

MicroRNA-382-5p Targets Nuclear Receptor Subfamily 3 Group C Member 1 to Regulate Depressive-Like Behaviors Induced by Chronic Unpredictable Mild Stress in Rats

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Background: Depression is an emotional disorder characterized by depression, lack of pleasure, and cognitive and sleep disorders. It is a systemic disease with a complex pathogenesis. In this study, we will be focused to investigate their associations and the exact functional mechanisms of miR-382-5p and NR3C1 in depression.

Materials and Methods: We measured the expressions of microRNA-382-5p (miR-382-5p) and NR3C1 in the hippocampus by chronic unpredictable mild stress (CUMS). Depression behavior test including novelty-suppressed feeding test (NSFT), sucrose preference test (SPT), and forced swim test (FST) on rats have been conducted to examine the roles and functions of miR-382-5p and NR3C1 on depression-like behaviors by lentivirus vectors.

Results: Up-regulation of miR-382-5p and down-regulation of NR3C1 were observed in rats' hippocampus induced by CUMS. miR-382-5p targeted NR3C1 and inhibited the expressions of NR3C1 in rats' hippocampus. miR-382-5p could significantly change the depression behaviors induced by CUMS. NR3C1 downstream BDNF and p-TrkB were also oppositely associated with miR-382-5p in rats' hippocampus.

Conclusion: Through our experiments and analysis, we found that the associations between miR-382-5p and NR3C1 could affect the depression-like behaviors.

Keywords: miRNA-382-5p, depression, hippocampus, NR3C1

Background

Depression is an emotional disorder characterized by a lack of pleasure, cognitive, and sleep disorders.^{1,2} It is a systemic disease with a complex pathogenesis.^{3,4} Compared with the current first-line treatments targeting monoamine transmitters, the development of drugs that has a therapeutic impact on multiple pathogenesis is a new topic.⁵ In recent years, studies have shown that endogenous non-coding small RNAs with regulatory functions are abnormally expressed in tissues and body fluids of animal models and depressed patients, and in drug therapy response, synaptic plasticity, neuron production, cognition, learning and memory functions.^{6,7} Among them, microRNAs-based transcriptomics studies have made progress in the discovery of clinical depression biomarkers and potential drug targets.⁸

MicroRNAs (miRNAs) are a class of endogenous non-coding RNAs found in eukaryotes that are about 22 nt in length and have regulatory functions,⁹ which are

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able to complement the 3' non-coding region of target genes by sequence complementation.^{10,11} Accumulative evidence suggest that miRNA is involved in multiple classical pathogenesis of depression, by targeting multiple nodal genes, thereby regulating the expressions of key proteins, which means that miRNA itself has great potential as a therapeutic target for depression and a prospective biomarker.^{12,13} In a recent report, Lopozp et al discussed that miRNAs in depression-like behaviors,¹⁴ which shed light to the potential of utilizing many miRNAs in the development or treatment of depression. It has been reported that several miRNAs including miR-9-5p, miR-128-1-5p, and miR-382-5p that are significantly increased in chronic mild stress.¹⁵ As an important member of miRNAs, miR-382-5p has been demonstrated to play important roles in liver cancer metastasis,¹⁶ ischemic stroke,¹⁷ and stem cell differentiation.¹⁸ In 2015, R.J. Chen reported that miR-382-5p could act as a biomarker of resilience or vulnerability to stress,¹⁹ which gives us a clue in the depression. Herein, we are interested in the exact role of miR-382-5p in depression behaviors.

Hippocampus has been considered as a core factor in the pathophysiology of depression, and previous studies have revealed that hippocampal glucocorticoid receptor gene nuclear receptor subfamily 3 group C member 1 (NR3C1) DNA methylation can mediate part of pre-conception paternal stress effects in rat offspring.²⁰ It was also revealed that there exist genetic and epigenetic associations of MAOA and NR3C1 with depression.²¹ Besides, NR3C1 promoter was proved to be hypermethylated in Thai females with major depressive disorder.²² The preliminary bioinformatics analysis revealed that miR-382-5p could target NR3C1. We hypothesis that miR-382-5p may exert a modulation role by interacting with NR3C1 in depression. Therefore, we will be focused to investigate their associations and the exact functional mechanisms.

Materials and Methods

Experimental Animals

Male Wistar rats with weights at around 200 grams were provided by Shanghai Animal Center, China. They were maintained in half day light and half day night at ~22Celsius and 55% humidity, with freedom to eat and drink. The experiments had been approved by the Institute for Experimental Animals of People's Hospital of Shenzhen Baoan District, and our study followed the guidelines of the National Institutes of Health.

Chronic Unpredictable Mild Stress (CUMS) Rats

Rats in CUMS groups had various stress factors, such as 1 day's starvation, 1 day's water deprivation, 5 minutes' cold swimming, and 1 minute's tail pinch randomly for 28 days. Control group was kept in a separate place. The rats were given behavioral tests before being sacrificed. For euthanasia, rats were anesthetized by intraperitoneal injection with 3% sodium pentobarbital (30 mg/kg body weight, Sigma Chemical Co., St. Louis, MO, USA) and sacrificed by cervical dislocation.

Lentivirus Vectors and Stereotaxic Injection

Construction of NR3C1 lentiviral vector (LV-NR3C1) and subsequent production of lentivirus were completed by Gene Pharma Company (Shanghai, China). The empty vector (LV-Mock) served as the negative control. LV-miR-382-5p/LV-si-miR-382-5p (108 TU/mL) also purchased from the Gene Pharma Company (Shanghai, China). All viral injection procedures followed the previous study.²³ For stereotaxic surgery test, rats were anesthetized with a 100 mg/kg ketamine and 10 mg/kg xylazine mixture and installed in a stereotaxic framework. One milliliter of the virus solution was bilaterally infused into rats using a precision Hamilton micro-syringe with a needle of 26 G, according to the following coordinates: hippocampus [The first injection: 4.8 mm posterior from Bregma, 2.5 mm lateral from the medial suture, 3.5 mm ventral to the surface of the skull. The second injection: 4.8 mm posterior from Bregma, 5 mm lateral from the medial suture, 6 mm ventral to surface of the skull]. Rats recovered 1 week before exposure to CUMS.

Depression Behavioral Test

Novelty-suppressed feeding test (NSFT): the NSFT was performed 4 weeks after CUMS exposure. The test instrument consisted of a plastic box (35 cm x 35 cm). No food was given to the rats 24 h before the test. At the start of the test, a single pellet of food was put on a white paper platform in the middle of the box. We put a rat in a corner of the maze and immediately activated a stopwatch. Interest test was started when the rats grabbed the food with their fore-paws and began to eat. As a control value, we measured the food consumption in home cages within 90 min after the completion of the test; Sucrose preference test (SPT): Rats were trained to adapt to a sucrose solution (1%, w/v) before this test. Two bottles of sucrose solution were placed for 24

h in an individual cage, and then one bottle of sucrose solution was changed into water for 24 h. After adaptation, rats were fasted on water and food for 24 h. During the test, rats were kept in separate cages and were free to take two bottles of sucrose solution and water. The sucrose solution and water consumption were measured after 24 h; Forced swim test (FST): the FST was performed 24 h after SPT. Firstly, pour tap water (22–26°C) into glass beakers. Rats were then put into that glass beakers, where they could not escape or rest though touching the bottom of the beaker. The test lasted 6 min (360 s) and recorded the duration of immobility. Mobility was defined as any action beyond what was necessary to keep the head above water. Data were expressed in the term of the average time of immobility, swimming and climbing over the observation period (360 s).

Primary Hippocampal Neuronal Cultures

To start, we took the hippocampi rat's brain. The neuronal cells were digested, re-suspended, and diluted to 100 cells/mL. Three-milliliter cell suspensions were cultured for 2 h in 5% CO₂ at 37 Celsius for 14 days, with medium refreshed with 3 mL of neurobasal/B27 medium. After cultured neurons were treated with LV-miR-382-5p or LV-si-miR-382-5p for 48 h, protein expression levels of NR3C1, BDNF and TrkB were detected by Western blot.

qRT-PCR

Hippocampus was dissected and stored at –80 Celsius. RNA was extracted by TRIzol (Invitrogen, USA), and cDNA was generated by PrimeScript[®] (Takara, China). qRT-PCR was carried out to measure miRNAs and mRNA expressions by SYBR II (Takara, China). The relative expressions were calculated by $2^{-\Delta\Delta CT}$, using U6 snRNA and GAPDH as references. The primers are displayed in Table 1.

Western Blotting

Proteins were separated by SDS-PAGE and transferred to PVDF membrane (Bio-Rad, USA). We blocked the membranes and incubated them with anti-NR3C1 (1:500,

sc-12763), anti-BDNF (1:500, sc-546), anti-TrkB (1:500, sc-7268), p-TrkB (1:500, sc-8058), which were purchased from Santa Cruz Biotechnology, USA. GAPDH (1:1000, A9044) from Sigma, USA was used as control. After washing, we incubated the blots with HRP-conjugated secondary antibodies. Chemiluminescent was used to quantify the signals.

Luciferase Assay

The possible target locations of the NR3C1 3'-untranslated region (3'-UTR) (WT-NR3C1) or mutated sequences (MT-NR3C1) were cloned into the pmirGLO Dual-Luciferase miRNA target expression vector (Promega, Madison, WI). The total 3'-UTR NR3C1 sequences (SwitchDB, Menlo Park, CA) were constructed using the transfection-ready luciferase reporter. Luciferase assays were operated in 293 T cells by the Dual-Luciferase Reporter 1000 Assay System (Promega). Using Normalized values (firefly activity/Renilla activity) for analysis.²⁴

Statistical Analysis

SPSS 19.0 was used for data analysis. Data were shown as means ± SD. The difference significance was determined by unpaired *t*-test (2 groups) or one-way ANOVA (>2 groups). Two-sided P values less than 0.05 were considered as statistically significant.

Results

Up-Regulation of miR-382-5p and Down-Regulation of NR3C1 in Rats' Hippocampus Induced Through CUMS

We assessed the transcriptional and translational level of miR-382-5p and NR3C1 in rats' hippocampus to investigate the expression level of miR-382-5p in CUMS model. As shown in Figure 1A, CUMS induced miR-382-5p expressions, which increased further with time passing by (n=6 per group. P<0.05, P<0.01). Differently, Figure 1B and C showed that hippocampus NR3C1 was down-regulated in CUMS rats as time passing by (P<0.05, P<0.01).

Table 1 Sequences of Primers Used in qRT-PCR

Gene	Forward Primer (5'-3')	Reversed Primer (5'-3')
miR-382-5p	ATCCGTGAAGTTGTTTCGTGG	TATGGTTGTAGAGGACTCCTTGAC
U6	CTCGCTTCGGCAGCACAC	AACGCTTCACGAATTTGCGT
NR3C1	CGAGCATGAGACCAGATGTA	CGACTGCTCTTTTGAAGAAA
GAPDH	TGCACCACCAACTGCTTAGC	GGCATGGACTGTGGTCATGAG

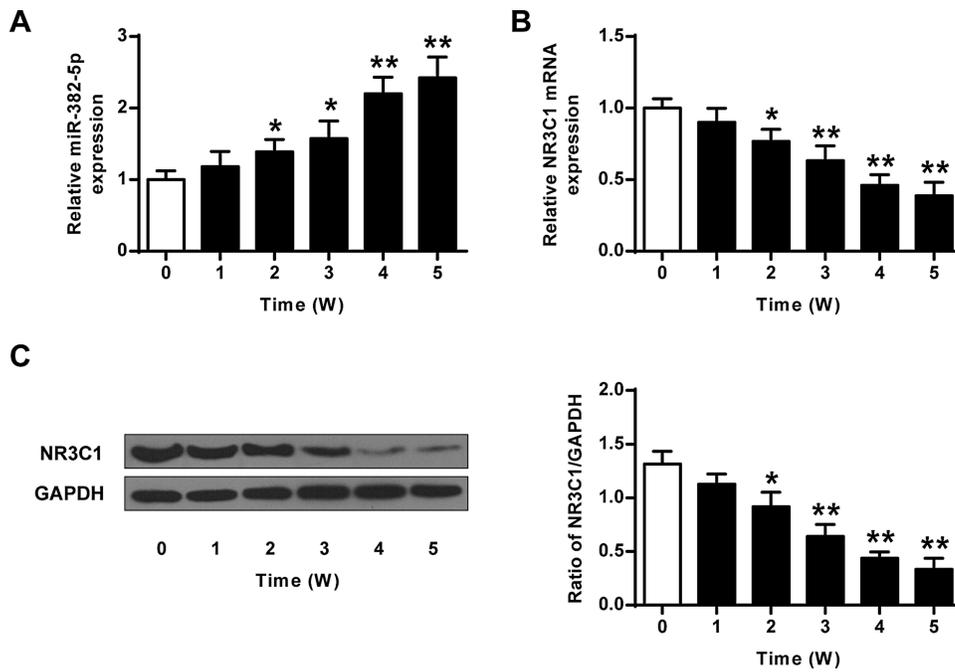


Figure 1 Dysregulated miR-382-5p and NR3C1 expressions in rats' hippocampus induced by CUMS. **(A)** Expressions of miR-382-5p in rats' hippocampus by CUMS. **(B)** mRNA expression of NR3C1 in rats' hippocampus by CUMS. **(C)** Protein levels of NR3C1 in rats' hippocampus by CUMS. N=6 per group. *P<0.05, **P<0.01 vs control.

Impact of miR-382-5p Over-Expressions on the Behaviors Induced by CUMS

In contrast with rats transfected with LV-Mock, rats with miR-382-5p over-expressions had elevated latency to feed (P<0.01) (Figure 2A) and immobility time (P<0.01) (Figure 2E), and lower sucrose preference (P<0.01)

(Figure 2C) and swimming time (P<0.01) (Figure 2F), which suggested more depression. Inhibition of miR-382-5p had the opposite effects. Food intake (Figure 2B) and total water intake (Figure 2D) did not show any significant change. Our results indicated that miR-382-5p can significantly enhance the CUMS induced depression behaviors.

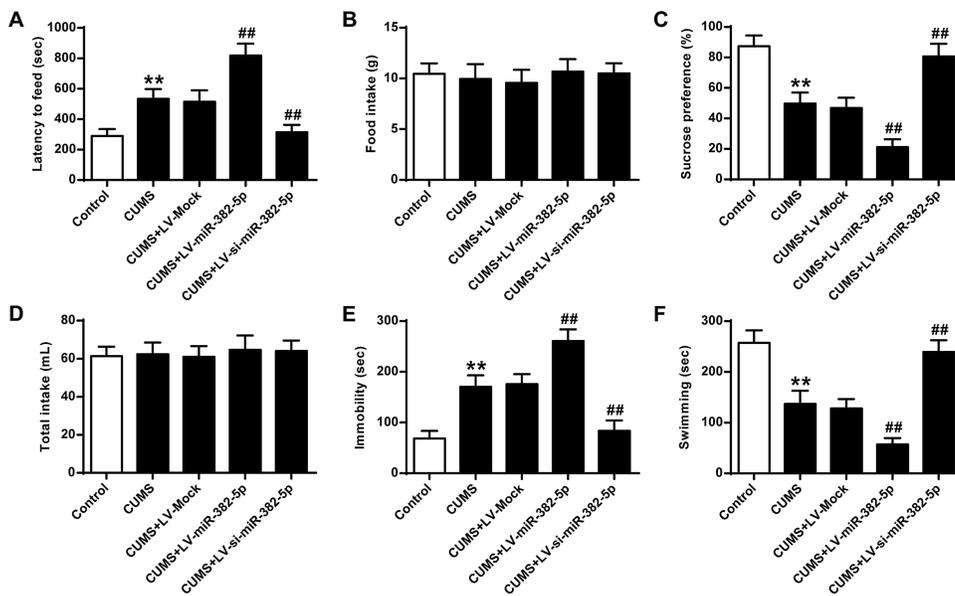


Figure 2 Impact of miR-382-5p over-expressions on the behaviors induced by CUMS. For rats with miR-382-5p over-expressions: **(A)** latency to feed, **(B)** food intake, **(C)** sucrose preference, **(D)** total water intake, **(E)** immobility time, and **(F)** swimming time. n = 6. **P<0.01 vs control; ###P<0.01 vs CUMS+LV-Mock.

miR-382-5p Down-Regulates the Expressions of NR3C1 in Rats' Hippocampus

To evaluate the influence of miR-382-5p on the expression of NR3C1, we conducted gain and loss function experiments. **Figure 3A** finds decreased or enhanced expressions of miR-382-5p in rats' hippocampus by LV-si-miR-382-5p and LV-miR-382-5p ($P<0.01$). **Figure 3B–D** revealed that NR3C1 expressions were significantly lowered in miR-382-5p and elevated in si-miR-382-5p ($P<0.01$). **Figure 3E** and **F** indicated that the NR3C1 downstream BDNF and p-TrkB were also oppositely associated with miR-382-5p in rats' hippocampus ($P<0.05$).

NR3C1 is Targeted by miR-382-5p

Further investigation of miR-382-5p and NR3C1 were conducted. As shown in **Figure 4A**, bioinformatics used to predict that NR3C1 was a target of miR-382-5p. **Figure 4B** uses luciferase reporter assays and found that NR3C1-mut abolished its abilities to bind with the miR-382-5p 3'-UTR ($P>0.05$). **Figure 4C** shows cultured neuronal cells were treated with LV-miR-382-5p or LV-si-miR-382-5p ($P<0.01$). **Figure 4D–H** demonstrated that NR3C1, BDNF and p-TrkB were elevated with LV-si-miR-382-5p

treatments and lowered with LV-miR-382-5p ($P<0.05$, $P<0.01$). From these results, we could conclude that NR3C1 is targeted by miR-382-5p.

NR3C1 Over-Expressions on CUMS-Related Depression Behaviors in Rats

To further illustrate the function of NR3C1 over-expression on CUMS, we analyzed the level of NR3C1 in rats. According to the qPCR and Western blotting results, we found that NR3C1 expressions were significantly elevated under LV-NR3C1 ($P<0.01$) (**Figure 5A–C**). **Figure 5B, D, and E** demonstrates that NR3C1 downstream targets BDNF and p-TrkB were also elevated in the LV-NR3C1 group ($P<0.05$).

Then, the depression behaviors of Rats described in previous studies^{25,26} were also assessed in the delay in the latency to feed (**Figure 6A**), food intake (**Figure 6B**), sucrose preference (**Figure 6C**), total water intake (**Figure 6D**), immobility time (**Figure 6E**), and swimming time (**Figure 6F**) under treatments of Control, CUMS, CUMS+LV-Mock, CUMS+LV-NR3C1. Treatments with LV-NR3C1 lowered the latency to feed ($P<0.05$), elevated sucrose preference ($P<0.01$), decreased immobility time

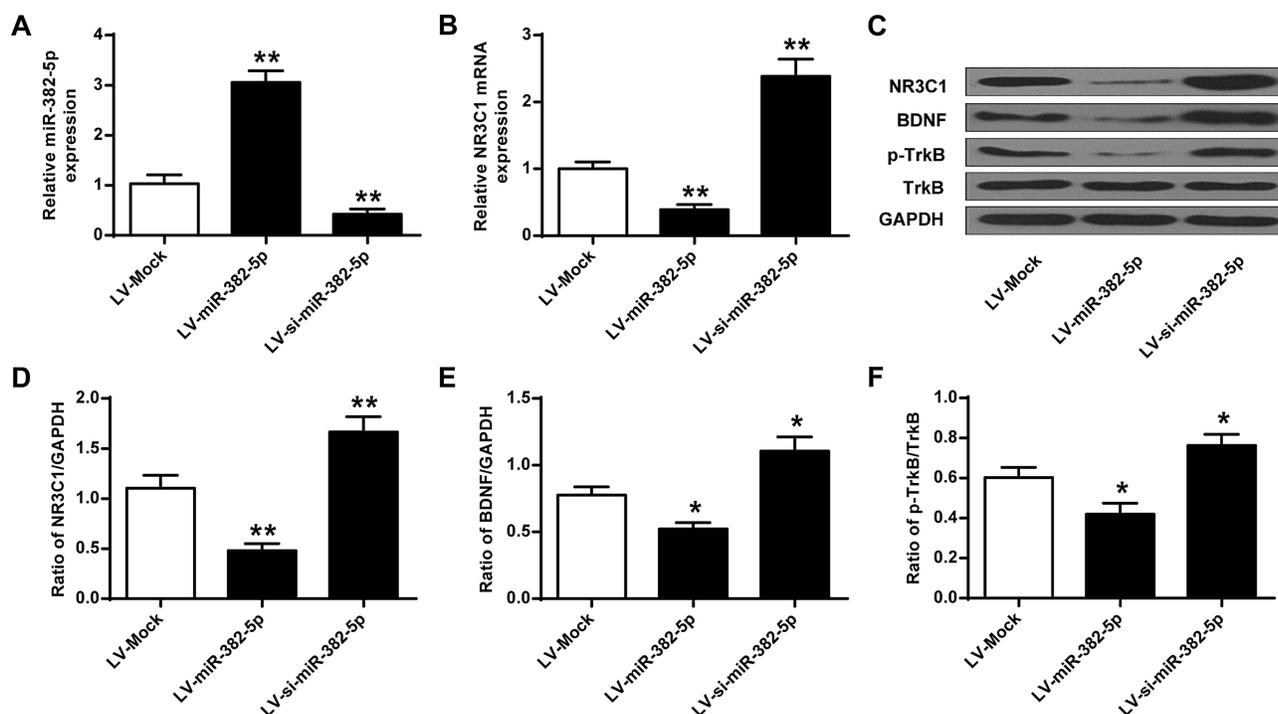


Figure 3 miR-382-5p inhibited the expressions of NR3C1 in rats' hippocampus. **(A)** miR-382-5p level in under LV-miR-382-5p or LV-si-miR-382-5p treatments. **(B)** NR3C1 in rats' hippocampus under LV-miR-382-5p or LV-si-miR-382-5p treatments. **(C)** LV-miR-382-5p on NR3C1, BDNF and p-TrkB protein expressions in rats' hippocampus. **(D–F)** Protein expressions of NR3C1, BDNF and p-TrkB. $n = 6$. * $P<0.05$, ** $P<0.01$ vs LV-Mock.

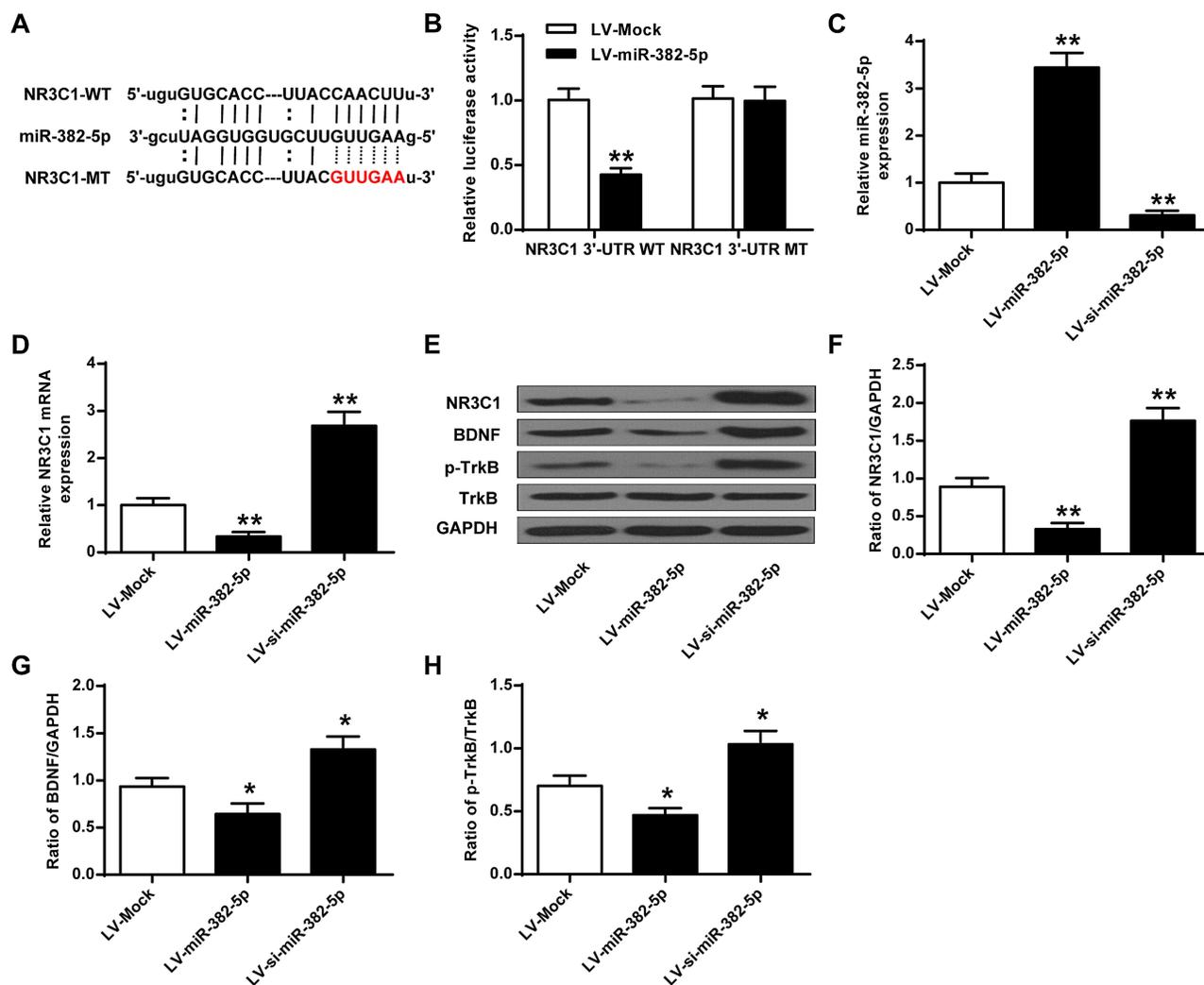


Figure 4 NR3C1 is targeted by miR-382-5p. **(A)** Common sequences between miR-382-5p and NR3C1-MT. **(B)** Luciferase activity of NR3C1-MT or NR3C1-WT with LV-miR-382-5p or LV-Mock. **(C)** Expressions of miR-382-5p in neurons under LV-miR-382-5p or LV-si-miR-382-5p. **(D)** Expressions of NR3C1 in hippocampus under LV-miR-382-5p or LV-si-miR-382-5p treatments. **(E)** Protein expressions of NR3C1, BDNF and p-TrkB by si-miR-382-5p. **(F-H)** NR3C1, BDNF and p-TrkB protein level. * $P < 0.05$, ** $P < 0.01$ vs LV-Mock.

($P < 0.05$), and elevated swimming time ($P < 0.01$). No obvious changes were observed in food intake and water intake by NR3C1 over-expressions.

Discussions

MiRNAs have specific expressions in neural progenitor cells, neurons and glial cells during neurodevelopment. For instance, researchers have revealed that miR-1202,²⁷ miR-137,²⁸ and miR-144-5p²⁹ may be involved in physiological processes such as axon guidance, synaptic plasticity regulation, and neurodegenerative diseases and depression.³⁰ From our study, we found that CUMS induced the promotion of miR-382-5p expressions in a dose-dependent manner. Differently, hippocampus NR3C1 was lowered by CUMS with time passing by. It

was obvious that miR-382-5p was up-regulated and NR3C1 was down-regulated in the hippocampus of rats induced by CUMS. From these data, we believe that alteration of miR-382-5p and NR3C1 in the hippocampus may be related to stress responses in rats.

Previous studies have demonstrated that miRNAs played an important role in neuronal development and differentiation, synaptic plasticity, cognition and learning and memory functions.^{31,32} Some miRNAs are associated with the development of various central nervous system diseases.^{7,33} In contrast with rats transfected with LV-Mock, rats with miR-382-5p over-expressions had elevated latency to feed and immobility time, and lower sucrose preference and swimming time, which suggested more depression. Inhibition of miR-382-5p had the

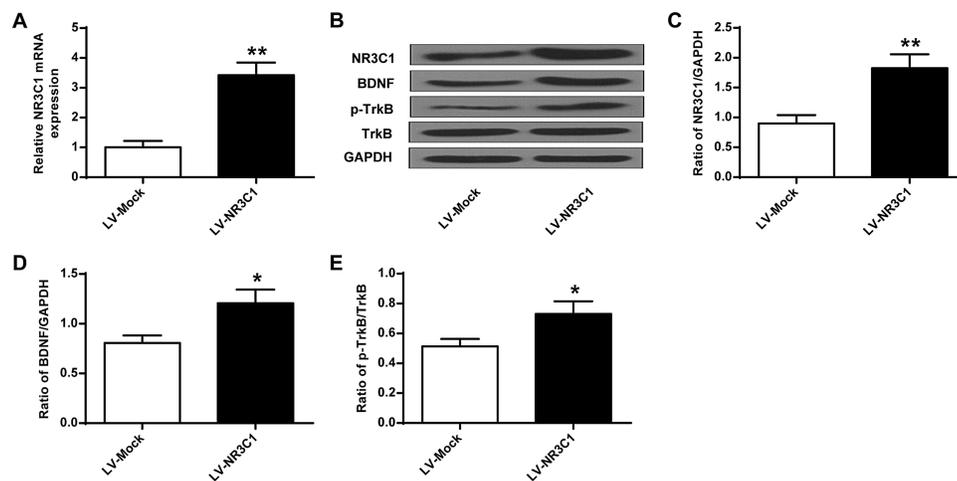


Figure 5 The change of NR3C1, BDNF and p-TrkB protein in rats' hippocampus after LV-NR3C1 treatments. **(A)** mRNA level of NR3C1 in rats' hippocampus response to LV-NR3C1 treatments. **(B)** Impact of LV-NR3C1 modulation on NR3C1, BDNF and p-TrkB expressions in rats' hippocampus. **(C-E)** Quantitative analysis of NR3C1, BDNF and p-TrkB protein level. $n = 6$. * $P < 0.05$, ** $P < 0.01$ vs LV-Mock group.

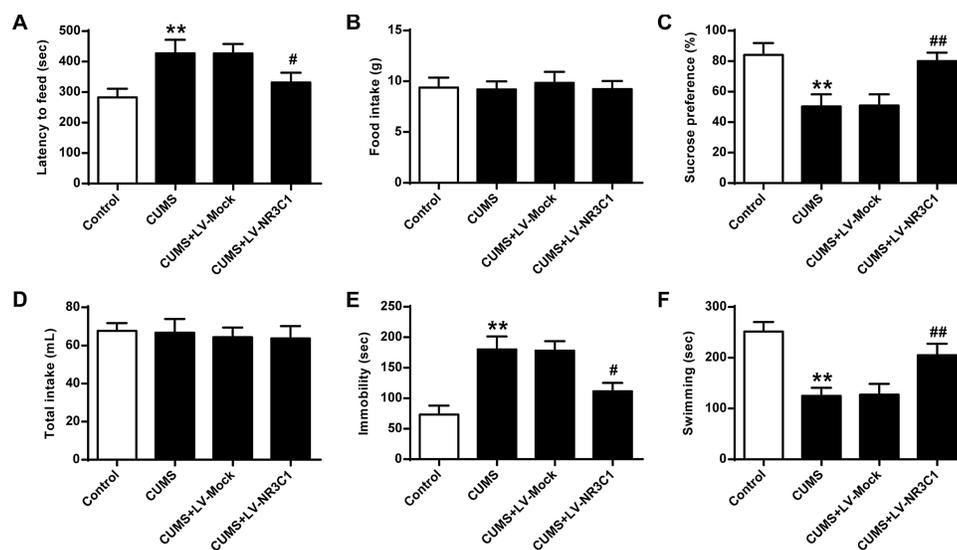


Figure 6 Impact of lentiviral-mediated NR3C1 over-expressions on CUMS-related depression behaviors in the NSFT, sucrose preference test and forced swimming test. Under treatments of Control, CUMS, CUMS+LV-Mock, CUMS+LV-NR3C1: **(A)** Delay in the latency to feed, **(B)** Food intake, **(C)** Sucrose preference, **(D)** total water intake, **(E)** immobility time, and **(F)** swimming time. $n = 6$. ** $P < 0.01$ vs Control; ## $P < 0.05$, ### $P < 0.01$ vs CUMS+LV-Mock.

opposite effects. No significant change was found in food intake and total water intake.

It has been reported that depression factors such as childhood life unfortunate could affect the methylation level of the NR3C1 promoter region.^{34,35} The methylation level of the NR3C1 promoter region in patients with depression was positively correlated with the hippocampal subdivision volume.³⁶ In our experiments, we found decreased or enhanced expressions of miR-382-5p in rats' hippocampus by LV-si-miR-382-5p and LV-miR-382-5p. NR3C1 expressions were significantly lower in miR-382-5p and elevated in si-miR-382-5p. NR3C1

downstream BDNF and p-TrkB were also oppositely associated with miR-382-5p in rats' hippocampus. miR-382-5p inhibited the expressions of NR3C1 in rats' hippocampus, which proved the roles of miR-382-5p in depression.

Bioinformatics analysis predicted that NR3C1 was a target of miR-382-5p. Luciferase reporter assays found that NR3C1-mut abolished its abilities to bind with the miR-382-5p 3'-UTR. NR3C1, BDNF and p-TrkB were elevated with LV-si-miR-382-5p treatments and lowered with LV-miR-382-5p. According to established results, miRNAs can also directly affect the expressions and regulation of several other key components of depression-

related signaling pathways, such as brain-derived neurotrophic factor (BDNF), which is reduced in depression patients and stress animal models.^{1,35} Our data supported that NR3C1 was targeted by miR-382-5p, which could help modulate the levels of depression-related factors.

NR3C1 has been reported essential in the depressive disorders for a long time.³⁷ According to the qPCR and Western blotting results, NR3C1 downstream targets BDNF and p-TrkB were also elevated in the LV-NR3C1 group. Treatments with LV-NR3C1 lowered the latency to feed, elevated sucrose preference, decreased immobility time and elevated swimming time. No obvious changes were observed in food intake and water intake by NR3C1 over-expressions. In consistence with previous findings, we also found that NR3C1 could impact depression behaviors in rats.

Conclusion

Through our experiments and analysis, we found that the associations between miR-382-5p on NR3C1 could affect the depression-like behaviors.

Abbreviations

CUMS, chronic unpredictable mild stress; NR3C1, nuclear receptor subfamily 3 group C member 1.

Data Sharing Statement

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The experiments had approval by the Institute for Experimental Animals of People's Hospital of Shenzhen Baoan District.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests for this work.

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