mir 21

Mesenchymal stem cells deliver exogenous miR 21 via exosomes to inhibit nucleus pulposus cell apoptosis and reduce intervertebral disc degeneration [1].

---

miR-21 is a vital oncogenic MicroRNA that regulates drug resistance of tumor cells.

They might promote cell proliferation and inhibit cell senescence and apoptosis of human glioma cells by targeting SPRY1 via the PTEN/PI3K/AKT signaling pathway [2].

---

miR-21 enhances the resistance of human glioma cells to BCNU by decreasing the expression of Spry2 protein. Thus, Spry2 may be a novel therapeutic target for treating glioma BCNU-resistance [3]

Glioblastoma has a high level of miR-21 which could upregulate vascular endothelial growth factor (VEGF) expression.

Sun et al. hypothesized glioma stem cells (GSCs)-exosomes (EXs) can promote the angiogenic ability of endothelial cells (ECs) through miR-21/VEGF signal. GSCs were isolated from U-251 cells with stem cell marker CD133. GSCs transfected without or with scramble or miR-21 mimics were used to produce GSC-EXscon, GSC-EXssc and GSC-EXsmiR-21. Human brain ECs were co-cultured with vehicle, GSC-EXscon, GSC-EXssc or GSC-EXsmiR-21 plus VEGF siRNAs (siRNAVEGF). After 24 hours, the angiogenic abilities of ECs were evaluated. The levels of miR-21, VEGF and p-Flk1/VEGFR2 were determined. Results showed: 1) Over 90% of purified GSCs expressed CD133; 2) The levels of miR-21 and VEGF in GSCs and GSC-EXs were up-regulated by miR-21 mimic transfection; 3) Compared to GSC-EXscon or GSC-EXssc, GSC-EXsmiR-21 were more effective in elevating the levels of miR-21 and VEGF, and the ratio of p-Flk1/VEGFR2 in ECs; 4) GSC-EXsmiR-21 were more effective in promoting the angiogenic ability of ECs than GSC-EXscon or GSC-EXssc, which were remarkably reduced by siRNAVEGF pretreatment. In conclusion, GSC-EXs can promote the angiogenic ability of ECs by stimulating miR-21/VEGF/VEGFR2 signal pathway [4].

MicroRNA and aneurysm

The molecular mechanisms behind intracranial aneurysm formation and rupture remain poorly understood.

The MicroRNA and mRNA interactions and expression levels in cerebral aneurysm tissue from human subjects were profiled.

A prospective case-control study was performed on human subjects to characterize the differential expression of mRNA and MicroRNA in unruptured cerebral aneurysms in comparison with control tissue (healthy superficial temporal arteries [STA]). Ion Torrent was used for deep RNA sequencing. Affymetrix MicroRNA microarrays were used to analyze MicroRNA expression, whereas NanoString nCounter technology was used for validation of the identified targets.

Overall, 7 unruptured intracranial aneurysm and 10 STA specimens were collected. Several

differentially expressed genes were identified in aneurysm tissue, with MMP-13 (fold change 7.21) and various collagen genes (COL1A1, COL5A1, COL5A2) being among the most upregulated. In addition, multiple MicroRNAs were significantly differentially expressed, with miR 21 (fold change 16.97) being the most upregulated, and miR 143-5p (fold change -11.14) being the most downregulated. From these, miR-21, miR-143, and miR 145 had several significantly anticorrelated target genes in the cohort that are associated with smooth muscle cell function, extracellular matrix remodeling, inflammation signaling, and lipid accumulation. All these processes are crucial to the pathophysiology of cerebral aneurysms.

This analysis identified differentially expressed genes and MicroRNAs in unruptured human cerebral aneurysms, suggesting the possibility of a role for MicroRNAs in aneurysm formation. Further investigation for their importance as therapeutic targets is needed [5].

A study aimed to determine the changes associated with microRNA-21-5p (miR-21-5p) during epileptogenesis in a kainic acid rat model, and to assess whether the PTEN-mTOR pathway is a target of miR-21-5p.

Reverse transcription polymerase chain reaction (RT-PCR) was used to examine the quantitative expressions of miR-21-5p and PTEN, and Western blotting was used to test the activity of mTOR in the acute, latent, and chronic stages of epileptogenesis. The antagomir of miR-21-5p was injected into the intracerebroventricular space using a microsyringe. Neuronal death and epilepsy discharge were assessed by Nissl staining and electroencephalography (EEG), respectively. The Morris water maze (MWM) was used to assess the cognitive impairment in rats after status epilepticus (SE).

Both miR-21-5p and mTOR were upregulated and PTEN was downregulated in rats during acute, latent, and chronic stages of epileptogenesis when compared with those of the control. After using antagomir miR-21-5p in vivo, miR-21-5p and mTOR decreased and the expression of PTEN increased compared with that in the SE model. The silencing of miR-21-5p diminished the number of abnormal spikes on EEG and decreased the number of neuron deletions on Nissl staining. The cognitive and memory impairment caused by epilepsy could also be improved after miR-21-5p knockdown in vivo.

The results of the present study demonstrate that PTEN-mTOR is the target of miR-21-5p in a kainic acid model of epilepsy. The knockout of miR-21-5p decreases the neuronal damage in stages of epileptogenesis. The miR-21-5p/PTEN/mTOR axis may be a potential target for preventing and treating seizures and epileptic damage [6].

1)
Cheng X, Zhang G, Zhang L, Hu Y, Zhang K, Sun X, Zhao C, Li H, Li YM, Zhao J. Mesenchymal stem cells deliver exogenous miR-21 via exosomes to inhibit nucleus pulposus cell apoptosis and reduce intervertebral disc degeneration. J Cell Mol Med. 2017 Aug 14. doi: 10.1111/jcmm.13316. [Epub ahead of print] PubMed PMID: 28805297.
2)
Chai C, Song LJ, Han SY, Li XQ, Li M. MicroRNA-21 promotes glioma cell proliferation and inhibits senescence and apoptosis by targeting SPRY1 via the PTEN/PI3K/AKT signaling pathway. CNS Neurosci Ther. 2018 Jan 5. doi: 10.1111/cns.12785. [Epub ahead of print] PubMed PMID: 29316313.
3)
Wang GB, Liu JH, Hu J, Xue K. MiR-21 enhanced glioma cells resistance to carmustine via decreasing Spry2 expression. Eur Rev Med Pharmacol Sci. 2017 Nov;21(22):5065-5071. doi: 10.26355/eurrev_201711_13819. PubMed PMID: 29228450.
4)
Sun X, Ma X, Wang J, Zhao Y, Wang Y, Bihl JC, Chen Y, Jiang C. Glioma stem cells-derived exosomes

promote the angiogenic ability of endothelial cells through miR-21/VEGF signal. Oncotarget. 2017 Mar 29. doi: 10.18632/oncotarget.16661. [Epub ahead of print] PubMed PMID: 28410224.

5) Bekelis K, Kerley-Hamilton JS, Teegarden A, Tomlinson CR, Kuintzle R, Simmons N, Singer RJ, Roberts DW, Kellis M, Hendrix DA. MicroRNA and gene expression changes in unruptured human cerebral aneurysms. J Neurosurg. 2016 Dec;125(6):1390-1399. PubMed PMID: 26918470; PubMed Central PMCID: PMC5001931.

6) Tang C, Gu Y, Wang H, Wu H, Wang Y, Meng Y, Han Z, Gu Y, Ma W, Jiang Z, Song Y, Na M, Lu D, Lin Z. Targeting of microRNA-21-5p protects against seizure damage in a kainic acid-induced status epilepticus model via PTEN-mTOR. Epilepsy Res. 2018 May 4;144:34-42. doi: 10.1016/j.eplepsyres.2018.05.001. [Epub ahead of print] PubMed PMID: 29751355.