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Long noncoding RNA XIST enhances cerebral ischemia-reperfusion injury by regulating miR-486-5p and GAB2

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Abstract. – OBJECTIVE: LncRNA XIST has been reported to act as diverse function in different human diseases. Our study is designed to detect the role of lncRNA XIST and the regulatory mechanisms of XIST/miR-486-5p/GAB2 in cerebral I/R injury.

MATERIALS AND METHODS: In our article, SH-SY5Y cells were treated with oxygen-glucose deprivation reperfusion (OGDR) to mimic I/R injury. RT-qPCR assay was performed to detect the mRNA expression of XIST, GAB2 and miR-486-5p. The correlation between XIST and miR-486-5p, miR-486-5p and GAB2 were verified by RT-qPCR assay and Dual-Luciferase reporter assay. MTT assay was used to detect cell viability of SH-SY5Y cells treated with I/R. The protein expression of GAB2, apoptosis-related proteins (Bax/Bcl-2) were explored by Western blot assay.

RESULTS: XIST and GAB2 were significantly highly expressed, while miR-486-5p was low expressed in SH-SY5Y cells under I/R. XIST exacerbated the oxidative damage of I/R cells. Moreover, XIST was found to restrain cell viability and induce cell apoptosis. For our experiment, miR-486-5p was a target of XIST, and GAB2 was a downstream gene of miR-486-5p. Furthermore, miR-486-5p mimic promoted cell proliferation and inhibited cell apoptosis, while XIST co-transfection reversed the effect of miR-486-5p. In addition, XIST was found to impair the inhibitory effect of miR-486-5p on expression of GAB2 in I/R cells.

CONCLUSIONS: Our results indicated that XIST promoted cerebral I/R injury via modulating miR-486-5p and GAB2.

Key Words:
LncRNA XIST, MiR-486-5p, GAB2, Cerebral ischemia/reperfusion injury.

Introduction

The brain is the most sensitive organ to anoxia. Cerebral tissue ischemia will cause local brain tissue and function damage and is the main cause of cerebrovascular accidents[1]. Timely restoration of blood supply is conducive to reduce brain tissue damage. However, when blood reperfusion is restored, more serious damage to the structural and function of brain tissues occurs, which is called ischemia/reperfusion (I/R) injury[2]. Free radical damage, cell swelling, and apoptosis and necrosis are possible consequences of cerebral I/R injury. Above all, I/R injury is an intricate cascade-reactive pathophysiological process, which involves a variety of pathogenesis[3]. In consequence, it is instant to study the mechanisms of cerebral I/R injury, and to find new treatment methods for stroke patients.

LncRNAs play important roles in the regulation of cardiovascular and cerebrovascular protection. For instance, LncRNA N1LR was found to reduce neuronal apoptosis and neural cell loss in I/R by inhibiting p53 phosphorylation[4]. LncRNA NEAT1 was reported to inhibit cell growth and induce cell apoptosis in PC12 cells with I/R by inhibiting miR-874-3p expression[5]. Pan et al[6] discovered that lncRNA SNHG16 acted as a neuroprotection role in OGD/R SH-SY5Y cells by modulating miR-106b-5p/LIML1. X-inactive specific transcript (XIST) was reported to be abnormally expressed and be involved in cell progression of various human diseases. In osteosarcoma, XIST was attested to be high expressed, and enhance cell progression and epithelial-mesenchy-

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mal transition of osteosarcoma cells induced by oxidative stress through miR-153/SNAI1[7]. Zhou et al[8] found that XIST alleviated cardiomyocytes from hypoxia-induced injury by regulating miR-150-5p/Bax. However, the role of XIST in cerebral I/R has not been expounded.

LncRNAs can directly bind to miRNAs and weakening the latter's role in inhibiting gene expression in human diseases. In particular, H19 enhanced I/R injury by interplaying with miR-19a-3p to modulate PTEN[9]. MALAT1 knockdown was reported to project against cerebral I/R injury by regulating miR-145[10]. MiR-486-5p was found to participate in various biological progressions of human disease. Furthermore, miR-486-5p was down expressed and served as a tumor suppressor by regulating ARHGAP5 in lung cancer[11]. Moreover, Liu et al[12] reported that miR-486-5p restrained cell growth and promoted cell apoptosis by inhibiting EOXO1 in leukemia. In this research, we verified that miR-486-5p was a target of XIST in I/R injury.

In our work, we explored the role of XIST in cerebral I/R injury. Specifically, XIST was confirmed to enhance cerebral I/R injury by modulating miR-486-5p/GAB2. Our findings may provide a new target for the treatment of ischemic stroke.

Materials and Methods

Cell Culture and Cell Transfection

SH-SY5Y cells were acquired from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). The SH-SY5Y cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) medium supplement with 15% fetal bovine serum (FBS). The cells were cultured in an atmosphere at 37°C, 95% air and 5% CO_2.

XIST vector and siRNA, miR-486-5p mimic and miR-486-5p inhibitor, GAB2 were synthesized by GenePharma (Shanghai, China). We transfected them into SH-SY5Y cells by Lipofectamine 2000 according to the manufacturer's recommended protocol.

Establishment of Oxygen-Glucose Deprivation and Reperfusion Model (OGDR)

SH-SY5Y cells were cultured in a glucose-free Hanks' balanced salt solution under hypoxic conditions (1% O2/94% N 2/5% CO_2) at 37°C for 4 h to build an OGD model. After that, the cells were placed in a glucose medium with 10% FBS and cultured under normoxic conditions (95% air/5% CO_2) for 48 h for reperfusion. SH-SY5Y cells cultured under normoxic conditions were used as controls.

Real Time-Quantitative Polymerase Chain Reaction (RT-qPCR) Assay

Total RNA was obtained from the SH-SY5Y cells according to the TRIzol reagent. Then, cDNA was synthesized by PrimeScript RT Reagent Kit. RT-qPCR was used by the SYBR PrimeScript miRNA RT-PCR Kit on ABI 7500 Fast system. GAPDH and U6 were used as internal controls. The $2^{-\Delta\Delta Ct}$ method was performed to quantify the expression levels. The primers sequences were listed in Table I.

LDH, MDA, SOD Levels

The commercial kits for determining lactate dehydrogenase (LDH), malondialdelyde (MDA) and reactive oxygen species (ROS) were obtained from Jinkang Bioengineering (Shanghai, China). The level of LDH, SOD and MDA were used to measure the injury degree of SH-SY5Y cells with I/R.

Table I. Primer sequences in qRT-PCR.

Gene		Primers 5′-3′
XIST	Forward	5'-AGCTCCTCGGACAGCTGTAA-3'
	Reverse	5'-CTCCAGATAGCTGGCAACC-3'
miR-486-5p	Forward	5'-ACACTCCAGCTGGGTCCTGTACTGAGCTGCCC 3'
	Reverse	5' CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGCCCCG 3'
GAB2	Forward	5'-CGAAGAGAACTATGTCCCTATGC-3'
	Reverse	5'-AGGGGCAGGACTGTTCGT-3'
U6	Forward	5'-GCTTCGGCAGCACATATACTAAAAT-3'
	Reverse	5'-CGCTTCACGAATTTGCGTGTCAT-3'
GAPDH	Forward	5'-CCTGACCTGCGTGTGGACT-3'
	Reverse	5'-GCTGTGGATGGGGAGGTGTC-3'

MTT Assay

SH-SY5Y cells were cultured in 96-well plates at 37°C and 5% CO_2 for 48 h. Then, the cells were incubated with MTT reagent (20 μL/well) for 4 h. Then, dimethyl sulfoxide (DMSO; 100 μL) was added to each well. Finally, the Microplate reader at 490 nm was used to measure the absorbance.

Dual-Luciferase Reporter Assay

The pmirGLO luciferase plasmids of XIST-wt or XIST-mut, GAB2-wt or GAB2-mut and miR-486-5p mimic were transfected into SH-SY5Y cells. Cells were cultured in the incubator at 37°C, 5% CO_2, and 95% humidity. After 48 hours, the Luciferase activity was tested by the Dual-Luciferase reporter assay kit.

Western Blot

Total proteins were extracted from SH-SY5Y cells by radio immunoprecipitation assay (RIPA). Then, the membrane was incubated with specific antibodies after incubated with 5% skimmed milk. Finally, the protein signals were detected by enhanced chemiluminescence (ECL) Western Blotting Substrate.

Statistical Analysis

The data were presented as mean±standard deviation (SD). Each experiment was performed at least three times. And, SPSS 20.0 (IBM, Armonk, NY, USA) was performed to analyze data. The comparison between two groups was analyzed by *t*-test. ANOVA was carried out to assess the comparison between multiple groups. $p<0.05$ was considered as statistically significant.

Results

XIST and GAB2 Was High Expressed, While MiR-486-5p Was Low Regulated in I/R Cell

We detected the expression of XIST, miR-486-5p and GAB2 in I/R treated SH-SY5Y cells. RT-qPCR results showed that XIST was markedly high expressed in I/R cells (Figure 1A). Intriguingly, miR-486-5p was lower expressed in I/R group than in control group (Figure 1B). In addition, the mRNA expression of GAB2 was indicated to be high expressed in I/R cells (Figure 1C). Besides, the protein expression of GAB2 was upregulated in I/R cells by Western blot assay (Figure 1D). Our findings implied that XIST, miR-486-5p and GAB2 might be involved in cerebral I/R injury.

Upregulation of XIST Enhanced Cerebral I/R Injury

To detect the effect of XIST on cerebral I/R injury, XIST vector or XIST siRNA was transfected into SH-SY5Y cells under I/R. These results indicated that the expression of XIST was notably ascended

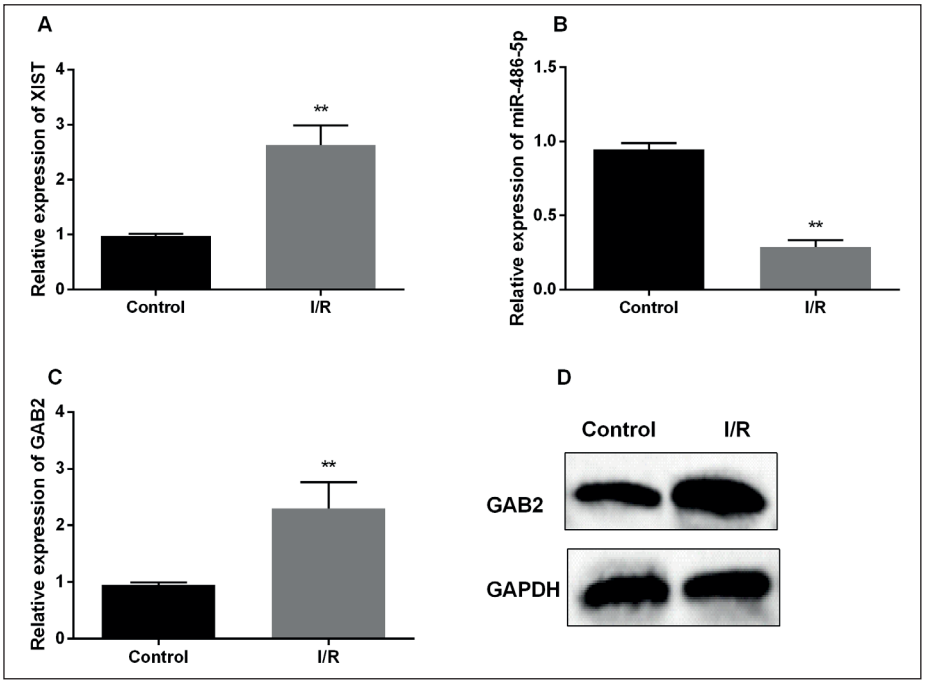

Figure 1. XIST and GAB2 were high expressed and miR-486-5p was low expressed in I/R treated SH-SY5Y cells. **A**, The expression of XIST was higher expressed in I/R than in control group. **B**, The expression of miR-486-5p was lower expressed in I/R than in control group. **C**, The mRNA expression of GAB was increased in I/R. **D**, The protein expression of GAB2 was ascended in I/R. $^{**}p<0.01$.

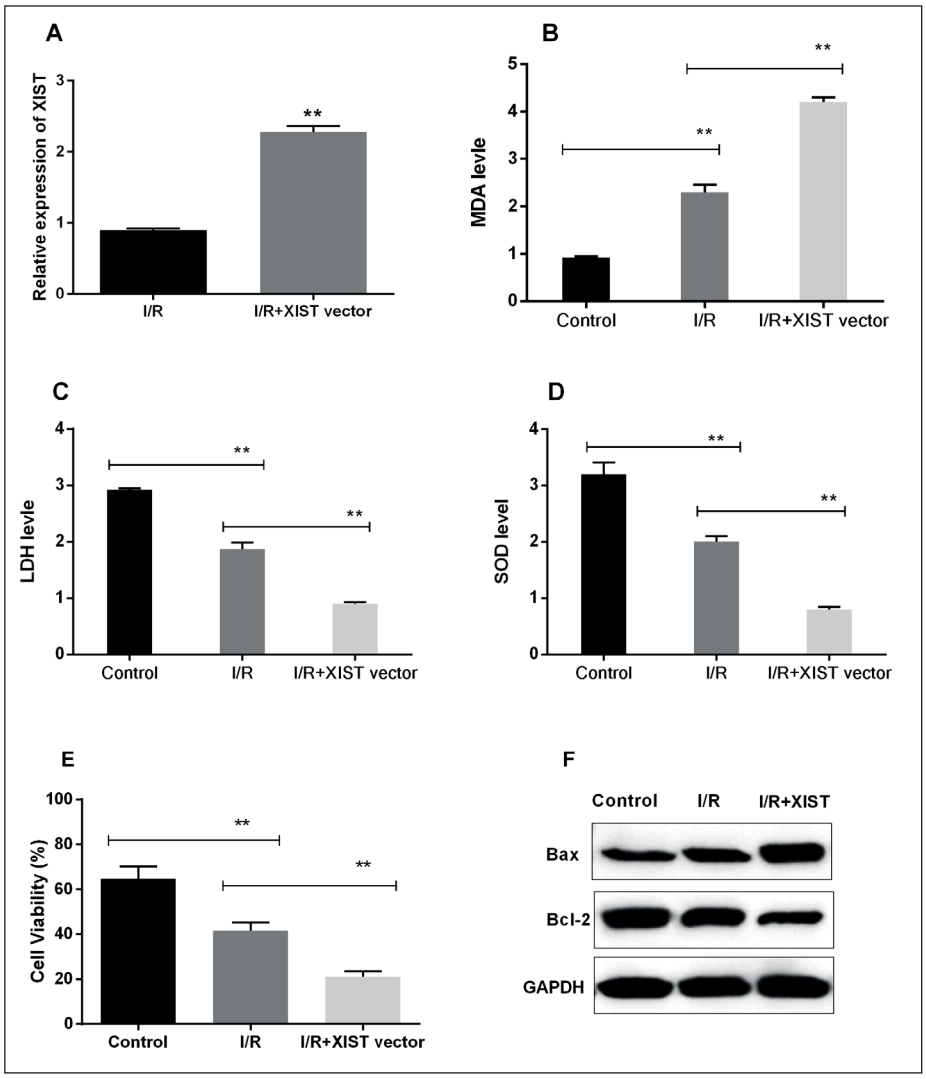

Figure 2. Upregulation of XIST enhanced cerebral I/R injury in SH-SY5Y cells. **A**, The expression of XIST was significantly increased by XIAT vector. **B**, XIST vector promoted the level of MDA in I/R treated SH-SY5Y cells. **C**, XIST vector reduced the level of LDH in I/R treated SH-SY5Y cells. **D**, XIST vector reduced the level of SOD in I/R treated SH-SY5Y cells. **E**, The cell viability was inhibited by XIST vector in I/R. **F**, The expression of Bax and Bcl-2 were detected in I/R group and I/R+XIST vector group. $^{**}p<0.01$.

by XIST vector, while descended by XIST siRNA (Figure 2A). Then, we measured the level of LDH, MDA, SOD in I/R group. We found that MDA level was notably upregulated in I/R group (Figure 2B). Additionally, the level of MDA was significantly increased by XIST vector in I/R group. Besides that, the level of LDH and SOD were reduced in I/R. The level of LDH and SOD were further decreased by XIST vector in I/R group (Figure 2C, D). Next, MTT assay was carried out to assess the effect of XIST on cell growth in I/R cells. Our findings displayed that cell proliferation was inhibited in I/R cells (Figure 2E). Meanwhile, we found that XIST vector further suppressed cell proliferation compared with I/R group. Furthermore, Western blot assay was adopted to measure the expression of apoptosis-related proteins (Bcl-2 and Bax). In I/R group, Bax expression was increased, while Bcl-2 expression was shortened compared with control group. In addition, XIST vector restrained the expression of Bcl-2 and ascended the expression of Bax in I/R cells (Figure 2F). Taken together, XIST was confirmed to enhance the cerebral I/R injury in I/R cells.

MiR-486-5p Was a Target of XIST

In the current work, miR-486-5p was predicted to be a target of XIST by StarBase. As shown in Figure 3A, there were special binding sites between miR-486-5p and XIST. To test the above hypothesis, RT-qPCR assay and dual luciferase reporter assay were implemented. Our results displayed that the luciferase activity of XIST-wt was weakened by miR-486-5p mimic transfection, but XIST-mut had no change by miR-486-5p mimic (Figure 3B). Furthermore, we transfected XIST vector or XIST siRNA, miR-486-5p mimic

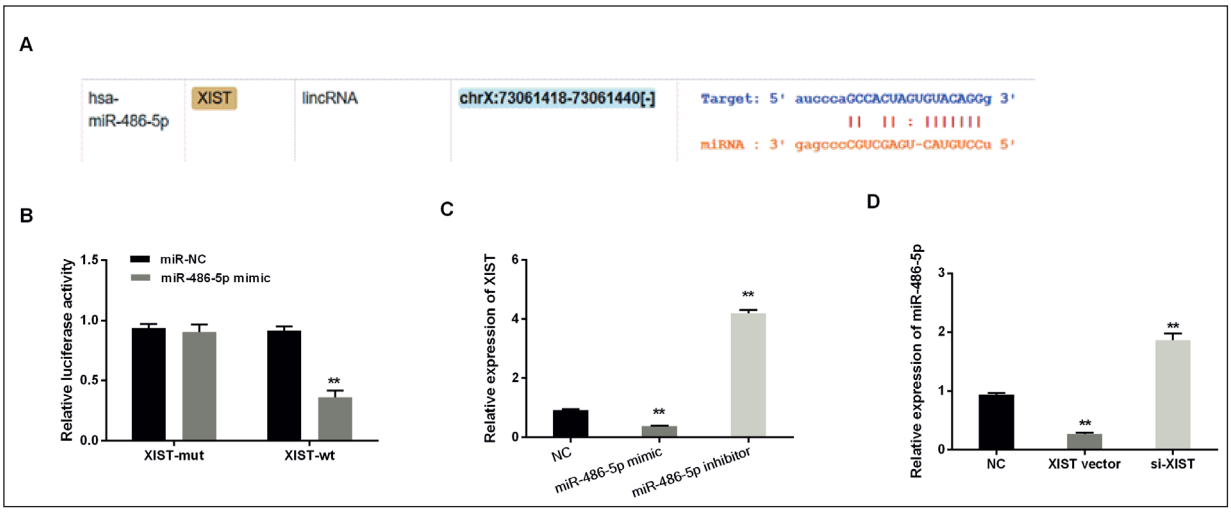

Figure 3. MiR-486-5p was a target of XIST. **A**, There were special binding sites between XIST and miR-486-5p. **B**, The relative luciferase activity of XIST-mut and XIST-wt. **C**, The expression of XIST was reduced by miR-486-5p inhibitor, while increased by miR-486-5p mimic. **D**, The expression of miR-486-5p was reduced by XIST vector, while increased by XIST siRNA. **$p<0.01$.

or miR-486-5p inhibitor into SH-SY5Y cells. We noticed that the expression of XIST was reduced by miR-486-5p mimic but ascended by miR-486-5p inhibitor (Figure 3C). Moreover, XIST vector inhibited miR-486-5p expression, whereas XIST siRNA promoted miR-486-5p expression (Figure 3D). Our data displayed that XIST acted as a ceRNA of miR-486-5p in I/R cells.

XIST Enhanced Cerebral I/R Injury by Inhibiting MiR-486-5p

We transfected XIST vector into SH-SY5Y cells under I/R. As shown in Figure 4A, miR-486-5p was reduced by XIST vector. MTT assay indicated that miR-486-5p mimic promoted cell growth, while XIST co-transfection inhibited the effect of miR-486-5p on cell growth (Figure 4B).

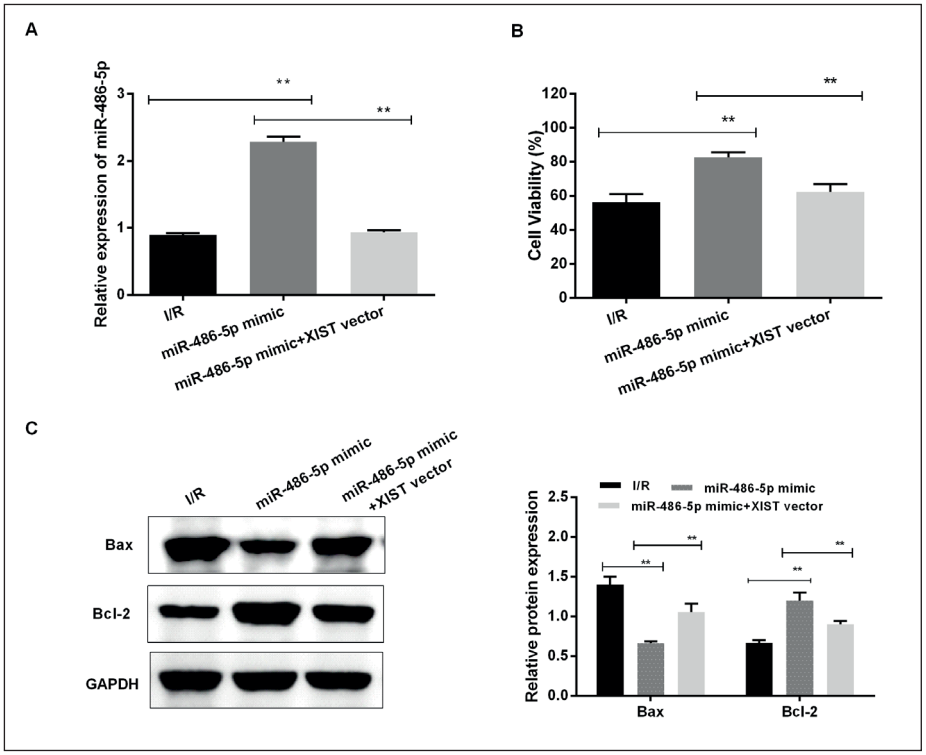

Figure 4. XIST enhanced cerebral I/R injury by inhibiting miR-486-5p in SH-SY5Y cells. **A**, The expression of miR-486-5p was increased by miR-486-5p mimic, but reduced by XIST co-transfection with miR-486-5p. **B**, The cell viability was detected in miR-486-5p mimic group and XIST vector co-transfection with miR-486-5p mimic group. **C**, The expression of Bax and Bcl-2 was detected in miR-486-5p mimic group and XIST vector + miR-486-5p mimic group.**$p<0.01$.

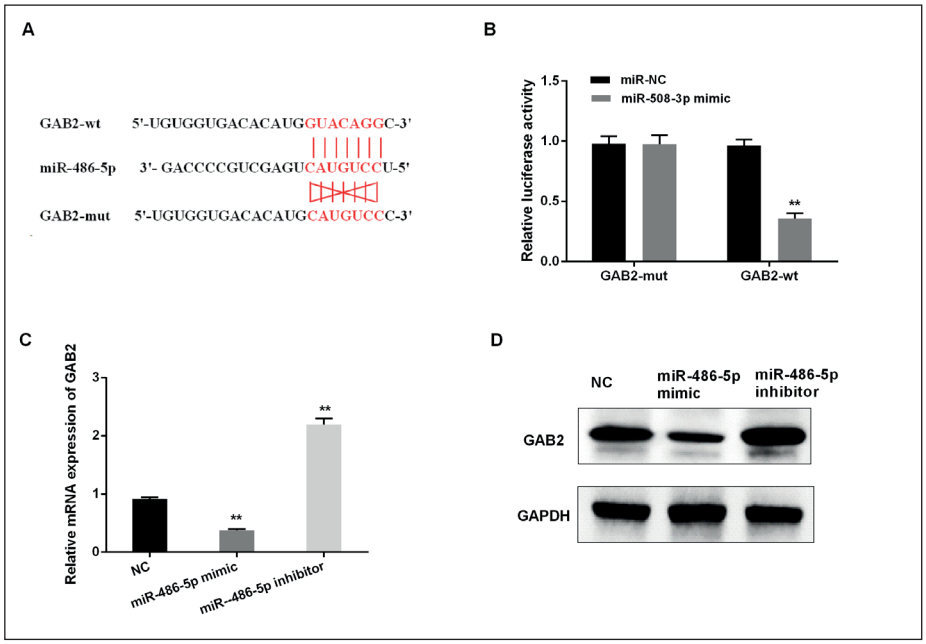

Figure 5. GAB2 was a downstream target gene of miR-486-5p. **A**, GAB2 had binding sites with miR-486-5p. **B**, The relative luciferase activity of GAB2-mut and GAB2-wt. **C**, The mRNA expression of GAB2 was reduced by miR-486-5p, but increased by miR-486-5p inhibitor. **D**, The protein expression of GAB2 was reduced by miR-486-5p, but increased by miR-486-5p inhibitor. $^{**}p<0.01$.

In addition, miR-486-5p mimic reduced the expression of Bax, while XIST vector impaired the inhibitory of miR-486-5p. Inversely, the expression of Bcl-2 was ascended by miR-486-5p mimic but inhibited by XIST co-transfection (Figure 4C). Our results indicated that XIST promoted cerebral I/R injury by inhibiting miR-486-5p expression.

GAB2 Was a Downstream Target Gene of MiR-486-5p

TargetScan software was adopted to search the target genes of miR-486-5p. Our results indicated that miR-486-5p had binding sites with GAB2 (Figure 5A). MiR-486-5p mimic was found to weaken the luciferase activity of GAB2-wt but have little effect on GAB2-mut (Figure 5B). In the next moment, RT-qPCR assay revealed that the mRNA expression of GAB2 was reduced by miR-486-5p mimic, while increased by miR-486-5p inhibitor (Figure 5C). In addition, miR-486-5p had the same effect on the protein expression of GAB2 (Figure 5D). In the current work, GAB2 was verified to be a downstream gene of miR-486-5p.

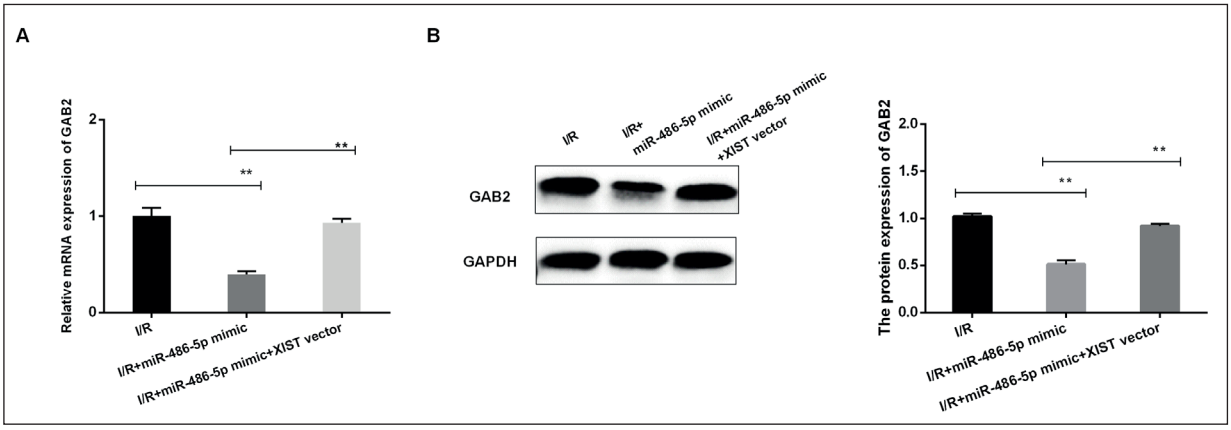

Figure 6. XIST aggravated the damage of I/R treated SH-SY5Y cells by regulating miR-486-5p/GAB2. **A**, The mRNA expression of GAB2 was reduced by miR-486-5p mimic, while XIST vector attenuated the effect of miR-486-5p in I/R cells. **B**, The protein expression of GAB2 was reduced by miR-486-5p mimic, while XIST vector impaired the effect of miR-486-5p mimic in I/R cells. $^{**}p<0.01$.

XIST Aggravated the Damage of I/R Cells by Regulating MiR-486-5p/GAB2

To verify the mechanism of XIST/miR-486-5p/GAB2 on cerebral I/R, XIST vector was co-transfected with miR-486-5p mimic into SH-SY5Y cells. We noticed that miR-486-5p mimic reduced the expression of GAB2, but XIST vector co-transfection attenuated the effect of miR-486-5p mimic on GAB2 expression (Figure 6A). Similarly, Western blot assay showed that XIST vector impaired the inhibitory effect of miR-486-5p mimic on protein expression of GAB2 (Figure 6B). Therefore, we indicated that XIST aggravated I/R injury by regulating miR-486-5p/GAB2.

Discussion

LncRNAs have been shown to play a curial part in cerebral I/R injury. ZFAS1 was proved to suppress oxidative stress, inflammation and cell apoptosis by regulating miR-582/NOS3 in cerebral I/R[13]. Zhong et al[14] found that SNHG14 enhanced inflammatory response by miR-136-5p/ROCK1 in cerebral I/R. In our study, XIST was noticed to be upregulated in SH-SY5Y cells under I/R. Moreover, overexpression of XIST enhanced the cerebral I/R injury. Similar to our findings, XIST silencing moderated hypoxia-induced injury by regulating miR-150-5p and Bax[8]. Functionally, knockdown of XIST was reported to repress cell growth, cell metastasis and induce cell apoptosis by modulating miR-142-5p/PAX6 in non-small cell lung cancer[15]. Furthermore, XIST knockdown protected spinal cord injury in rat by interplaying with miR-494[16]. Our results implied that XIST might be a curial regulator in cerebral I/R injury.

In the current investigation, we noticed that miR-486-5p was low expressed in I/R cells treated with I/R. Besides that, we verified that XIST acted as a ceRNA of miR-486-5p in I/R cells. Consistent with our findings, XIST competitively binding to miR-486-5p in colorectal cancer[17]. Furthermore, miR-486-5p restrained cell migration and invasion ability by regulating PIK3R1 in colorectal cancer[18]. Moreover, miR-486-5p was low expressed in hepatocellular carcinoma (HCC), and acted as a tumor inhibitor in HCC[19]. MTT assay indicated that miR-486-5p mimic accelerated cell growth, while XIST co-transfection reversed the effect of miR-486-5p. Meanwhile, miR-486-5p mimic reduced the expression of Bax, while XIST vector impaired the inhibitory of miR-486-5p. Inversely, the expression of Bcl-2 was ascended by miR-486-5p mimic but inhibited by XIST co-transfection. Consistent with our findings, miR-486-5p was proved to inhibit cell metastasis by regulating Snail in prostate cancer[20]. Our findings suggested that XIST enhanced cerebral I/R injury by inhibiting miR-486-5p expression.

GAB2, a member of the Grb-associated binders family, has been reported to act as a crucial role on biological progression in various human diseases[21]. GAB2 knockdown suppressed cell growth, EMT and cell metastasis in prostate cancer[22]. In addition, GAB2 knockdown was found to inhibit cell proliferation and increase quizartinib sensitivity in acute myeloid leukemia[23]. In this study, GAB2 was verified to be a downstream gene of miR-486-5p. Consistent with our results, miR-486-5p repressed cell growth and cell metastasis by restraining GAB2 in non-small cell lung cancer[24].

Conclusions

In sum, we first discovered that XIST was high expressed in I/R cells. Moreover, XIST enhanced the cerebral I/R injury by modulating miR-486-5p/GAB2. Therefore, we suggested that XIST might be a novel target for the treatment of cerebral I/R injury.

Competing interests

The authors declare that they have no competing interests.

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