M, Rinelli A, Macrì E, et al.: Type II estrogen binding sites and antiproliferative activity of quercetin in human meningiomas. Cancer. 1993, 71:193-8. 10.1002/1097-0142(19930101)71:1<193::aid-cncr2820710130>3.0.co;2-c

58. Ludwig N, Kim YJ, Mueller SC, et al.: Posttranscriptional deregulation of signaling pathways in meningioma subtypes by differential expression of miRNAs. Neuro Oncol. 2015, 17:1250-60. 10.1093/neuonc/nov014

59. Werner TV, Hart M, Nickels R, et al.: MiR-34a-3p alters proliferation and apoptosis of meningioma cells in vitro and is directly targeting SMAD4, FRAT1 and BCL2. Aging. 2017, 9:932-54. 10.18632/aging.101201

60. Heldin CH, Moustakas A: Role of Smads in TGFβ signaling . Cell Tissue Res. 2012, 347:21-36. 10.1007/s00441-011-1190-x

61. Lee SH, Lee EH, Lee SH, Lee YM, Kim HD, Kim YZ: Epigenetic role of histone 3 lysine methyltransferase and demethylase in regulating apoptosis predicting the recurrence of atypical meningioma. J Korean Med Sci. 2015, 30:1157-66. 10.3346/jkms.2015.30.8.1157

62. Abdelzaher E, El-Gendi SM, Yehya A, Gowil AG: Recurrence of benign meningiomas: predictive value of proliferative index, BCL2, p53, hormonal receptors and HER2 expression. Br J Neurosurg. 2011, 25:707-13. 10.3109/02688697.2010.522743

63. Childs G, Fazzari M, Kung G, et al.: Low-level expression of microRNAs let-7d and miR-205 are prognostic markers of head and neck squamous cell carcinoma. Am J Pathol. 2009, 174:736-45. 10.2353/ajpath.2009.080731

64. Su B, Zhao W, Shi B, et al.: Let-7d suppresses growth, metastasis, and tumor macrophage infiltration in renal cell carcinoma by targeting COL3A1 and CCL7. Mol Cancer. 2014, 13:206. 10.1186/1476-4598-13-206

65. Li H, Zhao J: let-7d suppresses proliferation and invasion and promotes apoptosis of meningioma by targeting AEG-1. Onco Targets Ther. 2017, 10:4895-904. 10.2147/OTT.S141008

66. Chang Y, Li B, Xu X, et al.: Lentivirus-mediated knockdown of astrocyte elevated gene-1 inhibits growth and induces apoptosis through MAPK pathways in human retinoblastoma cells. PLoS One. 2016, 11:0148763. 10.1371/journal.pone.0148763

67. Huang K, Li LA, Meng Y, You Y, Fu X, Song L: High expression of astrocyte elevated gene-1 (AEG-1) is associated with progression of cervical intraepithelial neoplasia and unfavorable prognosis in cervical cancer. World J Surg Oncol. 2013, 11:297. 10.1186/1477-7819-11-297

68. Li T, Ren J, Ma J, Wu J, Zhang R, Yuan H, Han X: LINC00702/miR-4652-3p/ZEB1 axis promotes the progression of malignant meningioma through activating Wnt/β-catenin pathway. Biomed Pharmacother. 2019, 113:108718. 10.1016/j.biopha.2019.108718

69. Xing H, Wang S, Li Q, Ma Y, Sun P: Long noncoding RNA LINC00460 targets miR-539/MMP-9 to promote meningioma progression and metastasis. Biomed Pharmacother. 2018, 105:677-82. 10.1016/j.biopha.2018.06.005

70. Zheng J, Pang CH, Du W, Wang L, Sun LG, Xing ZY: An allele of rs619586 polymorphism in MALAT1 alters the invasiveness of meningioma via modulating the expression of collagen type V alpha (COL5A1). J Cell Mol Med. 2020, 24:10223-32. 10.1111/jcmm.15637

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