PRELIMINARY EVALUATION OF THE THERAPEUTIC POTENTIAL OF MIR-30C MIMIC TREATMENT IN ACUTE ISCHEMIC STROKE: DOSE-RESPONSE AND THERAPEUTIC TIME WINDOW

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Background: Decreased expression of endogenous miR-30c has been implicated in many human diseases, such as different types of cancer, hyperlipidemia and atherosclerosis, hyperglycemia and diabetes. Therapeutic elevation of miR-30c via systemic administration of miR-30c mimic has been shown to reduce hyperlipidemia and atherosclerosis, in contrast, inhibition of hepatic miR-30c by anti-miR-30c increased hyperlipidemia and atherosclerosis in animal models, indicating that miR-30c may represent an attractive target for therapeutic intervention. In this study, we investigated the role and therapeutic potential of targeting miR-30c in ischemic stroke. **Methods and results:** Male adult mice were subjected to middle cerebral artery occlusion (MCAo) for 45 min followed by reperfusion. To test the dose-response and identify an optimal dose of miR-30c mimic for stroke treatment, animals were assigned randomly into the following groups: Control (no-treatment), sc-miR-30c (scramble) and miR-30c mimic at a dose of 0.5, 2.5, or 5 mg/kg. Equal amount of mi-R30c mimic or sc-miR-30c was administered intravenously at 3h after the onset of ischemia. The results showed that the systemic administration of miR-30c mimic reduced neurological deficits and decreased the infarct volume 72 h after MCAo in a dose-dependent manner. Infarct volumes were significantly reduced in mice treated with miR-30c mimic at a dose of 2.5 mg/kg ($p<0.05$), whereas a lower dose of 0.5 mg/kg miR-30c had no significant effect ($p>0.05$) compared to control (no-treatment) or sc-miR-30c treated groups. Importantly, the smaller infarct volumes translated into better neurological outcome. Animals treated with miR-30c mimic (2.5 or 5 mg/kg) showed significant improvement in neurological functions compared to controls. In addition, there was no significant difference between 2.5mg/kg and 5mg/kg of mi-R30c mimic-treated groups in infarct volumes and neurological deficits. Based on these data, miR-30c mimic at the dose of 2.5 mg/kg was used to investigate the therapeutic window of miR-30c mimic against ischemic stroke. The results showed that extended treatment with miR-30c mimic at 4.5 h after ischemia significantly improved the neurologic functions and decreased the infarct volumes 72 h after ischemia. However, administration of miR-30c mimic at 6 h or 9 h after ischemia had no significant neuroprotection. **Conclusions**: The present study demonstrates for the first time that systemic administration of miR-30c mimic may represent a promising intervention for the treatment of acute ischemic stroke. The underlying mechanisms of miR-30c in stroke pathophysiology are currently under investigation in our laboratory.

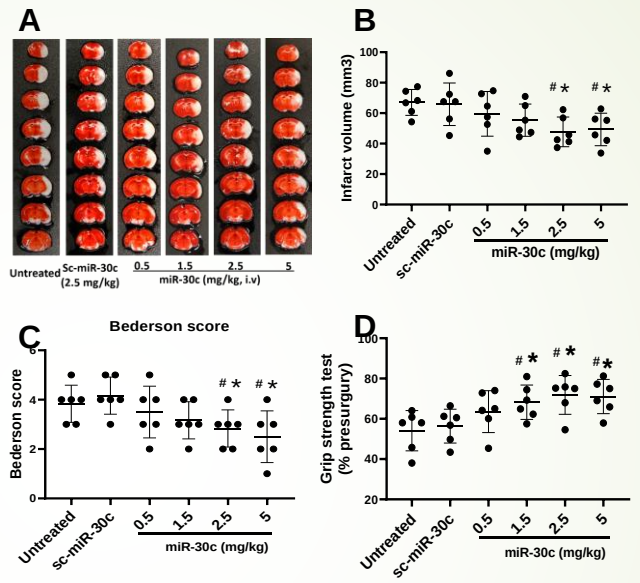

Fig. 1. Dose-response effects of miR-30c mimic in acute experimental ischemic stroke. A, Representative TTC staining; B, Infarct volume; C, Bederson score; D, Grip strength test, n=6 per group. Animals were subjected to MCAO for 45 min followed by reperfusion. All treatments were initiated at 3 hours after stroke onset, and data were collected on 3 day. One-way ANOVA followed by the Bonferroni post hoc test with selected multiple comparisons was used to compare infarct volume. Nonparametric functional scores were compared by Kruskal–Wallis test with post hoc Dunn corrections. *p<0.05 vs. untreated group, #p<0.05 vs. sc-miR-30c treated group.

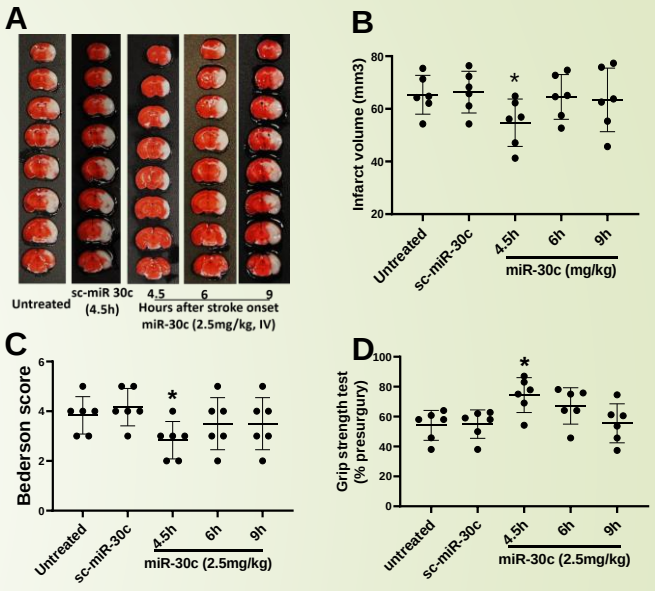

Fig. 2. Therapeutic window for mi-R-30c mimic treatment. A, Representative TTC staining; B, Infarct volume; C, Bederson score; D, Grip strength test, n=6 per group. Mice received mimic or scramble at 4.5, 6 or 9 hours after stroke onset and data were collected on 3 day. One-way ANOVA followed by the Bonferroni post hoc test with selected multiple comparisons was used to compare infarct volume. Nonparametric functional scores were compared by Kruskal–Wallis test with post hoc Dunn corrections. *p<0.05 vs. sc-miR-30c treated group.

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