miR 124

The miR-124 microRNA precursor is a small non-coding RNA molecule that has been identified in flies (MI0000373), nematode worms (MI0000302),mouse (MI0000150) and human (MI0000443).

The mature ~21 nucleotide microRNAs are processed from hairpin precursor sequences by the Dicer enzyme, and in this case originates from the 3' arm. miR-124 has been found to be the most abundant microRNA expressed in neuronal cells. Experiments to alter expression of miR-124 in neural cells did not appear to affect differentiation.

However these results are controversial since other reports have described a role for miR-124 during neuronal differentiation.

Visvanathan et al.. showed that miR-124 targets the mRNA of the anti-neural function protein SCP1 (small C-terminal domain phosphatase 1). Makeyev et al. showed that miR-124 directly targets PTBP1 (PTB/hnRNP I) mRNA, which encodes a global repressor of alternative pre-mRNA splicing in non-neuronal cells. Arrant et al. wrote that miR-124 changes glutamate receptor composition in the prefrontal cortex and can decrease social dysfunction in frontotemporal dementia.

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miR-124 is a brain-enriched microRNA that plays a crucial role in neural development and has been shown to be down-regulated in glioma and medulloblastoma, suggesting its possible involvement in brain tumor progression. Here, we show that miR-124 is down-regulated in a panel of different grades of glioma tissues and in all of the human glioma cell lines we examined. By integrated bioinformatics analysis and experimental confirmation, we identified SNAI2, which is often up-regulated in glioma, as a direct functional target of miR-124. Because SNAI2 has been shown to regulate stem cell functions, we examined the roles of miR-124 and SNAI2 in glioma cell stem-like traits. The results showed that overexpression of miR-124 and knockdown of SNAI2 reduced neurosphere formation, CD133(+) cell subpopulation, and stem cell marker (BMI1, Nanog, and Nestin) expression, and these effects could be rescued by re-expression of SNAI2. Furthermore, enhanced miR-124 expression significantly inhibited glioma cell invasion in vitro. Finally, stable overexpression of miR-124 and knockdown of SNAI2 inhibited the tumorigenicity and invasion of glioma cells in vivo. These findings reveal, for the first time, that the tumor suppressor activity of miR-124 could be partly due to its inhibitory effects on glioma stem-like traits and invasiveness through SNAI2 [1)].

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miR-124 function as a tumor suppressor miRNA and suppress tumor proliferation and aggression by directly targeting oncogenic CD164 signaling pathway in NSCLC [2)].

miR-124 regulates cell apoptosis and autophagy in dopaminergic neurons and protects them by regulating AMPK/mTOR pathway in Parkinson's disease [3)].

Kong et al have previously demonstrated the monotherapeutic effects of miR-124, which inhibits the signal transducer and activator of transcription 3 (STAT3) immune suppressive pathway, and immune stimulatory 4-1BB aptamers against a variety of malignancies, including genetically engineered immune competent high-grade gliomas. To evaluate potential synergy, we tested an immune

stimulatory aptamer together with microRNA-124 (miRNA-124), which blocks tumor-mediated immune suppression, and found survival to be markedly enhanced, including beyond that produced by monotherapy. The synergistic activity appeared to be not only secondary to enhanced CD3+ cell numbers but also to reduced macrophage immune tumor trafficking, indicating that a greater therapeutic benefit can be achieved with approaches that both induce immune activation and inhibit tumor-mediated immune suppression within the central nervous system (CNS) tumors [4)].

The aim of a study was to examine the Smad4-dependent effects of miR-124 on C6 glioma cell proliferation. In this study, the level of miR-124 was found to be enhanced in C6 cells upon transfection with miR-124 mimics, and the mechanisms of action of miR-124 in C6 cells were investigated by reverse transcriptase-quantitative polymerase chain reaction, MTT assay, western blot analysis and luciferase reporter assays in vitro. The results revealed that miR-124 expression was significantly lower in the C6 cells than in either normal rat brain tissue or astrocytes. Upon the overexpression of miR-124, the proliferation of the C6 cells decreased and Smad4 expression was significantly suppressed. Smad4 was identified as a direct target of miR-124 through luciferase reporter assays. Furthermore, miR-124 was found to modulate signal transducer and activator of transcription 3 (Stat3) by downregulating Smad4 expression. Using small interfering RNA targeting Smad4 mRNA, we also confirmed that miR-124 downregulated c-Myc by modulating Smad4 expression. In addition, caspase-3 expression was induced by miR-124 overexpression, but not via Smad4 downregulation. On the whole, our results demonstrate that miR-124 upregulation inhibits the growth of C6 glioma cells by targeting Smad4 directly. These findings may be clinically useful for the development of therapeutic strategies directed toward miR-124 function in patients with glioma [5)].

miR 124 and Intracerebral Hemorrhage Stroke

Stroke causes death or long-term disabilities and threatens the general health of the population worldwide. Recent studies have suggested that miRNAs are dysregulated and can be used as biomarkers for diagnosis and prognosis in stroke. The intracerebral hemorrhage (ICH) accounts for 15% of all the stroke cases. However, at present, little is known regarding the functions and clinical implications of miRNAs in ICH. In the present study, we established the collagenase-induced rat ICH model to mimic human ICH syndrome. We profiled the expression of 728 rat miRNAs at different time points in rat brain tissues and plasma post-ICH and identified a set human brain-enriched miRNAs that had changed expression level in the plasma of rat ICH. Among them, the expression levels of miR-124 displayed significantly synchronous alterations in rat plasma and brain tissue during ICH progression. They were significantly elevated at the acute injury phase (day 1 and 2), gradually decreased during the delayed recovery phase (day 7, 14 and 30), and finally restored to normal levels at late recovery phase (day 60). We further determined the plasma expression profile of miR-124 from human ICH patients. Similar to the pattern observed in rat ICH model, our results indicated that immediately after patients reached the hospital, the average plasma concentrations of miR-124 increased more than 100-fold in 24 h, then decreased gradually on day 2, 7, 14 and to near normal level on day 30. Taken together, these results strongly suggested that plasma concentration of miR-124 is a promising candidate biomarker for the early detection and predictive prognosis of human ICH [6)].

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