

Electroacupuncture Improves Rat Traumatic Brain Injury by Affecting Mitochondrial Function through the AMPK-PGC1 α /SIRT1 Pathway

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Abstract

Background and Purpose: Traumatic brain injury (TBI) is a common clinical craniocerebral injury. Not only does it affect the psychology and physiology of patient health, but it places a serious burden on the family and socioeconomic profile of patients. Although current studies have shown that electroacupuncture (EA) treatment is preliminarily effective for treating TBI, the specific mechanism is still unclear. Therefore, this study aimed to investigate the mechanism of action of EA in TBI. **Methods:** A rat TBI model was induced by controlled cortical impact (CCI). Rat brain tissue damage was evaluated by measuring the water content of the brain tissue. The assessment of neural function and the damage to learning and memory functions in rats was conducted through the modified neurological severity score (mNSS) and the Morris water maze experiment. ATP content was detected using a kit. Mitochondrial reactive oxygen species (mROS) levels and mitochondrial membrane potential were detected by flow cytometry. The expression of key genes and proteins was detected by RT-qPCR and Western blotting. **Results:** After TBI, the water content of the brain tissue significantly increased, and the neural, learning, and memory functions of the rats were impaired, which improved after EA treatment. In addition, after TBI, rats showed decreased ATP levels, mitochondrial membrane potential, and p-AMPK/AMPK, PGC-1 α , and SIRT1 expression, along with increased mROS levels. EA treatment reversed these effects. **Conclusion:** Our research indicates that EA can enhance mitochondrial function through the activation of the AMPK-PGC-1 α /SIRT1 pathway, thereby improving TBI-induced neurological dysfunction.

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Keywords

Traumatic Brain Injury, Electroacupuncture, Mitochondrial Function, AMPK, PGC-1 α , SIRT1

1. Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability worldwide, causing substantial health and economic burdens to patients, patients' families and society [1]. TBI is a chronic condition that can have lasting effects on multiple organ systems, accompanied by psychological distress related to emotional, cognitive, and other behavioral changes [2]. Currently, decompressive craniectomy and neurocritical care are common neurosurgical intervention strategies for TBI, which have been reported to reduce patient mortality [3]. However, there is still a lack of effective interventions in TBI clinical practice to improve the neurodegenerative process in patients [4], which highlights the importance of developing potential therapeutic interventions for TBI.

Acupuncture is an ancient healing method that originated in China and has been used to relieve pain [5]. As a supplementary form of acupuncture, electroacupuncture (EA) has been confirmed to significantly improve the treatment efficacy of traditional acupuncture for various diseases [6]. Current research indicates that EA has neuroprotective effects in animal models of Parkinson's disease [6] and ischemic stroke [7]. In TBI, although EA treatment has been confirmed to be effective at improving motor, sensorimotor and learning/memory deficits [8] and metabolic disorders [9] in the brain, the specific mechanism remains unclear.

Multiple studies have reported that mitochondrial dysfunction is a key mediator of the development of TBI-related pathophysiology [10]-[12]. Post-TBI intracellular physical and biochemical changes can lead to the impairment of mitochondrial membrane integrity, which results in the production and accumulation of reactive oxygen species (ROS) and the impairment of adenosine triphosphate (ATP) synthesis [13], further inducing inflammatory responses and cell death [14]. Importantly, previous studies have shown that EA may promote the recovery of brain function after brain injury by improving mitochondrial function [15]. In addition, evidence has shown that EA can improve cognitive function in mice by promoting the activation of AMP-activated protein kinase (AMPK) [16]. AMPK has been confirmed to play important regulatory roles in mitochondrial homeostasis and energy metabolism [17]. Notably, AMPK can enhance mitochondrial function by promoting the expression of peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α) [18]. In addition, AMPK can improve mitochondrial dysfunction by increasing the activity of silent information regulator 2-related enzyme 1 (SIRT1) [19]. Therefore, we speculated that EA may improve mitochondrial function by activating the AMPK-PGC1 α /SIRT1 pathway, thereby

promoting the recovery of neural function after TBI.

In summary, the present study aimed to investigate the effects of EA on neurological function after TBI and to elucidate the potential underlying mechanisms.

2. Materials and Methods

2.1. Construction of the TBI Rat Model and Electroacupuncture Intervention

The animal-related experiments in this study were approved by the Animal Ethics Committee of our hospital. Thirty 6 - 8-week-old male SD rats (body weight 200 - 250 g) were purchased from Hunan SJA Laboratory Animal Co., Ltd. Rats were bred in a specific pathogen-free (SPF) environment and allowed to eat and drink freely during this period. After 1 week of adaptive feeding, the rats were randomly divided into 3 groups ($n = 5/\text{group}$). The TBI group rats were induced with a TBI model through controlled cortical impact (CCI) as previously described [20]. Briefly, rats were anesthetized with 4% isoflurane and positioned in a stereotaxic frame. Subcutaneous bupivacaine was administered at the incision site for analgesia, followed by a 7-mm craniotomy (midline between bregma and lambda, 1.0 mm lateral to the midline). The bone flap was gently removed, and a cortical contusion was induced by impacting the dura mater with a pneumatically driven CCI device (velocity: 1.5 m/s; depth: 1.5 mm; dwell time: 100 ms). As a control, the Sham group underwent craniotomy only without CCI impact. For the TBI + EA group, after CCI induction, acupoints were located according to experimental animal acupuncture atlas and disinfected with alcohol. Acupuncture needles (diameter: 0.25 mm, length: 13 mm) were inserted at the designated acupoints, and electrical stimulation was delivered using an electroacupuncture apparatus (Model SDZ-V, Hwato, China). EA intervention was administered for 30 minutes per session, once daily, 5 times per week, for a total of 4 weeks. The electroacupuncture parameters were set as follows: dense-disperse wave, frequency of 1/20 Hz, and intensity of 1 mA. All rats were euthanized 4 weeks after CCI procedure, and brain tissues were collected for subsequent studies.

2.2. Detection of Brain Tissue Water Content

The rat's brain tissue was isolated and weighed, and the results were recorded as wet weight. Afterward, the brain tissue was transferred to an oven for drying, after which it was weighed again to obtain the dry weight. The water content of the brain tissue was calculated by the formula $(\text{wet weight} - \text{dry weight})/\text{wet weight} \times 100\%$.

2.3. Behavioral Examination

As mentioned previously [21], the neurological deficit was assessed using the modified neurological severity score (mNSS) at 1, 7, 14, 21, and 28 days post-TBI to evaluate motor, sensory, reflex, and balance functions. In this scoring system,

the total score ranges from 0 to 18 points (with 0 points indicating normal neurological function in Sprague-Dawley rats), where higher scores correspond to more severe neurological impairment.

In accordance with previous methods [22], after 2 weeks of CCI induction, the learning and memory function of the rats was evaluated by the Morris water maze test. Briefly, a plastic pool (180 cm in diameter, 60 cm in height) was filled with tap water to a depth of 28 cm. Titanium dioxide was added to render the water opaque. A platform (10 cm in diameter) was submerged 26 cm below the water surface in the southwest quadrant. During each trial, rats were released facing the pool wall from one of four starting positions (east, west, south, or north) and allowed to swim freely. Their movements were recorded for 60 seconds by a camera mounted above the maze. Rats that failed to locate the platform within the time limit were manually guided to it, and all animals remained on the platform for 30 seconds. Each rat underwent 4 tests every day, with each test lasting 5 minutes, for a total of 5 days. On the 6th day, the rats were released from one direction for testing, and their latency (the time taken to climb onto the platform) and swimming distance to the platform were measured using analysis software (San Diego Instruments, San Diego, CA).

2.4. Western Blot Analysis

Extract total protein from rat brain tissue using RIPA lysis buffer containing 1% protease inhibitors and phosphatase inhibitors (HY-K1001, MCE, USA). Quantify protein concentration using the BCA protein assay kit (KTD3010, Abbkine, China). Equal amounts of total proteins were separated by SDS-PAGE and transferred to PVDF membranes (ISEQ00010; Millipore, USA). The membrane was incubated in TBST blocking solution containing 5% skim milk powder for 1 h at room temperature. Then, the membranes were incubated with primary antibodies against p-AMPK (1:1000; PA5-17831; Invitrogen, USA), AMPK (1:1000; MA5-15815; Invitrogen, USA), PGC-1 α (1:1000; ab191838; Abcam, UK), SIRT1 (1:1000; ab189494; Abcam, UK), and β -actin (1:1000; ab8226; Abcam, UK) at 4°C for the entire night. The membrane was then treated with the corresponding secondary antibody for 1 h at room temperature. The enhanced ECL chemiluminescent detection reagent kit (36222ES60, Yeasen, China) was used to detect luminescent signals, and semi-quantitative analysis of protein bands was performed using ImageJ software.

2.5. Real-Time qPCR (RT-qPCR)

Total RNA was extracted from rat brain tissue using TRIzol™ reagent (15596018CN, Invitrogen, USA) and reverse transcribed into cDNA with a cDNA first strand synthesis kit (QP056, GeneCopoeia, USA). RT-qPCR was performed using TB Green Premix Ex Taq™ reagent (RR420A, Takara, Japan). The internal reference for this study was β -actin, and the experimental results were calculated using the $2^{-\Delta\Delta CT}$ method. The sequences of primers used in this study are listed in **Table 1**.

Table 1. List of primers.

Gene	Primers sequence (5'-3')
PGC-1 α	F: GTAGATCCTCTTCAAGATCCTG
	R: CATACAAGGGAGAATTGCGA
SIRT1	F: TTCCTGTGGGATACCTGACTTC
	R: CCCCCAAATAATGCTTCAATGCT
β -actin	F: GGTCAGGTCATCACTATCGG
	R: GGATTCCATACCCAGGAAGG

2.6. Determination of ATP Content

Take 1 g of brain tissue and homogenize it with 9 mL of sterile double-distilled water on ice, then centrifuge at 3500 g for 10 minutes to collect the supernatant. Subsequently, measure the ATP content in the rat brain tissue using the ATP detection kit (A095-1-1, Nanjing Jiancheng Bioengineering Institute, China) according to the manufacturer's instructions.

2.7. Flow Cytometry

The levels of mitochondrial ROS (mROS) and mitochondrial membrane potential in rat brain tissue were detected using a mROS detection kit (S0061S) and a mitochondrial membrane potential detection kit (C2006) from Beyotime, respectively. In simple terms, rat brain tissue was treated with 0.25% trypsin to prepare a single-cell suspension, which was then adjusted to 6×10^5 cells/mL. After that, 500 μ L of MitoSOTM Red staining working solution or JC-1 staining buffer was added to the cell suspension, and incubated at 37°C for 30 minutes. Subsequently, PBS was used to wash away excess dye, and the sample was analyzed on a flow cytometer.

2.8. Statistical Analysis

All experimental data are expressed as the mean $\pm$ standard deviation (mean $\pm$ SD). Statistical analysis was performed on the experimental data using GraphPad Prism 8.1 software (GraphPad Software Inc., San Diego, CA, USA). A *t* test was used to compare the data between two groups, one-way analysis of variance (ANOVA) was used to compare the data between multiple groups, and Tukey's post hoc test was used to perform multiple comparisons. A *P* value < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Electroacupuncture Improves the Developmental Process of Traumatic Brain Injury in Rats

First, we explored the effect of EA on the progression of TBI in rats. Analysis of the water content in the brain tissue revealed that the water content in the brain tissue significantly increased in the TBI rats and that the water content in the brain tissue significantly decreased after the EA intervention (**Figure 1(A)**). The mNSS score was

used to evaluate neurological impairment in the rats, and the neurological function of the TBI rats was severely impaired and improved after the EA intervention (**Figure 1(B)**). Results from the Morris water maze test showed that TBI rats exhibited significantly prolonged latency (time required to reach the platform) in water, whereas EA intervention reduced this latency (**Figure 1(C)**). Additionally, TBI rats demonstrated a significantly increased swimming distance to locate the platform, which was effectively shortened by supplementary EA treatment (**Figure 1(D)**). These results suggest that EA treatment can improve TBI-induced neurological dysfunction.

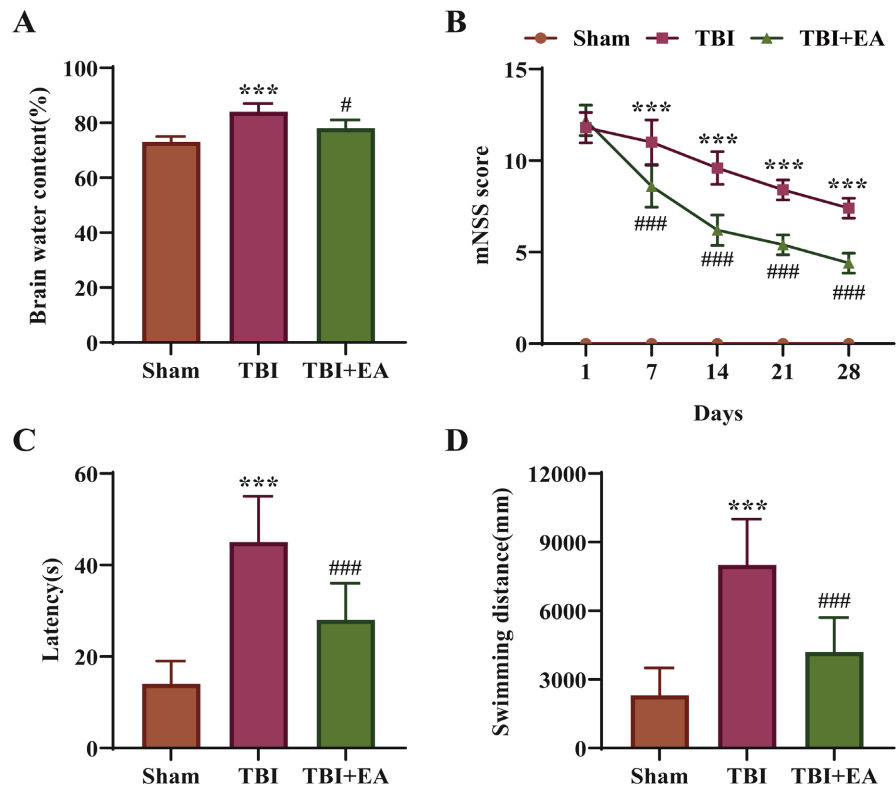


Figure 1. Electroacupuncture improves the developmental process of traumatic brain injury in rats. (A: Water content in rat brain tissue; B: Evaluation of neurological function in rats by the mNSS score; C: Statistical diagram of the latency period (time required to climb the platform) of the rats in the water maze; D: Statistical diagram of the swimming distance of the rats when they climbed the platform in the water maze. Compared with the Sham group, *** $P < 0.001$; compared with the TBI group, # $P < 0.05$, ### $P < 0.001$).

3.2. Electroacupuncture Treatment Restores Mitochondrial Function by Activating the AMPK-PGC1 α /SIRT1 Pathway

Previous studies have indicated that mitochondrial dysfunction is a key mediator of the development of TBI-related pathophysiology [10]-[12]. AMPK is a key regulator of mitochondrial homeostasis and energy metabolism [17] and is regulated and activated by EA [16]. Notably, AMPK can promote PGC-1 α [18] and SIRT1 expression to improve mitochondrial dysfunction [19]. Therefore, we further explored whether EA improves mitochondrial function by activating the AMPK-PGC1 α /SIRT1 pathway. The Western blot results showed that the expression levels of p-AMPK/AMPK,

PGC-1 α and SIRT1 in the brain tissue of TBI rats were significantly reduced, and the expression of these proteins was restored to some extent after EA treatment (**Figure 2(A)**). The mRNA expression of PGC-1 α and SIRT1 was detected by RT-qPCR. The mRNA expression of PGC-1 α and SIRT1 in the brain tissues of TBI rats was significantly downregulated, and the expression of PGC-1 α and SIRT1 mRNA was upregulated after EA intervention (**Figure 2(B)-(C)**). The ATP content was detected using a kit. The ATP content in the brain tissue of TBI rats was significantly reduced, and the ATP content was significantly upregulated after EA intervention (**Figure 2(D)**).

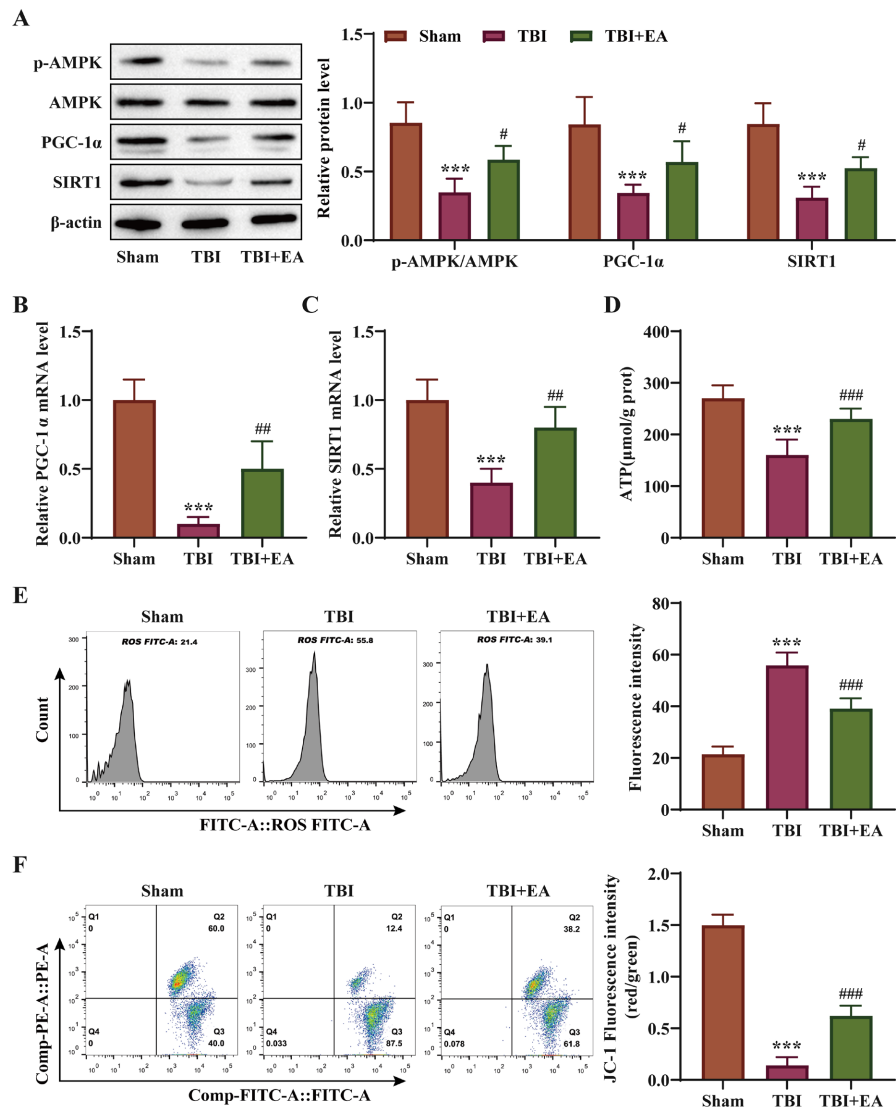


Figure 2. Electroacupuncture treatment restores mitochondrial function by activating the AMPK-PGC1 α /SIRT1 pathway. (A: The expression of p-AMPK/AMPK, PGC-1 α , and SIRT1 in rat brain tissues was detected by western blot; B: The mRNA expression of PGC-1 α and SIRT1 in rat brain tissues was detected by RT-qPCR; C: Detection of ATP content in rat brain tissue using the kit; D: mROS levels in rat brain tissue were detected by flow cytometry; E: Mitochondrial membrane potential levels in rat brain tissue were detected by flow cytometry. Compared with the Sham group, *** $P < 0.001$; compared with the TBI group, # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$).

The mROS levels and mitochondrial membrane potential were detected by flow cytometry. The result shows that the mROS levels in the brain tissue of TBI rats were significantly elevated, while the mitochondrial membrane potential levels were significantly reduced. However, after EA intervention, the mROS levels significantly decreased, and the mitochondrial membrane potential levels significantly increased (**Figure 2(E)-(F)**). These results indicate that EA restores mitochondrial function by activating the AMPK-PGC1 α /SIRT1 pathway.

4. Discussion and Conclusions

TBI is a common clinical disease of the central nervous system. Owing to the lack of interventions, the economic burden on the families and society of patients with TBI is still heavy [1]. The important finding of this study is that EA intervention can effectively improve neurological, learning, and memory dysfunctions induced by TBI, and the positive effects of EA are related to its activation of the AMPK-PGC-1 α /SIRT1 signaling pathway and the subsequent improvement in mitochondrial function.

EA is an extension of traditional acupuncture and moxibustion treatment and plays a key role in the treatment of central nervous system-related diseases. Multicenter studies have shown that EA treatment can effectively improve motor and defecation dysfunction in Parkinson's disease patients [23] and skeletal muscle pain [24]. In patients with Alzheimer's disease, EA treatment can also effectively improve cognitive dysfunction [25] and learning and memory ability [26]. In TBI, EA treatment also helps patients recover consciousness after surgery and has long-term efficacy [27]. In addition, existing basic studies have confirmed that EA improves TBI-induced neuronal injury [28] [29] and restores local blood flow [30]. Consistent with the results of previous studies, we found that EA treatment could reduce the water content in the brain tissue and improve neural, learning and memory functions in rats with TBI.

Mitochondria are important double-membrane organelles in cells that play key roles in the regulation of intracellular energy metabolism and lipid synthesis [31]. However, under the background of TBI, the function of mitochondria is often impaired, which can lead to neuronal apoptosis and oxidative stress [32], as well as impairments in movement and hippocampus-related spatial learning and memory functions [33]. Notably, Geng *et al.* [34] have shown that EA can improve cognitive function in mice by activating mitochondrial function. Therefore, we explored whether EA affects TBI progression through the regulation of mitochondrial function. We found that EA treatment could reduce the mROS level in the brain tissue of TBI rats, upregulate the mitochondrial membrane potential and promote ATP synthesis, indicating that EA improves TBI-related neurological dysfunction by improving mitochondrial function. In the process of exploring the mechanism underlying the improvement in mitochondrial dysfunction in TBI, we reviewed previous studies and reported that EA could improve energy metabolism disorders by activating AMPK [16]. AMPK is a key regulatory target of mitochondrial metabolism; its inac-

tivation or reduced activity can lead to an imbalance in mitochondrial homeostasis [35] and further lead to the accumulation of mROS and the subsequent development of cognitive dysfunction [36]. As a response element of AMPK signaling, PGC-1 α [18] and SIRT1 [19] are also critical for AMPK-mediated maintenance of mitochondrial function, and abnormalities in AMPK/PGC-1 α [37] and AMPK/SIRT1 [37] signal transduction lead to mitochondrial dysfunction. Importantly, PGC-1 α [38] and SIRT1 [39] loss of expression is associated with mitochondrial dysfunction after TBI. Therefore, we further explored the effect of EA on AMPK/PGC-1 α -SIRT1 signaling after TBI. We found that the expression of p-AMPK/AMPK, PGC-1 α , and SIRT1 in the brain tissue of rats after TBI was significantly downregulated, while EA treatment can reverse this phenomenon. Our study suggested that EA treatment may activate the AMPK/PGC-1 α -SIRT1 signaling pathway to enhance mitochondrial function and improve TBI-induced neural dysfunction.

In summary, our research reveals the strong potential of EA in improving neurofunctional disorders in TBI. We also confirm that the positive effects of EA partially depend on its activation of the AMPK/PGC-1 α -SIRT1 signaling pathway and the subsequent improvement of mitochondrial function. Our study provides a theoretical basis for the application of EA in TBI.

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Author Contributions

Conceptualization: Bingxue Zhang, Liangmin Gao; data curation: Pinwen Tu, Chaochao Yang; formal Analysis: Ya Li, Baocai Hong; funding acquisition: Hongbo Chen; investigation: Yinghong He; methodology: Ya Li, Baocai Hong, Xiongli Fu; project administration: Bingxue Zhang, Liangmin Gao; resources: Hongbo Chen; software: Yongqian Deng, Yunbin Sun; supervision: Yinghong He; validation: Bingxue Zhang, Yinghong He; visualization: Liangmin Gao, Hongbo Chen; writing—original draft: Bingxue Zhang, Liangmin Gao; writing—review & editing: Yinghong He, Hongbo Chen. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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

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