Bio-instructive hydrogel as an injectable tissue prosthesis for the repair and rehabilitation of impaired muscle

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Hydrogel-based injectable tissue prostheses connect and modulate the responses of surrounding cells and tissues after a tissue defect by reconstructing a bio-instructive microenvironment. This reconstruction is essential for maintaining homeostasis, which is crucial for tissue growth, repair, regeneration, and rehabilitation. Hydrogel-induced rehabilitation has received much attention in tissue function reconstruction from fundamental research and practical applications in recent years. In particular, bioactive hydrogels with special (bio) physicochemical characteristics, such as conductivity, appropriate diffusibility, biomimetic structure, bio-adapted biodegradation, and biocompatibility, are becoming increasingly desirable biomaterials for nerve and muscle rehabilitation.

Muscles sustaining an injury interrupts their connection to the neural system, resulting in impaired function. Conventional prosthetics fail to completely restore these connections for intended muscular contractions. The combination of biomedical engineering and materials science has resulted in the development of electroconductive hydrogels, which exhibit a response to electrical stimulation and show potential for tissue/organ rehabilitation. These hydrogels are soft and flowable, designed to be directly injected into injured muscles,[1] serving as a bridge between damaged tissue and neural circuitry. Their unique properties allow them to adapt to injury contours, filling voids from trauma. Critically, they transmit electrical signals bidirectionally, stimulating muscles to aid recovery and providing real-time feedback on rehabilitation progress. Recent advances in integrating electroconductive functionalities by adding conductive polymers or nanoparticles allow them to mimic natural tissues and dynamically respond to electrical signals—a crucial trait for interaction with biological systems. Several studies mentioned rapidly bondable conductive hydrogels for therapeutic cardiac patches,[2] injectable neural stimulation electrodes made from polymer/metal composites,[3] and multifunctional hydrogels containing MXene nanosheets (injectable, adhesive, self-healing, and conductive features) for spinal cord injury repair.[4]

In a recent article published in *Nature*, Jin et al.[5] introduced an innovative strategy to heal muscle injuries. This approach involves using injectable tissue prosthesis made of conductive hydrogels with a robot-assisted rehabilitation system. Conventional methods for rehabilitating these injuries have concentrated on creating a closed-loop gait rehabilitation system that uses wearable or implanted technology along with lightweight exoskeletons to help patients regain motion and sensory abilities compromised by nerve and muscle damage. However, current electronic materials with a rigid nature and mechanical properties commonly lead to friction and inflammation, hindering patient rehabilitation. To address these challenges, Jin et al.[5] explored the use of hyaluronic acid in developing an injectable hydrogel for tissue prosthesis. Hyaluronic acid is important in modulating cellular behaviour and tissue response due to its biocompatibility, viscoelastic properties, and ability to interact with cell surface receptors. Its presence in the injectable hydrogel enhances cell proliferation, migration, and differentiation, facilitating tissue regeneration and repair. These injectable tissue-interfacing prostheses hold promise for applications in tissue engineering and soft bioelectronics due to their various cross-linking strategies. These prostheses contain irreversible biphenyl linkage, reversible strong coordinate bonds with gold nanoparticles, and weak multivalent ionic interactions for effective energy dissipation and tissue interfacing (**Figure 1**). This hydrogel acts as a temporary filler for tissue voids caused by missing muscle

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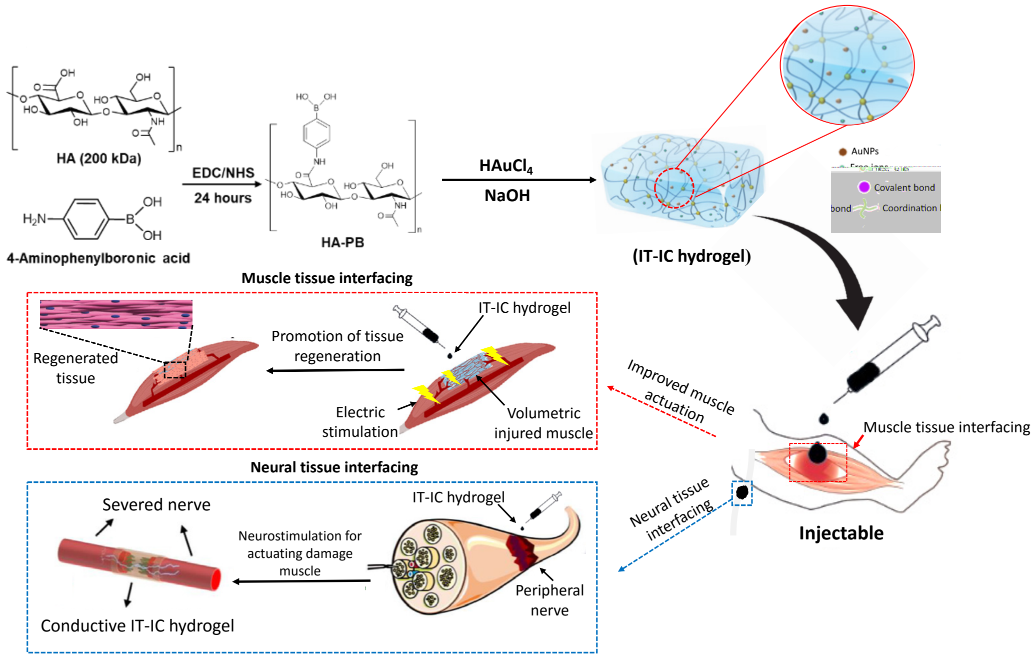

Figure 1. Schematic illustration of the design strategy and application of conductive IT-IC hydrogel. The preparation process and filling of the injured muscle (red dashed box) or nerve (blue dashed box) with IT-IC hydrogel contributes to tissue repair and rehabilitation. The chemical structure was drawn using KingDraw software, and the figure was created using Photoshop 2021 (version 22.1.0). HA: hyaluronic acid; IT-IC: injectable tissue-interfacing prostheses; PB: phenylborate.

or nerve tissues, promoting tissue repair. Its injectable nature presents a substantial benefit over conventional bioelectronics devices, which are not suitable for small, deep, and narrow spaces and thus require intrusive procedures.

Additionally, due to its remarkable biological characteristics, the developed hydrogel integrates smoothly with natural tissues and can be applied to inaccessible body regions without the need for surgical intervention. The hydrogel, possessing reversible and irreversible crosslinks, adjusts to withstand high shear stress during injection, providing exceptional bio-mechanical stability. Gold nanoparticles incorporated into the hydrogel provide it with decent electrical properties, facilitating the effective transmission of electrophysiological signals across injured tissues (**Figure 1**). Furthermore, the hydrogel is biodegradable, which eliminates the necessity for further surgical procedures.

Researchers view this bio-instructive hydrogel as a promising approach for rehabilitation owing to its mechanical characteristics similar to natural tissues, excellent tissue adhesion, and injectable properties. Jin et al.[5] validated this concept in rat models by simulating volumetric muscle loss injury, where they significantly improved gait in injured rats by administering the hydrogel via injection. Additionally, they combined robot assistance controlled by muscle electromyography signals with stretchable tissue interface devices for electrical sensing and stimulation. This approach, when coupled with robot assistance guided by muscle electromyography signals, improved gait without the need for nerve stimulation. Moreover, long-term muscle tissue repair was substantially enhanced after utilising the conductive hydrogel to fill muscle damage.

In summary, this study marks a significant advancement in rehabilitation medicine, biomaterial technology, and bioelectronics devices. Integrating an injectable tissue prosthesis with a closed-loop bioelectronics system holds great promise for patients with neurological and musculoskeletal disorders, offering improved rehabilitation prospects and potential applications for precise diagnosis and treatment across various medical conditions. The hydrogel's biodegradability and exceptional tissue adhesion further enhance its appeal as an innovative soft tissue prosthesis for medical use. Ultimately, the injectable hydrogel prosthesis allows for bidirectional cross-talk between peripheral nerve tissue and muscles, facilitating therapeutic rehabilitation for patients suffering from chronic tissue damage. This breakthrough has the potential to transform patient care, providing new possibilities and hope for individuals recovering from chronic injury.

Author contributions

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Conflicts of interest statement

None.

1. Han, I. K.; Song, K. I.; Jung, S. M.; Jo, Y.; Kwon, J.; Chung, T.; Yoo, S.; Jang, J.; Kim, Y. T.; Hwang, D. S.; Kim, Y. S. Electroconductive, adhesive, non-swelling, and viscoelastic hydrogels for bioelectronics. *Adv Mater.* **2023,** *35*, e2203431.
2. Liang, S.; Zhang, Y.; Wang, H.; Xu, Z.; Chen, J.; Bao, R.; Tan, B.; Cui, Y.; Fan, G.; Wang, W.; Wang, W.; Liu, W. Paintable and rapidly bondable conductive hydrogels as therapeutic cardiac patches. *Adv Mater.* **2018,** *30*, e1704235.
3. Trevathan, J. K.; Baumgart, I. W.; Nicolai, E. N.; Gosink, B. A.; Asp, A. J.; Settell, M. L.; Polaconda, S. R.; Malerick, K. D.; Brodnick, S. K.; Zeng, W.; Knudsen, B. E.; McConico, A. L.; Sanger, Z.; Lee, J. H.; Aho, J. M.; Suminski, A. J.; Ross, E. K.; Lujan, J. L.; Weber, D. J.; Williams, J. C.; Franke, M.; Ludwig, K. A.; Shoffstall, A. J. An injectable neural stimulation electrode made from an in-body curing polymer/metal composite. *Adv Healthc Mater.* **2019,** *8*, e1900892.
4. Yu, Q.; Jin, S.; Wang, S.; Xiao, H.; Zhao, Y. Injectable, adhesive, self-healing and conductive hydrogels based on MXene nanosheets for spinal cord injury repair. *Chem Eng J.* **2023,** *452*, 139252.
5. Jin, S.; Choi, H.; Seong, D.; You, C. L.; Kang, J. S.; Rho, S.; Lee, W. B.; Son, D.; Shin, M. Injectable tissue prosthesis for instantaneous closed-loop rehabilitation. *Nature.* **2023,** *623*, 58-65.

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