Forkhead box O1 (FOXO1)

Forkhead box protein O1 (FOXO1) is a FOX protein also known as forkhead in rhabdomyosarcoma is a protein that in humans is encoded by the FOXO1 gene.

FOXO1 is a transcription factor that plays important roles in the regulation of gluconeogenesis and glycogenolysis by insulin signaling, and is also central to the decision for a preadipocyte to commit to adipogenesis.

It is primarily regulated through phosphorylation on multiple residues; its transcriptional activity is dependent on its phosphorylation state.

Pre-stroke exercise conditioning reduces neurovascular injury and improves functional outcomes after stroke. The goal of this study was to explore if post-stroke exercise conditioning (PostE) reduced brain injury and whether it was associated with the regulation of gluconeogenesis. Adult rats received 2 h of middle cerebral artery (MCA) occlusion, followed by 24 h of reperfusion. Treadmill activity was then initiated 24 h after reperfusion for PostE. The severity of the brain damage was determined by infarct volume, apoptotic cell death, and neurological deficit at one and three days after reperfusion. We measured gluconeogenesis including oxaloacetate (OAA), phosphoenolpyruvate (PEP), pyruvic acid, lactate, ROS, and glucose via ELISA, as well as the location and expression of the key enzyme phosphoenolpyruvate carboxykinase (PCK)-1/2 via immunofluorescence. We also determined upstream pathways including forkhead transcription factor (FoxO1), p-FoxO1, 3-kinase (PI3K)/Akt, and p-PI3K/Akt via Western blot. Additionally, the cytoplasmic expression of p-FoxO1 was detected by immunofluorescence. Compared to non-exercise control, PostE (*p < .05) decreased brain infarct volumes, neurological deficits, and cell death at one and three days. PostE groups (*p < .05) saw increases in OAA and decreases in PEP, pyruvic acid, lactate, ROS, glucose levels, and tissue PCKs expression on both days. PCK-1/2 expressions were also significantly (*p < .05) suppressed by the exercise setting. Additionally, phosphorylated PI3K, AKT, and FoxO1 protein expression were significantly induced by PostE at one and three days (*p < .05). In this study, PostE reduced brain injury after stroke, in association with activated PI3K/AKT/FoxO1 signaling, and inhibited gluconeogenesis. These results suggest the involvement of FoxO1 regulation of gluconeogenesis underlying post-stroke neuroprotection [1)].

Forkhead box O1 (FOXO1) was predicted as a potential target of miR-660. The subsequent luciferase reporter assay indicated that miR-660 directly binds to the 3'-untranslated region of FOXO1. Furthermore, miR-660 inhibition increased the FOXO1 expression in OS cells at mRNA and protein levels. Moreover, FOXO1 was downregulated in OS tissues and this downregulation was negatively correlated with miR-660 levels. Besides, rescue experiments demonstrated that FOXO1 knockdown abolished the effects of miR-660 knockdown on OS cell proliferation and invasion. These results suggest that miR-660 may serve oncogenic roles in OS by directly targeting FOXO1. Targeting miR-660 may be an effective candidate for the treatment of patients with OS [2)].

A total of 50 pairs of glioma tissue samples and para-carcinoma tissue samples were collected.

Human glioma cell line (U251) and normal human astrocyte (NHA) were cultured. The expression of RNA and protein was detected by quantitative real-time polymerase chain reaction (qRT-PCR) and Western blot, respectively. Cell proliferation assay and transwell assay were used to detect the activities of proliferation and invasion. Luciferase reporter assays were carried out to determine the binding efficiency between forkhead box O1 (FOXO1) and miR 135a in U251 cells.

qRT-PCR results showed that miR-135a expression was significantly reduced while FOXO1 was up-regulated in glioma tissues. miR-135a overexpression in U251 cells could prominently inhibit proliferation and invasion according to the transwell assays. Moreover, FOXO1 was recognized as the target for miR-135a and may partially reverse the functions of miR-135a in U251 cells.

Shi et al., from the Yantaishan Hospital, Yantai, China, showed that miR-135a inhibits glioma cell proliferation and invasion by down-regulating the target gene FOXO1 [3].

miR-135A/B, and the target FOXO1, may be potential therapy targets for glioma treatment [4].

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