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Multifunctional injectable hydrogel enhances functional recovery after spinal cord injury in adult rats through upregulation of the NCK1/CDK1 pathway

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Abstract: **Background**: Spinal cord injury (SCI) leads to significant functional impairments and neurological deficits, profoundly impacting quality of life. Despite various neuroprotective and rehabilitative strategies, no universally accepted preventive treatment exists. **Objectives**: This study aims to elucidate the underlying mechanisms of SCI to guide the development of more effective preventative measures. **Methods**: We investigated the molecular mechanisms by which a multifunctional injectable hydrogel (MIH) improves SCI in a rat model, specifically focusing on the NCK adaptor protein 1 (NCK1)/cyclin-dependent kinase 1 (CDK1) pathway. After establishing the SCI model, rats in the MIH group received a 10μL injection of MIH, while control and model groups received sterile saline. We utilized immunofluorescence, HE staining, Western blot and qRT-PCR to analyze the effects of MIH on SCI and its regulation of the NCK1/CDK1 pathway. **Results**: This findings indicate that upregulating NCK1 and CDK1 contributes to preventing SCI progression by enhancing cell viability and promoting neurite development in spinal cord tissue. Conversely, downregulation of these pathways may exacerbate SCI progression. These targets suggest potential pathways for alleviating SCI. **Conclusion**: Enhancing the NCK1/CDK1 pathway may provide a promising approach to preventing SCI by improving cellular viability and facilitating neurite growth in spinal cord tissue.

Keywords: CDK1; Multifunctional injectable hydrogel; NCK1; Neuroprotection; Spinal cord injury

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INTRODUCTION

Spinal cord injury (SCI) is a severe condition that can lead to various functional impairments, including paralysis or weakness in different parts of the body, sensory function impairment, bladder dysfunction, autonomic dysfunction and loss of sexual function (Hu *et al.*, 2023; Karsy & Hawryluk, 2019). SCI not only affects the physical aspects but also has a profound impact on one's psychological well-being. Patients with SCI often face emotional and psychological challenges, such as depression, anxiety and adjustment disorders. The burden of SCI-related costs falls on both the families of individuals with SCI and society (Eli *et al.*, 2021; Jin *et al.*, 2021). The global incidence of spinal cord injury is increasing, primarily due to the rise in traumatic injuries resulting from accidents, violence and sports-related incidents (Ding *et al.*, 2022). The treatment of SCI involves a range of approaches, including both surgical and non-surgical interventions (Freyermuth-Trujillo *et al.*, 2022). Currently, there is no cure for SCI and the primary focus of treatment is on symptom management, complication prevention and promotion of functional recovery (Venkatesh *et al.*, 2019). However, the effectiveness of these treatments is limited due to the complex and poorly understood mechanism of spinal cord injury. Interestingly, some studies (Nie *et al.*, 2022; Yang *et al.*, 2022) have shown a correlation between the NCK adaptor protein 1 (NCK1)/cyclin-dependent kinase 1 (CDK1) pathway and functional recovery after SCI. Additionally, multifunctional injectable hydrogel (Luo *et al.*, 2021) (MHI) also presents great potential in treating SCI. Recent studies have demonstrated that the NCK1/CDK1 pathway plays a crucial role in cell survival and neurite outgrowth (Diab *et al.*, 2023; Nie *et al.*, 2022). Injectable hydrogels have shown promise in delivering therapeutic agents directly to injury sites, enhancing local tissue repair and functional recovery (Ji *et al.*, 2023). However, the mechanism of MHI and the NCK1/CDK1 pathway in SCI remains elusive and further studies need to be conducted.

The injectable hydrogel is a multifunctional material that can be delivered directly to the site of SCI. It is typically composed of biocompatible polymers or biomaterials that mimic the extracellular matrix, providing physical and biochemical cues for nerve cell growth. The hydrogel comprises hyaluronic acid, Gelatin methacryloyl (GelMA), PEG diacrylate and bioactive peptides for enhanced bioactivity and mechanical properties. The hydrogel has 10-20 kPa modulus, shear-thinning viscosity, biodegrades in 4-6 weeks and is MMP-degradable. The hydrogel can be easily injected into the injury site, where it forms a scaffold-like structure that supports the growth of new nerve tissue. The key mechanisms by which the injectable hydrogel promotes nerve regeneration is through its ability

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to provide a favorable microenvironment for axonal growth. The hydrogel can release growth factors and other bioactive molecules that stimulate the survival and growth of nerve cells. In addition, MHI also provides mechanical support and protects the regenerating nerves from further damage. However, the mechanism of the optimal formulation, delivery method and long-term effects of the injectable hydrogel in promoting nerve regeneration and functional recovery after SCI is still unclear and further research are needed.

NCK1 and CDK1 are both crucial molecules involved in various cellular processes. NCK1 is known to play a role in neurite outgrowth, synaptic plasticity and apoptosis, while CDK1 is primarily recognized as a master regulator of the cell cycle (Yang *et al.*, 2022). However, recent studies have shown that these molecules also have implications in spinal cord injury (SCI). Despite NCK1 and CDK1 are involved in SCI, the specific mechanism underlying the NCK1/CDK1 pathway in this context is not yet fully understood. While it is known that this pathway is relevant to functional recovery after SCI, the detailed interactions and processes involved remain elusive. Understanding these mechanisms is crucial for developing effective therapeutic interventions (Enserink & Chymkowitch, 2022). One intriguing avenue of research suggests that a multifunctional injectable hydrogel may have the ability to control the NCK1/CDK1 pathway. It is believed that the hydrogel may interact with the NCK1/CDK1 pathway, potentially influencing its activity and leading to improved outcomes in SCI (Lin *et al.*, 2021). Despite the intriguing potential of the multifunctional injectable hydrogel, the precise mechanism by which it regulates the NCK1/CDK1 pathway in SCI is not yet understood. Elucidating the mechanism by which the multifunctional injectable hydrogel regulates the NCK1/CDK1 pathway in SCI holds significant promise for the development of potential treatment options.

This study present a novel therapeutic strategy that integrates the use of a multifunctional injectable hydrogel with targeted modulation of the NCK1/CDK1 pathway to promote functional recovery after spinal cord injury (SCI). Unlike existing hydrogel-based treatments that primarily provide structural support or general neuroprotection, this approach uniquely combines a bioactive hydrogel capable of precise local delivery with the specific upregulation of the NCK1/CDK1 pathway. This dual-action strategy not only enhances cell viability and neurite outgrowth but also ensures that therapeutic agents are delivered directly to the injury site, maximizing their efficacy. Moreover, while previous therapies targeting the NCK1/CDK1 pathway often suffer from limited delivery precision, our method addresses this by embedding the pathway modulators within a supportive hydrogel matrix, thereby improving targeting and overall therapeutic outcomes. This integrated approach offers a significant advancement over existing methods, as shown in table 1(a), providing a more effective and targeted treatment for SCI. Here, we conducted an *in-vivo* study to investigate the molecular mechanisms of multifunctional injectable hydrogel regulating the NCK1/CDK1 pathway in AS.

MATERIALS AND METHODS

Spinal cord injury (SCI) animal model establishment

We acquired Sprague-Dawley (SD) rats weighing between 180-220 g from the animal center of our hospital. The animal study conducted in our hospital was approved by the Institutional Animal Care and Use Committee (IACUC) with approval number: IACUC-2023-045 in 2023. The study followed international ethical guidelines for the humane handling and care of animals. To ensure unbiased assignment, randomization was carried out using a computer-generated randomization schedule and the investigator responsible for the assessments was blinded to the group allocations. These rats were assigned into following three groups (n=6 per group): control, model and MIH groups. To establish the SCI model, we used a No. 11 surgical blade to induce a hemisection injury at the T10 level of the right half of the spinal cord in the rats. After the hemisection procedure, we sutured the deep and superficial muscle layers. Once the SCI rat model was established, the rats in the MIH groups received an injection of 10μL of MIH, control and model group rats received sterile saline. No predefined inclusion or exclusion criteria were applied to animals or data points. No animals or data points were excluded from the analyses. The multifunctional injectable hydrogel (MIH) comprises biocompatible materials with specific crosslinking chemistry, featuring 5-10 minute gelation time at 37°C and 2-4 week degradation period. The 10 μL injection volume was optimized to effectively fill lesion cavities and support tissue regeneration without causing additional spinal cord damage. Post-injury care included monitoring the rats for signs of distress and providing analgesics as needed. The rats were euthanized at specific time points post-injury 3 days to collect blood and spinal cord tissues for subsequent biochemical and histological analyses.

Immunofluorescence

First, fix and permeabilize the spinal cord tissue samples. Then, incubate the samples with primary antibodies. After the incubation period, wash away any unbound antibodies. Next, incubate with secondary antibodies, then wash to remove unbound antibodies. Finally, use a fluorescence microscope to examine the samples.

Hematoxylin and eosin (HE) staining

The spinal cord tissue obtained from all groups of rats was fixed in formalin and subsequently embedded in paraffin. Afterwards, the tissue samples were sliced into 5-μm sections for the purpose of HE staining. A pathologist then examined the outcomes using an optical microscope.

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Table 1(a): The differences between our approach and existing methods

Aspect	Existing treatments hydrogel-based	Existing NCK1/CDK1 pathway therapies	Our approach
Hydrogel composition	Often single-component or non-functionalized hydrogels (e.g., alginate, collagen)	Not applicable	Multifunctional injectable hydrogel with bioactive components
Delivery method	Injectable, but with limited targeting efficiency	Often systemic with limited local targeting	Targeted local injection ensuring precise delivery
Mechanistic focus	General neuroprotection and scaffold provision	Focused on cell cycle regulation and survival	Combined approach leveraging both neuroprotection and targeted pathway modulation
Efficacy in SCI models	Moderate improvement in functional recovery	Variable; often limited by delivery mechanism	Significant improvement in functional recovery as evidenced by upregulation of NCK1/CDK1
Novelty in target pathway	Limited or indirect modulation of signaling pathways	Direct targeting of cell cycle regulators, but without hydrogel benefits	Direct modulation of NCK1/CDK1 pathway within a supportive hydrogel matrix
Overall innovation	Incremental improvements in scaffold materials	Novel pathway targeting but lacks delivery precision	Integrated approach combining multifunctional hydrogel with targeted pathway modulation

Table 1(b): The primers sequence of NCK1, CDK1 and β-actin

Gene		Primer sequences (5'-3')
NCK1	Forward	GCTGGATATCAAGAAGAATG
	Reverse	GCGATGTAATGGATGTTATTG
CDK1	Forward	GTGGAATCTTTACAGGACTAT
	Reverse	GATTCAGAAATTGATCAACTC
β-actin	Forward	CGGTCAGGTCATCACTATC
	Reverse	CAGGGCAGTAATCTCCTTC

qRT-PCR

Total RNA was extracted using TRIzol Reagent (Beyotime). mRNA and cDNA were synthesized using the mRNA Reverse-Transcription Kit (Beyotime). SYBR Green PCR Mix (Vazyme) was used for quantitative assays on a Real-Time PCR System. Relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method and normalized to β-actin. The experiment was repeated three times. Primer sequences are in table 1(b).

Western blotting

The protein was separated using 10% SDS-PAGE. Subsequently, the proteins obtained were transferred to a PVDF membrane. The PVDF membrane was washed with TBST. Primary antibodies and β-actin were added to the membrane and incubated overnight at 4°C. Afterward, the membrane was washed again with TBST. A secondary antibody was introduced to the membrane and incubated for 2 hours at room temperature. The membrane was then washed with TBST to remove excess secondary antibodies. An ECL luminescent reagent was added to visualize the proteins and the bands on the membrane were analyzed.

Statistical analysis

Statistical analysis was carried out using Prism 8. The mean ± SD was used to exhibit all measurement data, which were repeated at least three times. A t-test was utilized to compare two groups, while an ANOVA was used to compare the difference among three or more groups.

RESULTS

Pathological results

To evaluate the impact of MIH on SCI in rats, we performed HE staining, shown in fig. 1. The results indicated that the model group exhibited significantly more cavitation and tissue loss in the spinal cord compared to the control group ($P<0.05$). However, the MIH group showed a marked reduction in these damages compared to the model group ($P<0.05$).

The effect of NCK1 and CDK1 protein in rats with SCI

To elucidate the role of NCK1 and CDK1 protein in rats with SCI, the NCK1 and CDK1 protein relative expression levels in the spinal cord tissue in all groups of rats were measured by WB, fig. 2 shows that the NCK1 and CDK1 protein expression levels in the model group were significantly lower than those in the control group ($P<0.05$). However, compared to model group, the NCK1 and CDK1 protein relative expression levels in MIH group were significantly increased ($P<0.05$).

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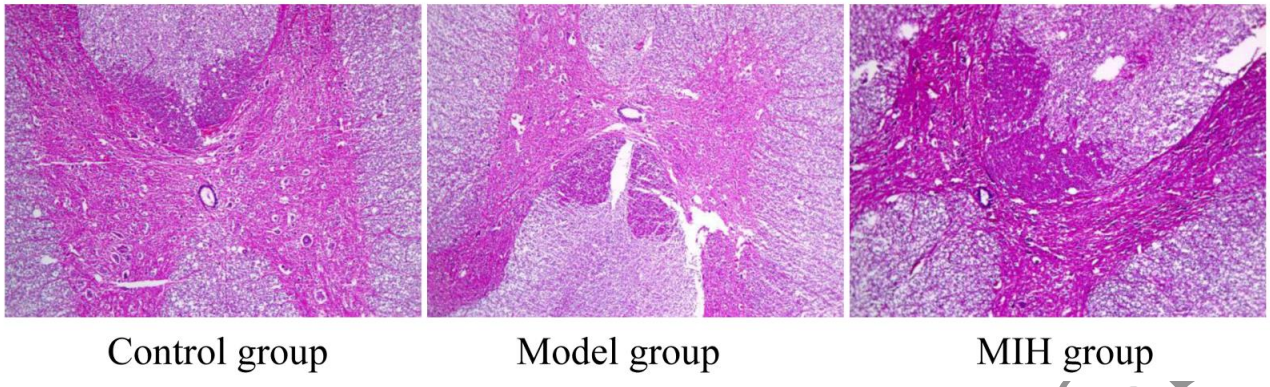


Fig. 1: The cavitation and tissue loss in the spinal cord tissue in all groups of rats were calculating by HE staining.

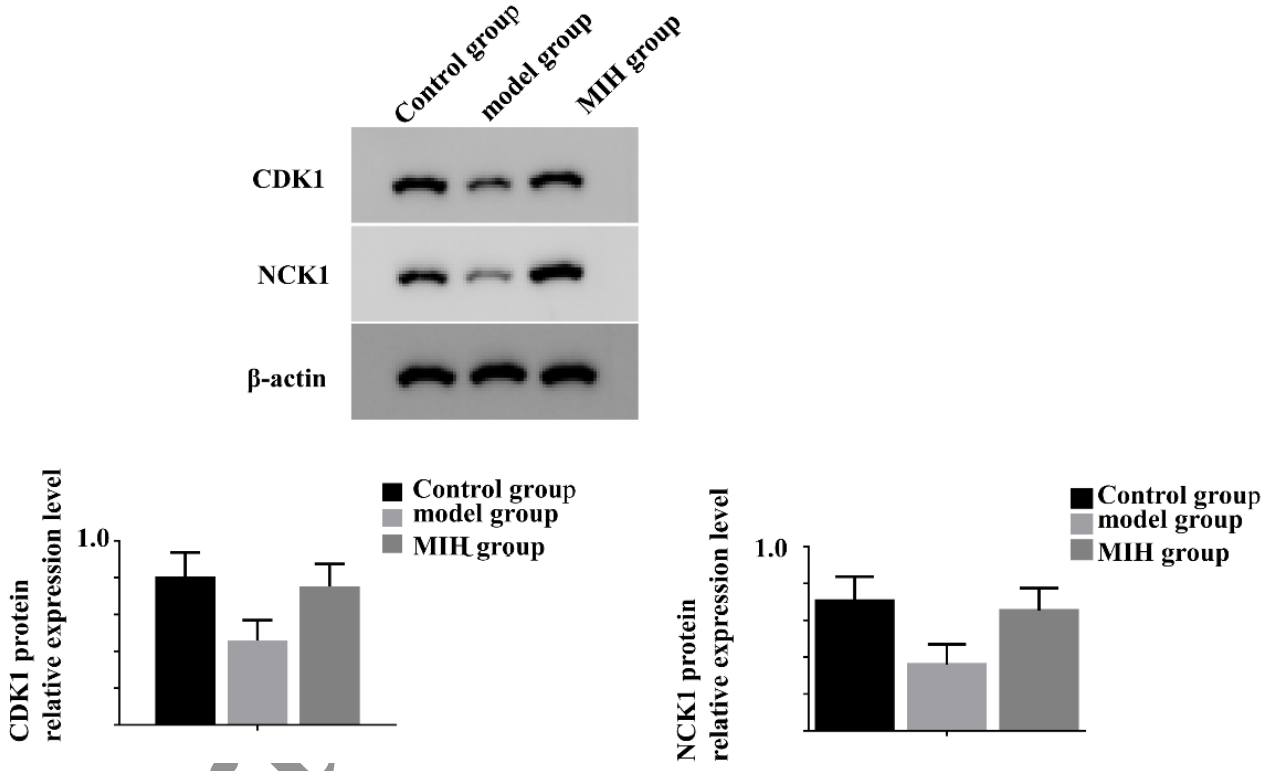


Fig. 2: The NCK1 and CDK1 protein relative expression levels in the spinal cord tissue in all groups of rats were measured by WB.

These results indicated that MIH might improve the cavitation and tissue loss in the spinal cord tissue in SCI rat by up-regulating NCK1 and CDK1 protein levels.

Immunofluorescence of the expression of NCK1 in the SCI rat

To evaluate the impact of NCK1 in rats with SCI, we conducted an immunofluorescence assay, shown in fig. 3. The assay detected NCK1 expression in various cell types at injury sites. The results revealed a significant reduction in NCK1-positive cells at the injury center in the model group compared to the control group ($P<0.05$). In contrast, the MIH group exhibited a notable increase in NCK1-positive cells compared to the model group ($P<0.05$).

The effect of NCK1 and CDK1 mRNA in rats with SCI

To clarify the effect of NCK1 and CDK1 mRNA in rats with SCI, the NCK1 and CDK1 mRNA relative expression levels in the spinal cord tissue in all groups of rats were measured by qRT-PCR, as shown in fig. 4. The results indicated that NCK1 and CDK1 mRNA expression levels were significantly lower in the model group compared to the control group ($P<0.05$). However, these levels were notably higher in the MIH group compared to the model group ($P<0.05$). This suggests that MIH may reduce cavitation and tissue loss in the spinal cord of SCI rats by upregulating NCK1 and CDK1 mRNA levels.

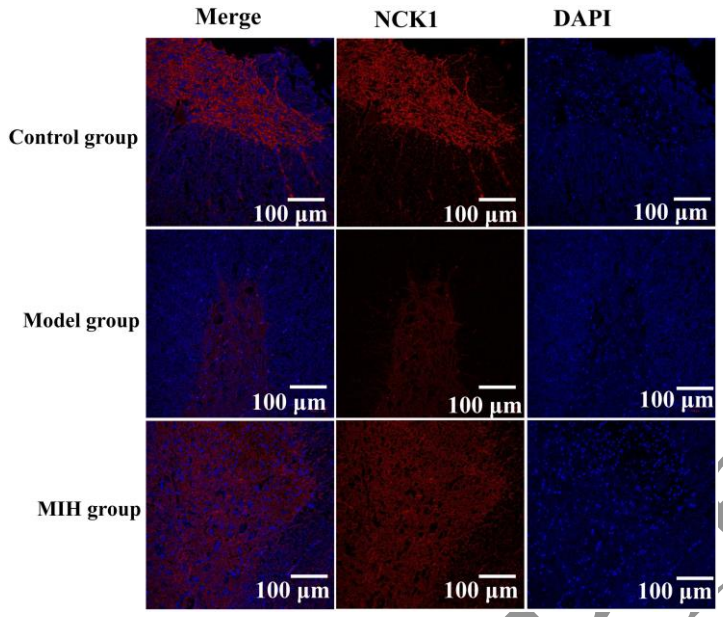


Fig. 3: The effect of NCK1 in the spinal cord tissue in all groups of rats were detected using immunofluorescence assay.

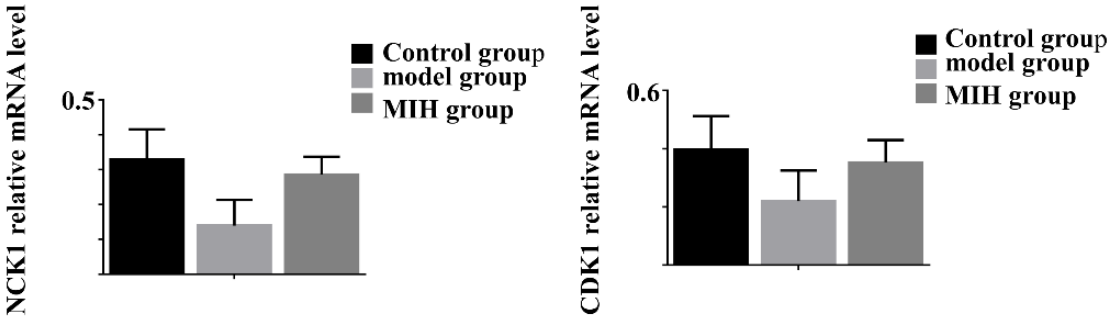


Fig. 4: The NCK1 and CDK1 mRNArelative expression levels in the spinal cord tissue in all groups of rats were measured by qRT-PCR.

DISCUSSION

SCI has a significant impact on the health and quality of life of patients. To enhance the effectiveness of SCI treatment, further research is required to elucidate the underlying mechanism. The use of MIH shows great prospect in promoting nerve regeneration in the damaged spinal cord of SCI patients. Additionally, the upregulation of the NCK1/CDK1 pathway holds potential for treating SCI patients. Moreover, while the control of the NCK1/CDK1 pathway by MIH has been implicated in various diseases, its role in SCI remains unclear. This study aims to uncover the mechanism by which MIH controls the NCK1/CDK1 pathway in SCI. The findings suggest that upregulating the NCK1/CDK1 pathway can improve SCI.

The MIH, which has multiple functions, shows promise as a treatment method for spinal cord injuries. One of its advantages is the ability to be directly injected into the affected area of the spinal cord. This targeted and precise delivery of the hydrogel to the injury site maximizes its potential therapeutic effects. The use of a multifunctional injectable hydrogel has shown promising results in preventing pathological damage in the spinal cord tissue (Cha *et al.*, 2022; Fang *et al.*, 2023). This hydrogel is intended to be directly injected into the affected area to create a protective barrier and stimulate tissue regeneration. These results in our study suggested that MIH can ameliorate the cavitation and tissue loss in the spinal cord of rats with SCI. Consistent with those described in previous studies (Xiao *et al.*, 2023; Zheng & Tuszynski, 2023), the MIH can prevent the SCI process by promote the neural regeneration after SCI. The multifunctional injectable hydrogel has been found to effectively prevent cavitation and tissue loss, thereby preserving the structural integrity of the spinal cord.

NCK1 plays a vital role in promoting nerve regeneration through its involvement in cell migration, cytoskeletal remodeling and axon guidance (Ilovich *et al.*, 2022). On the other hand, CDK1 serves as a crucial regulator of the cell cycle and contributes to neuronal differentiation,

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highlighting its significance in facilitating the growth and development of new neurons (Michowski *et al.*, 2020; Wang *et al.*, 2023). Both NCK1 and CDK1 are essential proteins involved in the regulation and signaling of cells. The NCK1/CDK1 pathway plays a role in various cellular processes, including cell migration, axon guidance and neuronal differentiation (Diab *et al.*, 2023; Zha *et al.*, 2021). The results in our studies suggested that the MIH can enhance nerve regeneration, leading to functional recovery and improvement in patients with spinal cord injury via activating the NCK1/CDK1 pathway. In addition, In the context of SCI, the expression levels of NCK1 and CDK1 have been observed to increase upon treatment with the MIH. In a study by Yang *et al*. (2022) , the role of NCK1 in rats after spinal cord injury (SCI) was investigated. The findings revealed a significant decrease in NCK1 protein level at 1th day post-SCI. Knockout of Nck1 resulted in decreased cell viability and neurite development in the spinal cord tissue. These results suggest that increasing NCK1 expression can improve SCI by enhancing cell viability and neurite development in the spinal cord tissue. Additionally, Nie *et al.* (2022) conducted an *in vivo* study that highlighted the role of CDK1 in SCI. The results demonstrated that downregulation of NCK1 suppressed the activity of anterior horn astrocytes and microglia in the spinal cord tissue, while upregulation of NCK1 enhanced their activity. This study suggests that upregulating NCK1 can improve SCI through the administration of a multifunctional injectable hydrogel to rats with SCI. Based on these findings, it can be concluded that the NCK1/CDK1 pathway is involved in the attenuation of SCI by multifunctional injectable hydrogel injection. One limitation of this study is that it only investigated the molecular mechanisms of the multifunctional injectable hydrogel and its regulation of the NCK1/CDK1 pathway in SCI through *in vitro* experiments. Further clinical studies are needed to validate these findings.

Limitations and future work

Model limitations

Our rodent model may not fully capture the complexity of human spinal cord injuries, necessitating further studies in larger animal models. *Hydrogel Formulation*: Potential variability in hydrogel properties requires optimization for consistent clinical application. *Future Research*: Future studies should focus on refining the hydrogel formulation, conducting mechanistic studies and planning for clinical trials to ensure safe and effective translation to human patients.

CONCLUSION

Our study demonstrates that the hydrogel exhibits promising stability at human body temperature (37°C), with favorable gelation time, degradation rate and mechanical strength, making it a viable candidate for clinical applications. The scalability of hydrogel production has been addressed, ensuring that large-scale manufacturing can maintain quality and consistency. Regulatory pathways for clinical translation have been mapped out, highlighting the importance of biocompatibility, safety and efficacy. However, it is essential to recognize the limitations of our current preclinical model. While the hydrogel shows potential in rodent models, significant anatomical, physiological and immunological differences between rodents and humans necessitate further preclinical validation. Future studies should focus on larger animal models to better mimic human spinal cord injuries and ensure the robustness of the hydrogel's therapeutic effects. In conclusion, while our findings are promising, further preclinical studies are required to validate the hydrogel's safety and efficacy before considering clinical trials. This evidence-based approach will help ensure that the hydrogel can be effectively and safely translated to human patients.

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Authors' contributions

Yan Zhang conceived the study, designed the experiments, and drafted the manuscript. Caili Bao established the rat spinal cord injury model, administered the treatments, and collected the tissue samples. Xiaolong Yang performed the immunofluorescence staining and histological analyses and contributed to manuscript drafting. Hongze Chang performed the Western blot experiments. Liang Liu performed the qRT-PCR experiments. Xiaodong Liu analyzed and interpreted the experimental data. Feng Cai supervised the study, contributed to the study design and interpretation of the results, and critically revised the manuscript. All authors reviewed and approved the final manuscript.

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Protocol registration

A study protocol outlining the research question, key design features, and analysis plan was prepared before the experiments. The protocol was not registered in a public registry.

Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

The animal ethic approval was reviewed and approved from the Ethics Committee of The Shanghai Yangpu Hospital affiliated to Tongji University (approval No.:

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IACUC-2023-045). All methods were carried out in accordance with relevant guidelines and regulations. This study was performed in adherence with the ARRIVE guidelines. See supplementary file for the ARRIVE checklist.

Consent to publish
All of the authors have consented to publish this research.

Conflict of interests
All authors declare no conflict of interest.

AI-use statement
No artificial intelligence tools were used in the preparation, analysis, editing, or figure production of this manuscript.

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