Mir 128

MiR-128 is a brain-enriched microRNA.

In a study, Zhou et al. from Kunming, established mouse models of Parkinson's disease (PD) to investigate the expression of microRNA-128 (miR 128) and mechanism through which it affects apoptosis of dopamine (DA) neurons and the expression of excitatory amino acid transporter 4 (EAAT4) via binding to axis inhibition protein 1 (AXIN1).

Gene expression microarray analysis was performed to screen differentially expressed MicroRNAs that are associated with PD. The targeting relationship between miR-128 and AXIN1 was verified via a bioinformatics prediction and dual luciferase reporter assay. After separation, DA neurons were subjected to a series of inhibitors, activators and shRNAs to validate the mechanisms of miR-128 in controlling of AXIN1 in PD. Positive protein expression of AXIN1 and EAAT4 in DA neurons was determined using immunocytochemistry. miR-128 expression and the mRNA and protein levels of AXIN1 and EAAT4 were evaluated via RT-qPCR and Western blot analysis, respectively. DA neuron apoptosis was evaluated using TUNEL staining.

They identified AXIN1 as an upregulated gene in PD based on the microarray data of GSE7621. AXIN1 was targeted and negatively mediated by miR-128. In the DA neurons, upregulated miR-128 expression or sh-AXIN1 increased the positive expression rate of EAAT4 together with mRNA and protein levels, but decreased the mRNA and protein levels of AXIN1, apoptosis rate along with the positive expression rate of AXIN1; however, the opposite trend was found in response to transfection with miR-128 inhibitors.

Evidence from experimental models revealed that miR-128 might reduce apoptosis of DA neurons while increasing the expression of EAAT4 which might be related to the downregulation of AXIN1. Thus, miR-128 may serve as a potential target for the treatment of PD [1)].

Frixa et al.showed that the miR-128-3p, which is up-regulated in lung cancer tissues, has Drosha and Dicer, two key enzymes of MicroRNAs processing, as the main modulation targets leading to the widespread downregulation of MicroRNA expression. They observed that the MicroRNAs downregulation induced by miR-128-3p contributed to the tumorigenic properties of lung cancer cells. In particular miR-128-3p-mediated MicroRNAs dowregulation contributed to aberrant SNAIL and ZEB1 expression thereby promoting the epithelial-to-mesenchymal transition (EMT) program. Drosha also resulted to be implicated in the control of migratory phenotype as its expression counteracted miR-128-3p functional effects. The study provides mechanistic insights into the function of miR-128-3p as a key regulator of the malignant phenotype of lung cancer cells. This also enforces the remarkable impact of Drosha and Dicer alteration in cancer, and in particular it highlights a role for Drosha in NSCLC cells migration [2)].

MiR-128 is an important suppressor of Polycomb Repressor Complex (PRC) activity, and its absence is an early event in gliomagenesis [3)].

Low miR-128 levels in serum and tissue were markedly correlated with high pathological grade and low Karnofsky Performance Status score (KPS). These findings proved that serum miR-128 could be a sensitive and specific biomarker of glioma [4)].

Overexpression of miR-128 inhibits cell proliferation by targeting E2F3a and Bmi-1, and reduces

neuroblastoma cell motility and invasiveness through inhibiting Reelin and DCX.

The plasma levels of miR-21, miR-128 and miR-342-3p were significantly altered in GBM patients compared to normal controls and could discriminate glioma from healthy controls with high specificity and sensitivity. However, these three MicroRNAs were not significantly changed in patients with other brain tumors such as meningioma or pituitary neuroendocrine tumor. Furthermore, the plasma levels of these three MicroRNAs in GBM patients treated by operation and chemo-radiation almost revived to normal levels. FWang et al., demonstrated that miR-128 and miR-342-3p were positively correlated with histopathological grades of glioma [5].

MicroRNA-128 was found to be decreased in glioblastoma, and knockout of the microRNA-128a gene could induce epilepsy in mice. Based on the Chinese Glioma Genome Atlas and previous study, Yuan et al., hypothesized that dysregulation of miR-128 expression may play a role in the pathogenesis of TAE in low-grade glioma.

Fifty-three low-grade glioma samples were analyzed for the expression levels of miR-128 using qRT-PCR, and candidate targets of miR-128 (Cacnge2, GRIK3, and GRIN2D) were detected by the 3'-UTR luciferase reporter assay. Four other miRs (miR-9, miR-192a, miR-92a, and miR-451) that showed dysregulation of glioblastoma in the CGGA data were also analyzed.

The microRNA-128 expression levels were down-regulated in low-grade glioma tissue (t-test; p=0.009). Dysregulation of miR-128 expression in low-grade glioma is associated with glioma-associated epilepsy (p=0.006). No statistical significance of miR-9, miR-192a, miR-92a, and miR-451 was found to be associated with LGG.

The results here, together with other recent lines of evidence, indicate that miR-128 is an extremely attractive target for therapy in glioma patients with seizure [6].

1)
Zhou L, Yang L, Li YJ, Mei R, Yu HL, Gong Y, Du MY, Wang F. MicroRNA-128 Protects Dopamine Neurons from Apoptosis and Upregulates the Expression of Excitatory Amino Acid Transporter 4 in Parkinson's Disease by Binding to AXIN1. Cell Physiol Biochem. 2018;51(5):2275-2289. doi: 10.1159/000495872. Epub 2018 Dec 7. PubMed PMID: 30537735.
2)
Frixa T, Sacconi A, Cioce M, Roscilli G, Ferrara FF, Aurisicchio L, Pulito C, Telera S, Carosi MA, Muti P, Strano S, Donzelli S, Blandino G. MicroRNA-128-3p-mediated depletion of Drosha promotes lung cancer cell migration. Carcinogenesis. 2017 Dec 11. doi: 10.1093/carcin/bgx134. [Epub ahead of print] PubMed PMID: 29236960.
3)
Peruzzi P, Bronisz A, Nowicki MO, Wang Y, Ogawa D, Price R, Nakano I, Kwon CH, Hayes J, Lawler SE, Ostrowski MC, Chiocca EA, Godlewski J. MicroRNA-128 coordinately targets Polycomb Repressor Complexes in glioma stem cells. Neuro Oncol. 2013 Sep;15(9):1212-24. doi: 10.1093/neuonc/not055. Epub 2013 Jun 3. PubMed PMID: 23733246; PubMed Central PMCID: PMC3748913.
4)
Sun J, Liao K, Wu X, Huang J, Zhang S, Lu X. Serum microRNA-128 as a biomarker for diagnosis of glioma. Int J Clin Exp Med. 2015 Jan 15;8(1):456-63. eCollection 2015. PubMed PMID: 25785017; PubMed Central PMCID: PMC4358472.
5)
Wang Q, Li P, Li A, Jiang W, Wang H, Wang J, Xie K. Plasma specific MicroRNAs as predictive biomarkers for diagnosis and prognosis of glioma. J Exp Clin Cancer Res. 2012 Nov 22;31:97. doi: 10.1186/1756-9966-31-97. PubMed PMID: 23174013; PubMed Central PMCID: PMC3554474.
6)
Yuan Y, Xiang W, Yanhui L, Ruofei L, Yunhe M, Jiewen L, Qing M. Dysregulation of microRNA-128

expression in WHO grades 2 glioma is associated with glioma-associated epilepsy: Down-regulation of miR-128 induces glioma-associated seizure. Epilepsy Res. 2016 Aug 11;127:6-11. doi: 10.1016/j.eplepsyres.2016.08.005. [Epub ahead of print] PubMed PMID: 27526390.