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Original Article

Small nucleolar RNA host gene 1 silence inhibits the lipopolysaccharide-induced microglial apoptosis and inflammation

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Abstract

Microglia activation is an early mediator of neuroinflammation and a major contributor to spinal damage and motor dysfunction. This study was designed to investigate the role of small nucleolar RNA host gene 1 (SNHG1) on the apoptosis and inflammatory response of microglial cell BV-2 and its underlying molecular mechanism. The C5 lamina contusion-induced mouse model of spinal cord injury (SCI) was constructed. Mouse microglia BV2 was stimulated by lipopolysaccharide (LPS) to establish the in vitro model of SCI. The quantitative reverse transcription polymerase chain reaction method was used to quantify RNA expression levels. Enzyme-linked immunosorbent assays were used to quantify concentrations of inflammatory cytokines. Protein levels were assessed by western blotting, and apoptosis was assessed by flow cytometry. Dual luciferase reporter gene assay and RNA pull-down assay were conducted to investigate the binding relationships between molecules. Upregulation of SNHG1 and downregulation of miR-195-5p were observed in the spinal cords of SCI mouse model. LPS treatment led to elevation of SNHG1 expression in BV2 cells, as well as accelerated apoptosis and inflammation. Evident mitigation of LPS-induced BV2 cell damage was observed after SNHG1 knockdown. MiR-195-5p was identified as a target of SNHG1. Inhibition of miR-195-5p restored the impact of SNHG1 knockdown on cell damage of LPS-treated BV2 cells. Furthermore, miR-195-5p can target activating transcription factor-6 (ATF6). In summary, SNHG1 knockdown ameliorates LPS-induced microglial apoptosis and inflammatory response via the miR-195-5p/ATF6 axis, providing a novel direction for SCI treatment.

Keywords: SNHG1, Molecular mechanism, BV2 microglia, Cell damage, Spinal cord injury.

1. Introduction

Traumatic spinal cord (SC) injury (SCI), as a destructive injury, is the most severe form of neurological damage due to direct or indirect external inducements [1]. Traumatic SCI is characterized by primary mechanical injury to the SC and subsequent secondary injury that may trigger apoptosis and excessive inflammatory responses [2, 3]. The prognosis of SCI is extremely dismal, with patients suffering from limb movement disorders, cognitive loss, and even paralysis in some cases, greatly compromising people's life quality [4]. The effect of the current strategies for SCI treatment remains to be desired. Therefore, seeking the underlying mechanism of SCI development and new markers of therapeutic response in SCI patients is paramount.

Long non-coding RNAs (lncRNAs), as over 200-nucleotide length long non-coding RNAs, can interfere with the occurrence and progression of a wide range of diseases [5]. In recent years, the role played by lncRNAs in SCI has attracted growing attention. For example, literature [6] has found that LncRNA Neat1 can promote post-SCI regeneration by targeting miR-29b. LncRNA small nucleolar RNA host gene 1 (SNHG1), as a well-known LncRNA, has been reported to be critical in multiple diseases. Xu M et al. [7] found that SNHG1 interfered with colorectal cancer cell growth through targeting miR-154-5p. Another research [8] found that SNHG1 promoted neuronal damage in a cellular model of Parkinson's disease via miR-181a-5p/CXCL12 axis. However, there is no detailed research regarding SNHG1's specific biological mechanism in SCI. Through bioinformatics analysis, we found the presence of binding loci between SNHG1 and miR-195-5p, as well as down-regulated miR-195 in SCI rats as indicated by previous studies [9]. Hence, we speculated that SNHG1 might influence microglia after SCI by sponging miR-195-5p.

In this study, we investigated SNHG1 expression in SCI mice, as well as its function on microglia and relevant mechanisms, in the hope of providing a novel target direction for SCI diagnosis and therapy.

2. Materials and Methods

2.1. Establishment of a mouse model of traumatic SCI

Adult female C57bl/6J mice were purchased from Vital

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River Center (Beijing, China) and stochastically assigned to SCI and sham groups, with 10 mice in each group. Before surgery, mice were anesthetized with pentobarbital through intraperitoneal injection. In the SCI group, the C5 lamina was incised along the neck to expose the spine, and then the SC was hit with an impactor, followed by hemostasis and layer-by-layer sutures. The C5 lamina of sham group mice was not impacted. The mice were narcotized a week after SCI for SC tissue collection for subsequent experiments. The Animal Research Ethics Committee of the First Affiliated Hospital of Harbin Medical University ratified this research, and all experiments followed the "National Institutes of Health" guidelines for the Care and Use of Laboratory Animals. The Basso, Beattie, and Bresnahan locomotor rating scale (BBB) was adopted to evaluate mouse hind limb motor function. The mice were placed on a test platform to observe the joint motion of the lower limbs, gait, trunk stability, paws fine motor, tail position and physical coordination. The score ranged from 0 points (complete paralysis without visible hindlimb movements) to 21 points (persistent palm movement, coordinated gait, grounding toes, stable trunk, rising tail, active paw position always parallel to the body during activity and completely normal activity).

2.2. Cell model establishment and transfection

BV2 cells purchased from Procell Life Science & Technology Co., Ltd. (Wuhan, China) were stimulated with 100 ng/mL lipopolysaccharide (LPS) for 24 h and then cultivated in a 10% fetal bovine serum and 100 g/ml penicillin/streptomycin-supplemented RPMI-1640 medium (Invitrogen, USA). They were then incubated under the conditions of 37℃ and 5% CO_2 and were collected for transfection when the cells grew to 80% adherence. Then, with Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA), BV2 cells were treated with transfections with the following vectors all synthesized by Genepharma (Shanghai, China): SNHG1 small interfering RNA (si-SNHG1), siRNA control (si-NC), miR-195-5p mimics and its control (NC), as well as miR-195-5p inhibitor and anti-NC. Six hours later, BV2 cells were intervened by 100 ng/mL LPS (Solarbio).

The TRIzol reagent (Invitrogen, CA, USA) was used for isolating total RNA from tissue and cell for cDNA synthesis by PrimeScript RT reagent (Takara), followed by real-time PCR using the SYBR Green Master Mix II and ABI 7900 Fast real-time PCR system (ABI, USA). The reaction system and reaction conditions were operated in accordance with the manufacturer's recommendations. GAPDH and U6 acted as controls in this experiment, and the $2^{-\Delta\Delta CT}$ method was utilized for quantification. Each test ran three times independently.

2.3. Enzyme-linked immunosorbent assay (ELISA)

ELISA kits quantified TNF-α, IL-1β and IL-6 contents in cells in compliance with the manuals. After determining the $absorbance_{450\ nm}$ with a microplate reader (Bio-RAD, USA), the above inflammatory cytokines' concentrations were quantified according to the standard curve.

2.4. Western Blotting (WB)

The cells gathered were lysed using RIPA (Beyotime, Beijing, China), and the protein concentration was measured via a bicinchoninic acid (BCA) protein quantification kit (Beyotime Biotechnology Inc., Shanghai, China). Then came SDS-polyacrylamide gel (10%) separation and transfer of proteins onto a polyvinylidene fluoride (PVDF) membrane. The membrane was then placed at room temperature and given 5% skim milk powder blocking that lasted for 2 h, and the subsequent overnight incubation (4°C) with I antibodies: activating Transcription Factor 6 (ATF6; 1: 1000; ab227830; Abcam), GAPDH (1: 1000; ab9485; Abcam). Next, HRP-bound anti-rabbit IgG (ab6721, Abcam) diluted at 1: 2000 was added to incubate at an ambient temperature for 2 hours. After 3 washes with TBST buffer, the conjugated secondary antibody was tested by the enhanced chemiluminescence (ECL) system (Pierce Biotechnology, USA). GAPDH served as a control in this experiment.

2.5. Apoptosis assay

After 0.25% trypsin digestion and two PBS rinses, the transfected cells were immersed in 100μL binding buffer to make into a $1*10^6$/mL suspension. After successive addition of Annexin V-FITC and PI, the mixture was incubated in darkness at an ambient temperature for 5 minutes, after which apoptotic cells were analyzed using an FC500 flow cytometer equipped with Cell Quest 3.0 software (BD Biosciences, USA).

2.6. Dual luciferase reporter (DLR) gene assay

Through starBase (https://starbase.sysu.edu.cn/) prediction, we found the presence of targeted binding site between SNHG1, miR-195-5p, and ATF6. After amplification of oligonucleotides containing SNHG1 and ATF6 target sequences, they were then cloned into pmirGLO plasmid (WT). The pmirGLO-SNHG1-3'UTR wild type (Wt), pmirGLO-ATF6-3'UTR-Wt, pmirGLO-SNHG1-3'UTR (Mut), and pmirGLO-ATF6-3'UTR-Mut were constructed and transferred to luciferase reporter gene downstream, respectively, for sequencing and identification. Lipofectamine 2000 was responsible for co-transfecting luciferase reporter plasmids with miR-195-5p-mimic or miR-NC into 239T cells. 24 h after culture, cells were gathered to measure luciferase activity using a luciferase detection kit, and the results were statistically analyzed.

2.7. RNA pull-down assay

The biotin-labeling of miR-195-5p was performed using Biotin RNA labeling Mix (Roche, Mannhei, Germany). MiR-195-5p was labeled with biotin and incubated with streptavidin beads (Thermo, CA, USA) at 4 °C overnight. The mixture was then centrifuged at 3000 rpm for 1 min and washed with wash buffer three times. A total of 2×10^7 cells were lysed. The bead-biotin complex was added to the lysates and incubated at room temperature for 1 h. After washing, the RNA that was bound to the bead was captured and extracted with Trizol for the subsequent qPCR assay.

2.8. Statistics and methods

SPSS19.0 and GraphPad Prism 8.0 were used for data analysis and mapping, respectively. Bio-repeats were run in triplicate. To identify statistical significance that was supposed to be indicated by $P<0.05$, the independent t-test, single factor analysis of variance, LSD-t, and repeated ANOVA were employed for inter-group, inter-group, post pairwise, and multi-time point comparisons, respectively.

Bonferroni was used for post-hoc tests.

3. Results

3.1. SCI mice show up-regulated SNHG1 and lowly expressed miR-195-5p

We utilized the BBB method to evaluate the post-SCI recovery of motor function in all mice. The results showed the obvious reduction of hind limb motor activity of SCI mice, with decreased BBB scores compared with the sham group (Figure 1A), suggesting the successful establishment of the mouse SCI model. Then, we used RT-qPCR to detect SNHG1 and miR-195-5p in SC tissues in both groups. It showed up-regulated SNHG1 and under-expressed miR-195-5p in the SC tissue of the SCI group versus sham group (Figure 1B-C). We then measured the contents of inflammatory factors in SCI mice, including TNF-α, IL-1β and IL-6, using ELISA, and found their statistically enhanced levels in SCI mice versus sham mice (Figure 1D-F). Overall, SNHG1 showed high expression and miR-195-5p showed low expression in SCI mouse model.

3.2. SNHG1 knock-down eliminates LPS-mediated BV2 apoptosis and inflammation

After knocking down SNHG1 in BV2 cells, we utilized LPS to treat the transfected cells to explore the role played by SNHG1 in LPS-stimulated microglia. Based on RT-qPCR analysis, LPS inducement led to statistically elevated SNHG1 in BV2 cells, but knocking down SNHG1 reversed this phenomenon (Figure 2A); SNHG1 knockdown greatly inhibited LPS-induced apoptosis of BV2 cells, as indicated by the flow cytometry analysis (Figure 2B); we further observed by ELISA that knocking down SNHG1 restored the up-regulation of TNF-α, IL-1β and IL-6 in LPS-induced BV2 (Figure 2C-E). Thus, SNHG1 knockdown can alleviate LPS-induced BV2 cell apoptosis and inflammation.

3.3. SNHG1 is a molecular sponge of miR-195-5p in BV2 cells

We found through online software starbase 2.0 analysis the targeted binding loci between miR-195-5p and SNHG1 (Figure 3A). Further, it was found by DLR assay that the SNHG1-wt luciferase activity was obviously inhibited by miR-195-5p-mimic; nut the SNHG1-mut luciferase activity had no obvious change (Figure 3B); increased miR-195-5p-WT and SNHG1 enrichment versus miR-NC and miR-195-5p-MUT was identified by the RNA pull-down experiment (Figure 3C). Thus, we proved that SNHG1 can bind to miR-195-5p in BV2 cells.

3.4. SNHG1 affects LPS-induced BV2 cell damage via sponging miR-195-5p

We treated LPS-induced BV2 with miR-195-5p inhibitor+si-SNHG1 co-transfection to further confirm that SNHG1 can affect LPS-induced BV2 cell damage via targeting miR-195-5p. Obviously up-regulated miR-195-5p in LPS-induced BV2 cells was observed after si-SNHG1 transfection, but this effect was reversed by the transfection of miR-195-5p inhibitor (Figure 4A). MiR-195-5p inhibitor also reversed Si-SNHG1 inhibited LPS-induced apoptosis of BV2 cells (Figure 4B) and up-regulated TNF-α, IL-1β, and IL-6 (Figure 4C-E). Thus, SNHG1 can affect LPS-induced BV2 cell damage via sponging miR-195-5p.

3.5. miR-195-5p specifically suppresses ATF6 in BV2

For the purpose of investigating the downstream mechanism of miR-195-5p, we predicted via Targetscan (https://www.targetscan.org/vert_72/) to find the binding loci between miR-195-5p and ATF6 (Figure 5A). A DLR

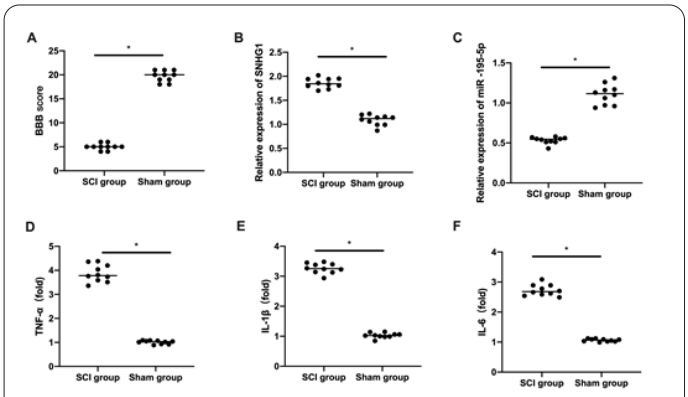

Fig. 1. SCI mice show up-regulated SNHG1 and lowly expressed miR-195-5p. A: BBB score of SCI mice; B: SNHG1 expression; C: miR-195-5p expression; D: TNF-α expression; E: IL-1β expression; F: IL-6 expression. * P<0.05.

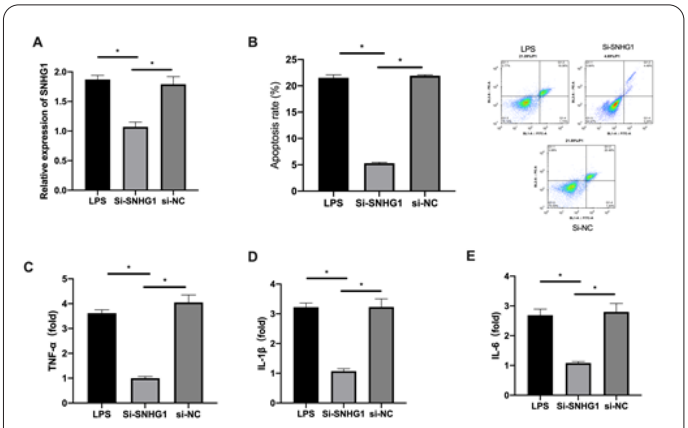

Fig. 2. SNHG1 knock-down eliminates LPS-mediated apoptosis and inflammation of BV2 cells. A: The knock-down efficiency of SNHG1; B: Impact of SNHG1 knock-down on LPS-mediated BV2 cell apoptosis; C-E: Impact of SNHG1 knock-down on TNF-α, IL-1β, and IL-6 in LPS-mediated BV2. * P<0.05.

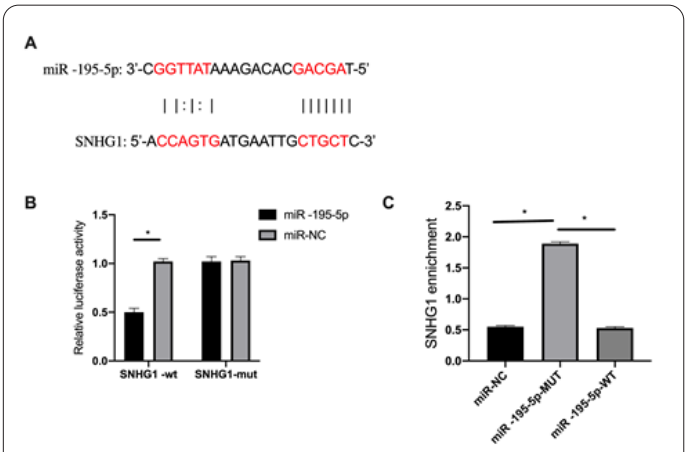

Fig. 3. SNHG1 is a molecular sponge of miR-195-5p in BV2. A-B: DLR assay confirmed the binding relationship between SNHG1 and miR-195-5p; C. SNHG1 and miR-195-5p enrichment capacity determined by RNA pull-down. * P<0.05.

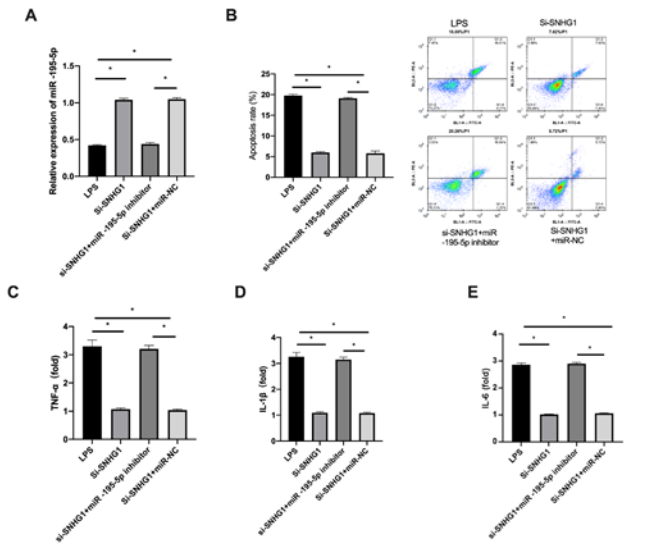

Fig. 4. SNHG1 affects LPS-induced BV2 cell damage by sponging miR-195-5p. A: Influence of miR-195-5p inhibitor + si-SNHG1 co-transfection on miR-195-5p levels; B: Influence of co-transfection of miR-195-5p inhibitor + si-SNHG1 on LPS-induced apoptosis of BV2 cells; C-E: Influence of co-transfection of miR-195-5p inhibitor + si-SNHG1 on inflammatory cytokines in BV2 cells with LPS inducement. * P<0.05.

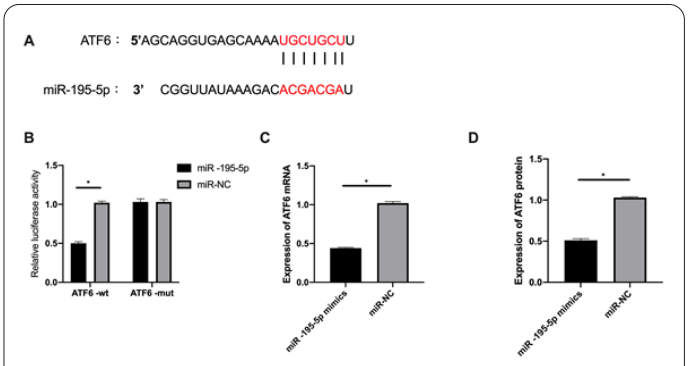

Fig. 5. miR-195-5p can specifically inhibit ATF6 in BV2 cells. A-B: Targeting relationship between miR-195-5p and ATF6 identified by DLR assay; C: Impact of overexpressing miR-195-5p in BV2 cells on ATF6 mRNA; D: Impact of overexpressing miR-195-5p in BV2 cells on ATF6 protein. * P<0.05.

assay was further used to determine their relationship. It showed that miR-195-5p mimics notably lowered the luciferase activity of ATF6-WT group cells but had no notable impact on the luciferase activity in ATF6-MUT group (Figure 5B). Subsequently, we utilized qRT-PCR and WB to measure ATF6 expression to observe the impact of miR-195-5p on ATF6 in BV2, and evidently decreased ATF6 at both mRNA and protein levels were found following miR-195-5p mimics transfection (Figure 5C-D). Overall, ATF6 could be targeted by miR-195-5p.

4. Discussion

It is well established that lncRNAs are crucial mediators in SCI, in which LPS-stimulated microglia are extensively used to investigate nosogenesis [10]. A mouse SCI model was successfully built in the present research, with which we found evidently elevated SNHG1 in SC tissues of SCI mice and under-expressed miR-195-5p. Besides, a SCI cell model was built by LPS stimulation of BV2 cells, and it was found that knocking down SNHG1 mitigated BV2 cell damage induced by LPS via regulating miR-195-5p/ATF6 axis.

In the past, SNHG1 was mostly studied as an oncogene. For example, a study [11] found that SNHG1 could interfere with esophageal squamous cell carcinoma progression through the miR-204/HOXC8 axis. Another study [12] indicated that SNHG1 was able to suppress p53 expression and promoted liver cancer development by binding DNMT1. In recent years, SNHG1's effects on microglia have also been gradually unveiled. For example, Dong J et al. [13] reported that SNHG1 accelerated LPS-induced microglial activation and inflammation by targeting miR-181b. Consistently, we found a marked increase of SNHG1 in BV2 under LPS inducement, and enhanced inhibition of cell apoptosis following SNHG1 knockdown. Furthermore, we observed the decreased contents of inflammatory factors in LPS-activated BV2 after SNHG1 knockdown, which indicated that knocking down SNHG1 weakened BV2 cell inflammation induced by LPS. Overall, SNHG1 knockdown accelerated the recovery from SCI by inhibiting apoptosis and inflammation. In addition to the above data, a previous study [14] proposed that SNHG1 could attenuate microglial activation through down-regulating miR-329-3p in an in vitro model of cerebral infarction, which is also consistent with our observations.

LncRNAs are known to exert their functions on cells by acting as ceRNAs of miRNAs [15]. In order to further explore the possible mechanisms of SNHG1 in SCI, we predicted that SNHG1 had binding loci with miR-195-5p through the online database Starbase and confirmed the targeting relationship between them by DLR and RNA pull-down assays. As a member of miRNAs, miR-195-5p has been indicated by previous research to be essential in tumor diseases. For example, the research by Liu X et al. [15] found the ability of miR-195-5p to prevent cervical carcinoma from malignant progression through targeting YAP1. Another study [16] exhibited that miR-195-5p could exert a tumor suppressor function in human lung carcinoma cells via targeting TrxR2. In recent years, its role in the body's inflammatory response has also received attention. For example, miR-195-5P was shown to reduce cerebral ischemia-reperfusion injury via modulating PTEN-AKT axis [17]. However, no research has been done on its role in SCI. We treated LPS-induced BV2 with miR-195-5p inhibitor + si-SNHG1 co-transfection to further confirm that SNHG1 can influence BV2 cell damage induced by LPS via targeting miR-195-5p. The results showed a great decrease in LPS-induced BV2 post si-SNHG1 transfection, while miR-195-5p inhibitor reversed the si-SNHG1-suppressed LPS-induced inflammation and apoptosis in BV2 cells. Hence, SNHG1 influences BV2 cell damage induced by LPS through regulating miR-195-5p.

To further probe into the downstream mechanism, we predicted by Targetscan to find the presence of binding loci between miR-195-5p and ATF6. ATF6 is a type II transmembrane protein in the endoplasmic reticulum (ER), and ATF6 target gene can enhance ER homeostasis and contribute to cell protection [18]. ATF6, which has been reported to be up-regulated in SCI rats, can effectively alleviate SCI-induced neuronal apoptosis and inflammation by regulating ER stress [19]. To get a deeper understanding of the connection between ATF6 and miR-195-5p, we first verified their relationship with DLR assay. Moreover, we found reduced mRNA and protein levels of ATF6 after miR-195-5p mimics transfection, and their ele-

vated levels following miR-195-5p inhibitor transfection, further demonstrating that miR-195-5p may affect apoptosis and inflammatory response of BV2 cells by targeting ATF6. Previous literature [20] has found that knockdown of RyR2 can down-regulate ATF6, thus alleviating mitochondrial dysfunction and endoplasmic reticulum stress after SCI. This may be another upstream mechanism of ATF6 in SCI, which needs further analysis.

5. Conclusion

In a word, the present paper found upregulated SNHG1 in LPS-activated BV2 cells and SCI mice. Knocking down SNHG1 ameliorated microglial apoptosis and inflammation induced by LPS via modulating the miR-195-5p/ATF6 axis. Our research reveals the protective role of SNHG1 knockdown in SCI, deepening our understanding of SCI management at the molecular level and providing novel ideas for SCI therapy.

Informed consent

The authors report no conflict of interest.

Availability of data and material

We declared that we embedded all data in the manuscript.

Authors' contributions

SH conducted the experiments and wrote the paper; GJ and LX analyzed and organized the data; SM conceived, designed the study and revised the manuscript.

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