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LncRNA SNHG14 Served as a Biomarker of Depression Disorder Patients and Regulated Depression-Like Behaviors via MiR-200a-3p

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Depression disorder has become a major mental disease and has attracted special attention globally. Identifying specific biomarkers for the diagnosis and severity of depression disorder would benefit its clinical management. This study focused on the significance of lncRNA SNHG14 in depression disorder and investigated its effect on depression-like behaviors, aiming to explore a potential biomarker for depression disorder occurrence and development. This study included 147 patients with depression disorder and 98 healthy individuals. The serum *SNHG14* in all participants was analyzed by PCR, and its diagnostic value was evaluated by receiver operatorating characteristic curve (ROC) analysis. The depression-like behaviors were induced via chronic social defeat stress (CSDS) and evaluated by sucrose preference, forced swimming, and open field tests. *SNHG14* was significantly upregulated in depression disorder patients relative to healthy individuals, which discriminated depression disorder patients with a relatively high efficiency. Depression disorder patients with severe conditions showed higher serum *SNHG14* levels, and a significantly positive correlation of *SNHG14* with PHQ9 score was demonstrated. In CSDS mice, increasing *SNHG14* and decreasing miR-200a-3p were observed. Silencing *SNHG14* and overexpressing miR-200a-3p could alleviate reduced sucrose preference, increased swimming immobility time, decreased standing times, and decreased traveling distance induced by CSDS. The knockdown of *SNHG14* promoted the expression of miR-200a-3p, and silencing miR-200a-3p could reverse the protective effect of *SNHG14* silencing on depression-like behaviors. *SNHG14* served as a biomarker for the occurrence and severity of depression disorder. Silencing *SNHG14* could alleviate depression-like behaviors via modulating miR-200a-3p.

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Introduction

Depression disorder is a nervous system disease with the behaviors of losing interest in activities, appetite disorders, and suicidal thoughts or even suicide. It was reported that the lifetime prevalence of depression disorder is as high as 11%, which exerted negative effects on the life quality of patients (Kessing 2007). During the period of delay and relapse, the cognitive function of depression disorder patients is continuously declining, which severely hinders the recovery of patients' social function (Greenberg et al. 2012; Demyttenaere and Heirman 2020). Depression disorder is a chronic disease involving various factors, such as genetics, epigenetics, endocrine biology, and environment (Ménard et al. 2016). The diagnosis and therapy of depression disorder are still challenging problems in clinical research. There is a lack of unified theory for the pathogenesis of depression disorder, and the inducing factors are diverse. Recently, it is widely known that the onset and progression of depression disorder involves nerve injury, which is regulated by a number of molecules (Caloc'h et al. 2023; Suárez-Rojas et al. 2023; Mehsein et al. 2024).

Non-coding RNAs (ncRNAs) have been revealed to mediate the proliferation, differentiation, and apoptosis of

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nerve cells and are closely associated with the progression of various nervous system diseases, such as neurodegenerative diseases, consciousness disorders, and cardiovascular diseases (Esteller 2011; Akhter 2018; Wu and Kuo 2020; van den Berg et al. 2020; Sun et al. 2022) . For depression disorder, there have been numerous studies confirmed the role of lncRNAs in disease development and identified functional lncRNAs (Cui et al. 2016). For example, both lncRNA NONHSAG004550 and lncRNA NONHSAT 125420 were found to be dysregulated in perinatal depression patients, and their combination showed significant diagnostic potential with relatively high sensitivity and specificity (Wang et al. 2021a). Previously, lncRNA SNHG14 has been identified as a critical neuro-related ncRNA that regulates cognitive impairment, modulates neuroinflammation, and participates in the progression of brain tumors (Lu et al. 2020; Duan et al. 2021; He et al. 2023). Therefore, *SNHG14* is hypothesized of great potential to act as a biomarker for depression disorder, which lacks confirming data. Modulating functional microRNAs (miRNAs) is the major regulatory mechanism underlying lncRNAs. Among predicted ceRNAs of *SNHG14*, miR-200a-3p was previously identified as a depression-related miRNA and was involved in the onset of neurodegenerative disease (Satyanarayanan et al. 2019; Wang et al. 2019; McKibben and Dwivedi 2021). Whether miR-200a-3p mediates the function of *SNHG14* in depression disorder was investigated in this study, to reveal the regulatory mechanism.

Furthermore, animal modeling is a commonly used method to investigate the regulator mechanism of ncRNAs in human diseases. Stress has been considered the major inducing factor for the pathology of depression disorder, which has been widely employed for the modeling of depression animals. There are various established methods reported, such as chronic pain, chronic social defeat stress, and chronic unpredictable mild stress. Chronic social defeat stress (CSDS) is a novel modeling method that has attracted special attention in recent studies to establish depression disorder rat models. CSDS could mimic the pathological mechanism of depression disorder in humans and induce corresponding depression-like behaviors, such as anhedonia, social avoidance, anxiety, and susceptibility to addiction (Wang et al. 2021b). More importantly, previous studies have demonstrated that the CSDS rat models showed consistent changes in brain function, neurotransmitters, and hormone levels in depression disorder patients (Veeraiah et al. 2014; Wingo et al. 2018).

According to the above, the significance of *SNHG14* in depression disorder remains unclear, which could provide a biomarker for the disease screening and severity evaluation. Additionally, with the employment of animal modeling, the regulatory mechanism underlying *SNHG14* was also investigated to provide novel ideas and insights into the therapy of depression disorder.

Materials and Methods

Study design

A total of 147 depression disorder patients were enrolled in People's Hospital of Dongxihu District from 2018-2021, and another 98 healthy volunteers with matched age and sex composition were included in the same period. This study has been approved by the Ethics Committee of People's Hospital of Dongxihu District, and all participants had signed informed consent. Depression disorder patients were diagnosed according to the Diagnostic Statistical Manual of Mental Disorders (American Psychiatric Association 2000) and confirmed by two psychiatrists. The severity of depression disorder patients was evaluated based on the Patient Health Questionnaire-9 (PHQ-9). Patients with one of the following items were excluded from the study: 1) psychotic disorder; 2) mental retardation; 3) limited capacity; 4) substance dependence.

Sample preparation

Blood samples were collected from all study subjects and stood for 20 min at room temperature. Serum was isolated by centrifugation at 1,500 × *g* for 10 min at 4°C and stored in liquid nitrogen at −80°C for the following analyses.

Depression disorder animal modeling

C57BL/6J mice (aged 5-8 weeks and weighted 24 ± 2 g, mean ± standard deviation, SD) were purchased from the Shanghai SLAC Animal Center and maintained at 24°C with 55% relative humidity. Depression disorder mice models were established with the CSDS modeling according previous studies (Golden et al. 2011; Munshi et al. 2022; Guan et al. 2023). Mice were supplied with free access to food and drink for 7 days to adapt to the environment. The *SNHG14*-knockdown lentivirus (OBio Technology, Shanghai, China), miR-200a-3p antagomir (Ribobio, Guangzhou, China), or their negative controls were microinjected into the hippocampus before modeling. The injection position was anterior/posterior (AP), −2.0 mm; medial/lateral (ML), ± 1.5 mm; and dorsal/ventral (DV), −2.0 mm. Then, mice were randomly divided into a control group and a stress group.

For the stress group, C57BL/6J mice were housed on the right side of the cage with a perforated partition and CD1 mice were housed on the left side as the attacker. On the first day, the C57BL/6J mice were placed on the left side together with CD1 mice and received attack for 5-10 min until showing obvious rigidity and avoidance. Then, the C57BL/6J mice were separated from CD1 mice using a perforated transparent plastic partition ensuring the C57BL/6J mice could observe the behavior, hear the sound, and smell CD1 mice and thus receive continuous stress. On the next day, the stress was repeated, and this cyclic mode lasted for 10 days. Then, the ethology of experimental mice was evaluated with corresponding tests.

Sucrose preference test

The sucrose preference test was performed to evaluate the degree of anhedonia in the first 48 h of the test, and the location of 1% sucrose solution and water was changed every 12 h, to avoid the effect of location on the testing results and ensure mice acclimate to the sucrose solution. The formal test was conducted with two bottles filled with water and 1% sucrose solution, respectively. The two bottles were weighed and placed in the primary location. C57BL/6J mice were free to drink and the two bottles were exchanged at the location every 12 h. The bottles were weighted after 24 h of testing. The preference rate was calculated according to the following equation: preference rate = sucrose consumption / (water and sucrose consumption) × 100%.

Forced swimming test

The forced swimming test was conducted to assess the severity of depression in mice. The C57BL/6J mice were forced to swim in warm water for 15 min and then wiped dry. After 24 h, the mice were forced to swim for 5 min and were unable to touch the bottom of the pool. The immobile time was recorded when the mice stopped struggling, only moved slightly with one forepaw, or kept the nose above the water occasionally.

Open field test

The purpose of the open field test was to assess the cognitive function of mice. The C57BL/6J mice were placed in the observation box (length of 100 cm, width of 70 cm, height of 50 cm without top) for 5 min after modeling. The total traveling distance and the number of standings were recorded.

Real-time quantitative PCR

After ethology testing, the hippocampal tissues of experimental mice or serum samples of study subjects were collected, and total RNA was extracted using the TRIzol reagent (1 mL/100 mg tisusses or 200 μL serum). The purity of isolated RNA was evaluated by the ratio of OD260/280, and the ratio ranging 1.8-2.2 indicated high-quality RNA. cDNA was generated from isolated RNA using ImProm-II Reverse Transcription System (for *SNHG14*, Promega, Madison, WI, USA) or TaqMan miR Rever Transcription kit (for miR-200a-3p, Applied Biosystem, Waltham, MA, USA). Then, amplification was performed on a real-time PCR system (7500 fast PCR system, Applied Biosystem) with GAPDH (forward 5′-GACTGAGATTGGCCCGATG-3′, reverse 5′-GACTGAGATTGGCCCGATG-3′) and U6 (forward 5′-CTCGCTTCGGCAGCACA-3′, reverse 5′-AACGCTTCACGAATTTGCGT-3′) as the internal reference for *SNHG14* (forward 5′-GGGTGTTTACGTAGACCAGAACC-3′, reverse 5′-CTTCCAAAAGCCTTCTGCCTTAG-3′) and miR-200a-3p (forward 5′-TAACACTGTCTGGTAACGATGT-3′, reverse 5′-CATCTTACCGGACAGTGCTGGA-3′), respectively. The relative levels of SNHG14 and miR-200a-3p were calculated by the $2^{-\Delta\Delta CT}$ method.

Statistical analyses

All data were analyzed by SPSS 22.0 software (IBM, Armonk, NY, USA) and GraphPad Prism 9.0 software (GraPhpad Prism, La Jolla, CA, USA). Difference comparison was conducted with the student's t-test and one-way ANOVA for two groups and multiple groups, respectively. The receiver operating curve (ROC) analysis was employed to assess the significance of *SNHG14* in diagnosing depression disorder patients. The sensitivity and specificity of diagnosis were obtained at the maximum Youden index. The correlation of *SNHG14* with PHQ9 score was analyzed by Pearson's correlation analysis to evaluate its association with disease severity of depression disorder patients. $P < 0.05$ indicates statistical significance.

Results

Upregulate SNHG14 predicts the occurrence and severity of depression disorder patients

Compared with healthy individuals, significant upregulation of *SNHG14* was observed in patients with depres-

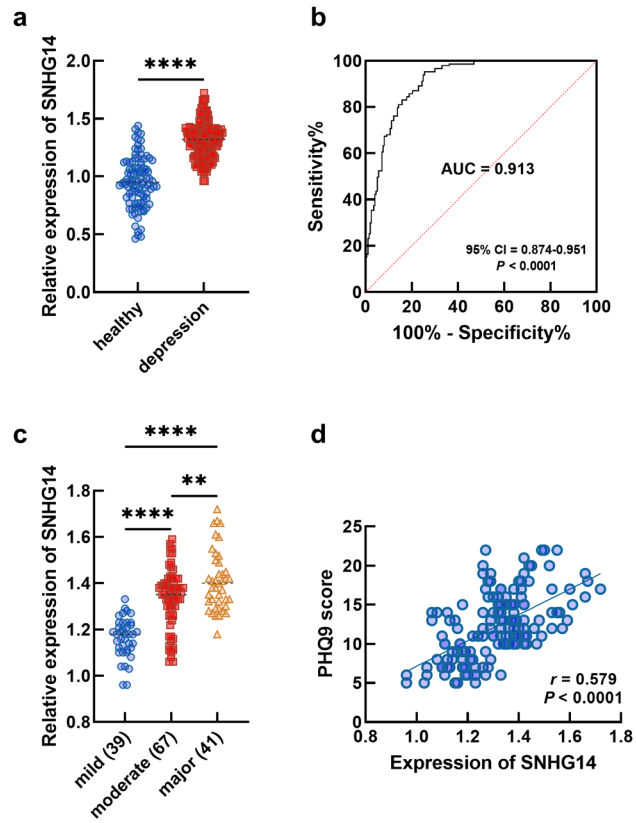

Fig. 1. Expression and significance of *SNHG14* in depression disorder patients.
a. Expression of *SNHG14* in healthy individuals and depression disorder patients. b. Significance of *SNHG14* in distinguishing depression disorder patients. c. Expression of *SNHG14* in depression disorder patients with different severity. d. Correlation of *SNHG14* with PHQ9 score of depression disorder patients. $^{**}P < 0.01$, $^{****}P < 0.0001$.

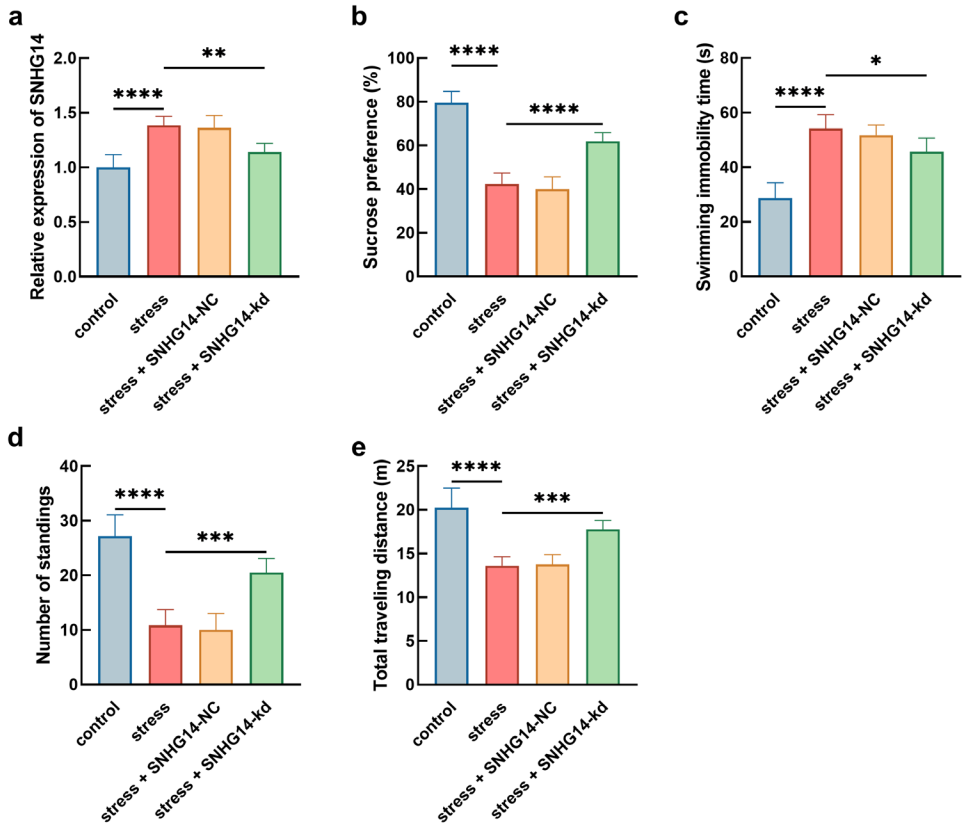

Fig. 2. Effect of *SNHG14* on depression-like behaviors in chronic social defeat stress (CSDS) mice models. a. Expressopm of *SNHG14* in CSDS mice. b-e. Behaviors tests on CSDS mice by sucrose preference test (b), forced swimming test (c), and open field test (d and e). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. Data were represented as mean ± SD (n = 6).

sion disorder (Fig. 1a), which could also discriminate depression disorder patients confirmed by ROC (AUC = 0.913, Fig. 1b). The severity of depression disorder patients was evaluated by the PHQ9 scores. Among the enrolled depression disorder patients, there were 39 patients diagnosed with mild depression disorder, 67 patients diagnosed with moderate depression disorder, and 41 patients diagnosed with major depression disorder. The depression disorder patients with increasing severity showed a significantly higher expression of *SNHG14* (Fig. 1c). Consistently, *SNHG14* was positively correlated with the PHQ9 score of depression disorder patients with a correlation coefficient of 0.579 (Fig. 1d).

Silencing SNHG14 suppresses depression-like behaviors

Mice that received CSDS showed a significantly increasing expression of *SNHG14*, which was silenced by the *SNHG14*-knockdown lentivirus (Fig. 2a). CSDS mice showed decreasing sucrose preference (Fig. 2b), increasing swimming immobility time in the forced swimming test (Fig. 2c), decreasing number of standings (Fig. 2d), and decreasing traveling distance (Fig. 2e) in the open field test, which are considered depression-like behaviors. The knockdown of *SNHG14* (SNHG14-kd) could alleviate the depression-like behaviors of CSDS mice, behaving as increasing sucrose preference (Fig. 2b), decreasing swimming immobility time (Fig. 2c), increasing standing times (Fig. 2d), and increasing traveling distance (Fig. 2e).

Overexpressing miR-200a-3p attenuated depression-like behaviors

In CSDS mice, miR-200a-3p was significantly downregulated, which was reversed by the injection of its angomir (miR-angomir) (Fig. 3a). Moreover, the overexpression of miR-200a-3p also showed significant protective effects on CSDS mice, which improves sucrose preference (Fig. 3b), reduces swimming immobility time (Fig. 3c), increases number of standings (Fig. 3d), and lengthens traveling distance (Fig. 3e) of CSDS mice.

SNHG14 regulates depression-like behavior via modulating miR-200a-3p

In CSDS mice, silencing *SNHG14* significantly increased the expression of miR-200a-3p, which was reversed by the injection of its antagomir (Fig. 4a). Meanwhile, the alleviation of depression-like behaviors by silencing *SNHG14* was dramatically reversed by the knockdown of miR-200a-3p, which was hypothesized as the

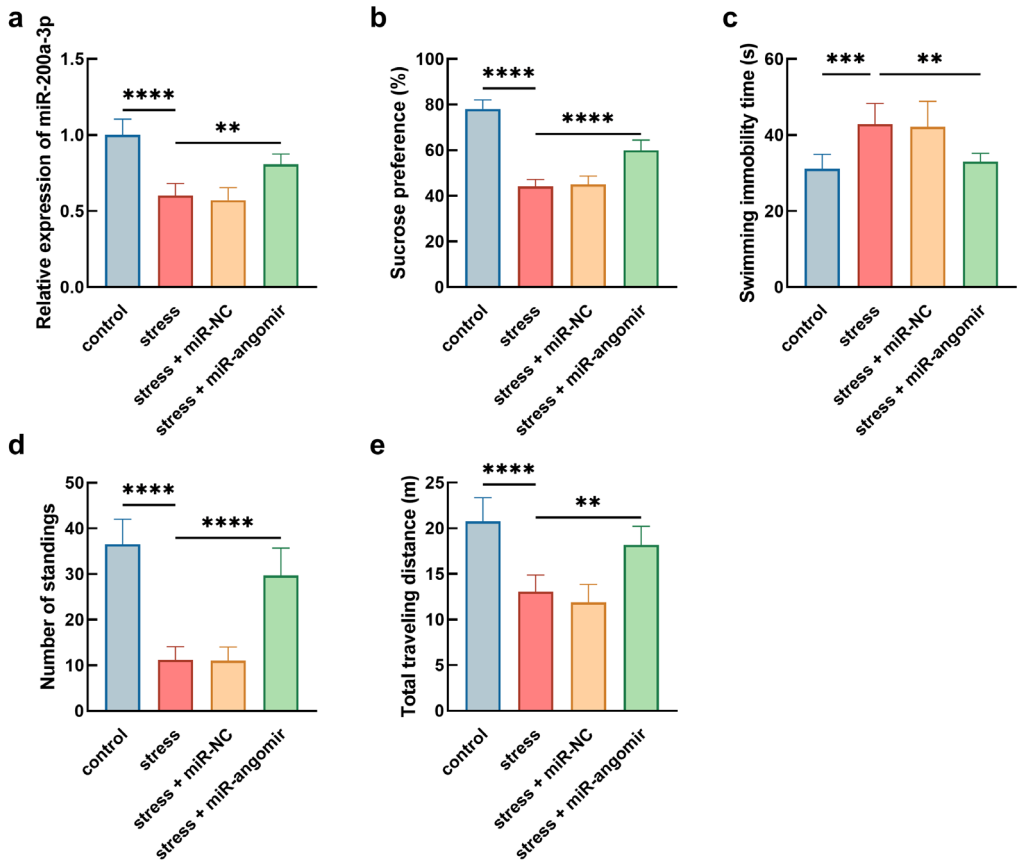

Fig. 3. Effect of miR-200a-3p on depression-like behaviors in chronic social defeat stress (CSDS) mice models. a. Expression of miR-200a-3p in CSDS mice. b-e. Behaviors tests on CSDS mice by sucrose preference test (b), forced swimming test (c), and open field test (d and e). $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. Data were represented as mean ± SD (n = 6).

potential regulatory mechanism underlying *SNHG14* (Fig. 4b-e).

Discussion

Depression disorder has become a major mental disease in China, which seriously threatens the life quality of patients. Although the treatment of depression disorder has developed rapidly in the past decades, there are still about one-third of depression disorder patients showing no alleviated symptoms after treatments with multiple medications (Cohn et al. 2011; Monroe and Harkness 2022). Exploring novel biomarkers for the diagnosis and development of depression disorder is of great clinical significance. The clinical significance of *SNHG14* in human diseases has attracted special attention in previous studies. In human cancers, *SNHG14* could promote cervical cancer progression and predict adverse prognosis of patients (Zhang et al. 2019b). *SNHG14* was also identified as a necroptosis-related lncRNA in glioma and could predict the prognosis and immune reaction of glioma patients (Wu et al. 2022). The prognostic value of *SNHG14* was also confirmed in acute myeloid leukemia which was associated with adverse overall survival (Gamaleldin et al. 2021). More importantly, *SNHG14* has also been identified as a neuro-related lncRNA that has been reported to regulate nerve cell apoptosis, protect cerebral injury, and regulate nervous system diseases, such as Parkinson's disease and neuroinflammation (Zhang et al. 2019a; Jiang et al. 2021; Sun et al. 2021; Tan et al. 2023). In the present study, the significant upregulation of *SNHG14* was observed in depression disorder patients relative to healthy individuals. Increasing *SNHG14* could distinguish between depression disorder patients and healthy volunteers with relatively high efficiency, indicating its diagnostic potential in depression disorder. Additionally, the expression of *SNHG14* showed a positive correlation with the PHQ9 score of depression disorder patients, which is a critical indicator assessing the severity of patients. According to the clinical results, increasing serum *SNHG14* could be considered a biomarker for the diagnosis and severity of depression disorder. Compared with other clinical examinations, the blood analyses could provide a more objective results, and PCR analysis is low-cost and fast. Therefore, increasing serum *SNHG14* levels is of great potential to be employed as a clinical indicator for depression disorder.

Through animal modeling, the regulatory mechanism

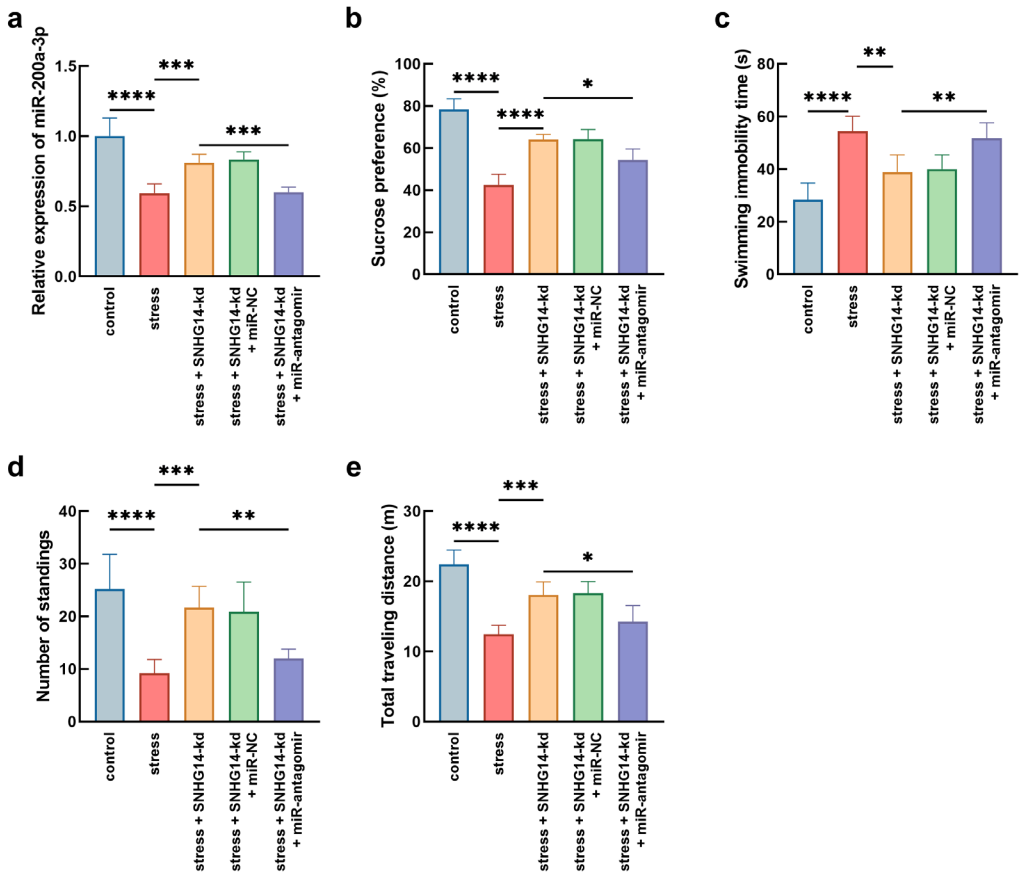

Fig. 4. Involvement of miR-200a-3p in the function of *SNHG14* in chronic social defeat stress (CSDS) mice model. a. Expression of miR-200a-3p regulated by *SNHG14*. b-e. Behaviors tests on CSDS mice by sucrose preference test (b), forced swimming test (c), and open field test (d and e). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. Data were represented as mean ± SD (n = 6).

of *SNHG14* was revealed. The response to environmental stress is a major cause of depression disorder (Menard et al. 2017). CSDS mouse modeling has been considered an effective animal model for inducing long-term depression-like behaviors (Wang et al. 2021b). The depression-like behaviors of CSDS mice were evaluated from three perspectives: anhedonia by sucrose preference (Liu et al. 2018), despairing behaviors by forced swimming (Yankelevitch-Yahav et al. 2015), and autonomy and exploratory behaviors by open field test (Sturman et al. 2018). As expected, CSDS showed significant anhedonia, despairing behaviors, and reduced autonomy and exploratory behaviors. *SNHG14* was significantly upregulated in CSDS mice, and silencing *SNHG14* could alleviate the depression-like behaviors, which is consistent with its association with the severity of depression disorder patients. Among the downstream ceRNAs of *SNHG14*, miR-200a-3p was previously suggested to show protective effects on Alzheimer's disease and was downregulated in chronic pain-induced depression (Satyanarayanan et al. 2019; Wang et al. 2019). Here, the downregulation of miR-200a-3p was observed in CSDS mice, and overexpressing miR-200a-3p could also alleviate depression-like behaviors. Hence, both *SNHG14* and miR-200a-3p were identified as regulators of depression-like behaviors, which are of potential to serve as therapeutic targets of depression disorder. Moreover, silencing *SNHG14* increased the expression of miR-200a-3p in CSDS mice. The antagomir of miR-200a-3p was employed to reverse the overexpression of miR-200a-3p, which also reversed the protective effect of *SNHG14* knockdown on CSDS-induced depression-like behaviors. Therefore, *SNHG14* was hypothesized to regulate depression-like behaviors in CSDS mice via modulating miR-200a-3p.

There are still some limitations in this study. On the one hand, although the diagnostic significance of *SNHG14* in depression disorder patients has been confirmed, the evaluation was performed based on its relative expression in the serum of depression disorder patients. There was a lack of analysis to estimate the absolute content and the threshold of *SNHG14* in the blood depression disorder patients has not been revealed, which would provide a direct reference for the application of *SNHG14* in the clinical diagnosis and prediction of depression disorder patients.

On the other hand, the regulatory mechanism underlying the function of *SNHG14* was only declaimed from the behavior level. Depression disorder is a kind of nervous system disease involving microglia-mediated neuroinflammation, synaptic plasticity, and synaptic transmission (Duman and Aghajanian 2012; Wang et al. 2022). Therefore, deep investigations are needed to confirm the absolute diagnostic cutoff and disclose the regulation of the pathogenesis of depression disorder by *SNHG14*.

Taken together, upregulated *SNHG14* in depression disorder patients served as a biomarker for diagnosing depression disorder and predicting disease severity. Silencing *SNHG14* could suppress depression-like behaviors in the CSDS mice model via enhancing miR-200a-3p.

Author Contributions

H.L.W. developed the original idea and the protocol, abstracted and analyzed data, wrote the manuscript, and is a guarantor. S.W.D. and J.B. contributed to the development of the protocol, abstracted data, and prepared the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

References

Akhter, R. (2018) Circular RNA and Alzheimer's disease. *Adv. Exp. Med. Biol.*, **1087**, 239-243.

American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision (DSM-IV-TR), Washington, DC.

Caloc'h, T., Le Saout, E., Litaneur, S., Suarez, A., Durand, S., Lefaucheur, J.P. & Nguyen, J.P. (2023) Treatment of cognitive and mood disorders secondary to traumatic brain injury by the association of bilateral occipital nerve stimulation and a combined protocol of multisite repetitive transcranial magnetic stimulation and cognitive training: a case report. *Front. Neurol.*, **14**, 1195513.

Cohn, A.M., Epstein, E.E., McCrady, B.S., Jensen, N., Hunter-Reel, D., Green, K.E. & Drapkin, M.L. (2011) Pretreatment clinical and risk correlates of substance use disorder patients with primary depression. *J. Stud. Alcohol Drugs*, **72**, 151-157.

Cui, X., Sun, X., Niu, W., Kong, L., He, M., Zhong, A., Chen, S., Jiang, K., Zhang, L. & Cheng, Z. (2016) Long non-coding RNA: potential diagnostic and therapeutic biomarker for major depressive disorder. *Med. Sci. Monit.*, **22**, 5240-5248.

Demyttenaere, K. & Heirman, E. (2020) The blurred line between anxiety and depression: hesitations on comorbidity, thresholds and hierarchy. *Int. Rev. Psychiatry*, **32**, 455-465.

Duan, R., Wang, S.Y., Wei, B., Deng, Y., Fu, X.X., Gong, P.Y., E, Y., Sun, X.J., Cao, H.M., Shi, J.Q., Jiang, T. & Zhang, Y.D. (2021) Angiotensin-(1-7) analogue AVE0991 modulates astrocyte-mediated neuroinflammation via lncRNA SNHG14/miR-223-3p/NLRP3 pathway and offers neuroprotection in a transgenic mouse model of Alzheimer's disease. *J. Inflamm. Res.*, **14**, 7007-7019.

Duman, R.S. & Aghajanian, G.K. (2012) Synaptic dysfunction in depression: potential therapeutic targets. *Science*, **338**, 68-72.

Esteller, M. (2011) Non-coding RNAs in human disease. *Nat. Rev. Genet.*, **12**, 861-874.

Gamaleldin, M.A., Ghallab, O. & Abo Elwafa, R.A. (2021) Prognostic significance of long non coding RNA ANRIL and SNHG14 in acute myeloid leukemia. *Asian Pac. J. Cancer Prev.*, **22**, 3763-3771.

Golden, S.A., Covington, H.E. 3rd, Berton, O. & Russo, S.J. (2011) A standardized protocol for repeated social defeat stress in mice. *Nat. Protoc.*, **6**, 1183-1191.

Greenberg, J., Tesfazion, A.A. & Robinson, C.S. (2012) Screening, diagnosis, and treatment of depression. *Mil. Med.*, **177**, 60-66.

Guan, W., Wu, X.Y., Jin, X., Sheng, X.M. & Fan, Y. (2023) miR-204-5p plays a critical role in the pathogenesis of depression and anti-depression action of venlafaxine in the hippocampus of mice. *Curr. Med. Chem.*, **31**, 3412-3425.

He, G., Ni, H., Wang, K., Gao, H., Li, Y., Gu, J., Ni, X., Wang, Z. & Bao, Y. (2023) Dexmedetomidine attenuates the neuroinflammation and cognitive dysfunction in aged mice by targeting the SNHG14/miR-340/NF-kappaB axis. *Biomed. Rep.*, **19**, 100.

Jiang, H., Ni, J., Zheng, Y. & Xu, Y. (2021) Knockdown of lncRNA SNHG14 alleviates LPS-induced inflammation and apoptosis of PC12 cells by regulating miR-181b-5p. *Exp. Ther. Med.*, **21**, 497.

Kessing, L.V. (2007) Epidemiology of subtypes of depression. *Acta Psychiatr. Scand. Suppl.*, 85-89.

Liu, M.Y., Yin, C.Y., Zhu, L.J., Zhu, X.H., Xu, C., Luo, C.X., Chen, H., Zhu, D.Y. & Zhou, Q.G. (2018) Sucrose preference test for measurement of stress-induced anhedonia in mice. *Nat. Protoc.*, **13**, 1686-1698.

Lu, J., Liu, X., Zheng, J., Song, J., Liu, Y., Ruan, X., Shen, S., Shao, L., Yang, C., Wang, D., Cai, H., Cao, S. & Xue, Y. (2020) Lin28A promotes IRF6-regulated aerobic glycolysis in glioma cells by stabilizing SNHG14. *Cell Death Dis.*, **11**, 447.

McKibben, L.A. & Dwivedi, Y. (2021) MicroRNA regulates early-life stress-induced depressive behavior via serotonin signaling in a sex-dependent manner in the prefrontal cortex of rats. *Biol. Psychiatry Glob. Open Sci.*, **1**, 180-189.

Mehsein, Z., Kobaïter-Maarrawi, S., Samaha, H., El Shami, M., Albeaini, S. & Maarrawi, J. (2024) Right posterior insular epidural stimulation in rats with neuropathic pain induces a frequency-dependent and opioid system-mediated reduction of pain and its comorbid anxiety and depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **128**, 110845.

Ménard, C., Hodes, G.E. & Russo, S.J. (2016) Pathogenesis of depression: insights from human and rodent studies. *Neuroscience*, **321**, 138-162.

Menard, C., Pfau, M.L., Hodes, G.E., Kana, V., Wang, V.X., Bouchard, S., Takahashi, A., Flanigan, M.E., Aleyasin, H., LeClair, K.B., Janssen, W.G., Labonte, B., Parise, E.M., Lorsch, Z.S., Golden, S.A., et al. (2017) Social stress induces neurovascular pathology promoting depression. *Nat. Neurosci.*, **20**, 1752-1760.

Monroe, S.M. & Harkness, K.L. (2022) Major depression and its recurrences: life course matters. *Annu. Rev. Clin. Psychol.*, **18**, 329-357.

Munshi, S., Ritger, A. & Rosenkranz, A.J. (2022) Induction of repeated social defeat stress in rats. *Bio Protoc.*, **12**, e4306.

Satyanarayanan, S.K., Shih, Y.H., Wen, Y.R., Palani, M., Lin, Y.W., Su, H., Galecki, P. & Su, K.P. (2019) miR-200a-3p modulates gene expression in comorbid pain and depression: molecular implication for central sensitization. *Brain. Behav. Immun.*, **82**, 230-238.

Sturman, O., Germain, P.L. & Bohacek, J. (2018) Exploratory rearing: a context- and stress-sensitive behavior recorded in the open-field test. *Stress*, **21**, 443-452.

Suárez-Rojas, I., Perez-Fernandez, M., Bai, X., Martinez-Martel, I., Intagliata, S., Pittala, V., Salerno, L. & Pol, O. (2023) The inhibition of neuropathic pain incited by nerve injury and accompanying mood disorders by new heme oxygenase-1 inducers: mechanisms implicated. *Antioxidants* (*Basel*), **12**, 1859.

Sun, B., Ou, H., Ren, F., Guan, Y., Huan, Y. & Cai, H. (2021)

Propofol protects against cerebral ischemia/reperfusion injury by down-regulating long noncoding RNA SNHG14. *ACS Chem. Neurosci.*, **12**, 3002-3014.

Sun, P., Hamblin, M.H. & Yin, K.J. (2022) Non-coding RNAs in the regulation of blood-brain barrier functions in central nervous system disorders. *Fluids Barriers CNS*, **19**, 27.

Tan, Q., Liu, L., Wang, S., Wang, Q. & Sun, Y. (2023) Dexmedetomidine promoted HSPB8 expression via inhibiting the lncRNA SNHG14/UPF1 axis to inhibit apoptosis of nerve cells in AD : the role of dexmedetomidine in AD. *Neurotox. Res.*, **41**, 471-480.

van den Berg, M.M.J., Krauskopf, J., Ramaekers, J.G., Kleinjans, J.C.S., Prickaerts, J. & Briede, J.J. (2020) Circulating microRNAs as potential biomarkers for psychiatric and neurodegenerative disorders. *Prog. Neurobiol.*, **185**, 101732.

Veeraiah, P., Noronha, J.M., Maitra, S., Bagga, P., Khandelwal, N., Chakravarty, S., Kumar, A. & Patel, A.B. (2014) Dysfunctional glutamatergic and gamma-aminobutyric acidergic activities in prefrontal cortex of mice in social defeat model of depression. *Biol. Psychiatry*, **76**, 231-238.

Wang, H., He, Y., Sun, Z., Ren, S., Liu, M., Wang, G. & Yang, J. (2022) Microglia in depression: an overview of microglia in the pathogenesis and treatment of depression. *J. Neuroinflammation*, **19**, 132.

Wang, L., Liu, J., Wang, Q., Jiang, H., Zeng, L., Li, Z. & Liu, R. (2019) MicroRNA-200a-3p mediates neuroprotection in Alzheimer-related deficits and attenuates amyloid-beta overproduction and tau hyperphosphorylation via coregulating BACE1 and PRKACB. *Front. Pharmacol.*, **10**, 806.

Wang, L., Zhang, M., Zhu, H., Sun, L., Yu, B. & Cui, X. (2021a) Combined identification of lncRNA NONHSAG004550 and NONHSAT125420 as a potential diagnostic biomarker of perinatal depression. *J. Clin. Lab. Anal.*, **35**, e23890.

Wang, W., Liu, W., Duan, D., Bai, H., Wang, Z. & Xing, Y. (2021b) Chronic social defeat stress mouse model: current view on its behavioral deficits and modifications. *Behav. Neurosci.*, **135**, 326-335.

Wingo, A.P., Velasco, E.R., Florido, A., Lori, A., Choi, D.C., Jovanovic, T., Ressler, K.J. & Andero, R. (2018) Expression of the PPM1F gene is regulated by stress and associated with anxiety and depression. *Biol. Psychiatry*, **83**, 284-295.

Wu, Y.Y. & Kuo, H.C. (2020) Functional roles and networks of non-coding RNAs in the pathogenesis of neurodegenerative diseases. *J. Biomed. Sci.*, **27**, 49.

Wu, Z., Liu, M., Fu, J., Li, J., Qin, L., Wu, L., Chen, H., Yan, X., Liu, Q. & Zheng, J. (2022) A novel necroptosis-related lncRNA signature for predicting prognosis and immune response of glioma. *Biomed Res. Int.*, **2022**, 3742447.

Yankelevitch-Yahav, R., Franko, M., Huly, A. & Doron, R. (2015) The forced swim test as a model of depressive-like behavior. *J. Vis. Exp.*, 52587.

Zhang, L.M., Wang, M.H., Yang, H.C., Tian, T., Sun, G.F., Ji, Y.F., Hu, W.T., Liu, X., Wang, J.P. & Lu, H. (2019a) Dopaminergic neuron injury in Parkinson's disease is mitigated by interfering lncRNA SNHG14 expression to regulate the miR-133b/ alpha-synuclein pathway. *Aging* (*Albany N. Y.*), **11**, 9264-9279.

Zhang, Y.Y., Li, M., Xu, Y.D. & Shang, J. (2019b) LncRNA SNHG14 promotes the development of cervical cancer and predicts poor prognosis. *Eur. Rev. Med. Pharmacol. Sci.*, **23**, 3664-3671.