Scientific Research Publishing

Advances in Bioscience and Biotechnology, 2022, 13, 336-346
https://www.scirp.org/journal/abb
ISSN Online: 2156-8502
ISSN Print: 2156-8456

miR-362-3p Knockdown Triggers Inflammation to Promote Neuropathic Pain by Modulating JMJD1A Expression

Miao Huo[1], Qian Zhang[2], Xingxing Zheng[1], Hui Wang[1], Guang Yang[1], Jiao Guo[1], Ziyu Zhao[1]*

[1]Department of Anesthesiology, Shaanxi Provincial People's Hospital, Xi'an, China
[2]Department of Burn and Plastic Surgery, Shaanxi Provincial People's Hospital, Xi'an, China
Email: *rubypan0218@163.com

How to cite this paper: Huo, M., Zhang, Q., Zheng, X.X., Wang, H., Yang, G., Guo, J. and Zhao, Z.Y. (2022) miR-362-3p Knockdown Triggers Inflammation to Promote Neuropathic Pain by Modulating JMJD1A Expression. *Advances in Bioscience and Biotechnology*, **13**, 336-346.
https://doi.org/10.4236/abb.2022.138021

Received: May 13, 2022
Accepted: August 27, 2022
Published: August 30, 2022

Abstract

Objective: When nerve injury or inflammatory injury, different miRNA-mediated signal pathways are activated or inactivated, causing pain or hyperalgesia. Therefore, miRNA has become a new direction of pain mechanism research. We aimed to investigate the effect and mechanism of miR-362-3p on neuropathic pain in rats with chronic sciatic nerve injury (CCI). **Methods:** Neuropathic pain CCI rat model was established. Real-time-quantitative polymerase chain reaction (RT-PCR), Western blot, immunofluorescence, intrathecal injection, Enzyme-linked immunosorbent assay (ELISA), and dual luciferase reporter gene assays were used to explore the role of miR-362-3p in neuropathic pain development and the relationship between miR-362-3p and JMJD1A (Jumonji domain-containing 1A). **Results:** In the CCI group, the miR-362-3p level was increased and JMJD1A level was reduced in spinal cords and isolated microglia. The paw withdrawal threshold (PWT) and paw withdrawal latency (PWL) values were increased, the secretion of inflammatory factors was reduced, and the microglial marker Iba1 expression was decreased after intrathecal administration of miR-362-3p. miR-362-3p was observed to target JMJD1A. JMJD1A elevation abolished the inhibitory effects of miR-362-3p on neuropathic pain development. **Conclusion:** Intrathecal administration of miR-362-3p significantly relieved neuropathic pain in CCI rats and inhibited neuroinflammation possibly through regulating JMJD1A.

Keywords

miR-362-3p, Neuropathic Pain, Neuroinflammation, JMJD1A, Rats

1. Introduction

Neuropathic pain (NP) is a chronic disease whose clinical features often manif-

est as hyperalgesia, spontaneous pain or allodynia, and so on, and is considered a new burden in the 21st century [1]. Neuropathic pain is caused by damage to the peripheral or central nervous system or by chronic pain resulting from disordered function. Nevertheless, the exact pathogenesis of neuropathic pain is still an enigma and there is no effective treatment. Since neuropathic pain is difficult to be effectively eradicated, it is currently a growing number of patients worldwide, causing enormous physical and mental suffering to patients, and has become an intractable health problem that cannot be ignored [2]. In the clinic, antidepressants, antiepileptics as well as local anesthetics are the mainstays for neuropathic pain treatment, and these drugs often have many side effects or even pain sensitization [3]. Therefore, clarifying neuropathic pain pathogenesis and accelerating highly effective and low toxicity drug development has become hot areas of clinical research.

The expression imbalance of gene sets is a key factor that causes neuropathic pain, and it is clinically instructive to elaborate on the pathogenesis of the disease from the gene level. MiRNAs are a class of endogenous factors in the human body that have the function of regulating genomic expression, participating in the regulation of cell fate, tissue differentiation, functional maintenance, and so on [4]. MiRNAs play a role in regulating gene expression levels in eukaryotic cells, mainly by binding to the 3 URT region of target mRNA. Since neuropathic pain can be considered essentially as a stress response of the nervous system to injury, the pathological changes that occur are closely associated with the expression of various proteins, including signal transduction molecules, neurotransmitters, inflammatory factors, and ion channel proteins, among others [5]. Therefore, miRNAs exert different regulatory effects on the pathological process of neuropathic pain by regulating the expression of proteins related to different signaling pathways. For example, miR-194 has been found to exert an inhibitory effect on the pathological progression of CCI-induced neuropathic pain by targeting Forkhead box A1 (FOXA1) expression [6]. In addition, the study of Huang *et al.* confirmed that miR-183 was also one of the aberrantly expressed miRNAs, and was considered as a closely related miRNA to neuropathic pain, and its effect was mainly through regulating the expression of Mitogen-activated protein kinase kinase kinase 4 (MAP3K4), thereby regulation of inflammatory factors TNF-α, COX-2 and IL-6 [7]. A recent study reported that miR-362-3p may be a potential therapeutic target for neuropathic pain [8]. Nevertheless, the mechanism of miR-362-3p in neuropathic pain progression has not been elucidated.

In this study, we focused on a rat model of chronic sciatic nerve injury (CCI) to clarify molecular details of miR-362-3p in neuropathic pain, with a view to providing an effective strategy for neuropathic pain treatment.

2. Materials and Methods

2.1. Animals

For this study, healthy adult male pathogen-free grade Sprague-Dawley rats (200

± 20 g) were selected as experimental animals, which were uniformly provided by the animal center of Shaanxi Provincial People's hospital. The provided mice were acclimatized for 4 weeks to carry out the corresponding studies, and the mouse housing room conditions were set as: room temperature 20˚C - 25˚C, relative humidity 50% - 70%, and free access to food and water. All animal experiments were designed and operated in compliance with international guidelines for laboratory animals.

2.2. Chronic Sciatic Nerve Injury (CCI) Rat Model

An animal model of neuropathic pain was established in rats by CCI [9]. Rats were anesthetized using an intraperitoneal injection of phenobarbital sodium (40 mg/kg) and subsequently placed prone on the experimental operating table. The skin was cut out using surgical scissors, the muscles were separated, and both sciatic nerves of the rats were exposed. A segment of the sciatic nerve was selected, and the two ends of the sciatic nerve were ligated using a 4 - 0 suture, cut at the middle portion of the ligated nerve, and the muscular and skin layers were sutured sequentially with sutures, sterilized, and wrapped. Sham group rats underwent blunt dissection to expose the sciatic nerve and branches after, but without ligation and transection.

2.3. Intrathecal Injection

After rats were anesthetized, a 30 gauge Hamilton syringe needle was inserted in the subarachnoid space of the spinal cord between L4 and L5. In order to induce bilateral hind limb paralysis, the intrathecal catheter implantation in the correct position was affirmed by injecting 2% lidocaine. MiR-362-3p mimic or LV-JMJD1A was delivered intrathecally using a microsyringe connected to an intrathecal catheter. At the end of the experiment, lumbar L4-L5 spinal cords were dissected for follow-up experiment.

2.4. Spinal Cord Microglia Cell Culture

Rat spinal cord tissue was first isolated and placed into cold Dulbecco′ s Modified Eagle's Medium (DMEM) medium, the tissue was sheared into small pieces of approximately 1 mm^3 and digested with trypsin solution into a cell suspension, the supernatant was removed by centrifugation, and the cells were resuspended in complete medium containing DMEM. After that, they were plated in T75 flasks with a final volume of 25 ml and placed in an incubator at 37˚C with 5% CO_2 for two weeks. Finally, microglia was separated from other cells by shaking the flask with mixed glial cells.

2.5. Rat Behavioral Assays

On days 0, 3, 7, and 14 after CCI surgery, rats were measured for mechanical paw withdrawal threshold (PWT) and paw withdrawal latency (PWL) according to previously described methods [10]. Rats were placed in cages before mea-

surements and acclimatized for 30 min. PWT determination: rats were stimulated on the bottom of the left hind foot with a probe from the electronic von Frey pain meter at stimulus intensities ranging from 0 to 50 g in 2.5 g/s increments, which were stopped when the rat had a lifting and paw withdrawal response, and measured three times in consecutive intervals for 5 min each, and the mean value was taken as the PWT value (g) of the rat. PWL determination: when the left hind limb of rats was stimulated by heat radiation, the duration of paw retraction and heat radiation stimulation was recorded (s). The duration of paw retraction and heat radiation stimulation was measured continuously for 5 times with an interval of 20 min. The mean value was the PWL value of rats (s).

2.6. Enzyme Linked Immunosorbent Assay (ELISA)

Treated rat spinal cord tissues were lysed with RIPA lysis buffer. According to the instructions of the respective ELISA kits, the concentrations of interleukin (IL)-6 and tumour necrosis factor-α (TNF-α) were measured.

2.7. Immunofluorescence

After the rats were sacrificed, they were quickly perfused with 4% paraformaldehyde through the ascending aorta. Subsequently, spinal cord segments were collected, fixed, cryopreserved in 30% sucrose, embedded in cryostat (Sakura, 4583), and sectioned at 16 μm thick tissue sections. After sections were blocked with 4% normal Donkey Serum, primary antibody Iba1 were added for overnight incubation, followed by secondary antibody incubation. Subsequently, DAPI were added into prolong gold antifade reagent, which was then added dropwise to the sections and the images were acquired under a fluorescence microscope (Olympus).

2.8. Western Blotting

Total protein was extracted from L4-L5 segments by utilized lysis buffer. The protein content was determined with a BCA kit. 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) was used to separate the protein suspension, and polyvinylidene difluoride (PVDF) membranes were used to transfer the protein band. Primary antibodies for JMJD1A, Iba1 and GAPDH were used to incubate the membranes after they had been blocked with 5% nonfat milk. After washing with Tris-buffered saline containing 0.1% tween-20 (TBST) buffer, HRP-conjugated goat anti-rabbit IgG was performed to incubate for 1 h. After washing with TBST, the protein bands were visualized with ECL detection reagent, the intensity of the protein bands was quantitatively analyzed using image software, and the relative expression of the protein of interest was calculated.

2.9. Real Time-Quantitative Polymerase Chain Reaction (RT-qPCR)

Total RNA was obtained from spinal cord tissue of rats through TRIzol reagent

(Takara), extracted RNA was reverse transcribed to cDNA using primescript RT reagent kit. The single-strand cDNA was prepared employing Prime Script RT reagent Kit. Importantly, the software was then run in an ABI 7900HT RT-PCR system using the SYBR Premix Ex Taq II program. Ultimately, $2^{-\Delta\Delta CT}$ method was used to calculate the expression of miR-362-3p.

2.10. Luciferase Reporter Assay

The targeted binding sites between miR-362-3p and JMJD1A were predicted using Starbase bioinformatics tool. And miR-362-3p mimics or negative control were cotransfected with wild type JMJD1A (JMJD1A-wt) and mutant JMJD1A (JMJD1A-mut) luciferase reporter vectors into cells using Lipofectamine™ 3000, followed by incubation 48 h and then detection luciferase activity.

2.11. Statistical Analysis

Each experiment was independently repeated three times, and the results were expressed as mean ± standard deviation (SD) and analyzed using SPSS 21.0, with student's t-test for differences between two groups and ANOVA for multiple groups. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. miR-362-3p Level is Decreased in Spinal Cord after CCI

To examine the potential role of miR-362-3p in neuropathic pain, we established a rat model of CCI and further examined PWT and PWL at 0, 3, 7, and 14 days. The results demonstrated that CCI treatment caused a remarkable mechanical allodynia and thermal hyperalgesia (**Figure 1(a)** and **Figure 1(b)**). Moreover, RT-qPCR was performed to assess miR-362-3p expression in the spinal cord at segments L4-L5 and isolated microglias of CCI rats on day 0, 3, 7, and 14 following CCI. The results showed that downregulation of miR-362-3p was uncovered both in L4-L5 segments and isolated microglias (**Figure 1(c)** and **Figure 1(d)**).

3.2. Elevation of miR-362-3p Repressed Neuropathic Pain in Rats after CCI

Rats underwent CCI or sham surgery on day 3 after intrathecal injection of LV-miR-miR-362-3p or LV-NC. RT-qRCR demonstrated that injection of LV-miR-miR-362-3p lead to an effective increase on miR-miR-362-3p level (**Figure 2(a)**). The results of behavioral measurement of rats showed that miR-362-3p overexpression significantly reduced the PWT and PWL (**Figure 2(b)** and **Figure 2(c)**). Upregulation of miR-362-3 pdramatically increased IL-6 and TNF-α production in the L4-L5 segments of rats with CCI (**Figure 2(d)** and **Figure 2(e)**). Moreover, immunofluorescence revealed that overexpression of miR-362-3p markedly suppressed the expression of microglial marker Iba1 in the spinal L4-L5 segments of CCI rats (**Figure 2(f)**).

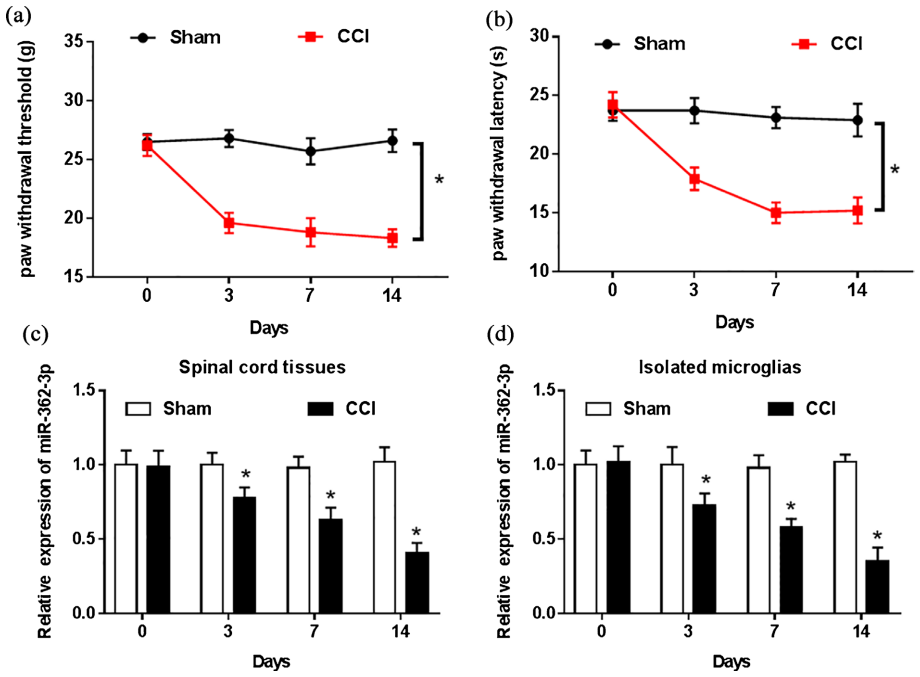

Figure 1. Downregulation of miR-362-3p was found in CCI rats. (a) The mechanical paw withdrawal threshold was test at, 3, 7, and 14 days after CCI; (b) The paw withdrawal latency was test at 0, 3, 7, and 14 days after CCI; (c) and (d) RT-qPCR analysis of miR-362-3p level in spinal cord tissue and microglias of rats at 0, 3, 7, and 14 days after CCI, respectively. *P < 0.05 vs sham group.

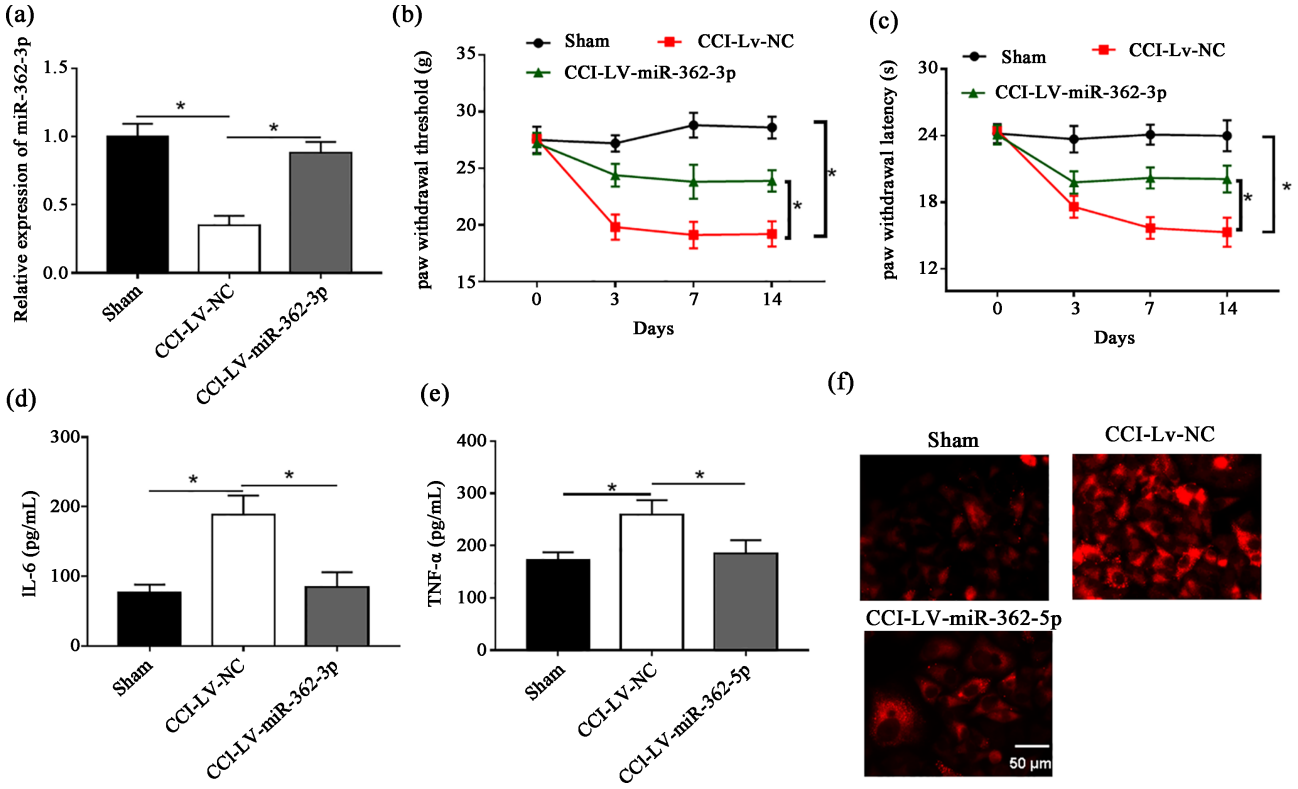

Figure 2. Overexpression of miR-362-3 relieved the development of neuropathic pain in CCI rats. (a) RT-qPCR analysis of miR-362-3p level in spinal cord tissue; (b) The mechanical paw withdrawal threshold was test; (c) The paw withdrawal latency was test; (d) and (e): ELISA analysis of IL-6 and TNF-*α* level; (f) Immunofluorescence analysis of Iba1 expression. *P < 0.05 vs sham group or CCI-LV-NC group.

3.3. miR-362-3p Directly Targets the 3'UTR of JMJD1A

Through starbase databases retrieval, we found that there were highly conserved binding sites between miR-362-3p and JMJD1A, which suggested that JMJD1A might be a potential target of miR-362-3p (Figure 3(a)). Surprisingly, miR-362-3p mimics significantly reduced the luciferase activity of wild type JMJD1A, whereas the luciferase activity of mutant JMJD1A was not changed (Figure 3(b)). Moreover, miR-362-3p mimics downregulated JMJD1A protein expression, whereas miR-362-3p inhibitor upregulated JMJD1A protein expression ($P < 0.01$) (Figure 3(c)). All the results indicated that JMJD1A was the target gene of miR-362-3p.

3.4. miR-362-3p Restrained Neuropathic Pain in CCI Rat Models by Regulating JMJD1A

To study whether JMJD1A plays an active part in miR-362-3p-mediated biological function in neuropathic pain development, we injected LV-miR-362-3p alone or together with LV-JMJD1A in CCI rats. We first found that JMJD1A expression was increased both in L4-L5 segments and isolated microglias following CCI (Figure 4(a) and Figure 4(b)). miR-362-3p elevation remarkably reduced JMJD1A level in CCI rats, which was counteracted by the JMJD1A overexpression (Figure 4(c)). JMJD1A overexpression substantially abolished miR-362-3p-mediated neuropathic pain-like behaviors in CCI rats (Figure 4(d) and Figure 4(e)).

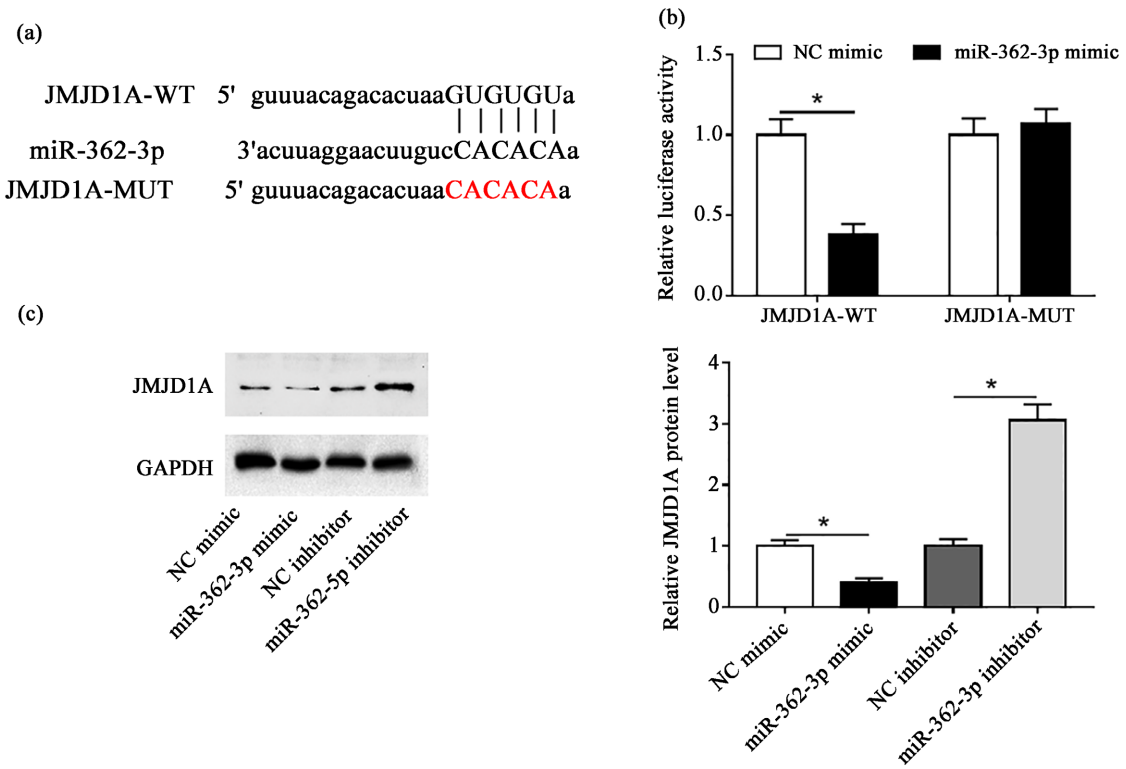

Figure 3. miR-362-3p bound with JMJD1A. (a) Starbase analysis of the binding of miR-362-3p and JMJD1A; (b) Luciferase reporter assay analysis of the relationship of miR-362-3p and JMJD1A; (c) Western blotting analysis of JMJD1A level. *$P < 0.05$ vs NC mimic or NC inhibitor.

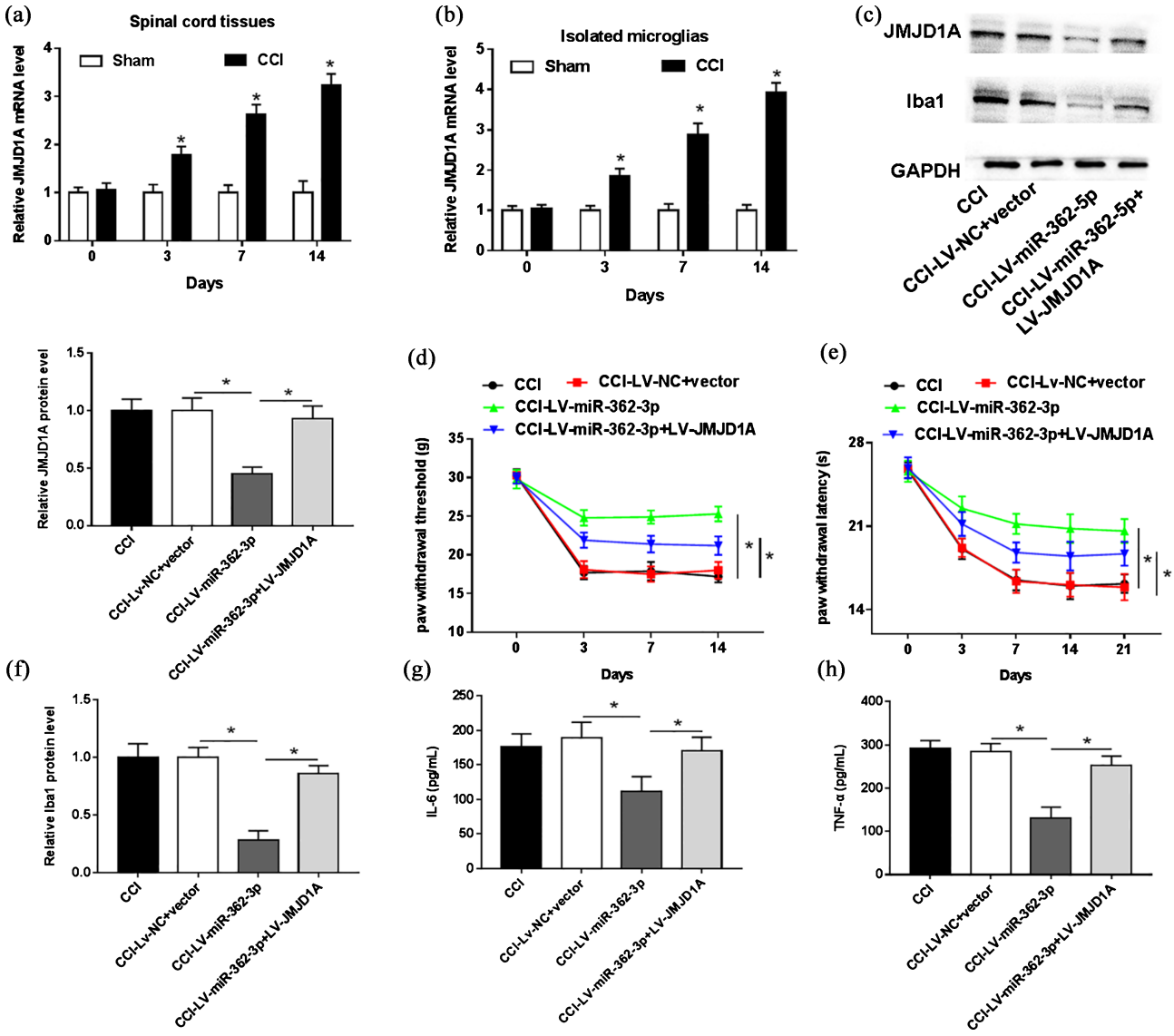

Figure 4. JMJD1A overexpression restored miR-362-3-mediated the impact of neuropathic pain in CCI rats. (a) and (b): RT-qPCR analys is of JMJD1A mRNA level in spinal cord tissue and microglias following CCI. LV-miR-362-3p or/and LV-JMJD1A were injected to rats before CCI; (c) Western blotting analysis of JMJD1AT protein expression; (d) The mechanical paw withdrawal threshold was test; (e) The paw withdrawal latency was test; (f) Western blotting analysis of Iba1 expression; (g) and (h): ELISA analysis of IL-6 and TNF-α level. *P < 0.05 vs CCI-LV-NC + vector or CCI-LV-miR-362-3p.

ELISA and western blotting demonstrated miR-362-3p overexpression suppressed IL-6 and TNF-α secretion and Iba1 expression in CCI rats, whereas JMJD1A overexpression could inverted these changes (Figures 4(f)-(h)).

4. Discussion

The pathogenesis of neuropathic pain is complex and involves peripheral or central nervous system sensitization, nerve conduction block, and neuroinflammation, and there is still a lack of effective treatments in the clinic [11]. Activated inflammatory responses in the nervous system are important contributors to neuropathic pain, and it is now known that IL-6, IL-1β, TNF-α and other in-

flammatory factors are involve in pathogenesis of neuralgia [12]. Accumulating evidence indicates that modulation of multiple miRNAs is able to reduce inflammatory factor secretion in the nervous system and relieve neuropathic pain [13] [14]. Recently, it was found that XIST acted as a competitive endogenous RNA of miR-362, and inhibition of XIST was helpful in alleviating cerebral ischemia-reperfusion injury by alleviating reduced inflammation and neuronal apoptosis by upregulating miR-362 expression [15]. Xie *et al.* reported that curcumin alleviated LPS-induced inflammatory factors secretion in microglial BV2 by inhibiting TRL4 via increasing the expression of miR-362-3p [16]. In spinal cord injury (SCI) rats, miR-362-3p alleviated SCI-induced secondary neuroinflammation, and decreased the degree of neuronal apoptosis to improve the motor function of SCI rats by targeted inhibition of ERK-p38 signaling [8]. Similarly, the present study found that the expression levels of miR-362-3p were significantly decreased in CCI rats. Upregulation of miR-362-3p expression inhibited the secretion of inflammatory factors and activation of microglia, alleviated neuropathic pain in CCI rats.

JMJD1A, also known as KDM3A, is a key member of the jumonji C family of histone demethylases, which play a role in many diseases. Accumulated evidences suggest that JMJD1A acted as an oncogene and contributed to tumor growth and drug resistance development [17] [18] [19]. JMJD1A could induce the expression of proinflammatory mediators through the NF-κB/P65 signaling pathway in cardiomyocytes, exacerbating high glucose-mediated myocardial injury [20]. Zhang *et al.* revealed that JMJD1A was involved in promoting MAPK/NF-κB-dependent inflammation in vascular smooth muscle cell injury induced by high concentrations of insulin [21]. JMJD1A was shown to exacerbate inflammatory damage in diabetes and vascular disease [22]. More importantly, our previous study found that pcat19 enhances neuroinflammation and thus exacerbates neuropathic pain by targeting the miR-182-5p/JMJD1A axis [23]. In this study, we found neuropathic pain (decreased PWT and PWL) as well as neuroinflammation in CCI rats, and this sequence of changes was accompanied by upregulation of JMJD1A expression. Furthermore, JMJD1A was inferred as miR-362-3p downstream target gene, and overexpression of the miR-362-3p effectively restrained JMJD1A expression. Ectopic expression of JMJD1A reverses the impact of miR-362-3p on neuropathic pain development.

5. Conclusion

In summary, the present study observed that in CCI rats, the miR-362-3p level was downregulated, while JMJD1A was upregulated, accompanied by the development of neuropathic pain (decreased PWT and PWL) as well as neuroinflammation in CCI rats. miR-362-3p overexpression significantly suppressed mechanical allodynia and thermal hyperalgesia and downregulated JMJD1A as well as neuroinflammation. Our experimental results provide new research ideas for neuropathic pain treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Woolf, C.J. and Mannion, R.J. (1999) Neuropathic Pain: Aetiology, Symptoms, Mechanisms, and Management. *Lancet* (*London*, *England*), **353**, 1959-1964. https://doi.org/10.1016/S0140-6736(99)01307-0

[2] Van Hecke, O., Austin, S.K., Khan, R.A., Smith, B.H. and Torrance, N. (2014) Neuropathic Pain in the General Population: A Systematic Review of Epidemiological Studies. *Pain*, **155**, 654-662. https://doi.org/10.1016/j.pain.2013.11.013

[3] De Gast, H., Torrensma, B., Fitzgerald, E. and Stevens, H. (2016) The Treatment of Chronic Neuropathic Pain: Bio (Regenerative) Pain Treatment through Lipofilling. A Short Communication Case Series. *Pain Physician*, **19**, E495-E498. https://doi.org/10.36076/ppj/2019.19.E495

[4] Hayes, J., Peruzzi, P.P. and Lawler, S. (2014) MicroRNAs in Cancer: Biomarkers, Functions and Therapy. *Trends in Molecular Medicine*, **20**, 460-469. https://doi.org/10.1016/j.molmed.2014.06.005

[5] Colloca, L., Ludman, T., Bouhassira, D., Baron, R., Dickenson, A.H., Yarnitsky, D., Freeman, R., Truini, A., Attal, N., Finnerup, N.B., Eccleston, C., Kalso, E., Bennett, D.L., Dworkin, R.H. and Raja, S.N. (2017) Neuropathic Pain. *Nature Reviews. Disease Primers*, **3**, Article No. 17002. https://doi.org/10.1038/nrdp.2017.2

[6] Zhang, X., Chen, Q., Shen, J., Wang, L., Cai, Y. and Zhu, K.R. (2020) miR-194 Relieve Neuropathic Pain and Prevent Neuroinflammation via Targeting FOXA1. *Journal of Cellular Biochemistry*, **121**, 3278-3285. https://doi.org/10.1002/jcb.29598

[7] Huang, L. and Wang, L. (2020) Upregulation of miR-183 Represses Neuropathic Pain through Inhibition of MAP3K4 in CCI Rat Models. *Journal of Cellular Physiology*, **235**, 3815-3822. https://doi.org/10.1002/jcp.29276

[8] Hu, Y., Liu, Q., Zhang, M., Yan, Y., Yu, H. and Ge, L. (2019) MicroRNA-362-3p Attenuates Motor Deficit Following Spinal Cord Injury via Targeting Paired Box Gene 2. *Journal of Integrative Neuroscience*, **18**, 57-64. https://doi.org/10.31083/j.jin.2019.01.12

[9] Li, X., Kang, L., Li, G., Zeng, H., Zhang, L., Ling, X., Dong, H., Liang, S. and Chen, H. (2013) Intrathecal Leptin Inhibits Expression of the P2X2/3 Receptors and Alleviates Neuropathic Pain Induced by Chronic Constriction Sciatic Nerve Injury. *Molecular Pain*, **9**, Article No. 65. https://doi.org/10.1186/1744-8069-9-65

[10] Xu, M., Cheng, Z., Ding, Z., Wang, Y., Guo, Q. and Huang, C. (2018) Resveratrol Enhances IL-4 Receptor-Mediated Anti-Inflammatory Effects in Spinal Cord and Attenuates Neuropathic Pain Following Sciatic Nerve Injury. *Molecular Pain*, **14**, 1-11. https://doi.org/10.1177/1744806918767549

[11] Sommer, C., Leinders, M. and Üçeyler, N. (2018) Inflammation in the Pathophysiology of Neuropathic Pain. *Pain*, **159**, 595-602. https://doi.org/10.1097/j.pain.0000000000001122

[12] Moalem, G. and Tracey, D.J. (2006) Immune and Inflammatory Mechanisms in Neuropathic Pain. *Brain Research Reviews*, **51**, 240-264. https://doi.org/10.1016/j.brainresrev.2005.11.004

[13] Andersen, H.H., Duroux, M. and Gazerani, P. (2014) MicroRNAs as Modulators and Biomarkers of Inflammatory and Neuropathic Pain Conditions. *Neurobiology*

of Disease, **71**, 159-168. https://doi.org/10.1016/j.nbd.2014.08.003

[14] Zhang, Y., Mou, J., Cao, L., Zhen, S., Huang, H. and Bao, H. (2018) MicroRNA-142-3p Relieves Neuropathic Pain by Targeting High Mobility Group Box 1. *International Journal of Molecular Medicine*, **41**, 501-510. https://doi.org/10.3892/ijmm.2017.3222

[15] Wang, J., Fu, Z., Wang, M., Lu, J., Yang, H. and Lu, H. (2021) Knockdown of XIST Attenuates Cerebral Ischemia/Reperfusion Injury through Regulation of miR-362/ROCK2 Axis. *Neurochemical Research*, **46**, 2167-2180. https://doi.org/10.1007/s11064-021-03354-6

[16] Xie, P., Deng, M., Sun, Q., Jiang, B., Xu, H., Liu, J., Zhou, Y., Ma, Y. and Chen, Z. (2020) Curcumin Protects BV2 Cells against Lipopolysaccharide-Induced Injury via Adjusting the miR-362-3p/TLR4 Axis. *Molecular Biology Reports*, **47**, 4199-4208. https://doi.org/10.1007/s11033-020-05543-y

[17] Jeon, H.Y., Ryu, H., Pornour, M. and Qi, J. (2022) Histone Demethylase JMJD1A in Cancer Progression and Therapeutic Resistance. *Molecular Carcinogenesis*, **61**, 392-396. https://doi.org/10.1002/mc.23390

[18] Tang, D.E., Dai, Y. and Xu, S.H. (2020) Histone Demethylase JMJD1A Promotes Tumor Progression via Activating Snail in Prostate Cancer. *Molecular Cancer Research*: *MCR*, **18**, 698-708. https://doi.org/10.1158/1541-7786.MCR-19-0889

[19] Peng, K., Su, G., Ji, J., Yang, X., Miao, M., Mo, P., Li, M., Xu, J., Li, W. and Yu, C. (2018) Histone Demethylase JMJD1A Promotes Colorectal Cancer Growth and Metastasis by Enhancing Wnt/β-Catenin Signaling. *The Journal of Biological Chemistry*, **293**, 10606-10619. https://doi.org/10.1074/jbc.RA118.001730

[20] Zhang, B., Zhang, J., Liu, G., Guo, X., Liu, X. and Chen, J. (2022) KDM3A Inhibition Ameliorates Hyperglycemia-Mediated Myocardial Injury by Epigenetic Modulation of Nuclear Factor Kappa-B/P65. *Frontiers in Cardiovascular Medicine*, **9**, Article ID: 870999. https://doi.org/10.3389/fcvm.2022.870999

[21] Zhang, B.F., Jiang, H., Chen, J., Guo, X., Hu, Q. and Yang, S. (2018) KDM3A Inhibition Attenuates High Concentration Insulin-Induced Vascular Smooth Muscle Cell injury by Suppressing MAPK/NF-κB Pathways. *International Journal of Molecular Medicine*, **41**, 1265-1274. https://doi.org/10.3892/ijmm.2017.3351

[22] Zhao, M., Wang, S., Zuo, A., Zhang, J., Wen, W., Jiang, W., Chen, H., Liang, D., Sun, J. and Wang, M. (2021) HIF-1α/JMJD1A Signaling Regulates Inflammation and Oxidative Stress Following Hyperglycemia and Hypoxia-Induced Vascular Cell Injury. *Cellular & Molecular Biology Letters*, **26**, Article No. 40. https://doi.org/10.1186/s11658-021-00283-8

[23] Huo, M., Zheng, X., Bai, N., Xu, R., Yang, G. and Zhao, Z. (2022) LncRNA PCAT19 Regulates Neuropathic Pain via Regulation of miR-182-5p/JMJD1A in a Rat Model of Chronic Constriction Injury. *Neuroimmunomodulation*, **29**, 161-170. https://doi.org/10.1159/000518847