MiR-199-3p Suppressed Inflammatory Response by Targeting MECP2 to Alleviate RTX-Induced PHN in Mice

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Abstract

Varicella zoster virus–induced postherpetic neuralgia (PHN) can be alleviated by limited medications with serious side effects. This study aims to investigate the underlying molecular mechanism of miR-199-3p in mediating PHN in mice. 293T cells were transfected with miR-199-3p vectors (mimic/inhibitor). The target relationship between miR-199-3p and MECP2 was confirmed using luciferase reporter assay. PHN mouse model was established by RTX injection. Animal behaviors were evaluated using Hargreaves test and Von Frey test. Western blot was used for protein analysis, and quantitative reverse transcription polymerase chain reaction was performed for messenger RNA quantification. Serum levels of inflammatory mediators were determined using ELISA. Increased thermal withdrawal latency (TWL) and decreased mechanical withdrawal threshold (MWT) were observed in resiniferatoxin-induced PHN mice. Downregulated miR-199-3p and upregulated MECP2 were found in PHN mice. Upregulated miR-199-3p increased PWL and MWT, but inhibited MECP2 in PHN mice. Besides, increased miR-199-3p suppressed proinflammatory indicators and activated anti-inflammatory mediators. It also found that MECP2 was the target of miR-199-3p. Further study showed miR-199-3p enhanced PWL and MWT, and supported inflammatory response via targeting MECP2. miR-199-3p regulated inflammation by targeting MECP2 to alleviate RTX-induced PHN in mice.

Keywords

PHN, inflammation, MECP2, miR-199-3p

Introduction

Nerve injury might induce neuropathic pain. As the most common neuropathic pain, postherpetic neuralgia (PHN) is usually caused by the infection of herpes zoster for more than 3 months¹. In the last decades, limited medications have been used for the treatment of PHN due to various side effects, and it has become an intractable issue in modern practice². Hence, deeper investigations are needed to reveal the pathogenesis of PHN.

Inflammation is closely associated with the pathophysiology of neuropathic pain³. Various researches revealed the essential roles of inflammatory cytokines in neuropathic pain, such as polyneuropathies⁴, fibromyalgia syndrome⁵, complex regional pain syndrome⁶, and PHN⁷. Upregulated serum IL-1β was observed in PHN patients⁸. Obvious correlations were found between the incidence of PHN and inflammatory cytokines including C-reactive protein (CRP) and lymphocyte count in patients with acute herpes zoster–induced PHN⁹. Recent evidence shows significant association between microRNA (miRNA) and the development of neuropathic pain and neuronal inflammation. Suppression of miRNA-155 alleviated mechanical and thermal allodynia, and proinflammatory cytokine expression through targeting SOCS1 in neuropathic pain¹⁰. Elevation of miR-199-3p inhibited the expression of tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 via IKKβ/NF-κB axis in diabetic nephropathy¹¹. A previous study demonstrated that Methyl-CpG-binding protein 2 (MeCP2) served an important role in neuronal differentiation and development and implicated neuropathic pain¹². Enhanced DNA methylation and MeCP2 in spinal cord after...
nerve damage contributed to neuropathic pain in rats\textsuperscript{13}. Bioinformatics analysis predicted MeCP2 was the target of miR-199-3p; hence, we hypothesized that miR-199-3p might regulate inflammation by targeting MeCP2 in PHN.

In this study, we investigated the regulatory mechanism of miR-199-3p in PHN. Our results demonstrated that overexpression of miR-199-3p suppressed inflammatory cytokines and enhanced thermal and mechanical hyperalgesia by targeting MECP2 to alleviate RTX-induced PHN in mice.

**Methods and Materials**

**Cell Lines, Animals, and Drug**

293T cells were purchased from ATCC and cultured in RPMI-1640 with 5% CO\textsubscript{2} at 37°C for the following luciferase reporter analysis.

A total of 48 male C57BL/6 J mice (8 weeks, 25–30 g) were kept under standard housing conditions with free access to water and food under controlled temperature. Resiniferatoxin (RTX) was purchased from Xiyuan-Bio (Shanghai, China).

**Construction of gene expression vectors.** The adenoviruses vectors (lenti-miR-199-3p-mimics, lenti-NC-mimics pcD513B-MECP2, and pcD513B-NC) were designed and constructed by Shanghai Genechem Co., Ltd. Subsequently, PHN mice received 100 μl of lenti-miR-199-3p-mimics, lenti-NC-mimics pcD513B-MECP2, or pcD513B-NC via tail vein injection. The experiments followed the Guidelines of International Association for the Study of Pain and obtained the approval from the Ethics Review Committee of the First Affiliated Hospital of Nanchang University.

**Group and RTX-Induced PHN**

All the mice were randomly divided into four groups (\(n = 8\) for each group): (1) control; (2) RTX; (3) RTX + miR-119-3p mimics; (4) RTX + NC mimics. The control group received a single intraperitoneal injection of the same volume of normal saline, whereas the other three groups received intraperitoneal injection of the above mixture supplemented with 200 μg/kg RTX to induce PHN mouse model.

**Evaluation of Thermal Hyperalgesia**

Hargreaves test was used to assess thermal hyperalgesia in mice at 0, 2, 4, 7, 14, 21 and 28 days. In brief, mice were placed on a glass surface and the plantar surface of one hind paw was irradiated with light. Thermal withdrawal latency (TWL) was defined as the time from the onset of the light to the response of clear paw flinching, paw licking, or jumping. A cutoff of 25 s was set to prevent from tissue damage. The experiments were conducted five times for each mouse to calculate the average value.

**Evaluation of Mechanical Hyperalgesia**

The Von Frey test was used to evaluate mechanical hyperalgesia at 0, 2, 4, 7, 14, 21, and 28 days. Mice were placed in acrylic cages with wire grid floors in a quiet room. A filament was pressed against the ventral paw from below and the pressure gradually increased from 0.57 g to 15 g. The end-point was defined as paw withdrawal followed by clear movements of paw flinching or licking. The test was performed at least three times for each paw with an interval of more than 15 s. The value of mechanical withdrawal threshold (MWT) was defined as the average of three measurements.

**ELISA**

Serum levels of IL-4, IL-6, IL-1β, and TNF-α in rats were determined using ELISA. The detection was conducted using commercial ELISA kits: Rat IL-4 ELISA Kit (H005, range = 5-100 ng/l), rat IL-6 ELISA Kit (H007-1-1, 3-100 pg/ml), rat IL-1β ELISA Kit (H002, 0.8-40 ng/l), and TNF-α ELISA Kit (15-300 ng/l).

**Western Blot**

Serum sample was collected for the analysis of MECP2. Briefly, total proteins were extracted from the serum samples and quantified using protein assay reagent from Bio-Rad. Subsequently, the extracted proteins were loaded on SDS-PAGE (sodium dodecyl sulfate–polyacrylamide gel electrophoresis) and transferred onto polyvinylidene fluoride (PVDF) membranes. After blocking, the membranes were incubated with primary antibody MECP2 (1/1000, ab252840, Abcam) at 4°C overnight, followed by incubation of secondary antibody goat anti-mouse IgG H&L pre-adsorbed (1/2,000, ab7063, Abcam) at 37°C for 45 min. The blots were visualized using an ECL kit and quantified using Image-Pro plus software.

**RNA Extraction and qRT-PCR Analysis**

Serum levels of MECP2 and miR-199-3p were determined using quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay. Briefly, total RNA was extracted using TRIzol reagent. RNA was converted into complementary DNA (cDNA) for miRNA and messenger RNA (mRNA) using a high-capacity cDNA reverse transcription kit (Applied Biosystems) and TaqMan Reverse Transcription kit (Thermo Fisher Scientific). For the quantification of miR-199-3p, Mir-X miRNA First Strand Synthesis Kit (Takara) on CFX96™ Real-Time PCR Detection System was used in quantitative real-time PCR. For the detection of MECP2, an SYBR Green Master Mix (SYBR Green) performed on StepOne Real-Time PCR System (Applied Biosystems) was used in PCR. Primer sequences were as follows: MECP2, F 5’-GTGTCTTGAACATACCAACTA-3’ and R 5’-CAT CCTAGCCTTCCCACCCACCTG-3’; miR-199-3p, F 5’-CGC...
GATTGGTTACACGTCTG-3′ and R 5′-AGTGCAGGGTCCGAGGTATT-3′; U6, F 5′-CTCGCTTCGGCAGCACA-3′ and R 5′-AACGCTTCACGAATTTGCGT-3′; β-actin, F 5′-TGGAATCCTGTGGCATCCATGAAAC-3′, and R 5′-ACGCACTTACAGTCCG-3′. Relative RNA was quantified using 2-ΔΔCq method.

Dual Luciferase Reporter Assay

The binding site between miR-199-3p and MECP2 was analyzed using dual luciferase reporter assay. The wild-type (WT)/mutant (MUT) fragments of MECP2 with the predicted binding site of miR-199-3p were amplified and subcloned into a p-MIR-report plasmid. 293T cells were co-transfected with the reporter plasmid and miR-199-3p mimics/inhibitor or the corresponding NC. Luciferase intensity was assessed using a TransDetect® Double-Luciferase Reporter Assay Kit (TransGen Biotech Co., Ltd) with value normalized to Renilla luciferase activity after transfection for 48 h.

Data Analysis

The normally distributed data were presented as mean ± SD. Comparison between the two groups was made using the Student t-test. A P value of <0.05 was considered to be statistically significant. All experiments were conducted for more than three times. All the analyses and graph were made using Prism software 6.0.

Results

Overexpression of miR-199-3p Attenuated RTX-Induced PHN in Mice

To study the role of miR-199-3p in RTX-induced PHN in mice, the PHN mice were injected with lenti-miR-199-3p mimics to increase miR-199-3p overexpression. Behavioral tests showed increased TWL and decreased MWT in RTX group, however, miR-199-3p mimics increased MWT but didn’t affect TWL in RTX-induced mice (Fig. 1A, B). An around 2-fold decrease in serum miR-199-3p was found in the RTX group compared with the control group, while an approximately 3-fold elevation was observed in RTX-induced mice injected with lenti-miR-199-3p mimics (Fig. 1C). The findings indicated that elevated miR-199-3p obviously attenuated RTX-induced PHN in mice.

Overexpression of miR-199-3p Inhibited the Expression of MECP2 and Inflammatory Response in RTX-Induced PHN in Mice

The MECP2 expression of RTX-induced PHN in mice was studied. Compared with the control group, an around 3.5-fold increased MECP2 expression was revealed in the RTX group, which was reduced by four times in the miR-199-3p mimics group compared with the NC group (Fig. 2A). Consistent results were observed in qRT-PCR analysis (Fig. 2B). Inflammatory response was also evaluated. The results revealed an about 4.5-fold elevation of IL-1β, TNF-α, and IL-6 and 2.5-fold reduction of IL-4 in the RTX group compared with controls. The injection of lenti-miR-199-3p mimics remarkably downregulated the serum levels of IL-1β, TNF-α, and IL-6 but upregulated serum IL-4 in RTX-induced PHN in mice (Fig. 2C). The above results suggested that increased miR-199-3p obviously suppressed MECP2 expression and inflammatory response in RTX-induced PHN in mice.

MiR-199-3p Negatively Regulated MECP2 Expression

The targeting relationship between miR-199-3p and MECP2 was investigated in 293T cells. Bioinformatics analysis predicted the binding site for miR-199-3p and MECP2 in Fig. 3A. Luciferase intensity of MECP2-WT was reduced in cells transfected with miR-199-3p mimics and enhanced by miR-199-3p inhibitor. The luciferase intensity of MECP2-MUT was not affected by miR-199-3p vectors (Fig. 3B). In addition, the level of MECP2 mRNA was downregulated by around 3.8 folds by miR-199-3p mimics but upregulated 4.5 folds by miR-199-3p inhibitor (Fig. 3C). Similar results were found in the analysis of western blot (Fig. 3D). These findings illustrated that MECP2 expression was negatively regulated by miR-199-3p.

Overexpression of miR-199-3p Alleviated RTX-Induced PHN by Targeting MECP2 in Mice

We further studied the molecular mechanism of miR-199-3p for regulating PHN in mice. Behavior assessment showed that elevated MWT induced by miR-199-3p mimics were reversed by pcD513B-MECP2, however, neither miR-199-3p mimics nor pcD513B-MECP2 affected TWL in RTX-induced mice (Fig. 4A, B). PCR data revealed miR-199-3p was up regulated in mice infected with lenti-miR-199-3p mimics; meanwhile, pcD513B-MECP2 did not show an obvious effect on miR-199-3p expression in mice (Fig. 4C). All the findings demonstrated that elevated miR-199-3p alleviated RTX-induced PHN by targeting MECP2 in mice.

Overexpression of miR-199-3p Alleviated Inflammatory Response by Targeting MECP2 in RTX-Induced PHN Mice

Our study also investigated the molecular mechanism of miR-199-3p for mediating inflammatory response in PHN mice. It showed that miR-199-3p mimics decreased the protein level of MECP2 by around 4 folds in RTX-induced mice, which was rescued by pcD513B-MECP2 infection (Fig. 5A). This finding was confirmed in PCR analysis (Fig. 5B). ELISA data revealed miR-199-3p mimics
significantly reduced serum levels of IL-1β, TNF-α, and IL-6 and enhanced IL-4 expression, which was reversed by pcD513B-MECP2 (Fig. 5C). The above data illustrated that upregulated miR-199-3p supported inflammatory response by targeting MECP2 in RTX-induced PHN mice.

**Discussion**

Despite the development of pharmacological treatments for PHN, patients still suffer from persistent spontaneous pain with thermal and mechanical hyperalgesia due to limited analgesic effect and serious side effects\(^\text{14}\). Although numerous authors have conducted studies on neuropathic pain\(^\text{15,16}\), the underlying molecular of PHN is still uncertain and novel therapeutic targets are still needed. Recently, the role of MECP2 in neuropathic pain and inflammation attracted more and more attention. MiR-199-3p is also reported to be involved in inflammatory response in various diseases. However, no studies illustrated the regulating mechanism of MECP2 in PHN. In the present study, we demonstrated that suppressed inflammatory response by targeting MECP2 alleviates PHN in mice.

Several studies have reported that MECP2 is involved in the development and maintenance of pain in different diseases. Elevated expression of MeCP2 was observed in mouse dorsal root ganglia with peripheral nerve injury\(^\text{17}\). Knockdown of MeCP2 in mouse central nucleus of the amygdala suppressed persistent pain\(^\text{18}\). A previous study

![Figure 1. Upregulated miR-199-3p attenuated RTX-induced PHN in mice. Mice were divided into 4 groups: (1) control; (2) RTX; (3) RTX + miR-199-3p mimics; (4) RTX + NC mimics. (A) Evaluation of TWL. (B) Evaluation of MWT. (C) Quantification of serum miR-199-3p using qRT-PCR assay. RTX: resiniferatoxin; PHN: postherpetic neuralgia; TWL: thermal withdrawal latency; MWT: mechanical withdrawal threshold; qRT-PCR: quantitative polymerase chain reaction; NC: negative control. *p < 0.05; **p < 0.01; ***p < 0.001.](image-url)
Figure 2. Upregulated miR-199-3p inhibited the expression of MECP2 and inflammatory response in RTX-induced PHN in mice. (A) Determination of MECP2 using western blot. (B) Determination of MECP2 using qRT-PCR assay. (C) Calculation of serum IL-4, IL-6, IL-1β, and TNF-α using ELISA. MECP2: Methyl-CpG-binding protein 2; RTX: resiniferatoxin; PHN: postherpetic neuralgia; TNF-α: tumor necrosis factor-α; IL: interleukin; qRT-PCR: quantitative polymerase chain reaction; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; NC: negative control. **p < 0.01; ***p < 0.001.

Figure 3. miR-199-3p negatively regulated MECP2 expression. (A) Predicted binding site between miR-199-3p and MECP2. (B) Luciferase intensity of MECP2-WT and MECP2-MUT in control, miR-199-3p mimic, miR-199-3p inhibitor, and NCs. (C) Detection of MECP2 using qRT-PCR assay. (D) Protein expression of MECP2 was analyzed using western blot. MECP2: Methyl-CpG-binding protein 2; qRT-PCR: quantitative polymerase chain reaction; WT: wild type; MUT: mutant; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; NC: negative control. *p < 0.05; **p < 0.01; ***p < 0.001.
revealed that the decrease of MeCP2 in maternal mice with neuropathic pain alleviated pain sensitization in offspring; however, the increase in MeCP2 aggravated hyperalgesia for the next generation, suggesting the essential role of MeCP2 in transgenerational transmission of chronic pain. Our findings also showed upregulated MeCP2 in PHN mice. Moreover, increased MeCP2 reduced MWT in PHN mice. MeCP2 is also considered to accelerate inflammatory response in various diseases. MeCP2 knockdown inhibited the expression of IL-6 and TNF-α; meanwhile, overexpression of MeCP2 exhibited proinflammatory effect on IL-6 and TNF-α in the mice model of acute liver injury.

Another study also showed that upregulated MECP2 activated the proinflammatory response in BV2 cells in neuroinflammation. Our results showed increased MECP2 suppressed inflammatory indicators in PHN mice, consistent with previous research works.

Recent evidence suggests that miRNA expression is associated with pain sensitivity and inflammation in various diseases, such as glomerular endothelial injury, lung inflammation, rheumatoid arthritis, and neuropathic pain. Emerging evidence suggests the involvement of miR-199-3p in processes of inflammatory diseases. Overexpressed miR-199-3p enhanced cell proliferation and

Figure 4. Overexpression of miR-199-3p alleviated RTX-induced PHN by targeting MECP2 in mice. Mice were divided into five groups: (1) RTX; (2) RTX + miR-199-3p mimics; (3) RTX + NC mimics; (4) RTX + miR-199-3p mimics + pcD513B-MECP2; (5) RTX + miR-199-3p mimics + pcD513B-NC. (A) Evaluation of TWL. (B) Evaluation of MWT. (C) qRT-PCR analysis for miR-199-3p. PHN: postherpetic neuralgia; MECP2: Methyl-CpG-binding protein 2; TWL: Thermal withdrawal latency; MWT: mechanical withdrawal threshold; RTX: resiniferatoxin; qRT-PCR: quantitative polymerase chain reaction; NC: negative control. **p < 0.01; ***p < 0.001.
suppressed cell apoptosis in chondrocytes to attenuate knee osteoarthritis in mice. miR-199-3p was found to be elevated in allergic rhinitis; the inhibition of miR-199-3p was proven to alleviate allergic rhinitis via Dnmt3a/STAT3 signal pathway in mouse. In addition, miR-199-3p activated ERK1/2 pathway and IL-10 generation through targeting

Figure 5. Overexpression of miR-199-3p alleviated inflammatory response by targeting MECP2 in RTX-induced PHN mice. (A) Protein expression of MECP2 was analyzed using western blot. (B) Detection of MECP2 using qRT-PCR assay. (C) Determination of serum IL-4, IL-6, IL-1β, and TNF-α using ELISA. MECP2: Methyl-CpG-binding protein 2; PHN: postherpetic neuralgia; RTX: resiniferatoxin; TNF-α: tumor necrosis factor-α; IL: interleukin; qRT-PCR: quantitative polymerase chain reaction. ***p < 0.01; ****p < 0.001.
PARP-1 in systemic lupus erythematosus, indicating the anti-inflammatory effect of miR-199-3p\(^\text{29}\). However, up to now, the role of miR-199-3p in PHN has not been illustrated. In our study, increased miR-199-3p was found in PHN mice. The regulation between miRNA and MECP2 was also reported in recent research works. The inhibition of miR-132 was responsible for the upregulation of MECP2 in rats with chronic cerebral hypoperfusion\(^\text{30}\). Another study found that MECP2 contributed to the alteration of mechanical sensitivity in dorsal root ganglia; meanwhile, overexpressed MECP2 was reduced by miR-132, miR-19a, and miR-301 in dorsal root ganglia\(^\text{31}\). Consistent with previous studies, our finding revealed that MECP2 served as the target of miR-199-3p in PHN. In addition, miR-199-3p attenuated inflammatory response and thermal and mechanical hyperalgesia through targeting MECP2 in RTX-induced PHN mice. This is the first study to demonstrate the molecular mechanism of miR-199-3p in the biological and pathological processes of PHN.

**Conclusion**

In summary, the present study revealed decreased miR-199-3p and increased MECP2 in RTX-induced PHN in mice. We for the first time illustrated that miR-199-3p suppressed inflammatory response by targeting MECP2 to alleviate PHN in mice. Our findings provided helpful insights for the pathology of PHN, suggesting miR-199a-3p as a potential therapeutic target for PHN.

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**Author Contributions**

Each author has made an important scientific contribution to the study and has assisted with the drafting or revising of the manuscript.

**Availability of Data and Materials**

All data can be obtained from the manuscript or by requesting the author.

**Ethical Approval**

Ethics approval was obtained from the Ethic Committee of The First Affiliated Hospital of Nanchang University.

**Statement of Human and Animal Rights**

All animal experiments were approved by the Animal Research Ethics Committee of the First Affiliated Hospital of Nanchang University.

**Statement of Informed Consent**

There are no human subjects in this article and informed consent is not applicable.

**Consent to Publish**

All the authors have consented to publish this research.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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