



Long non-coding RNA SNHG1 mediates neuronal damage in Parkinson's disease model cells by regulating miR-216a-3p/Bcl-2-associated X protein

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Background: Parkinson's disease (PD) is a common central nervous system degenerative disease in middle-aged and elderly people. Our study aimed to illuminate the relationship and mechanism of long-chain non-coding RNA SNHG1 and miRNA (miR)-216a-3p in PD.

Methods: Human neuroblastoma cell lines were treated with MPP⁺ to construct a PD model. Real-time fluorescent quantitative PCR was used to detect the cellular expression of SNHG1. Neuronal cell activity and apoptosis were compared before and after SNHG1 knock-down, as was neuronal miR-216a-3p expression. Further, a luciferase reporter gene experiment was performed to verify BAX as the target of miR-216a-3p. Anti-miR-216a-3p and BAX were co-transfected into PD model cells, and neuronal cellular activity and apoptosis were observed. Finally, the potential regulatory network of SNHG1/miR-216a-3p/BAX in PD was investigated.

Results: The expression of miR-216a-3p was decreased in the PD model cells, and re-expression reversed the high apoptotic rate and cell vitality inhibition in PD model cells. SNHG1 interacted with miR-216a-3p and negatively regulated its upstream molecules, while miR-216a-3p attenuated the effect of SNHG1 knock-down on neurons. The overexpression of BAX in the PD cell model blocked the damage by miR-216a-3p to neurons. At the same time, SNHG1 acted as a coordinator, mediating the regulation of BAX via miR-216a-3p, thereby affecting the activity and apoptotic rate of neurons in the PD model.

Conclusions: SNHG1 interacts with miR-216a-3p to regulate the expression of BAX. This SNHG1/miR-216a-3p/BAX molecular regulatory network is implicated in the pathogenesis of PD.

Keywords: SNHG1; miR-216a-3p; BAX; Parkinson's disease model (PD model); neuronal damage

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Introduction

Parkinson's disease (PD) is an extremely common neurodegenerative disease, the general clinical characteristics of which include muscle stiffness, slow movement, resting tremor, and staggering (1). PD is

characterized by the selective loss of substantia nigra nerve cells in the brain, resulting in a decrease in substantia nigra dopamine neurons. Despite long-term and in-depth clinical, physiological, and biochemical research on PD having been conducted, the exact cause of the pathological changes

associated with the disease has remained unclear. Many factors, including environmental, age-related, and heredity factors, can contribute to the degeneration and death of dopaminergic neurons (2,3). There is still no clinically effective drug for the treatment of PD. Therefore, clinically, drugs are often used for the treatment of PD. Doctors prescribe drugs with the aims of delaying the development of the disease and maintaining the patient's quality of life (4-6). Therefore, further clarification of the pathogenesis of PD is urgently needed.

Long non-coding RNAs (lncRNAs) are non-coding RNAs that cannot be transcribed to produce cellular protein. In recent years, an increasing number of studies have demonstrated that lncRNAs are important regulators in the pathogenesis of PD (7,8). Small nucleolar RNA host gene 1 (SNHG1) is one of the lncRNAs that have been studied more in recent years. A number of references report that it plays an important role in lung cancer and liver cancer, participates in many signal pathways, and becomes a target site for cancer detection (9). MicroRNAs (miRNAs or miRs) are another type of non-coding RNA with a length of 18 to 24 nt that cannot be transcribed to produce cellular protein. Through transcriptional and post-transcriptional regulation, miRNAs play important roles in multiple malignant physiological cellular processes, such as oncogenesis, and participate in various cellular activities (10). Numerous studies have shown that miR-216a-3p inhibits cell proliferation and invasion as well as other cellular activities in a variety of cancer cells by regulating its target genes. Cancer cells have a high rate of apoptosis and autophagy, and miR-216a-3p has the potential to become a molecular marker in the detection of some cancers. However, whether or not miR-216a-3p plays an equally important role in the occurrence of PD has yet to be determined. Therefore, the present study explored the biological roles of lncRNA SNHG1 and miR-216a-3p in the pathogenesis of PD, as well as their relationship and mechanism in the progression of the disease. We present the following article in accordance with the MDAR reporting checklist (available at <http://dx.doi.org/10.21037/atm-21-1613>).

Methods

Cell culture and PD model establishment

The human neuroblastoma cell line SK-N-SH was purchased from the Shanghai Institute of Life Sciences.

The SK-N-SH cells were cultured in high-sugar Dulbecco's Modified Eagle Medium (Thermo Fisher Scientific, USA) containing working concentrations of fetal bovine serum and penicillin-streptomycin of 10% and 1%, respectively. Cell culture was carried out in an incubator with the temperature set at 37 °C and a CO₂ concentration of 5%. To establish a PD cell model, cells were treated with 0.25, 0.5, or 1 mM 1-methyl-4-phenylpyridinium (MPP⁺) for 24 hours.

Plasmid transfection

1×10⁵ of cells in the logarithmic growth phase were seeded on a 48-well plate and cultured until reaching 40–60% confluence. Mixtures containing 50 μL serum-free medium and 3 μL Lipofectamine 2000, and 50 μL serum-free medium and 400 ng plasmid mixture were prepared for transfection, which was the amount of one hole of the 48-well plate. Each of the 2 mixtures was mixed and stood at room temperature for 5 minutes. After that, each mixture was mixed for a second time and left to stand at room temperature for 20 minutes. The reagents were configured according to the number of holes in the experiment.

The BAX overexpression plasmid was purchased from addgene, and the plasmid name was pCEP4-HA-BAX (Plasmid # 16587). The siRNA was synthesized in Shanghai Jima Pharmaceutical Co., Ltd. (China). The siRNA specific sequences were: siSNHG1-1: target sequence + 2nt overhang: CAGCTTGTGCTATATACCATTG; 21 nt guide (5'-3'): AUGGUAUUAAGCAACAAGCUG; 21 nt passenger (5'-3'): GCUUGUUGCUAUUAACCAUUG. siSNHG1-2: target sequence + 2 nt overhang: CTGAGCAAATAAGGTGTATAAAA; 21 nt guide (5'-3'): UUAUACACCUUAUUUGCUCAG; 21 nt passenger (5'-3'): GAGCAAUAAGGUGUAUAAAA.

Extraction of total cell RNA and polymerase chain reaction analyses

Total RNA was extracted from SK-N-SH cells using TRIzol reagent; following extraction, the quality of the RNA was tested and quantified. Then, reverse transcription and real-time fluorescent quantitative polymerase chain reaction (qRT-PCR) were performed using the relevant kits following the manufacturers' instructions. To detect the expression level of miR-216a-3p, due to the short lengths of miRNAs, the tailing miScript II RT Kit (Qiagen, Germany) was used for reverse transcription. To detect

the mRNA expression level of Bcl-2-associated X protein (BAX), a HiScript 1st Strand cDNA Synthesis Kit (Nanjing Novozan Biotechnology Co., Ltd.) was used for reverse transcription. The primer used for miR-216a-3p detection was a matching primer designed according to the Qiagen tailing reverse transcription kit. The primers used for the detection of the SNHG1 gene and other related genes were: SNHG1-F: 5'-CTGTTCCCGTCATGAGCCTT-3'; SNHG1-R: 5'-GCAAGGCCCTGAATGAGCTA-3'; BAX-F: 5'-CATGGGCTGGACATTTGGACT-3'; BAX-R: 5'-AAAGTAGGAGAGGAGGCCGT-3'; GAPDH-F: 5'-GACAGTCAGCCGCATCTTCT-3'; GAPDH-R: 5'-GCGCCCAATACGACCAAATC-3'; U6-F: 5'-CTCGCTTCGGCAGCACA-3'; U6-R: 5'-AACGCTTCACGAATTTGCGT-3'.

Western blot

First, SK-N-SH cells were collected in an Eppendorf tube. Considering the location of the protein to be detected in the cell, the cells were lysed with RIPA lysis buffer at an appropriate strength. The bicinchoninic acid assay (BCA) method was used for protein quantification. Equal amounts of protein were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). After separation, the proteins were transferred to a membrane, which was blocked, and incubated with primary and then secondary antibodies. Finally, the protein bands were developed and quantified.

Cell viability experiment

To detect cell viability, a cell counting kit-8 (CCK-8) assay was performed. Briefly, cells were seeded in a 96-well culture plate at 2×10^4 /mL for 24 hours. Then, 10 μ L of CCK-8 solution was added to each well, and the cells were incubated for 2 hours. Finally, the absorbance value was measured at 450 nm with a microplate reader.

Cell apoptosis experiment

For the cell apoptosis assay, cells were digested with trypsin and centrifuged to remove the supernatant. Then, the cells were resuspended in binding buffer and stained with isothiocyanate (FITC) and propidium iodide (PI) in the dark at room temperature. Finally, according to the manufacturer's instructions, a flow cytometer was used to detect cell apoptosis, and the percentage of apoptotic cells

was recorded.

Luciferase reporter gene

psiCHECK2TM plasmids containing fragments of miR-216a-3p target sites on the three prime untranslated region (3'UTR) of SNHG1 and Bcl-2-associated X protein (BAX, including MUT) were constructed and were denoted as psiCHECK2TM-SNHG1 and psiCHECK2TM-BAX, respectively. Human embryonic kidney (HEK) 293T cells were seeded in a 24-well plate and cultured to 50–60% confluence. Anti-miR-216a-3p synthesized in Shanghai Jima Pharmaceutical Co., Ltd. (China) and the constructed related reporter gene plasmid were simultaneously transfected into the same well. The negative control (NC) group was transfected with NC (bundled with anti-miRNA synthesis) and related reporter gene plasmids. After 24 hours, the supernatant was removed, and the cell pellets were collected. Then, the cells were lysed with passive lysis buffer, and centrifuged; 20 μ L of the supernatant was obtained in a 96-well white plate. After that, Firefly luciferase activity was detected using Luciferase Assay Reagent II. Stop & Glo Reagent reagents were added to inhibit luciferase activity and Renilla luciferase activity was detected.

Data analysis

Data were collected and statistically analyzed in GraphPad Prism 5.0 software, and relevant histograms were also generated using the software.

Results

Knock-down of SNHG1 affected the cell activity and apoptosis of neurons in the PD model cells

The PD cell model was constructed using MPP⁺ to treat the human neuroblastoma cell line SK-N-SH. Observation of the changes in SNHG1 expression before and after treatment revealed that the expression level of SNHG1 was positively correlated with the dose of MPP⁺ (Figure 1A). In the subsequent experiments, MPP⁺ was used at a concentration of 1 mM to construct an *in vitro* simulated PD cell model. The expression of SNHG1 was found to be significantly increased in the PD model cells. To establish whether SNHG1 expression was related to the growth of neurons in the model, we knocked out neuronal

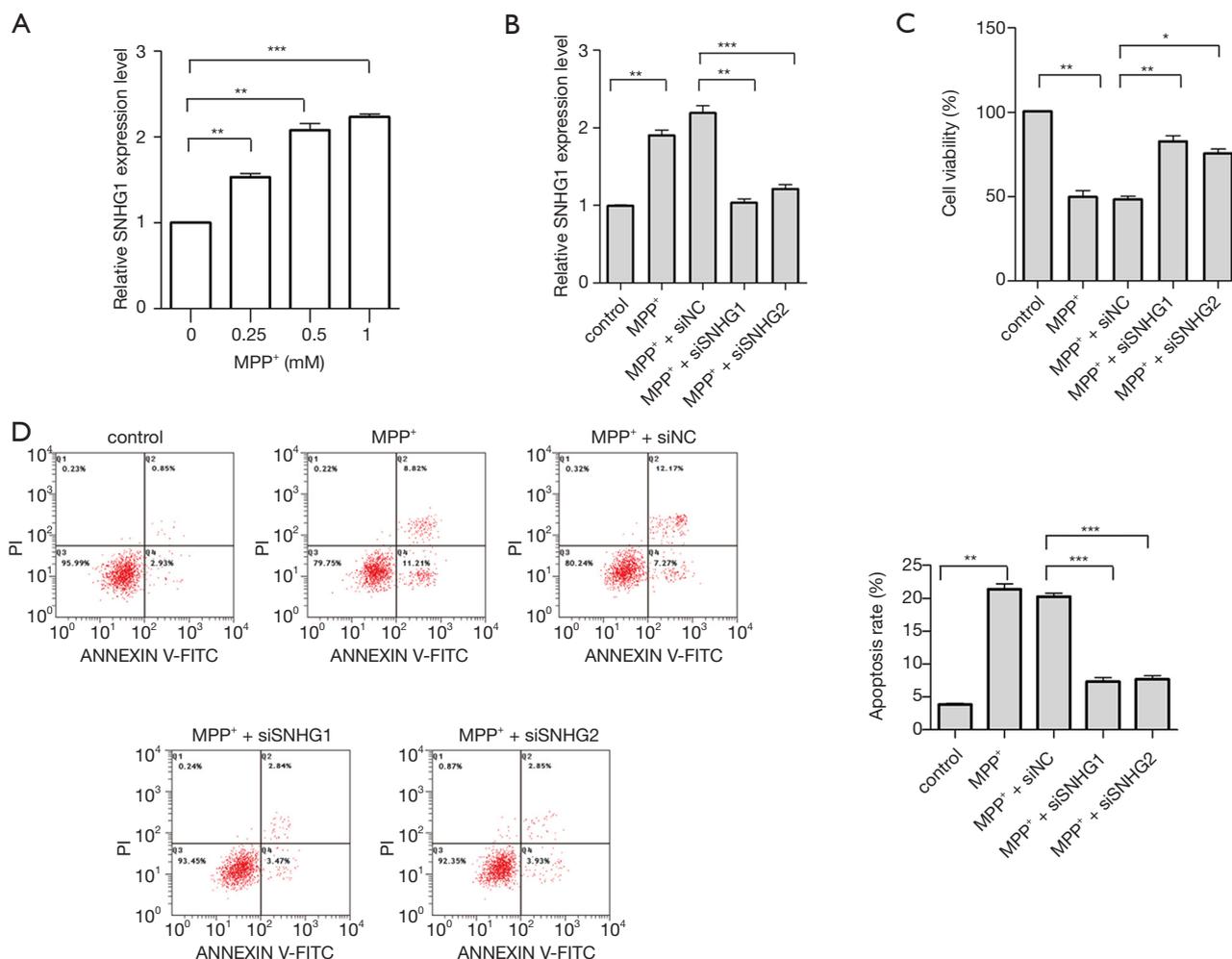


Figure 1 The effects of knock-down of SNHG1 on neuronal cell activity and apoptosis in the PD cell model. (A) The expression levels of SNHG1 in cells treated with different concentrations of MPP⁺. (B) The expression of SNHG1 after SNHG1 knock-down in the PD cell model constructed using 1 mM MPP⁺. (C) Cell viability of PD model cells after SNHG1 knock-down. (D) Apoptotic rate of PD model cells after SNHG1 knock-down, as detected by flow cytometry. *, P<0.05; **, P<0.01; ***, P<0.001. PD, Parkinson's disease; MPP⁺, 1-methyl-4-phenylpyridinium.

expression of SNHG1. After SNHG1 knock-down, the cell activity of the PD model cells increased, while the apoptotic rate decreased (Figure 1B,C,D).

The interaction between SNHG1 and miR-216a-3p

To further explore the role of SNHG1 in neurons in the PD model, we screened miR-216a-3p as the target of SNHG1 in the database (TarBase and miRWalk) (Figure 2A). The luciferase reporter gene experiment was used to verify the interaction between SNHG1 and miR-216a-3p (Figure 2B). The results of qRT-PCR showed that the expression of

miR-216a-3p was upregulated after knock-down of SNHG1 (Figure 2C). Together, the above experimental results suggested that SNHG1 could directly bind to miR-216a-3p to negatively regulate its expression level.

miR-216a-3p alleviated neuronal damage in the PD cell model after SNHG1 knock-down

After confirming the interaction and negative regulatory relationship between SNHG1 and miR-216a-3p, we attempted to establish whether miR-216a-3p was involved in the effect exerted by SNHG1 on neuronal cell activity

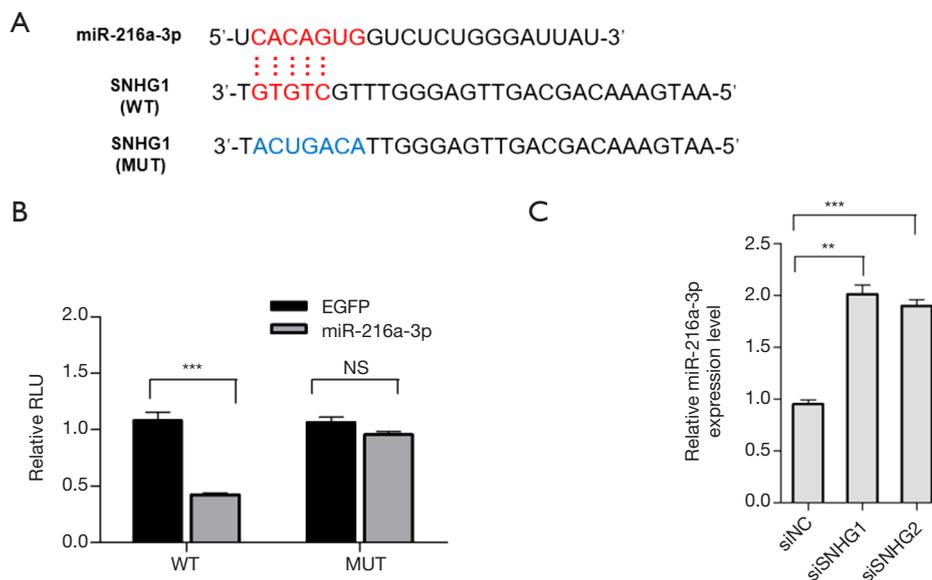


Figure 2 The interaction between SNHG1 and miR-216a-3p. (A) Sequence pairing relationship between SNHG1 and miR-216a-3p. (B) Luciferase reporter gene assay was used to verify the interaction between SNHG1 and miR-216a-3p. (C) The expression level of miR-216a-3p in PD model cells after SNHG1 knock-down. **, $P < 0.01$; ***, $P < 0.001$. PD, Parkinson's disease; NS, no significant.

and apoptosis. In the MPP⁺-treated PD model cells, the expression of miR-216a-3p was downregulated; however, after knock-down of SNHG1, the expression level of miR-216a-3p increased (Figure 3A). However, in cells transfected with anti-miR-216a-3p, miR-216a-3p expression was low even after SNHG1 knock-down. After knock-down of SNHG1, cell activity in the PD model cells increased, while the decline in the apoptotic rate was alleviated (Figure 3B,C,D).

BAX is a target of miR-216a-3p

Combining the predicted sequence of miR-216a-3p with the existing database, we predicted BAX to be a target of miR-216a-3p in PD (Figure 4A). A luciferase reporter gene experiment was used to verify the relationship between miR-216a-3p and BAX, and the experimental results confirmed that BAX was indeed a target of miR-216a-3p in PD (Figure 4B).

BAX reversed the increase in neuronal activity and the decrease in apoptosis in PD model cells when miR-216a-3p was overexpressed

The results of our experiments so far had shown that the

overexpression of miR-216a-3p changed the cell conditions in the PD cell model caused by SNHG1 knock-down. However, whether the mitigation effect of miR-216a-3p could be achieved by regulating its target BAX was unclear. Therefore, we sought to verify this in our next experiment. First, the effective expression of pCEP4-HA-BAX and miR-216a-3p mimics after transfection into cells was verified (Figure 5A,B). Then, BAX was overexpressed in cells also overexpressing miR-216a-3p. The results of qRT-pCR showed that in these cells, the expression of BAX was increased, the cell viability was reduced, and the apoptosis rate was increased compared to cells only overexpressing miR-216a-3p (Figure 5C,D,E).

Discussion

PD, also known as tremor paralysis, is an extremely common neurodegenerative disease, which mostly affects older people (1-4). Since PD was first discovered, many clinical and biological studies have been conducted; however, the exact cause of the pathological changes in PD is still unclear. Numerous researches have shown that PD occurrence is related to environmental and genetic factors working together. Therefore, from the perspective of genetic molecular biology, the transcriptional

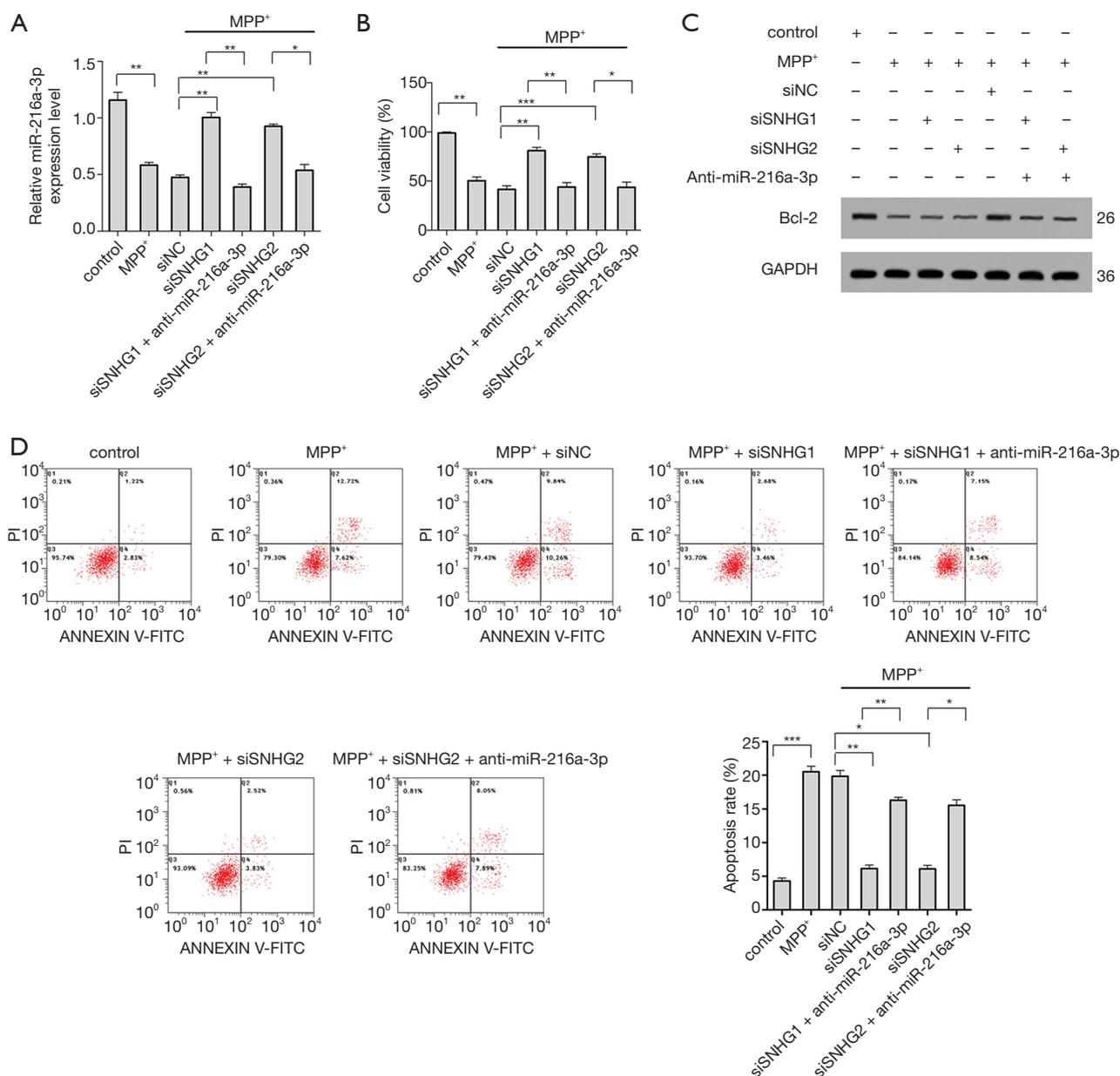


Figure 3 miR-216a-3p can alleviate neuronal damage in PD model cells after SNHG1 knock-down. (A) The expression of miR-216a-3p changes in PD model cells after knock-down of SNHG1, while transfection with anti-miR-216a-3p decreases miR-216a-3p expression. (B) Cell activity in PD model cells transfected with anti-miR-216a-3p after SNHG1 knock-down. (C) SNHG1 was knocked out in PD model cells transfected with anti-miR-216a-3p to decrease the expression of the cancer suppressor Bcl-2. (D) SNHG1 was knocked out in PD model cells transfected with anti-miR-216a-3p to decrease the expression of miR-216a-3p, and the apoptosis rate was detected by flow cytometry. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. PD, Parkinson's disease.

and translational regulation of related genes or genetic molecules plays an important role in the occurrence and development of PD.

Existing studies have shown that lncRNAs are involved

in the development of the brain and in the maintenance of neuronal function and life activities. For instance, lncRNA UCA1 can aggravate the damage to dopaminergic neurons in rats with PD by activating the PI3K/Akt signaling



Figure 4 BAX is a target of miR-216a-3p in PD. (A) The sequence matching relationship between the 3'UTR of BAX and miR-216a-3p. (B) The luciferase reporter gene assay was used to verify BAX as a target of miR-216a-3p in PD. ***, $P < 0.001$. BAX, Bcl-2-associated X protein; PD, Parkinson's disease; NS, no significant.

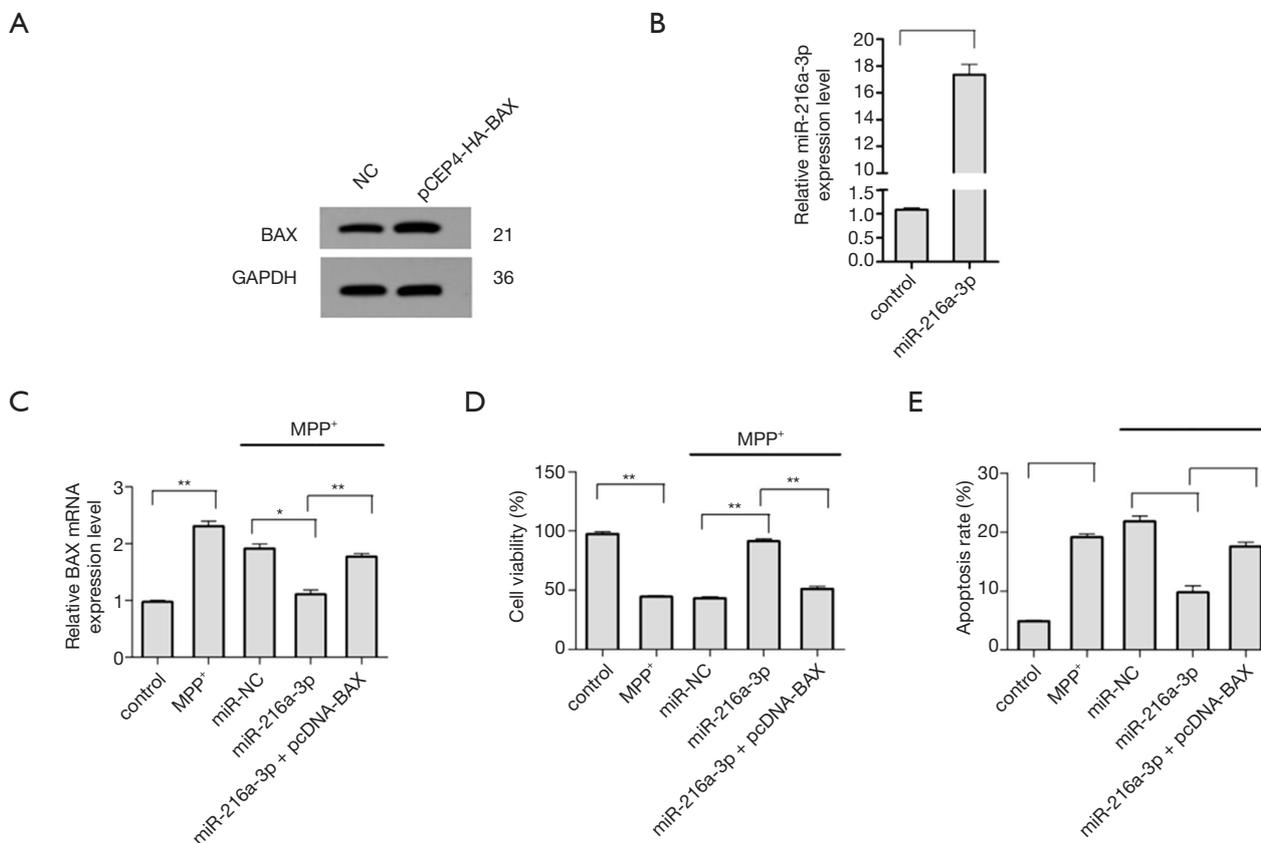


Figure 5 BAX can reverse the increased neuronal activity and decreased apoptotic rate in PD model cells when miR-216a-3p is overexpressed. (A) WB verification of BAX overexpression after pCEP4-HA-BAX transfected cells; (B) qPCR verification of miR-216a-3p overexpression after miR-216a-3p mimics transfected cells. (C) The expression level of BAX when miR-216a-3p was overexpressed in PD model cells simultaneously transfected with BAX. (D) Cell activity when miR-216a-3p was overexpressed in PD model neurons simultaneously transfected with BAX. (E) Apoptotic rate when miR-216a-3p was overexpressed in PD model neurons simultaneously transfected with BAX. *, $P < 0.05$; **, $P < 0.01$. BAX, Bcl-2-associated X protein; PD, Parkinson's disease.

pathway, causing inflammation and oxidative stress, while down-regulating lncRNA HOTAIR can suppress the development of PD by regulating the expression of LRRK2 (11,12). Therefore, lncRNAs have gradually become the

main biomarkers in exploration of the pathogenesis and treatment strategies of PD.

Apoptosis is an important cellular life process which is responsible for maintaining homeostasis in the brain.

Abnormalities in apoptosis have a particular impact on the occurrence and development of PD and are considered to be an important sign of PD-related neuronal degradation (13). Therefore, regulating cell apoptosis may provide new ideas for the effective clinical treatment of PD.

In recent years, studies have shown that the lncRNA SNHG1 may be involved in the pathogenesis of PD (14,15). In the present study, we treated human neuroblastoma cell lines with MPP⁺ to construct a PD cell model, and further studied the role of SNHG1 in the development of PD. Our results demonstrated that the expression of SNHG1 was increased in the PD model cells. Knock-down of SNHG1 inhibited cell viability in the model cells while increasing the apoptotic rate. Through sequence alignment, we predicted the miRNA target of SNHG1 and found that SNHG1 can be used as an auxiliary device for miR-216a-3p; thus, miR-216a-3p became a target molecule of study in this research. In this study, the expression of miR-216a-3p was reduced in PD model cells, and re-expression could reverse the high apoptosis rate and inhibition of cell vitality observed in the PD model. These findings indicate that SNHG1 is an upstream molecule that can adsorb and negatively regulate miR-216a-3p, and that miR-216a-3p can attenuate the effect of SNHG1 knock-down on neurons.

To further explore the specific network roles of SNHG1 and miR-216a-3p in the development of PD, we turned our attention to BAX, as 1 of the targets of miR-216a-3p. BAX, a member of the BAL-2 family, is a regulator of cell apoptosis that participates in various activity relating to neuronal injury, which can lead to neuronal damage and cell apoptosis (16-19). However, there are few studies on its relationship with PD occurrence and development. The results of our research showed that the overexpression of BAX blocked the neuronal damage by miR-216a-3p. At the same time, SNHG1 acted as a coordinator by mediating the regulation of BAX by miR-216a-3p, thereby affecting the activity and apoptosis of neurons in the PD model. These interactions form a SNHG1/miR-216a-3p/BAX molecular regulatory network, which plays a role in the pathogenesis of PD.

In conclusion, the present study has shown that SNHG1 interacts with miR-216a-3p and that BAX is a target of miR-216a-3p in PD. The expression of miR-216a-3p increases in PD model cells following SNHG1 knock-down, while the expression of BAX decreases with miR-216a-3p overexpression. Therefore, the expression of BAX in PD model cells decreases after SNHG1 knock-

down. We have also confirmed that SNHG1 can indirectly regulate the expression of BAX via miR-216a-3p, thereby affecting neuronal damage in PD model cells. Through this study, we have discovered the SNHG1/miR-216a-3p/BAX molecular regulatory network in the pathogenesis of PD, which provides us with strong evidence for further research and treatment of PD. This study has only obtained relevant conclusions in the Parkinson's model of cells, but this molecular regulatory network in animal models is still to be studied. Therefore, there is still a long way to go for the treatment of PD caused by the network-related factors.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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