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LNC01296 Regulates Apoptosis Genes Birc2 and Bak1 by Targeting miRNA-29c and Participates in Neuroprotection During Cerebral Ischemia/Reperfusion Injury in Rats

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ABSTRACT

AIM: To explore the extent to which LNC01296 inhibits the miRNA-29c expansion genes Birc2 and Bak1 from causing damage induced by brain expansion and reimplantation.

MATERIAL and METHODS: A total of 120 adult male experimental rats were divided to verify the effects of miRNA-29c and LNC01296 on brain expansion/reimplantation injury.

RESULTS: miRNA-29c can inhibit the Birc2/Bak1 pathway and aggravate the brain expansion/reimplantation damage. LNC01296 blocks miRNA-29c from entering the brain to protect it from expansion after reimplantation.

CONCLUSION: Our findings show that LINC01296 can alleviate the injury induced by cerebral ischemia and reimplantation by preventing the inhibitory effect of miR-29c on Birc2 and Bak1. Our research also provides new strategies and goals for the clinical treatment of patients with cerebral ischemia–reperfusion.

KEYWORDS: LNC01296, miRNA-29c, Apoptotic gene, Cerebral ischemia–reperfusion injury, Neuroprotection

ABBREVIATION: CIRI: Cerebral ischemia–reperfusion injury, **LncRNA:** Long noncoding RNA, **TTC:** Triphenyltetrazolium chloride

INTRODUCTION

Cerebral ischemia–reperfusion injury (CIRI) refers to cerebral ischemia. If blood perfusion in the ischemic area is not restored within a certain period of time, the brain function does not recover. It is further aggravated, causing related functional damage (21). Cerebral ischemia–reperfusion accounts for >80% of ischemic stroke and is also the cause of several stroke-related complications. Therefore, improving the poor prognosis of patients with ischemic stroke and the treatment of recurrent stroke depend on further research in this area and a better understanding of the underlying complex molecular mechanisms regulating the processes (2,20).

In recent years, research interest on long noncoding RNA (lncRNA), a type of noncoding single-stranded RNA with a length of >200 nucleotides (12,13), has increased. Various functions of lncRNA have been identified, including its role in epigenetic changes, transcriptional regulation, post-transcriptional modification, and targeted regulation of microRNAs (miRNA) and proteins resulting in various diseases (5). LINC01296, a newly discovered member of the lncRNA family (7,11), has been found to control the proliferation and apoptosis of the human neuroblastoma cell SK-N-SH by regulating the Wnt/β-catenin signaling pathway, migration, and invasion (23). There are limited studies on the mechanism of CIRI. miRNA-29c is involved in the overall process of focal ischemia in

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adult rats (10). Studies have shown that miRNA exhibits highly specific expression profiles in many human diseases, such as tumors and vascular diseases, and plays a role in the pathogenesis of several diseases (15). Specifically, miRNA29c has a decreased expression pattern in the middle cerebral artery occlusion (MCAO) model and plays a role in regulating ischemic brain injury (18). This study aims to determine a potential targeting relationship between LINC01296 and miRNA-29c and identify a specific mechanism of action to provide possible ideas for the clinical treatment of patients with CIRI.

MATERIAL and METHODS

Animal Experiment

We purchased 120 adult male rats weighing 220–280 g from Jicui Yaokang Company (Jiangsu, China). All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. This study was approved by our College.

The remaining 72 rats were selected and divided into 6 groups, each consisting of 12 rats. The six groups were MCAO (cerebral ischemia–reperfusion model) group, MCAO+pc-DNA-LINC01296 group, MCAO+pc-DNA3.1 group, MCAO+Sh-LINC01296 group, MCAO+Sh-NC group, and sham group. In the first five groups, 4% isoflurane was used to anesthetize the rats in medical oxygen and cut their right common carotid artery. After ligating the common and external carotid arteries, a silicon-containing 4.0 nylon suture was gently inserted. The internal carotid artery was approximately 20 mm in length. After 2 hours of ischemia, the line plug was withdrawn for reperfusion. In the sixth group (sham group), the same steps were performed except that the origin of the middle cerebral artery was not blocked. All rats were injected intracranially with the same amounts of normal saline, pc-DNA-LINC01296, pc-DNA-NC, Sh-LINC01296, and Sh-NC after the models were established. Two days hours after the injection, all rats were euthanized humanely according to the ethical guidelines. Subsequently, the brain tissue and blood of these rats were collected for evaluation.

2,3,5-Triphenyltetrazolium Chloride (TTC) Staining

TTC staining distinguished between the surviving and infarcted brain tissues after stroke. The brain tissue was washed with phosphate buffered saline (PBS) and kept at –20°C for 10 minutes. The tissue was then cut along the coronal axis and incubated with TTC solution for 30 minutes. After staining, the brain sections were fixed with 4% paraformaldehyde (Wako Pure Chemical Industries, Ltd., Osaka, Japan). ImageJ software (National Institutes of Health) was used to obtain pictures and analyze the slices for the white area, which represents the infarcted brain tissue, and other normal tissue areas.

Cerebral infarction rate (%) = infarct area/total area × 100%

Terminal Deoxynucleotidyl Transferase dUTP Nick end Labeling (TUNEL) Staining

The rat brain tissue was sliced, deparaffinized, and hydrolyzed with proteinase K for 30 minutes. The sections were then washed thrice with PBS and incubated in terminal deoxynucleotidyl transferase buffer for 10 minutes. The TUNEL reaction mixture (Roche, Switzerland) was added to each part and incubated for 1 hour at room temperature. The sections were then washed thrice with cold PBS and incubated with diaminobenzidine chromogen to develop color. An optical microscope (OLYMPUS, Japan) was used to capture the images at 400 × magnification.

Luciferase Reporter Gene Detection

The PC12 cells were obtained from American Type Culture Collection (Massanas, Virginia, USA) for use in luciferase reporter gene detection assay. The cells were cultured in Dulbecco's modified Eagle's medium (DMEM, USA) containing 10% fetal bovine serum. By conducting a search in the LncBase v.2 database, we found that RCC2 is a potential target gene of miR-29c and that miR-29c is a target of LINC01296. A luciferase reporter gene assay was performed to confirm these findings, and a commercial kit (Promega, USA; E1910) was used to detect the fluorescence. The fluorescence intensity was measured with a spectrophotometer (Thermo Fisher Scientific, USA); all steps were executed according to the manufacturer's instructions.

Reverse Transcription Polymerase Chain Reaction (RT-PCR)

The total RNA was extracted using the Trizol method (Thermo Fisher Scientific, USA). The mRNA was reverse transcribed into cDNA using a commercially available kit (Roche, Switzerland; 11483188001). SYBR Green Realtime PCR Master Mix (TaKaRa, Japan) was used to measure the fluorescence signal. The cDNA was amplified using the ABI 7500 system (Thermo Fisher Scientific, USA), and the relative expression of the target gene was analyzed using the 2-ΔΔCt method.

The following primers were used in this study:

miRNA-29c forward primer: ATAGCGGGCCGCAGATCCATGGA

reverse primer: ATACTCGAGGAAGTTAGGAA

LINC01296 forward primer: 5′-AACTGGCACCAGCCTCACT-3′

reverse primer: 5′-CGGCCAACTTCTTTACCATC-3′

Birc2 forward primer: 5′-CATAGTAGCTTGTTCAGTGGT-3′

reverse primer: 5′-CTCTAGAATTAAGAGGGTTTGGAG-3′

Bak1 forward primer: 5′-CATCCCCCACCCTCATCC-3′

reverse primer: 5′-CTACCCCAAACCCT-3′

Statistical Analysis

GraphPad Prism 7.0 (GraphPad Software Company, USA) software was used to analyze the data. The experimental result $p<0.05$, and the difference between the groups was considered statistically significant. The data were expressed as mean ± standard deviation.

RESULTS

LINC01296 Expression Decreased in the Cerebral Infarction Model Created by Cerebral Ischemia–Reperfusion

To clarify LINC01296's role in the ischemia–reperfusion injury model, we designed the sham group, MCAO group, MCAO+PBS group, MCAO+pc-DNA-LINC01296 group, MCAO+Sh-LINC01296 group, and the corresponding negative control group. The level of LINC01296 in the mouse brain tissue was measured. The results showed that when compared with the sham group, the level of LINC01296 in the brain tissue of the rats in the MCAO model group was reduced. After the injection of pc-DNA-LINC01296, the expression of LINC01296 increased; however, after the injection of Sh-LINC01296, the expression of LINC01296 decreased (Figure 1).

LINC01296 Reduced Cerebral Infarction Caused by Cerebral Ischemia and Reperfusion

We used TTC staining to determine the infarction rate of the rats in each group to further clarify the role of LINC01296 in the ischemia–reperfusion injury model. We found that the cerebral infarction rate decreased after the injection of pc-DNA-LINC01296 but increased after the injection of Sh-LINC01296 (Figure 2).

TUNEL staining was used to determine the apoptotic rate of the brain cells. The results showed that the injection of Sh-LINC01296 aggravated the apoptosis of the brain cells, while the injection of pc-DNA-LINC01296 alleviated the apoptosis (Figure 3).

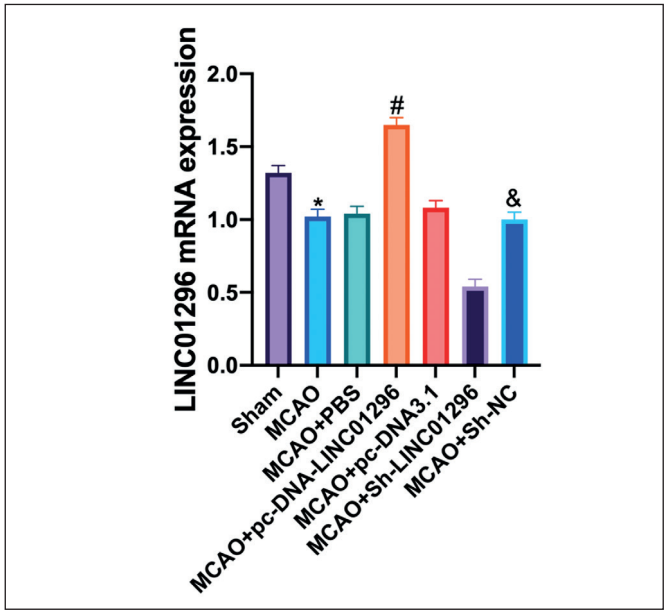

Figure 1: The expression of LINC01296 in a cerebral infarction model caused by cerebral ischemia and reperfusion. **Sham group:** control group, **MCAO group:** cerebral infarction model caused by cerebral ischemia–reperfusion, **MCAO+PBS group:** cerebral infarction model caused by cerebral ischemia–reperfusion plus solvent group, **MCAO+pc-DNA-LINC01296 group:** cerebral infarction model caused by cerebral ischemia–reperfusion + overexpression of LINC01296, **MCAO+Sh-LINC01296 group:** cerebral infarction model caused by cerebral ischemia–reperfusion + low expression of LINC01296. *p<0.05 *vs.* the sham group; #p<0.05 *vs.* MCAO+pc-DNA3.1 group; and p<0.05 *vs.* MCAO+Sh-NC group

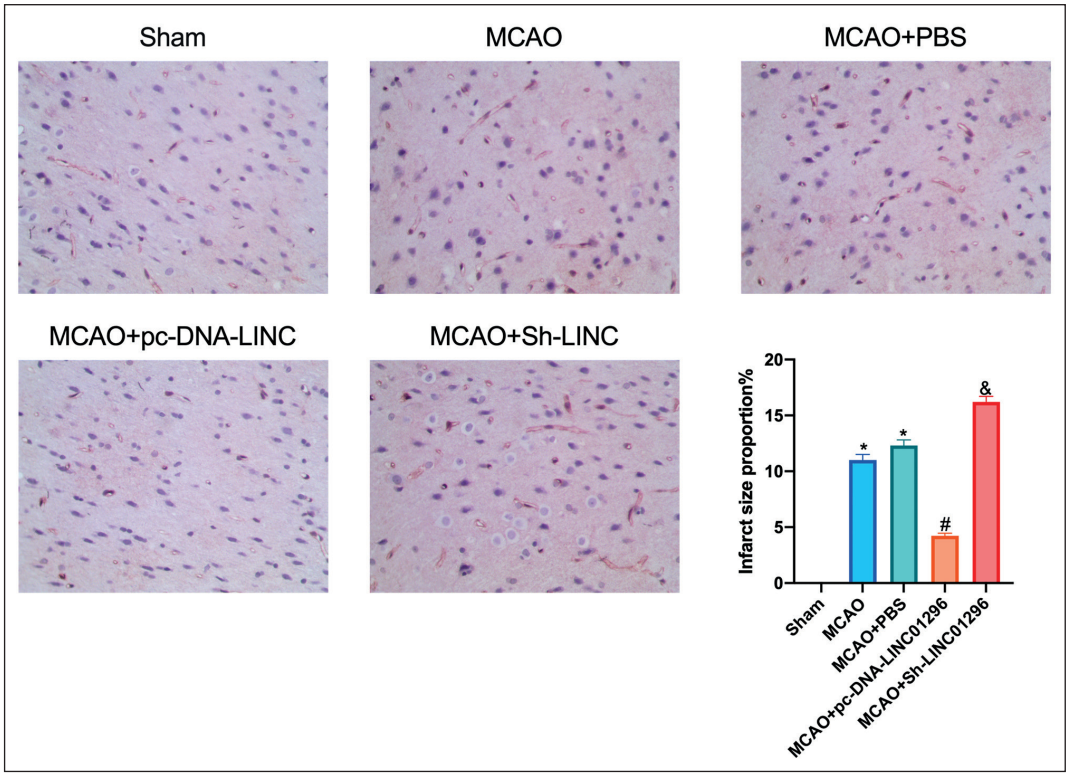

Figure 2: Triphenyltetrazolium chloride staining for the determination of the infarct rate in each group of rats. **Sham group:** control group, **MCAO group:** cerebral infarction model caused by cerebral ischemia–reperfusion, **MCAO+PBS group:** cerebral infarction model caused by cerebral ischemia–reperfusion plus solvent group, **MCAO+pc-DNA-LINC01296 group:** cerebral infarction model caused by cerebral ischemia–reperfusion + overexpression of LINC01296, **MCAO+Sh-LINC01296 group:** cerebral infarction model caused by cerebral ischemia-reperfusion + low expression of LINC01296. *p<0.05 *vs.* the sham group; #p<0.05 *vs.* MCAO+PBS group; and p<0.05 *vs.* pc-DNA-LINC01296 group.

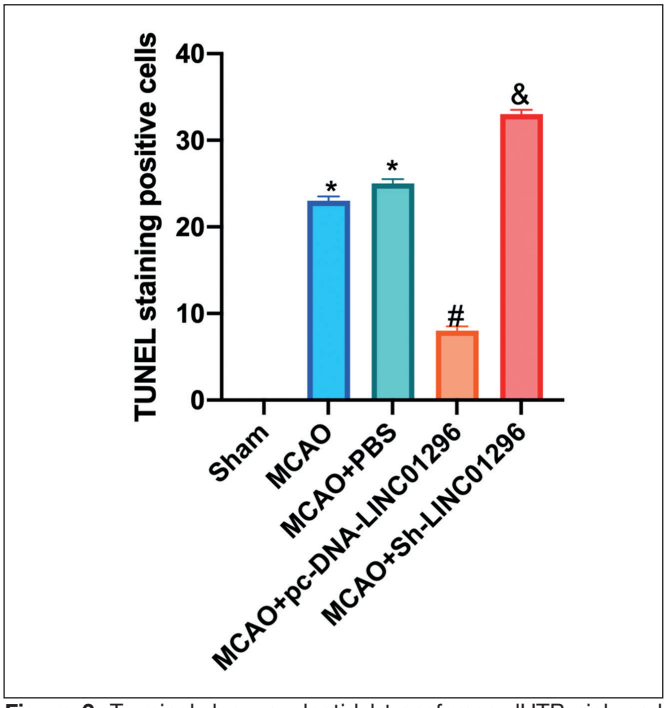

Figure 3: Terminal deoxynucleotidyl transferase dUTP nick end labeling staining for the determination of the infarct rate in each group of rats. **Sham group:** control group, **MCAO group:** cerebral infarction model caused by cerebral ischemia-reperfusion, **MCAO+PBS group:** cerebral infarction model caused by cerebral ischemia–reperfusion plus solvent group, **MCAO+pc-DNA-LINC01296 group:** cerebral infarction model caused by cerebral ischemia–reperfusion + overexpression of LINC01296, **MCAO+Sh-LINC01296 group:** cerebral infarction model caused by cerebral ischemia–reperfusion + low expression of LINC01296. *p<0.05 *vs.* the sham group; #p<0.05 *vs.* MCAO+PBS group; and p<0.05 *vs.* pc-DNA-LINC01296 group.

Western blot was used to detect the expression of apoptosis-related genes. In the Sh-LINC01296 group, the expressions of Birc2 and BAK1 were observed to be decreased. On the other hand, after the injection of pc-DNA-LINC01296, the expression levels increased (Figure 4).

LINC01296 Relieved CIRI by Regulating the Apoptotic Genes Birc2 and Bak1

LINC01296 can target and inhibit the miR-29c expression in endometrial cancer cells. We observed that overexpressed miR-29c can interfere with and inhibit the expression of Birc2 and Bak1, thereby aggravating many types of cell apoptosis and worsening CIRI. The luciferase reporter gene detection method was used in this study to verify the targeting effect of LINC01296 on miR-29c in the PC12 cells. In the LINC01296 and miR-29c analog systems, the fluorescence intensity was low. The targeting effect of miR-29c on Birc2 and Bak1 demonstrated reduced fluorescence intensity in the wild-type miR-29c mimic system.

These results indicate that LINC01296 targets and reduces the expression of miR-29c and that the targeted inhibition of miR-29c ultimately promotes the expressions of Birc2 and Bak1.

LINC01296 Promoted the Expression of Birc2 and Bak1 by Targeting the miR-29c Pathway and Alleviated CIRI

RT-PCR was performed to determine the level of miR-29c in the brain of each group of rats to explore the role of LINC01296 in cerebral ischemia–reperfusion-induced injury. We found that after LINC01296 overexpression, the expression of miR-29c decreased compared to that of the MCAO group (Figure 5). miR-29c antagomir was administered to the rats, and TTC staining was used to determine brain cell apoptosis. We observed that miR-29c antagomir inhibited the protective effect of LINC01296 on cerebral ischemia–reperfusion brain

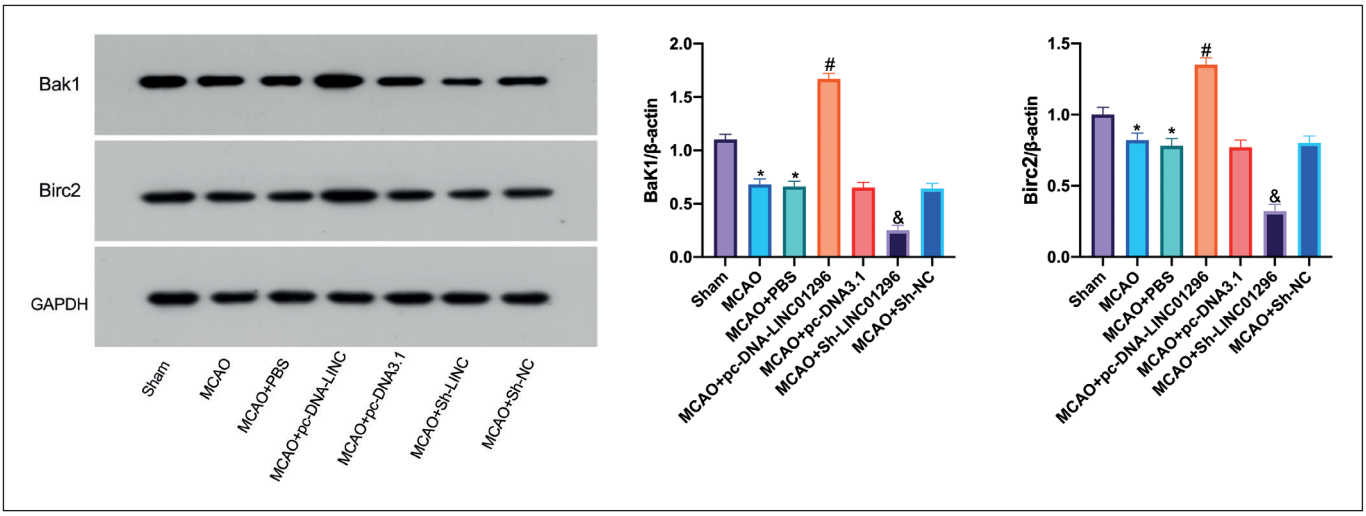

Figure 4: Detecting the expression of apoptosis-related genes by western blot. Sham group: control group, MCAO group: cerebral infarction model caused by cerebral ischemia-reperfusion, **MCAO+PBS group:** cerebral infarction model caused by cerebral ischemia–reperfusion plus solvent group, **MCAO+pc-DNA-LINC01296 group:** cerebral infarction model caused by cerebral ischemia–reperfusion + overexpression of LINC01296, **MCAO+Sh-LINC01296 group:** cerebral infarction model caused by cerebral ischemia–reperfusion + low expression of LINC01296. *p<0.05 *vs.* the sham group; #p<0.05 *vs.* MCAO+pc-DNA3.1 group; and p<0.05 *vs.* MCAO+Sh-NC group

cells (Figure 6). In addition, we identified that the expressions of Birc2 and Bak1 in the brain tissues were enhanced after miR-29c antagomir intervention (Figure 7). Therefore, we believe that LINC01296 overexpression inhibits the expression of miR-29c, while the reduction of miR-29c levels promotes the expressions of Birc2 and Bak1.

DISCUSSION

As a global public health threat, CIRI has severely affected patients' quality of life, for example, those with difficulties in memory, learning, speech, and mobility (24,25). Under normal circumstances, the body's brain tissue can activate endogenous antioxidation and anti-ischemic mechanisms when subjected to harmful stimuli, such as hypoxia and ischemia. These mechanisms can protect the dying nerve cells and promote the recovery of nerve function (6). However, when the body lacks exogenous intervention, the initiation of endogenous neuroprotection is relatively slow. The content of protective media and the duration of action are very much limited; the damage mechanism has an absolute advantage, often surpassing the endogenous neuroprotective effects (8,14). Therefore, it is necessary to apply external environmental stimuli to the body. Through a series of neural reflexes, the brain's tolerance to noxious stimuli, such as ischemia and hypoxia, can be increased significantly. It can

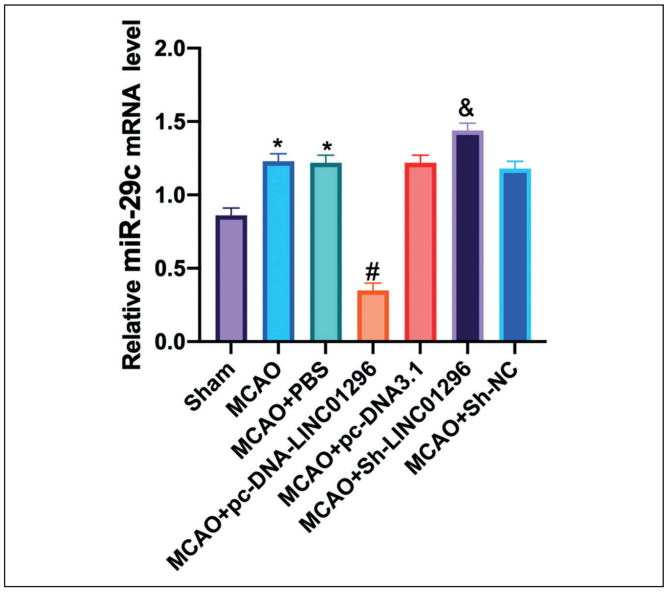

Figure 5: Reverse transcription polymerase chain reaction to determine the level of miR-29c in the brain of each group of rats. **Sham group:** control group, **MCAO group:** cerebral infarction model caused by cerebral ischemia–reperfusion, **MCAO+PBS group:** cerebral infarction model caused by cerebral ischemia–reperfusion plus solvent group, **MCAO+pc-DNA-LINC01296 group:** cerebral infarction model caused by cerebral ischemia–reperfusion + overexpression of LINC01296, **MCAO+Sh-LINC01296 group:** cerebral infarction model caused by cerebral ischemia–reperfusion + low expression of LINC01296. *p<0.05 *vs.* the sham group; #p<0.05 *vs.* MCAO+pc-DNA3.1 group; and p< 0.05 *vs.* MCAO+Sh-NC group.

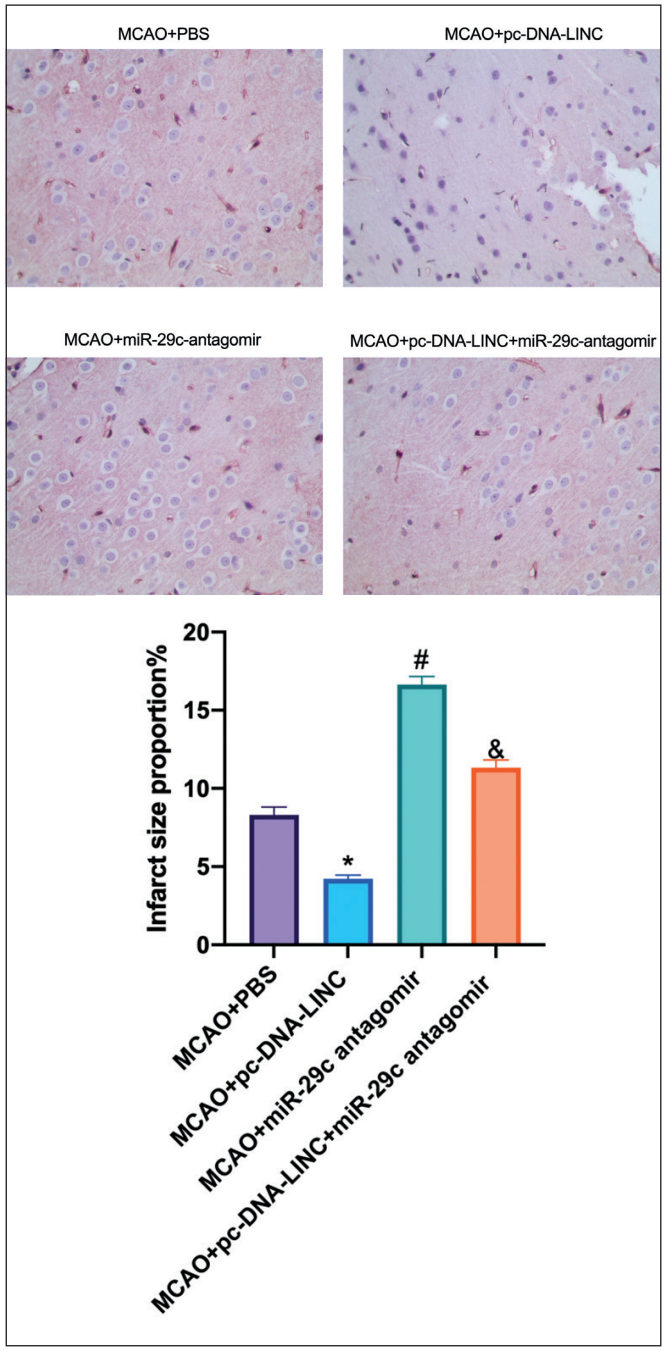

Figure 6: Triphenyltetrazolium chloride staining for determining the apoptosis of the brain cells. **MCAO+PBS group:** cerebral infarction model caused by cerebral ischemia–reperfusion plus solvent group, **MCAO+pc-DNA-LINC01296 group:** cerebral infarction model caused by cerebral ischemia–reperfusion + overexpression of LINC01296, **MCAO+miR-29c-antagomir group:** cerebral infarction model caused by cerebral ischemia–reperfusion + miR-29c-antagomir. **MCAO+pc-DNA-LINC01296+miR-29c-antagomir group:** cerebral infarction model caused by cerebral ischemia–reperfusion + miR-29c-antagomir + overexpression of LINC01296. *p<0.05 *vs.* MCAO+PBS group; #p<0.05 *vs.* MCAO+pc-DNA3.1 group; and p<0.05 *vs.* MCAO + miR-29c-antagomir group.

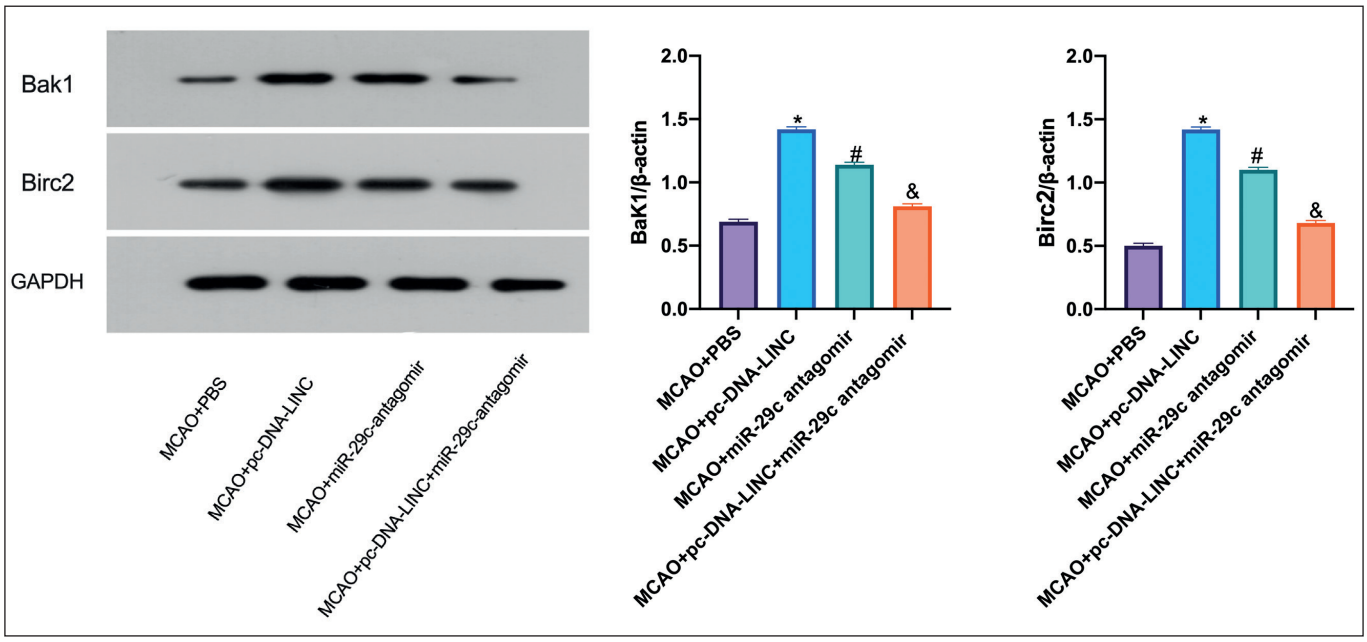

Figure 7: Detecting the expression of the apoptosis-related genes by western blot. **MCAO+PBS group:** cerebral infarction model caused by cerebral ischemia–reperfusion plus solvent group, **MCAO+pc-DNA-LINC01296 group:** Cerebral infarction model caused by cerebral ischemia–reperfusion + overexpression of LINC01296, **MCAO+miR-29c-antagomir group:** cerebral infarction model caused by cerebral ischemia–reperfusion + miR-29c-antagomir. **MCAO+pc-DNA-LINC01296+miR-29c-antagomir group:** cerebral infarction model caused by cerebral ischemia–reperfusion + miR-29c-antagomir + overexpression of LINC01296. *p<0.05, compared with MCAO+PBS group; #p<0.05 *vs.* MCAO+pc-DNA3.1 group; and p<0.05 *vs.* MCAO+ miR-29c-antagomir group.

last for some time, thereby significantly reducing the tissue damage caused by focal cerebral ischemia (17). This study analyzed the correlation among LINC01296, miR-29c, Birc2, Bak1, and CIRI and found that Birc2 and Bak1 can work concertedly to alleviate CIRI in rats. While miR-29c inhibits the expressions of Birc2 and Bak1 and aggravates brain damage, LINC01296 protects the rats from CIRI by targeting miR-29c.

miRNA is a type of endogenous noncoding RNA that regulates gene expression via RNA-induced silencing complexes and plays a role in many cell functions such as cell proliferation, differentiation, and apoptosis (3,4). miR-29c is one of the significantly differentially expressed miRNAs in CIRI, which can play a regulatory role at the transcriptional level (19). For example, miR-29c family members can target at least 16 different target genes related to the extracellular matrix (1). Some researchers have confirmed that miR-29c can negatively regulate the two target genes of Birc2 and Bak1 and aggravate the infarct area in patients with cerebral infarction (16). Huang et al. found that after receiving miR-29c antagonist therapy, neuronal apoptosis in patients with cerebral infarction decreased significantly and the neurological function score improved significantly, while the performance of rats injected with activator was completely the opposite (9). Xu et al. examined ovarian cancer tissues and found that LINC01296 can significantly increase the proliferation, invasion, and migration of OVCAR3 and SKOV3 cells by inhibiting miR-29c-3p (22).

This study has established that LINC01296 can perform biological functions by targeting and regulating the miR-29c cells, which confirms that LINC01296 is capable of controlling miR-29c. However, the difference between the levels of LINC01296 and miR-29c and the level of cerebral ischemia–reperfusion and the results of the relationship study are not yet available.

This study has shown that LINC01296 can target and inhibit the function of miR-29c, which is consistent with the above research results. In addition, the overexpression of LINC01296 eliminated the inhibitory effect of miR-29c and protected the nerve cells in the brain. The overexpression of LINC01296 also resulted in the upregulation of Birc2 and Bak1 levels. These results indicate that LINC01296 can relieve the nervous system damage caused by cerebral ischemia and reperfusion by nullifying the inhibitory effect of miR-29c on Birc2 and Bak1.

CONCLUSION

In summary, our research has demonstrated that LINC01296 can alleviate the injury caused by cerebral ischemia and reperfusion by inhibiting the inhibitory effect of miR-29c on Birc2 and Bak1. Furthermore, our findings have provided new strategies and goals for the clinical treatment of patients with cerebral ischemia–reperfusion. Based on the results, it is evident that miR-29c aggravates CIRI by interfering with Birc2 and Bak1 pathways and that the injury effect is assuaged after the injection of the miR-29c antagonist. The injury effect is enhanced after agonist injection.

AUTHORSHIP CONTRIBUTION

Study conception and design: LM, YQ
Data collection: YQ, KD, XZ
Analysis and interpretation of results: YQ, KD, XZ
Draft manuscript preparation: LM
Critical revision of the article: LM, YQ
All authors (LM, YQ, KD, XZ) reviewed the results and approved the final version of the manuscript.

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