miR 181a

Shi et al., showed that hsa-miR-181a and hsa-miR-181b functioned as tumor suppressors which triggered growth inhibition, induced apoptosis and inhibited invasion in glioma cells. Furthermore, the tumor-suppressive effect of hsa-miR-181b in glioma cells was more apparent than the effect of hsa-miR-181a. These findings suggest aberrantly down-regulated hsa-miR-181a and hsa-miR-181b may be critical factors that contribute to malignant appearance in human gliomas [1)].

ATP2B2 target gene could be regulated by has-mir-181a to involve in calcium signaling pathway [2)].

Ma et al., identified microRNA-181a (miR-181a) as a critical MicroRNA in opening BTB. MicroRNA-181a expression was upregulated in glioma endothelial cells (GECs), which were obtained by coculturing endothelial cells (ECs) with glioma cells. Overexpression of miR-181a resulted in an impaired and permeability increased BTB, and meanwhile reduced the expression of zonula occluden (ZO)-1, occludin, and claudin-5. Kruppel-like factor 6 (KLF6), a transcription factor of the zinc-finger family, was downregulated in GECs. Mechanistic investigations defined it as a direct and functional downstream target of miR-181a, which was involved in the regulation of BTB permeability and the expression of ZO-1, occludin, and claudin-5. Furthermore, luciferase assays and chromatin immunoprecipitation assays showed that KLF6 upregulated the promoter activities and interacted with the promoters of ZO-1, occludin, and claudin-5 in GECs. Collectively, we showed the possibility that overexpression of miR-181a contributes to the increased permeability of BTB by targeting KLF6, thereby revealing potential therapeutic targets for the treatment of brain gliomas [3)].

Wu et al., identified miR 181a, which may have a biological function, particularly during the early stages after nerve allotransplantation under FK506 immunosuppression [4)].

In HMOX1-transfected astrocytes, rno-miR-140*, rno-miR-17, and rno-miR-16 were significantly up-regulated, and rno-miR-297, rno-miR-206, rno-miR-187, rno-miR-181a, rno-miR-138 and rno-miR-29c were down-regulated, compared to sham-transfected controls [5)].

Sharma et al., measured six downstream MicroRNA targets of EZH2 and found significant downregulation of four (miR-181a/b and 200b/c) in GBM [6)].

Huang et al., showed that miR-181a and it targets ANGPT2 and LAMC1 might be predictors of prognosis in GBM patients [7)].

CASC2 could inhibit the miR-181a expression by direct targeting in TMZ-resistant glioma cells. CASC2 up-regulated PTEN protein and down-regulated p-AKT protein through regulating miR-181a, and the effect of CASC2 on PTEN and p-AKT could be partially restored by miR-181a. With TMZ-resistant glioma tissues, miR-181a was up-regulated while PTEN was down-regulated. Taken together, these observations suggest CASC2 up-regulates PTEN through direct inhibiting miR-181a and plays an important role in glioma sensitivity to TMZ and may serve as a potential target for cancer diagnosis and treatment [8)].

High Notch2 expression together with low miR-181a expression was correlated with a shorter median overall survival for GBM patients. Together, these data show that miR-181a may play an essential role in GSC formation and GBM progression by targeting Notch2, suggesting that Notch2 and miR-181a have potential prognostic value as tumor biomarkers in GBM patients [9)].

A transient increase in miR-181a expression was observed after conditioned fear conditioning (CFC)

and object location task (OLT) training. Selective overexpression or inhibition of miR-181a in the dorsal hippocampus (DH) via the injection of a miR-181a agomir or antagomir enhanced or impaired the CFC- and OLT-dependent memory formation, respectively. Using bioinformatics and luciferase assays, we identified PRKAA1 as a potential target gene of miR-181a. After CFC or OLT training, the expression and activity of PRKAA1 decreased as miR-181a expression increased and was effectively blocked by the miR-181a antagomir. Moreover, microinjection of the PRKAA1 agonist AICAR or inhibitor compound C in the DH reversed the roles of the miR-181a agomir or antagomir in CFC- and OLT-dependent memory formation. In conclusion, this work provides novel evidence describing the role and mechanism of miR-181a in hippocampus-dependent memory formation, which sheds light on the potential regulation of cognition and future treatments for cognitive disorders [10].

miR 181a plays critical roles in multiple cancers; however, its precise mechanisms in glioma have not been well clarified. The goal of a study of Wang et al., from the Harbin Medical University, Harbin, China, was to evaluate the interaction between Kaiso and miR-181a in glioma.

Quantitative real-time PCR (qRT-PCR) was performed to detect the levels of Kaiso and miR-181a in glioma tissues and cell lines. Cell proliferation, invasion, and the Epithelial-mesenchymal-transition (EMT) were evaluated to analyze the biological functions of miR-181a and Kaiso in glioma cells. The mRNA and protein levels of Kaiso were measured by qRT-PCR and western blotting, respectively. Meanwhile, luciferase assays were performed to validate Kaiso as a miR-181a target in glioma cells.

They found that the level of miR-181a was the lowest among miR-181a-d in glioma tissues and cell lines, and the low level of miR-181a was closely associated with the increased expression of Kaiso in glioma tissues. Moreover, transfection of miR-181a significantly inhibited the proliferation, invasion, and EMT of glioma cells, whereas knockdown of miR-181a had the opposite effect. Bioinformatics analysis predicted that Kaiso was a potential target gene of miR-181a, and the luciferase reporter assay demonstrated that miR-181a could directly target Kaiso. In addition, Kaiso silencing had similar effects as miR-181a overexpression in glioma cells, whereas overexpression of Kaiso in glioma cells partially reversed the inhibitory effects of the miR-181a mimic.

miR-181a inhibited the proliferation, invasion, and EMT of glioma cells by directly targeting and downregulating Kaiso expression [11].

1)
Shi L, Cheng Z, Zhang J, Li R, Zhao P, Fu Z, You Y. hsa-mir-181a and hsa-mir-181b function as tumor suppressors in human glioma cells. Brain Res. 2008 Oct 21;1236:185-93. doi: 10.1016/j.brainres.2008.07.085. Epub 2008 Jul 30. PubMed PMID: 18710654.
2)
Yu J, Cai X, He J, Zhao W, Wang Q, Liu B. Microarray-based analysis of gene regulation by transcription factors and microRNAs in glioma. Neurol Sci. 2013 Aug;34(8):1283-9. doi: 10.1007/s10072-012-1228-1. Epub 2012 Dec 5. PubMed PMID: 23212403.
3)
Ma J, Yao Y, Wang P, Liu Y, Zhao L, Li Z, Li Z, Xue Y. MiR-181a regulates blood-tumor barrier permeability by targeting Krüppel-like factor 6. J Cereb Blood Flow Metab. 2014 Nov;34(11):1826-36. doi: 10.1038/jcbfm.2014.152. Epub 2014 Sep 3. PubMed PMID: 25182666; PubMed Central PMCID: PMC4269760.
4)
Wu SC, Rau CS, Yang JC, Lu TH, Wu YC, Chen YC, Tzeng SL, Wu CJ, Lin CW, Hsieh CH. Identification of Circulating MicroRNAs in a Mouse Model of Nerve Allograft Transplantation under FK506 Immunosuppression by Illumina Small RNA Deep Sequencing. Dis Markers. 2015;2015:863192. doi: 10.1155/2015/863192. Epub 2015 Sep 8. PubMed PMID: 26435568; PubMed Central PMCID: PMC4578739.

5)
Lin SH, Song W, Cressatti M, Zukor H, Wang E, Schipper HM. Heme oxygenase-1 modulates microRNA expression in cultured astroglia: implications for chronic brain disorders. Glia. 2015 Jul;63(7):1270-84. doi: 10.1002/glia.22823. Epub 2015 Mar 25. PubMed PMID: 25820186.
6)
Sharma V, Purkait S, Takkar S, Malgulwar PB, Kumar A, Pathak P, Suri V, Sharma MC, Suri A, Kale SS, Kulshreshtha R, Sarkar C. Analysis of EZH2: micro-RNA network in low and high grade astrocytic tumors. Brain Tumor Pathol. 2016 Apr;33(2):117-28. doi: 10.1007/s10014-015-0245-1. Epub 2016 Jan 8. PubMed PMID: 26746204.
7)
Huang SX, Zhao ZY, Weng GH, He XY, Wu CJ, Fu CY, Sui ZY, Zhong XM, Liu T. The correlation of microRNA-181a and target genes with poor prognosis of glioblastoma patients. Int J Oncol. 2016 Jul;49(1):217-24. doi: 10.3892/ijo.2016.3511. Epub 2016 May 9. PubMed PMID: 27176932.
8)
Liao Y, Shen L, Zhao H, Liu Q, Fu J, Guo Y, Peng R, Cheng L. LncRNA CASC2 Interacts With miR-181a to Modulate Glioma Growth and Resistance to TMZ Through PTEN Pathway. J Cell Biochem. 2017 Jul;118(7):1889-1899. doi: 10.1002/jcb.25910. Epub 2017 Feb 13. PubMed PMID: 28121023.
9)
Huang SX, Zhao ZY, Weng GH, He XY, Wu CJ, Fu CY, Sui ZY, Ma YS, Liu T. Upregulation of miR-181a suppresses the formation of glioblastoma stem cells by targeting the Notch2 oncogene and correlates with good prognosis in patients with glioblastoma multiforme. Biochem Biophys Res Commun. 2017 May 13;486(4):1129-1136. doi: 10.1016/j.bbrc.2017.04.008. Epub 2017 Apr 4. PubMed PMID: 28389242.
10)
Zhang SF, Chen JC, Zhang J, Xu JG. miR-181a involves in the hippocampus-dependent memory formation via targeting PRKAA1. Sci Rep. 2017 Aug 16;7(1):8480. doi: 10.1038/s41598-017-09095-3. PubMed PMID: 28814760; PubMed Central PMCID: PMC5559581.
11)
Wang L, Ma J, Wang X, Peng F, Chen X, Zheng B, Wang C, Dai Z, Ai J, Zhao S. Kaiso (ZBTB33) Downregulation by MicroRNA-181a Inhibits Cell Proliferation, Invasion, and the Epithelial-Mesenchymal Transition in Glioma Cells. Cell Physiol Biochem. 2018 Jul 23;48(3):947-958. doi: 10.1159/000491963. [Epub ahead of print] PubMed PMID: 30036882.