

Stimuli-Responsive Hydrogels for Nerve Repair: Advances in Multimodal Systems and Advanced Manufacturing Technologies

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Abstract: Stimuli-responsive hydrogels, including photo-responsive, magnetic-responsive, thermo-responsive, and enzyme-responsive systems, have emerged as promising biomaterials for nerve repair and regeneration. This paper encapsulates recent developments in the utilization of intelligent hydrogels for nerve healing, emphasizing their regenerative capabilities and the principal limitations identified in the current literature and data. To highlight the potential for nerve repair, further analysis is provided on the innovative applications of advanced manufacturing technologies, such as microfluidics and 4D printing, in enhancing the fabrication precision and biocompatibility of stimulus-responsive hydrogels. Although challenges remain regarding biocompatibility, mechanical strength, and in vivo translation, the application of these technologies can help overcome current limitations. The paper highlights how the combination of smart hydrogels and advanced manufacturing techniques can significantly improve their potential for neural tissue engineering. Future directions prioritize hybrid systems, multi-stimuli integration, and 4D bioprinting. The findings provide valuable insights and technical references for future research on intelligent hydrogels in nerve regeneration medicine.

Keywords: Nerve repair, Nerve regeneration, Stimuli-responsive hydrogels, 4D printing, Microfluidics

1. Introduction

With the continuous advancements in biomaterials science and regenerative medicine, hydrogels have emerged as a major focus in the repair of neurological disorders, such as spinal cord injury (SCI), owing to their high water content, three-dimensional network structure, biodegradability, biocompatibility, and tunability[1]. Due to their superior water retention capabilities and physical characteristics akin to real soft tissues, hydrogels have been utilized as three-dimensional scaffolds in tissue engineering to furnish cells with an in vivo-like environment, thus facilitating tissue regeneration and repair[2]. Traditional hydrogel scaffolds can offer mechanical support to the injury site under static conditions, however, their fixed physical and chemical properties are insufficient to accommodate the dynamic spatiotemporal changes of the microenvironment following nerve injury, limiting their effectiveness in nerve repair. Recent investigations on hydrogel swelling qualities have revealed that hydrogels can experience volumetric alterations in reaction to environmental stimuli, including pH, temperature, light, magnetic fields, and enzymes, thereby producing dynamic

responses. Consequently, hydrogels are regarded as "smart materials" that can actively react to external stimuli or environmental alterations. This distinctive characteristic holds significant potential in nerve healing.

Despite the growing body of research on the application of smart hydrogels in nerve injury repair, there remains a notable gap in comprehensive reviews that systematically address the progress of various smart hydrogels in regulating the neural microenvironment. Specifically, there is a lack of detailed discussion on how advanced manufacturing technologies, such as microfluidic technology and 4D printing, contribute to enhancing the precision and biocompatibility of hydrogels. The existing deficiencies in current scholarship provide a foundational rationale and impetus for this research endeavor. This paper will focus on the application progress of stimuli-responsive hydrogels in nerve injury repair, with an emphasis on their potential in neural tissue engineering, the challenges associated with their use, and future research directions. The aim is to offer comprehensive theoretical support and practical guidance, contributing valuable insights to researchers in related fields.

2. Stimuli-responsive hydrogels

2.1. Photo-responsive hydrogels

Among various types of stimuli-responsive hydrogel materials, photo-responsive hydrogels have emerged as a research focus due to the advantages of light stimulation, such as non-invasiveness, precise spatiotemporal control, and adjustable energy[3]. These hydrogels undergo structural, volumetric, and physicochemical changes in response to external light stimuli. To achieve this, the synthesis strategies typically involve covalent modification to introduce photosensitive groups or the integration of photothermal nanoparticles, both of which enable the light-controlled regulation of the hydrogel structure. Photo-responsive hydrogels have proven to be exceptional scaffolding for soft actuators, healing materials, adaptable surfaces, dynamic cellular microenvironments, and drug delivery systems.

Photo-responsive hydrogels constitute a promising approach for nerve repair and regeneration. Recent advancements in photo-responsive hydrogels for nerve restoration can be classified into the following functional domains. Zhou has presented an injectable and photocurable methacrylate-silk fibroin hydrogel infused with basic fibroblast growth factor (bFGF) for spinal cord regeneration[4]. The study demonstrated that this hydrogel exhibits favorable biocompatibility and controlled drug release properties, enabling it to play a significant role in SCI treatment. In a separate study, Zhao employed a complete SCI animal model to evaluate the efficacy of a novel, visible light-induced, crosslinkable gelatin (GL)/hyaluronic acid (HA) hybrid scaffold[5]. The results revealed that this photo-responsive hydrogel effectively reduced both inflammation and glial scar formation at the injury site. Furthermore, the optimized composition of the hydrogel not only mitigated these adverse effects but also enhanced the activation of endogenous neural stem cells, thereby promoting neuronal maturation and facilitating axonal regeneration. In the context of precise, localized, and non-invasive delivery of bioactive molecules to manipulate neural activity both in vitro and in vivo, a study by Li proposed a novel approach for controlling bio-molecule delivery using a near-infrared (NIR) triggered nanocomposite hydrogel platform[6]. This system leverages the photo-thermal properties of polypyrrole (PPy) nanoparticles embedded in microscale hydrogels, allowing for spatiotemporal regulation of molecule release in response to NIR light. In vivo, it has been demonstrated that this platform can control brain activity in the auditory cortex of rats without the need for genetic modification. The ability of photo-responsive hydrogels mechanical compatibility and capacity to modulate the inflammatory response, positions them as effective materials in the field of regenerative medicine, particularly for spinal cord injuries and other nerve damage conditions.

2.2. Thermo-responsive hydrogels

Temperature fluctuations, particularly those around body temperature (37°C) or variations in environmental set temperatures, serve as a mild stimulus for controlling stimuli-responsive hydrogels. The core characteristic of thermo-responsive hydrogels arises from their phase transition behavior at the lower critical solution temperature (LCST) or upper critical solution temperature (UCST), enabling reversible swelling or shrinkage at specific temperatures. This behavior allows for the modulation of their physical properties, such as adhesiveness, mechanical strength, and porosity[7]. Thermo-responsive hydrogels have developed as a novel material due to its capacity to react to temperature fluctuations in physiological settings, facilitating the targeted transport of medications and cells. These hydrogels have emerged as a focal point of research in recent years.

Poly(N-isopropylacrylamide) (PNIPAM) hydrogels are the most thoroughly investigated thermo-responsive hydrogel materials, with widespread applications in drug delivery, tissue engineering, and cell engineering. In recent years, the reversible temperature-induced expansion of PNIPAM and its derivatives has been utilized in various smart sensors for nerve repair and regeneration. Yang et al. developed a PNIPAM/DM hydrogel by loading dopamine-modified multi-walled carbon nanotubes into PNIPAM hydrogels, resulting in a material with excellent hydrophilicity and reversible photothermal responsiveness[8]. Experimental results demonstrated that this hydrogel effectively promoted the growth of neural cells, enhanced the release of neurotrophic factors, and significantly increased the gene expression related to myelination and the cytoskeleton, offering promising potential to further improve nerve repair capabilities.

In addition, many studies have focused on exploring the applications of various types of temperature-responsive hydrogels in nerve repair. Zhang et al. developed a therapeutic system based on a temperature-responsive PLEL hydrogel, loaded with extracellular vesicles (EVs) derived from M2 microglia, which achieved sustained release of EVs through in situ gelation triggered by body temperature[9]. Research findings show that, after 28 days of treatment, the Basso, Beattie, Bresnahan (BBB) motor score of the PLEL/EVs group was 14 ± 2 , significantly higher than the other groups. The spinal cord injury area in the PLEL/EVs group was significantly reduced (0.025 ± 0.007 cm²), half the size of the injury in the hydrogel-only group. Toluidine blue and MAP2 staining showed better tissue integrity and more myelin in the PLEL/EVs group compared to the SCI and PLEL-only groups. EVs induced M2 polarization, significantly suppressing the expression of the inflammatory markers iNOS and COX-2. Furthermore, the system upregulated the anti-apoptotic protein Bcl-2, while inhibiting Bax and cleaved caspase-3, reducing neuronal apoptosis by 73% compared to the SCI group. These results collectively validate the synergistic regulation of thermo-responsive PLEL hydrogel and EVs, effectively improving the spinal cord injury microenvironment and promoting the recovery of neural function post-SCI.

The Alizadeh team further advanced the utilization of this material in spinal cord injury healing by investigating the synergy between nerve growth factor (NGF)-overexpressing adipose-derived mesenchymal stem cells (hADSCs) and a thermo-responsive hydrogel (CS/ β -GP/HEC)[10]. This approach efficiently facilitated stem cell migration and differentiation, markedly enhancing motor function recovery. Wang's study concentrated on optic nerve healing, developing a chitosan-based thermo-responsive hydrogel co-loaded with ciliary neurotrophic factor (CNTF) and FK506, an immunosuppressant. This technique accomplished prolonged drug release, enhancing the survival of retinal ganglion cells (RGCs) and efficiently suppressing excessive microglial activation[11].

These studies demonstrate the tremendous potential of thermo-responsive hydrogels in nerve repair, especially in the repair of spinal cord and optic nerve injuries, offering advantages that are difficult to match by traditional treatment methods. However, despite these promising results, thermo-responsive hydrogels still face challenges, particularly regarding the stability of long-term

drug release and how to address the impact of temperature fluctuations on hydrogel performance. To enhance the stability and adaptability of these hydrogels, future research may combine various crosslinking techniques, such as dynamic covalent bonds (e.g., boronate ester bonds) or hybrid crosslinking strategies, to improve the long-term stability and biocompatibility of the hydrogels[12]. Additionally, with the advancement of 3D/4D bioprinting technologies, thermo-responsive hydrogels are expected to play a greater role in personalized treatments, enabling the high-precision printing of individualized nerve repair scaffolds, thereby promoting clinical translation and application.

2.3. Magnetic-responsive hydrogels

The fabrication of magnetic-responsive hydrogels typically involves incorporating magnetic nanomaterials (e.g., iron oxide nanoparticles) into the polymer network through physical or chemical crosslinking. These hydrogels, capable of responding to external magnetic fields, allow for non-invasive remote control, adapting to the repair needs of different tissues and are particularly suitable for nerve repair and regeneration.

In SCI repair, magnetic-responsive hydrogels direct the growth of neural progenitor cells (NPCs), promote axon regeneration, and reduce inflammation. The study by Anarkoli introduced a novel injectable hydrogel, Anisogel, which aligns magnetic-responsive short fibers in a low magnetic field[13]. This system supports neuronal growth along the fiber direction and induces spontaneous electrical activity. The material incorporates low-toxicity superparamagnetic iron oxide nanoparticles (SPIONs), ensuring safety for in vivo applications, particularly in treatments requiring directional regeneration, such as spinal cord injury. Tran's research focused on magnetic-responsive self-assembling peptide-based hydrogels, specifically designed to respond to magnetic fields during polymerization to arrange fibers[14]. The research indicated that hydrogels seeded with human mesenchymal stem cells (hMSCs) enhanced axon development, provided directional guidance, and diminished inflammation in a spinal cord injury model, underscoring their potential in regenerative medicine.

In recent years, Zhang et al. further revealed the molecular mechanisms by which magnetic-responsive hydrogels regulate neural stem cell (NSC) differentiations[15]. By constructing a chitosan hydrogel containing gradient concentrations of magnetic nanoparticles (MNPs), the study found that 50 $\mu\text{g/mL}$ MNPs (MCS-M) optimally promoted NSC differentiation into neurons and significantly accelerated functional recovery following spinal cord hemisection injury in vivo. Proteomics analysis indicated that MNPs regulate the composition of the hydrogel's protein corona, enriching functional proteins associated with "neuronal differentiation," "receptor activation," and "protein kinase activity," thereby activating the RAS-MAPK/PI3K signalling cascade. Additionally, the synergistic application of an external magnetic field further enhanced neurogenesis efficiency by upregulating chemokine signalling pathways, providing a theoretical basis for the multimodal regulation of nerve repair by magnetic-responsive materials.

Despite the significant advantages of magnetic-responsive hydrogels, their clinical application still faces challenges, particularly regarding the toxicity of MNPs and the difficulties associated with large-scale production. Additionally, the homogeneous dispersion of magnetic particles in hydrogels is still difficult. Therefore, future research will focus on reducing nanoparticle toxicity, optimizing the biocompatibility of the hydrogels, and exploring new directions such as multifunctionality and integration of bioactive factors to further enhance their effectiveness in nerve repair.

2.4. Enzyme-responsive hydrogels

Enzyme-responsive hydrogels have become a key area of research in nerve repair and regeneration, owing to their inherent biocompatibility and responsiveness, making them ideal candidates for tissue engineering scaffolds.

A primary characteristic of enzyme-responsive hydrogels is their capacity to undergo enzymatically induced sol-gel transitions in response to specific enzymes, providing significant versatility for tissue engineering. Li et al.'s research illustrated the efficacy of gelatin hydrogels (GH) crosslinked by dual enzymes as scaffolds for nerve regeneration[16].

The hydrogel was crosslinked using horseradish peroxidase (HRP) and choline oxidase (ChOx), establishing a responsive environment that supported the survival, differentiation into neural cells, and neurotrophic factor secretion of bone marrow-derived mesenchymal stem cells (BMSCs). This enzymatic crosslinking mechanism not only enhanced cell viability but also facilitated neural differentiation and amplified the therapeutic effects of BMSCs, thereby promoting recovery from traumatic brain injury. Furthermore, the enzyme-responsive degradation of the hydrogel not only controls the release of drugs or cells but also promotes the repair of neural tissue. A peptide-based injectable hydrogel (SFNV) proposed by Adak et al. was shown to respond to matrix metalloproteinase-9 (MMP-9), releasing neuroprotective peptides at the nerve injury site, significantly promoting the growth of neural protrusions and aiding nerve repair[17].

Despite the broad potential of enzyme-responsive hydrogels in nerve repair, several challenges remain. Specifically, further optimization and research are needed in areas such as the long-term stability, degradation rate, and compatibility with the extracellular matrix of hydrogels. Precisely controlling the degradation process to ensure spatiotemporal specificity in nerve repair will be an important direction for future development.

3. Advanced fabrication technologies for stimuli-responsive hydrogels

3.1. Microfluidic technology

The rapid advancement of microfluidic technology has provided a powerful platform for the processing and application of stimuli-responsive hydrogels, particularly in biomedical fields such as nerve repair. By enabling precise manipulation of fluids at the microscale, microfluidic systems allow for efficient fluid management and biological sample control in biomedical applications involving stimuli-responsive hydrogels. These hydrogels, particularly those responsive to external stimuli like temperature, pH, or light, exhibit dynamic responses in microfluidic environments, hence improving the precision and adaptability of therapeutic systems. Under external stimulation, these hydrogels can alter their physical properties (e.g., swelling, shrinking, wettability), making them ideal functional components for implementing valves, pumps, and drug delivery systems within microchannels.

Photolithography and micromolding techniques are widely used in microfluidic systems to fabricate patterned pH- or temperature-responsive hydrogels, such as thermos-responsive microvalves and micropumps[18]. These active components regulate fluid flow and direction within microchannels through the swelling and contraction of the hydrogels. Such designs not only enable effective control of fluid dynamics but also allow for precise manipulation of biological samples in specific environments. For example, the switchable wettability of light-responsive hydrogels enables directional fluid guidance on open surfaces. However, the practical application of these systems remains challenged by issues such as the response speed and mechanical stability of the hydrogels, which limit their use in high-precision and high-stability environments. To address these limitations, various strategies have been proposed, such as incorporating carbon nanotubes to enhance thermal

conductivity or applying metallic coatings to reinforce mechanical strength, thereby optimizing the response characteristics and overall stability of the systems.

In the context of nerve repair, the integration of microfluidic technology with stimuli-responsive hydrogels has demonstrated notable advantages. In a study conducted by Lin et al., a dual temperature-controlled microfluidic system (TSTC-MS) was developed to continuously fabricate decellularized extracellular matrix (dECM) hydrogel microspheres through a temperature-sensitive sol-gel transition mechanism[19]. These microspheres, created without supplementary crosslinkers, facilitated the three-dimensional proliferation and differentiation of Schwann cells and neural stem cells. The dimensions of the microspheres could be meticulously regulated by modifying the fluid flow rate. This method not only provided a highly biocompatible vehicle for nerve repair but also enabled controlled drug release and targeted delivery through size modulation, offering an effective therapeutic strategy for peripheral nerve regeneration. Furthermore, the requirements for hydrogel morphology in nerve repair scenarios are becoming increasingly stringent, necessitating materials capable of matching the three-dimensional contours of injury sites or guiding the directional growth of axons—making shape modulation of hydrogels a critical focus of current research.

3.2. 4D printing technology

4D printing technology, as an advancement of 3D printing, has achieved notable advancements in the creation of stimuli-responsive hydrogels, particularly within biomedicine and tissue engineering. In contrast to conventional 3D printing, which produces static structures, 4D printing incorporates a temporal element, enabling the printed hydrogels to undergo morphological transformations in response to certain external stimuli, like temperature, pH, and humidity. This dynamic morphological alteration grants 4D-printed hydrogels significant potential in drug administration, tissue repair, sensing, and various medicinal applications.

Based on existing research and the aforementioned review, stimuli-responsive hydrogels can be classified into various types, with thermos-responsive and pH-responsive hydrogels being the primary focus of 4D printing studies. LCST hydrogels, represented by PNIPAM, undergo a dramatic volume shrinkage near the critical temperature of 32°C. Their biocompatibility has been verified through 3T3 fibroblast cell experiments, and the LCST can be precisely tuned to the physiological temperature range (36–38°C) by copolymerizing with oligo(ethylene glycol) methacrylate (OEGMA), making them suitable for in vivo drug release applications. This demonstrates the potential of PNIPAM in drug delivery applications for 4D printing. On the other hand, pH-responsive hydrogels exhibit different deformation behaviors through protonation or deprotonation of acidic or basic groups on the polymer chains. The variable pH levels in different tissues and cellular compartments of the human body enable pH-responsive hydrogels in 4D printing to accurately regulate medication release to targeted areas under specified conditions[20]. Specifically, pH-responsive hydrogels can respond to dynamic pH conditions present in different parts of the body, such as the gastrointestinal tract under steady-state conditions (with a gastric pH of 1.2 and intestinal pH ranging from 6.8 to 7.4), the vagina (pH ranging from 4.5 to 5.5), and blood vessels (pH of 7.4). These pH ranges closely match the pKa values (4.5 to 5.5) of common anionic hydrogels, such as polyacrylic acid, enabling targeted drug release triggered by physiological pH gradients[21]. In conclusion, the pH-responsive swelling and deswelling behavior of these hydrogels effectively regulates drug release in response to local pH variations.

The selection of hydrogel materials and printing methodologies is essential in the execution of 4D printing technology. Current research emphasizes laser-based methodologies (including stereolithography, digital light processing, and two-photon polymerization) alongside extrusion-based printing techniques (such as direct inkjet printing and fused deposition modeling) for the fabrication of responsive hydrogels[22].

These techniques enable high-resolution printing, and when combined with stimuli-responsive hydrogels, they allow the printed structures to undergo shape changes under external stimuli, enhancing the functionality and adaptability of the hydrogels. For example, when using thermo-responsive hydrogels for 4D printing, the printed hydrogels can expand or contract at specific temperatures, simulating dynamic biological tissue changes.

Despite the significant advantages of 4D printing technology in the application of stimuli-responsive hydrogels, some challenges remain. For example, improving the response speed and shape recovery capability of the hydrogels, as well as achieving the translation from laboratory to clinical applications, are critical issues that need to be addressed. On the other hand, the biocompatibility and degradability of the hydrogels must also be fully considered during design to ensure their safety and efficacy *in vivo*. Some studies have introduced multiple stimuli-responsive properties (such as temperature, pH, and humidity) to create multifunctional hydrogels, enhancing their application in complex biological environments[23].

4. Challenges and future perspectives

Despite significant advancements in the development of stimuli-responsive hydrogels for neural tissue engineering, several challenges persist that impede their widespread clinical application. One of the primary obstacles is the limited translation of these hydrogels into *in vivo* environments. While promising results have been observed in preclinical studies, the *in vivo* microenvironment presents unique challenges, such as the need for hydrogels to sustain their dynamic properties under stable physiological conditions. For example, methylcellulose is a thermo-responsive material with an initial gelation temperature of 60°C. By adjusting the salt content, its gelation temperature can be lowered to near physiological temperature (37°C). However, the non-biodegradability of methylcellulose limits its use in long-term applications[24]. Additionally, many current stimuli-responsive hydrogels exhibit a one-time, non-reversible response upon implantation, which limits their applicability for long-term clinical use.

A notable challenge is the biocompatibility of the employed materials. The porosity of crosslinked collagen scaffolds increases; yet, the randomly oriented pores result in disorganized axonal development. Other hydrogels, especially those originating from synthetic polymers, demonstrate challenges like insufficient cell adherence and suboptimal integration with adjacent tissues. Polyethylene glycol (PEG) and poly(2-hydroxyethyl methacrylate) (PHEMA) frequently exhibit inadequate cell adherence owing to the lack of natural protein constituents[24]. Enhancing the bioactivity of these hydrogels generally requires their combination with natural biomaterials or their amalgamation with natural polymers.

Although some stimuli-responsive hydrogels exhibit good biocompatibility, they often suffer from insufficient mechanical strength, which may compromise their ability to effectively support neural tissue regeneration. For example, studies have shown that maintaining the hydrogel scaffold structure at the injury site for at least four weeks is crucial for physically supporting and guiding axonal growth and regeneration[25]. While the elastic modulus of PEGDA-GelMA scaffolds is 260-300 kPa, similar to that of normal spinal cord tissue (200-600 kPa), long-term implantation may still lead to structural collapse due to degradation[26].

Looking forward, the integration of 4D bioprinting and microfabrication techniques presents promising solutions to some of these challenges. The ability to print complex hydrogel structures with high resolution and dynamic properties could facilitate the development of scaffolds that more accurately replicate the intricate architecture of the brain. However, significant efforts are required to optimize these techniques for scalable and cost-effective production. Furthermore, the incorporation of multiple stimuli-responsive mechanisms into a single hydrogel system—such as responsiveness to

light, temperature, and mechanical cues—has the potential to greatly enhance the versatility of these materials in various therapeutic applications.

5. Conclusion

Stimuli-responsive hydrogels have emerged as potential materials for the healing and regeneration of brain injuries due to their capacity to dynamically react to many environmental stimuli, such as light, temperature, magnetic fields, and enzymes. This study emphasizes current progress in the development of these hydrogels, specifically regarding their regeneration capabilities and the obstacles encountered in neural tissue engineering. The incorporation of new production methods, including microfluidics and 4D printing, has facilitated notable advancements in the precision, biocompatibility, and functional characteristics of these hydrogels, thus augmenting their utility in nerve healing. Despite substantial progress, several limitations persist in the application of stimuli-responsive hydrogels in neural tissue engineering. One of the primary challenges is the limited long-term stability and reversibility of these hydrogels under physiological conditions. Additionally, ensuring the mechanical strength and stability of hydrogels, particularly those based on natural polymers, remains a significant hurdle. Furthermore, the inherent complexity of neural microenvironments and the difficulty in accurately replicating their dynamic changes in vivo continue to present challenges for the development of more effective hydrogel-based scaffolds. Future research should focus on addressing these limitations by exploring the development of hybrid hydrogels that combine the advantages of both synthetic and natural polymers, offering enhanced mechanical properties and improved biocompatibility. Additionally, incorporating multiple stimuli-responsive mechanisms within a single hydrogel system could enhance its adaptability to the dynamic nature of the neural environment. Moreover, continued advancements in manufacturing technologies, particularly 4D bioprinting, will be crucial for fabricating complex, highly functional scaffolds that more closely mimic the neural extracellular matrix. These innovations will pave the way for the successful clinical application of stimuli-responsive hydrogels in nerve repair and regeneration.

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