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miR-142-3p is a Potential Therapeutic Target for Sensory Function Recovery of Spinal Cord Injury

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Spinal cord injury (SCI), which is a leading cause of disability in modern society, commonly results from trauma. It has been reported that application of sciatic nerve conditioning injury plays a positive role in repairing the injury of the ascending spinal sensory pathway in laboratory animals. Because of the complexity of SCI and related ethics challenges, sciatic nerve conditioning injury cannot be applied in clinical therapy. Accordingly, it is extremely important to study its mechanism and develop replacement therapy. Based on empirical study and clinical trials, this article suggests that miR-142-3p is the key therapeutic target for repairing sensory function, based on the following evidence. Firstly, studies have reported that endogenous cAMP is the upstream regulator of 3 signal pathways that are partially involved in the mechanisms of sciatic nerve conditioning injury, promoting neurite growth. The regulated miR-142-3p can induce cAMP elevation via adenylyl cyclase 9 (AC9), which is abundant in dorsal root ganglia (DRG). Secondly, compared with gene expression regulation in the injured spinal cord, inhibition of microRNA (miRNA) in DRG is less likely to cause trauma and infection. Thirdly, evidence of miRNAs as biomarkers and therapeutic targets in many diseases has been reported. In this article we suggest, for the first time, imitating sciatic nerve conditioning injury, thereby enhancing central regeneration of primary sensory neurons via interfering with the congenerous upstream regulator AC9 of the 3 above-mentioned signal pathways. We hope to provide a new clinical treatment strategy for the recovery of sensory function in SCI patients.

MeSH Keywords: **8-Bromo Cyclic Adenosine Monophosphate • Adenylate Cyclase • Spinal Cord Injuries**

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Background

The cost of spinal cord injury (SCI) is enormous emotionally, socially, and financially. The pathophysiology of the SCI is a complex series of reactions of events, responses, and processes, affecting the nervous, vascular, and immune systems [1]. Regardless of whether the spinal cord injury is complete or partial, aberrant sensations, including paresthesia, dysesthesia, and chronic neuropathic pain, always develop within a few months after injury [2]. Aberrant sensations are torturous experience that may make the patients suffer more serious impairments in daily life than dyskinesia alone [3]. Evidence from previous research suggests that aberrant sensations could affect cortical arousal and subsequently induce cognitive deficiency [4] and psychological problems [5]. Some scholars reported that single or combined application of sciatic nerve conditioning injury plays a positive role in repairing the injury to the ascending spinal sensory pathway [6,7]. Due to the complexity of the occurrence of SCI and ethics challenges, sciatic nerve conditioning injury cannot be applied in clinical therapy.

Accordingly, to clinically apply sciatic nerve conditioning injury, it is necessary to investigate and imitate the mechanism and effect of sciatic nerve conditioning injury, promoting repair of dorsal column lesions. Cai et al. [8] reported that cyclic adenosine monophosphate (cAMP) causes axonal regeneration on myelin-associated glycoprotein (MAG) and myelin, accomplished by polyamine synthesis and polyamines, which can further affect cytoskeleton assembly to induce axonal elongation. It has been indicated that cAMP elevation induced by peripheral nerve injury can antagonize the effect of myelin-associated inhibitory molecules via inhibiting Rho and further abolish the cytoskeleton organization inhibition by Rho [9]. Furthermore, IL-6, which can promote neurite growth through activating growth-associated protein 43 (GAP-43), has been validated as one of the downstream signaling pathways of cAMP [10,11]. Thus, cAMP is interesting candidates in studies aimed at stimulating the repair of the ascending spinal sensory pathway [12–21]. However, research on administration of exogenous cAMP has had no recent breakthroughs. The elevation of cAMP has 2 deficiencies: time limitation and the limited effect induced by time limitation [22,23]. To overcome these deficiencies, it is necessary to study the molecular biological mechanism of elevated cAMP levels induced by sciatic nerve conditioning injury. It has been shown that miR-142-3p and adenylyl cyclase 9 (AC9) exist in the dorsal root ganglia (DRG) [22]. AC9 converts adenosine-5-triphosphate (ATP) into cAMP and pyrophosphate and this reaction can be regulated by miR-142-3p through targeting AC9 mRNA [24].

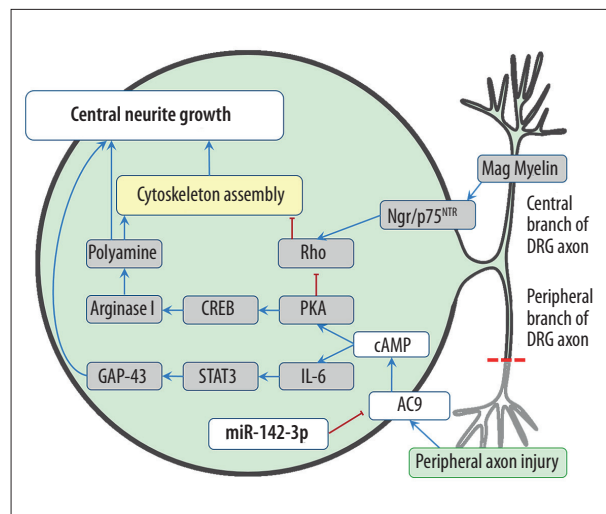


Figure 1. The hypotheses that peripheral axon injury promotes central neurite growth via miR-142-3p. Peripheral axon injury resulted in the elevation of cAMP, a PKA that, when activated by cAMP, further activates CREB. Activated CREB upregulates transcription of Arginase I. Arginase I induces the generation of polyamines, which may directly control cytoskeleton assembly or induce further neurite growth. Activation of PKA also antagonizes MAG- or myelin-derived inhibition via inhibiting Rho. The elevation of cAMP increases IL-6, which promotes the expression of GAP-43 through STAT3.

Hypothesis

Here, we hypothesize that miR-142-3p is the upstream molecular basis for sciatic nerve transection enhancing central regeneration of primary sensory neurons, and that it is a potential therapeutic target for sensory function recovery of spinal cord injury.

Cyclic Adenosine Monophosphate

Previous research has reported 3 signal pathways that partially mediate the mechanisms of sciatic nerve conditioning injury, promoting neurite growth (1). Activated protein kinase A (PKA) activates cAMP response element, binding protein (CREB) [25], which further upregulates transcription of regeneration-related genes such as Arginase I. Arginase I induces the generation of polyamines, which may directly control cytoskeleton assembly or further induce neurite growth on MAG and myelin (Figure 1) [26]. (2) Activation of PKA can antagonize the effect of myelin-associated inhibitory molecules via inhibiting Rho and further abolish the cytoskeleton organization inhibition by Rho (Figure 1) [9] (3). Increased interleukin-6 (IL-6), through STAT3, promotes the expression of regeneration-related genes, for example GAP-43 (Figure 1) [10,26]. The 3 above-mentioned

signal pathways have a homo-regulator cAMP. Therefore, it is important to study the regulation of cAMP.

Blesch et al. proved that the elevation of cAMP occurred as early as 1 day after sciatic nerve conditioning injury and remained elevated 1 week later [27]. Other researchers have indicated that the level of cAMP was increased by 1 day after conditioning injury and decreased to control levels by 1 week after injury [28]. More generally, the limited action time of cAMP results in the limited effect of axonal regeneration, whereas microRNA intervention, which may substitute sciatic nerve conditioning injury, can avoid ethics problems, overcome the above defects, and enhance the effect of axonal regeneration.

miR-142-3p

MicroRNAs (miRNAs), a family of non-coding RNAs, were discovered to regulate gene expression at the translational level by combining with the 3' untranslated region of target mRNAs, resulting in their degradation or translational inhibition [29–31]. The capacity of miRNAs to regulate cell function and state through translationally silencing genes plays a pivotal role in pathophysiology of SCI [1]. Recently, some researchers have begun to focus on miRNAs as biomarkers and therapeutic targets in many diseases [31]. The 2'-O-methyl-modified oligonucleotides are locked nucleic acids (LNA), which is the most common oligonucleotide modification, have been confirmed to be effective inhibitors in primary neurons [30]. Miravirsen, an LNA-modified DNA phosphorothioate antisense oligonucleotide targeting miR-122, has been in phase 2a clinical trials for viral hepatitis type C and may become the miRNA therapeutic target in humans [32].

miR-142-3p is a miRNA that is associated with cell differentiation and development [33,34]. It has been confirmed that the expression of miR-142-3p in DRG was downregulated at 9 h

after sciatic nerve conditioning injury and its percent change ranked third in all downregulated miRNAs [22]. It is computationally predicted by TargetScan (<http://www.targetscan.org>) that AC9, whose expression is abundant in DRG, is the target of miR-142-3p, which has also been confirmed in the literature [24]. cAMP can be produced by intracellular AC9 [24]; therefore, the miR-142-3p/AC9/cAMP signal pathway can efficiently imitate the repair effect of the ascending sensory pathway promoted by sciatic nerve conditioning injury and avoid ethics problems. Compared with gene expression regulation in the injured region of the spinal cord, intervention in DRG causes less trauma and infection and can efficaciously avoid trauma reaction, such as local inflammation and edema, which may inhibit the effect of miRNA intervention. Because a single miRNA may have more than 1 target gene, it is necessary to examine the influence of miR-142-3p on other genes by using mRNA microarray. During administration of miR-142-3p in DRG, it is necessary to avoid injury to the DRG neurons.

Conclusions

The downregulation of miR-142-3p can effectually upregulate the final level of cAMP via upregulating the expression of AC9 in injured neurons of DRG and further regulate the 3 signal pathways simultaneously through inhibition of Rho, activation of CREB, and increase of IL-6. It is a novel regulatory gene of upstream molecular mechanism for sciatic nerve conditioning injury, enhancing central regeneration of primary sensory neurons, and is of potential importance in gene therapy for the sensory function recovery of SCI. To test this hypothesis, further study is needed.

Conflict of interest

We declare that we have no conflict of interest.

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