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Effects of LncRNA GAS5/miR-137 general anesthesia on cognitive function by TCF4 inflammatory bodies in patients undergoing lumbar spinal canal decompression

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Abstract

Lumbar spinal stenosis is a common orthopedic disease in clinical practice at present. Postoperative cognitive dysfunction (POCD) refers to the phenomenon of impaired memory. However, whether long noncoding RNA (LncRNA) GAS5 contributes to the mechanism of cognitive function in undergoing lumbar spinal canal decompression remains unknown. Thus, the present study investigated the precise details of LncRNA GAS5 involvement in Postoperative cognitive dysfunction of patients undergoing lumbar spinal canal decompression. Patients undergoing lumbar spinal canal decompression with cognitive function and Normal healthy volunteers were obtained. C57BL/6 mice were maintained with a 2% concentration of sevoflurane in 100% oxygen at a flow rate of 2 L minute-1 for 4 hours. LncRNA GAS5 gene expression were up-regulated in patients undergoing lumbar spinal canal decompression. In mice model, LncRNA GAS5 gene expression also increased. LncRNA GAS5 promoted neuroinflammation in vitro model. LncRNA GAS5 raised cognitive impairment and increased neuroinflammation in mice model. LncRNA GAS5 suppressed miR-137 in vitro model. MiR-137 reduced neuroinflammation in vitro model. MiR-137 suppressed TCF4 protein expression in vitro model. Transcription factor TCF4 activates the expression of bHLH. Taking together, this experiment provide the first experimental and clinical evidence that LncRNA GAS5/miR-137 promoted anesthesia-induced cognitive function to increase inflammatory bodies in patients undergoing lumbar spinal canal decompression, suggesting it may be a biomarker of POCD and a potential therapeutic target for POCD.

Abbreviations: FISH = fluorescence in situ hybridization, LncRNA = long noncoding RNA, POCD = postoperative cognitive dysfunction.

Keywords: LncRNA GAS5, miR-137, postoperative cognitive dysfunction, TCF4

1. Introduction

Lumbar spinal stenosis is a common orthopedic disease in clinical practice at present.[1] Compression of the spinal cord can cause such irreversible pathological changes as numbness of the lower limbs, weakness in walking, paralysis and incontinence of urine and feces, which seriously impacts the patients' quality of life.[2–4]

Surgery is the main treatment for lumbar spinal stenosis, while epidural anesthesia and general anesthesia are the main intraoperative anesthesia methods.[5] However, there is some controversy about which anesthesia in conjunction with surgical treatment yields better results.[6,7]

Postoperative cognitive dysfunction (POCD) refers to the phenomenon of impaired memory and slow cognitive recovery of patients after surgery.[8] This condition is common in elderly postoperative patients, with a high incidence.[9] It can easily lead to Alzheimer's disease if not treated in time, affecting the socialization and communication of patients after hospital discharge.[10] Existing research has shown that the depth of anesthesia has an impact on the incidence of postoperative POCD. Some scholars believe that low depth of anesthesia is beneficial to the recovery of postoperative cognitive function.[11]

Long non-coding (lnc) RNAs refer to a class of non-protein-coding transcripts longer than 200 nt, which exert important functions in the cellular and disease processes, including differentiation of embryonic stem cells, development of brain functions, chromatin remodeling, as well as cancer and

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

All patients were informed and signed informed consent voluntarily. This study was approved by the ethics committee of the Second Affiliated Hospital of Hainan Medical College and complied with the guidelines outlined in the declaration of Helsinki were followed. The written consent was received from all participants.

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neurodegenerative diseases.[12] Research has demonstrated that some lncRNAs play a role in transcriptional and epigenetic mechanisms by aggregating transcription factors and chromatin modification complexes at specific genome binding sites.[13–15]

MiRNAs are involved in diverse physiological and pathological processes in the central nervous system, including neuronal plasticity, apoptosis, lipid metabolism and mitochondrial function.[16–18] Thus, the present study investigated the precise details of long noncoding RNA (LncRNA) GAS5 involvement in Postoperative cognitive dysfunction of patients undergoing lumbar spinal canal decompression.

2. Materials and Methods

2.1. Clinical trial

Patients undergoing lumbar spinal canal decompression with cognitive function and Normal healthy volunteers were obtained at The Second Affiliated Hospital of Hainan Medical College from May 2019 to November 2019. The written informed consents were obtained from all the subjects and this study was approved by the Ethics Committee of The Second Affiliated Hospital of Hainan Medical College. All the samples were immediately stored at – 80°C. No patients had received chemotherapy or pre-operative radiotherapy.

2.2. Mice experiment

C57BL/6 mice were housed in barrier cages under controlled environmental conditions (22–23 °C, 12/12 hours of light/dark cycle, 55% ± 5% humidity). At model group, C57BL/6 mice were received with LPS (30 mg/kg, i.p.,). At sham group, C57BL/6 mice were received with normal saline. After induction sepsis, mice was recorded survival rate at every day for 3 days. At 3 days, all mice were anaesthetized using 5% sevoflurane in a mixture of O_2 and N_2 (50%/50%), maintained with a 2% concentration of sevoflurane in 100% oxygen at a flow rate of 2 L minute-1 for 4 hours by an anesthetic system (Prisma SP Alpa, Penlon Limited, Oxon, UK), and then sacrificed using cervical spondylectomy.

2.3. Lentivirus injection

The lentiviral vectors carrying LncRNA GAS5 and a negative controlRNA (Control) were designed and chemically synthesized by Hanyin Biotechnology Limited Company (Shanghai, China). The constructs were diluted to a total volume of 100 μL containing 4 × 107 TU (transducing units) and administered into the mice through intracerebral injection. The sequences of LncRNA GAS55'-CAAAAAAA GGAAAATTCAGA GAGTAACTGA-3' and 5'- AGACACTG TTTTAAAAAAAAAA-3'; Actb forward, 5'-TCACTATCG GCAATGAGCGG-3'; reverse, 5'-TTGGCTACAA CTACAGGG CT-3'. After injection at 48 hours, mice were anaesthetized using 5% sevoflurane in a mixture of O_2 and N_2 (50%/50%), maintained with a 2% concentration of sevoflurane in 100% oxygen at a flow rate of 2 L minute-1 for 4 hours by an anesthetic system (Prisma SP Alpa, Penlon Limited, Oxon, UK), and then sacrificed using cervical spondylectomy.

Morris water maze test. Every experiment mice was trained twice per day and performed blindly for 5 days. Swimming was video tracked, and latency, path length, swim speed, and cumulative distance from the platform were recorded. Mean swim latency for every experiment rat was evaluated at each day. After a probe trial, the mean time spent in the correct quadrant containing the platform and the mean number of time that mice crossed the former platform position during 120 seconds were performed.

Hematoxylin and eosin (HE) staining. The brain tissues were removed, and the cerebral hemisphere was separated at the ice, immediately fixed with 4% paraformaldehyde for 24 hours. The tissues were paraffn-embedded, and serial coronal sections (10 μM) were cut behind the optic chiasm. Sections was stained with hematoxylin and eosin.

2.4. Quantitative PCR

The total RNA was extracted from serum and cell samples using a TRIZOL reagent (Life Technologies Inc.). qRT-PCR assays were performed using Light Cycler® 480 SYBR Mix (Roche, Germany) using LightCycler® 480 real-time PCR system. The expression levels of mRNA was normalized to the GAPDH expression using the 2–ΔΔct method.

2.5. Microarray analysis

Total RNA was extracted from serum samples, and the amount of RNA was quantified by use of NanoDrop 1000. Total RNA of each sample was used for reverse transcription using an Invitrogen SuperScript double stranded cDNA synthesis kit. Double-stranded cDNA was executed with a NimbleGen 1-color DNA labeling kit and then executed for array hybridization using NimbleGen hybridization system and washing with the NimbleGen wash buffer kit. Axon GenePix 4000B microarray scanner (Molecular Devices) was used for scanning.

2.6. Cell culture and RNA interference

Human neuroglioma cells H4 cells were cultured in RPMI 1640 medium (Gibco, Carlsbad, CA) supplemented with 10% fetal calf serum (FCS, Gibco, Carlsbad, CA) in a humidified atmosphere of 5% CO_2 at 37°C. Plasmids were transfected into PBMCs using Lipofectamine 2000. After 48 hours of transfection, H4 cells were gassed with 4.1% sevoflurane for 6 hours.

2.7. ELISA kits

The IL-1β, IL-6, INF-γ and TNF-α levels were performed according to the instructions of the ELISA kit (Beyotime Institute of Biotechnology, China). The absorbance value was quickly read using the microplate reader at a detection wavelength of 450 nm.

2.8. Western blot analysis

Total protein was extracted from lung samples or cell samples using Radio-Immunoprecipitation Assay and PMSF reagent (Beyotime, Beijing, China). Protein lysates were separated based on their molecular weight on SDS/PAGE gels and transferred onto a Polyvinylidene Fluoride (PVDF, Millipore) membrane. The membrane was blocked with nonfat-milk (5%) for 2 hours at room temperature and incubated with ant-TCF4 antibody, anti-bHLH antibody and anti-β-actin antibody at 4°C overnight. Then first antibodies were removed and TBST wash membrane using TBST. Membrane were incubated with the secondary antibody for 2 hours at room temperature. The bound antibodies were detected using enhanced chemiluminescence with β-actin used as a control.

2.9. Luciferase reporter assay

HEK293T cells were used to measure luciferase reporter. After 48 hours transfection with miR-137 mimics or inhibitor, 500 ng pcDNA3.1 vector or pcDNA3.1- LncRNA GAS5, along with 1 ng pRL-TK and 200 ng pGL3- TCF4 plasmid, HEK293T cells were harvested for luciferase activity assessment using a dual-luciferase reporter assay system (Promega).

2.10. Subcellular location analysis

RNA was isolated from nucleus and cytoplasmic fractions using PARIS Kit (Invitrogen, Carlsbad, CA) following the manufacturer's protocol. The RNA of nuclear and cytoplasmic fractions were eluted and then detected using RT-qPCR. For the Fluorescence in situ hybridization (FISH), Cy3-labeled LncRNA GAS5 probes and FAM-labeled miR-137 probes were synthesized by GenePharma (Shanghai, China). FISH was performed using a FISH kit (GenePharma) according to the manufacturer's instructions. Nuclear were stained by DAPI. The images of was obtained using a Zeiss Axioplan 2 fluorescent microscope (carl Zeiss AG, Oberkochen, Germany) and analysis was performed using Image-pro plus 6.0 (Media Cybernetics, Inc., Rockville, MD) software.

2.11. Statistical analysis

Graphad Prism 6 was used for the statistical analysis. All values are expressed as means ± SEM unless specified. $P < .05$ was considered statistically significant. The differences between groups were analyzed using Student's *t*-test.

3. Results

LncRNA GAS5 expression in patients undergoing lumbar spinal canal decompression.

We firstly measured that the expression levels of lncRNA GAS5 in patients undergoing lumbar spinal canal decompression. We collected patients undergoing lumbar spinal canal decompression (n = 12, Fig. 1A). LncRNA GAS5 gene expression were up-regulated in patients undergoing lumbar spinal canal decompression (Fig. 1A). In mice model, LncRNA GAS5 gene expression also increased (Fig. 1B). Taken together, these results suggested that LncRNA GAS5 played an repair factor in anesthesia-induced cognitive impairment.

3.1. LncRNA GAS5 promoted neuroinflammation in vitro model

The experiment determined that the effects of LncRNA GAS5 on neuroinflammation in model of anesthesia-induced cognitive impairment. LncRNA GAS5 plasmid the expression of LncRNA GAS5 in vitro model (Fig. 2A). Si- GAS5 mimics reduced lncRNA GAS5 in vitro model (Fig. 2B). Over-expression of lncRNA GAS5 induced IL-1β, IL-6, INF-γ and TNF-α levels in vitro model (Fig. 2C–2F). Down-regulation of lncRNA GAS5 reduced IL-1β, IL-6, INF-γ and TNF-α levels in vitro model (Fig. 2G–2J). Taken together, our data suggest that lncRNA GAS5 promoted neuroinflammation in vitro model.

3.2. LncRNA GAS5 raised cognitive impairment and increased neuroinflammation in mice model

We examined that the function of lncRNA GAS5 in cognitive impairment and neuroinflammation in mice model. LncRNA GAS5 increased freezing times, latency times and immobility, and reduced time spent and BDNF levels in target quadrant in mice model (Fig. 3A–3F). LncRNA GAS5 increased IL-1β, IL-6, INF-γ and TNF-α levels in hippocampal tissue of mice model (Fig. 3G–3J). Furthermore, data suggests that LncRNA GAS5 raised cognitive impairment and increased neuroinflammation in mice model.

3.3. LncRNA GAS5 suppressed miR-137 in vitro model

The study confirmed that mechanism of LncRNA GAS5 in vitro model. Subcellular analysis demonstrated that lncRNA GAS5 was primarily located in the cytoplasmic portion, suggesting the potential post-transcriptional regulation (Fig. 4A). Online bioinformatics tools were used to analyze miRNAs might effectively interact with lncRNA GAS5, miR-137 may be a target spot for anesthesia-induced cognitive impairment (Fig. 4B). The subcellular location analysis was measured using RNA-FISH and results demonstrated that lncRNA GAS5 and miR-137 were both mainly distribute in cytoplasm (Fig. 4C). Subsequently, the wild type (WT) and corresponding mutant (Mut) of lncRNA GAS5 were constructed targeting miR-137. Moreover, luciferase reporter assay illustrated that lncRNA GAS5 wild type closely correlated with miR-137 (Fig. 4D–4E). Over-expression of lncRNA GAS5 suppressed miR-137 expression levels in vitro model (Fig. 4F). Down-regulation of lncRNA GAS5 increased miR-137 expression levels in vitro model (Fig. 4G). In conclusion, these finding indicate that LncRNA GAS5 suppressed miR-137 in vitro model of anesthesia-induced cognitive impairment.

3.4. MiR-137 reduced neuroinflammation in vitro model

Furthermore, we examined that the function of miR-137 affected anesthesia-induced cognitive impairment. MiR-137 plasmid the expression of miR-137 in vitro model (Fig. 5A). Si- miR-137 mimics reduced miR-137 in vitro model (Fig. 5B). Over-expression of miR-137 reduced IL-1β, IL-6, INF-γ and TNF-α levels in vitro model (Fig. 5C–5F). Down-regulation of miR-137 increased IL-1β, IL-6, INF-γ and TNF-α levels in vitro model (Fig. 5G–5J). Taken together, our data suggest that miR-137 reduced neuroinflammation in vitro model.

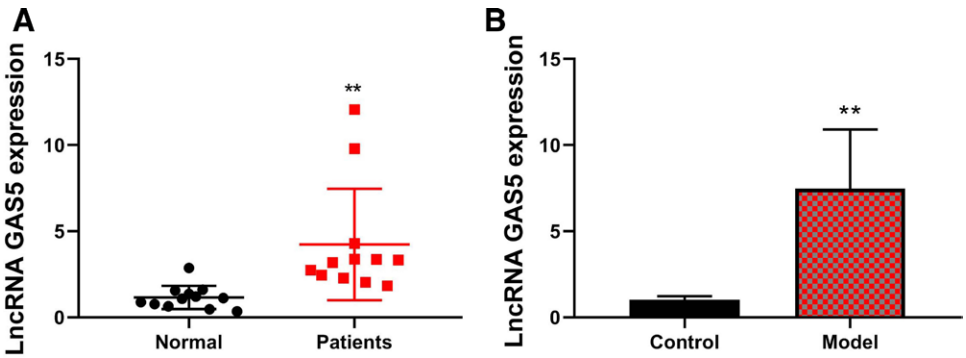

Figure 1. LncRNA GAS5 expression in patients undergoing lumbar spinal canal decompression. LncRNA GAS5 expression level in patients undergoing lumbar spinal canal decompression (A); LncRNA GAS5 expression level in mice with sevoflurane (B). Normal, normal volunteer group; patients, patients with undergoing lumbar spinal canal decompression; Sham, sham control group; model, mice with sevoflurane; Data were showed as mean ± SD. $^{**}P < .01$ compared with normal volunteer group or sham control group. LncRNA = long noncoding RNA.

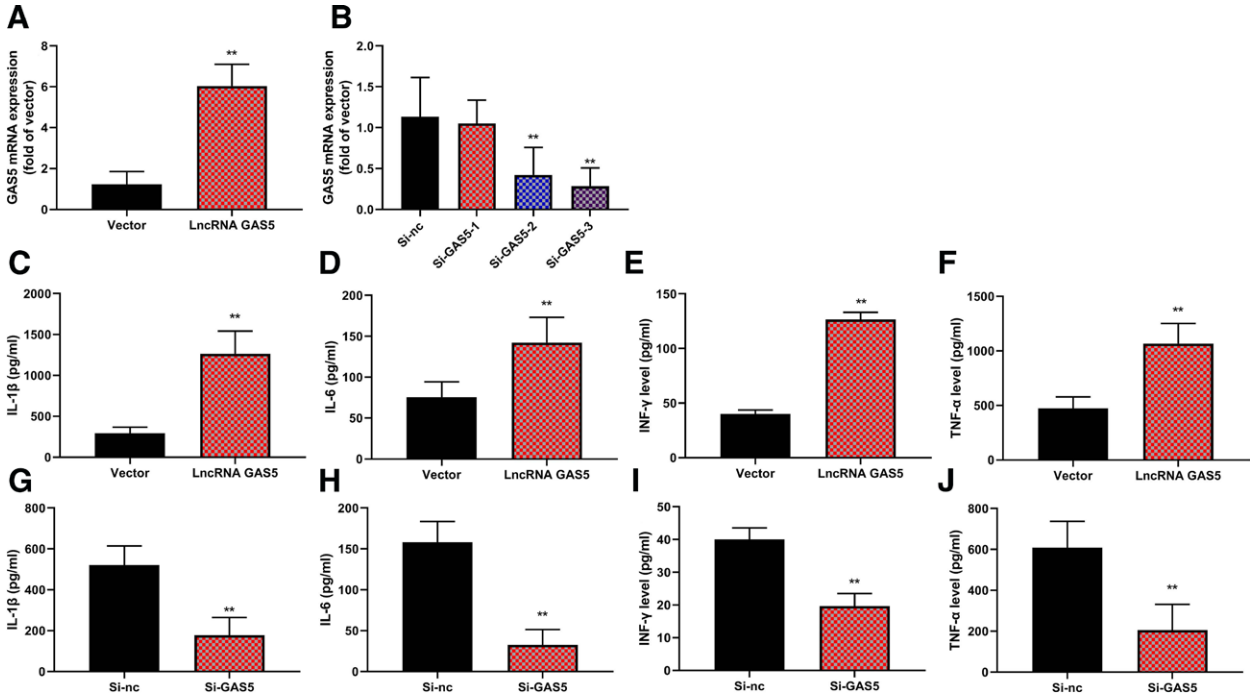

Figure 2. LncRNA GAS5 promoted neuroinflammation in vitro model. LncRNA GAS mRNA expression in vitro model (A and B); IL-1β (C), IL-6 (D), INF-γ (E) and TNF-α (F) levels in vitro model by over-expression of lncRNA GAS; IL-1β (G), IL-6 (H), INF-γ (I) and TNF-α (J) levels in vitro model by down-regulation of lncRNA GAS. Vector, negative control group; LncRNA GAS, over-expression of lncRNA GAS5 group; Si-nc, si-negative control group; si-GAS5, down-regulation of lncRNA GAS5 group. $^{**}P < .01$ compared with negative control group or si-negative control group. LncRNA = long noncoding RNA.

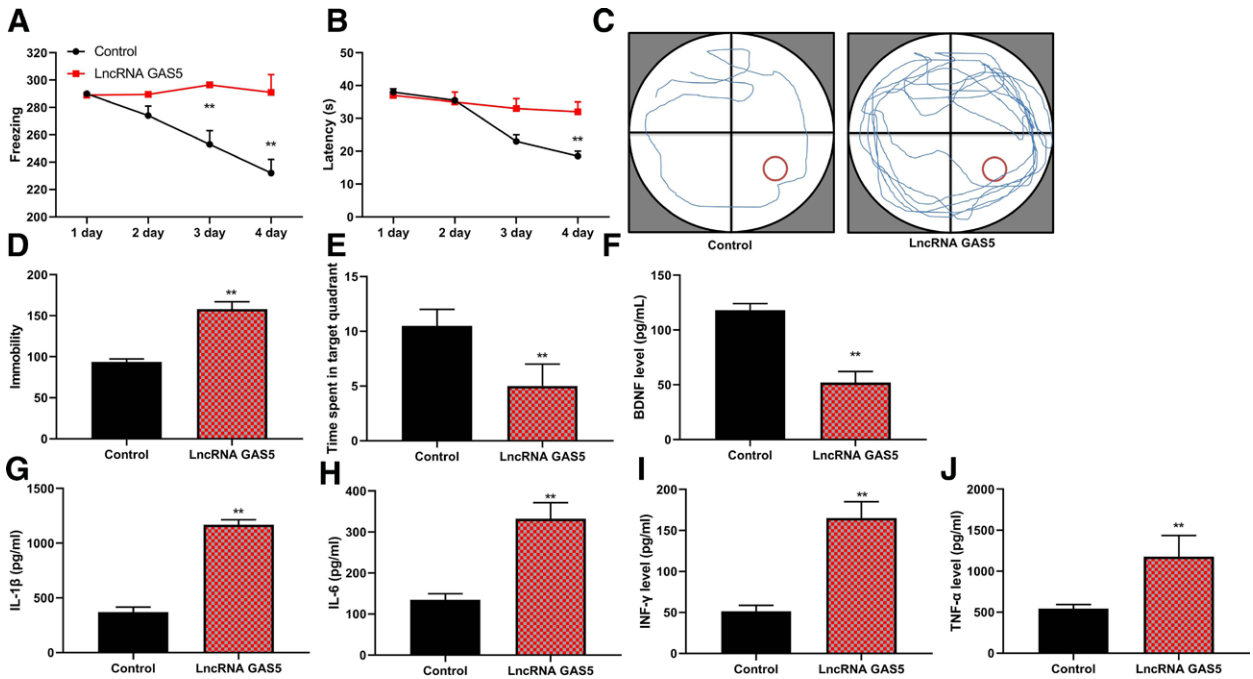

Figure 3. LncRNA GAS5 raised cognitive impairment and increased neuroinflammation in mice model. Freezing times (A), latency times (B), Morris water maze (C), immobility (D), time spent of target quadrant (E), BDNF levels (F), IL-1β (G), IL-6 (H), INF-γ (I) and TNF-α (J) levels in hippocampal tissue of mice model. Control, mice with sevoflurane; LncRNA GAS5, mice with sevoflurane and LncRNA GAS5. $^{**}P < .01$ compared with mice with sevoflurane group. LncRNA = long noncoding RNA.

3.5. MiR-137 suppressed TCF4 protein expression in vitro model

We assess that the mechanism of miR-137 on anesthesia-induced cognitive impairment. RT-qPCR analysis showed that LncRNA GAS5 overexpression enforced the TCF4 mRNA, while miR-137 mimics reduced the TCF4 mRNA expression. In addition, the co-transfection of LncRNA GAS5 overexpression and miR-137 mimics recued the TCF4 mRNA expression (Fig. 6A). Moreover, online bioinformatics tools (StarBase, http://starbase.sysu.edu.cn/) found that miR-137 target the 3'-UTR of TCF4 mRNA (Fig. 6B–6C). Over-expression of miR-137 suppressed

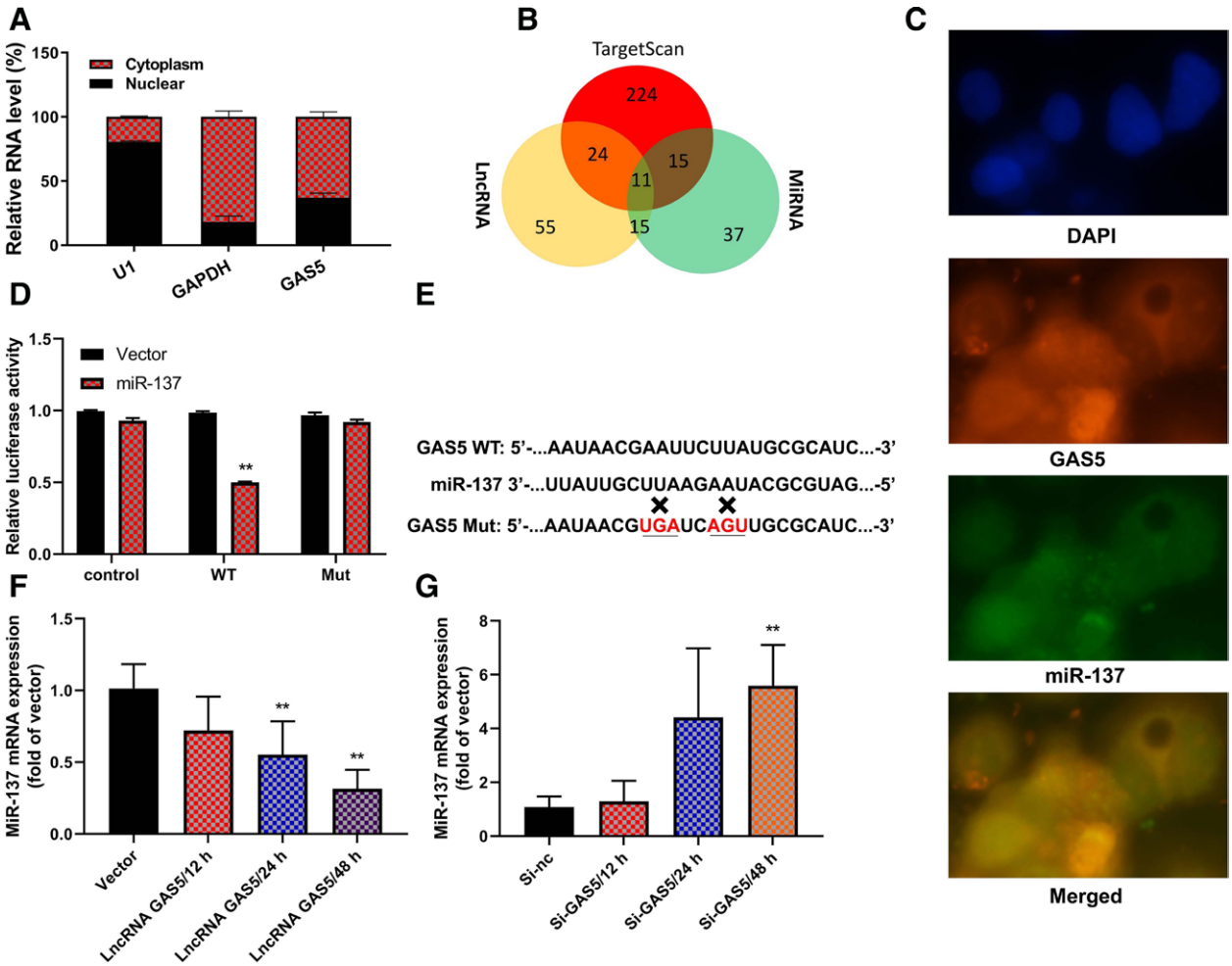

Figure 4. LncRNA GAS5 suppressed miR-137 in vitro model. LncRNA GAS5 expression in cytoplasm and nuclear (A), Online bioinformatics tools (TargetScan, RegRNA, CircNet) found that several miRNAs might effectively interact with LncRNA GAS5, including microRNA-137 (B), RNA-FISH demonstrated the distribution of LncRNA GAS5 and miR-137 in cytoplasm and nuclear (C), luciferase reporter levels (D), LncRNA GAS5 constructed targeting miR-137 (E), MiR-137 expression (F and G). Vector, negative control group; LncRNA GAS, over-expression of lncRNA GAS5 group; Si-nc, si-negative control group; si-GAS5, down-regulation of lncRNA GAS5 group. showed as mean ± SD. $^{**}P < .01$. FISH = Fluorescence in situ hybridization, LncRNA = long noncoding RNA.

TCF4 mRNA expression levels in vitro model (Fig. 6D). Down-regulation of miR-137 increased TCF4 mRNA expression levels in vitro model (Fig. 6E). However, Over-expression of LncRNA GAS5 induced TCF4 mRNA expression levels in vitro model (Fig. 6F). Down-regulation of LncRNA GAS5 suppressed TCF4 mRNA expression levels in vitro model (Fig. 6G). In conclusion, these finding indicate that LncRNA GAS5 targets miR-137/TCF4 in in vitro model of anesthesia-induced cognitive impairment.

3.6. TCF4 is 1 transcription factor to activate the expression of bhlh

TCF4 target the promoter region of bHLH gene (Fig. 7A). TCF4 and bHLH promoter was, showed the molecular interaction within TCF4 and bHLH (Fig. 7B). Luciferase activity of bHLH promoter and TCF4 promoted the promoter luciferase activity of WT sequence (Fig. 7C). TCF4 induced bHLH protein expression in vitro model (Fig. 7D). In conclusion, these findings implied that TCF4 activates the expression of bHLH in cognitive function by anesthesia.

4. Discussion

As a common orthopedic disease, lumbar spinal stenosis frequently occurs among middle-aged and elderly people.[19] With the intensification of population aging and the continuous change of lifestyle, its incidence has been increasing year by year, which seriously threatens people's quality of life.[2,20] Currently, surgery is the main treatment for patients with lumbar spinal stenosis.[21] Moreover, we found that LncRNA GAS5 gene expression were up-regulated in patients undergoing lumbar spinal canal decompression. Michele Salemi indicated that the occurrence of lncRNA GAS5 over-expression in Klinefelter syndrome (KS) patients.[22] Similarly, LncRNA GAS5 played an repair factor in anesthesia-induced cognitive impairment.

After surgery, elderly patients often experience changes in cognitive function, manifested as confusion, anxiety, personality changes, as well as memory impairment.[23] Such postoperative change is called POCD, which is a type of mild cognitive impairment (MCI).[24] Its diagnosis requires neuropsychological testing.[25] Herein, this experiment showed that LncRNA GAS5 raised cognitive impairment and increased neuroinflammation in mice model. Zhao et al suggests silencing GAS5 protects against brain injury in hypoxia/ischemia model.[26] Indeed, the above support our hypothesis that LncRNA GAS5 is a key player in POCD.

An lncRNA sequencing study found the presence of certain differential expression between the brain tissue samples of POCD patients and the well-matched elderly brain tissues, with observation of 24 up-regulated and 84 down-regulated lncRNAs in POCD patients.[27–29] Besides, recent research has shown that

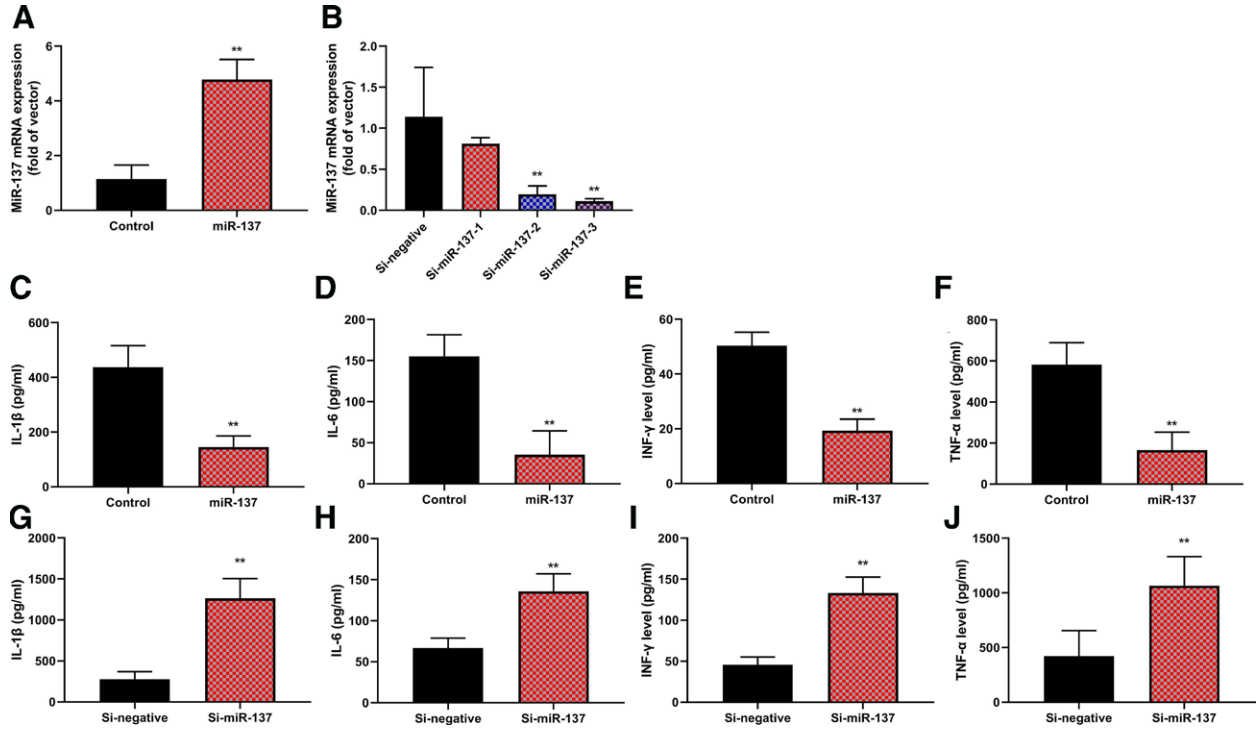

Figure 5. MiR-137 reduced neuroinflammation in vitro model. MiR-137 mRNA expression in vitro model (A and B); IL-1β (C), IL-6 (D), INF-γ (E) and TNF-α (F) levels in vitro model by over-expression of miR-137; IL-1β (G), IL-6 (H), INF-γ (I) and TNF-α (J) levels in vitro model by down-regulation of miR-137; Vector, negative control group; miR-137, over-expression of miR-137 group; Si-nc, si-negative control group; si-miR-137, down-regulation of miR-137 group. $^{**}P < .01$ compared with negative control group or si-negative control gro.

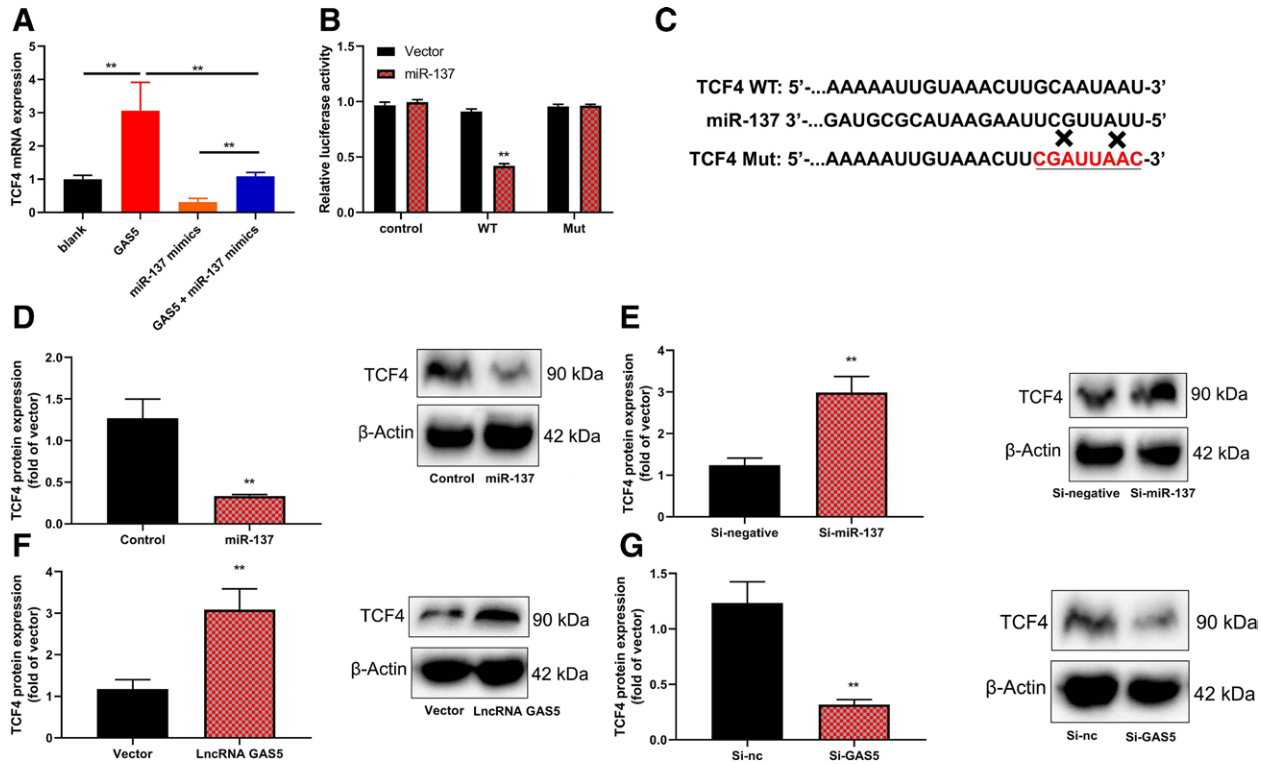

Figure 6. MiR-137 suppressed TCF4 protein expression in vitro model. TCF4 mRNA expression (A), luciferase reporter levels (B), TCF4 constructed targeting miR-137 (C), TCF4 protein expressions (D) in over-expression of miR-137 group; TCF4 protein expressions (E) in down-regulation of miR-137 group; TCF4 protein expressions (F) in over-expression of LncRNA GAS5 group; TCF4 protein expressions (G) in down-regulation of LncRNA GAS5 group. Vector, control group; LncRNA GAS5, over-expression of LncRNA GAS5; Sh-NC, Sh-control group; Sh-GAS5, down-regulation of LncRNA GAS5. Vector, control group; microRNA-137, over-expression of microRNA-137; Sh-NC, Sh-control group; Sh-miR-137, down-regulation of LncRNA GAS5. Data were showed as mean ± SD. $^{**}P < .01$. LncRNA = long noncoding RNA.

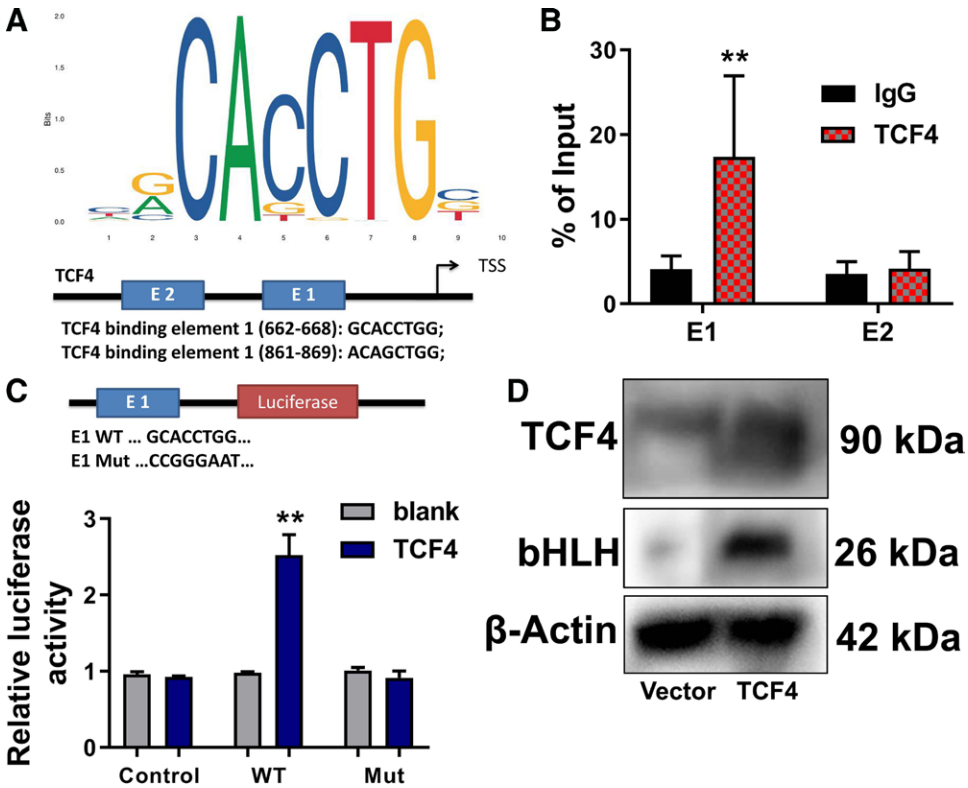

Figure 7. Transcription factor TCF4 activates the expression of bHLH. TCF4 could target the promoter region of bHLH gene (A); ChIP assay was performed to identify the binding relation between TCF4 and bHLH promoter (B); Mutant and wild type sequences of bHLH first element were respectively constructed and Luciferase reporter (C); TCF4 and bHLH protein expression levels in vitro model (D). Sector, control group; TCF4, over-expression of TCF4, the number of vitro model = 3. Data were showed as mean ± SD. $^{**}P < .01$.

changes in miRNA expression exert a certain effect on the biological mechanism of POCD.[30,31] More importantly, we show that LncRNA GAS5 suppressed miR-137 in vitro model. Gao et al reported that GAS5 is up-regulated in knee osteoarthritis, and can induce chondrocyte apoptosis through down-regulating miR-137.[32] Therefore, LncRNA GAS5 suppressed miR-137 to raised cognitive impairment in vitro model of POCD.

Existing pharmaceutical treatments for ameliorating POCD are classified into 3 strategies: blocking neuroinflammation by inhibiting inflammatory mediators (anti-neuroinflammation), preventing neuroinflammation by anti-oxidant constituents (anti-oxidation) and protecting neurons preoperatively and promoting neuronal health (neuronal therapy).[24,33–35] We found that LncRNA GAS5 promoted neuroinflammation in vitro model, and miR-137 reduced neuroinflammation in vitro model. Zhang et al showed that GAS5 knockdown suppresses neuroinflammation induced by oxidized low-density lipoprotein in macrophages.[36] Therefore, LncRNA GAS5 pathway is crucial for neuroinflammation in model of POCD.

TCF4, as a widely expressed protein, acts as a transcription factor to regulate other genes involved in the cell differentiation, survival and neurodevelopment.[37] According to recent research, the role of TCF4 in central nervous system diseases has become a hot topic receiving general attention, which exerts an important function in the neuronal regulation.[38,39] In the present study, LncRNA GAS5 induced TCF4 protein expression in vitro model by miR-137. Transcription factor TCF4 activates the expression of bHLH. Wang et al showed that miR-137 targets the suppression of TCF4 to reverse the progression of osteoarthritis,[40] suggesting it may be a therapeutic target for POCD.

Taking together, this experiment provide the first experimental and clinical evidence that LncRNA GAS5/miR-137 promoted anesthesia-induced cognitive function to increase inflammatory bodies in patients undergoing lumbar spinal canal decompression. Moreover, LncRNA GAS5 promotes neuroinflammation and prevents anesthesia-induced cognitive impairment, suggesting it may be a biomarker of POCD and a potential therapeutic target for POCD.

Author contributions

Conceptualization: Chunli Zhang.
Data curation: Chunli Zhang.
Formal analysis: Dingzhong Chen.
Methodology: Dingzhong Chen, Yuntao Gu, Tao Wang, Cong Wang.
Writing – original draft: Yuntao Gu, Cong Wang.
Writing – review & editing: Dingzhong Chen, Tao Wang.

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