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Application of smart hydrogels scaffolds for bone tissue engineering

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ABSTRACT

Recent attention in the biomedical and orthopedic sectors has been drawn towards bone defects, emerging as a prominent focus within orthopedic clinics. Hydrogels, due to their biocompatibility, elevated water content, softness, and flexibility, are increasingly acknowledged in tissue regeneration research. Advanced biomaterials offer numerous advantages over traditional materials, notably the capacity to respond to diverse physical, chemical, and biological stimuli. Their responsiveness to environmental cues, such as three-dimensional (3D) morphology and phase conditions, holds promise for enhancing the efficacy of localized bone lesion repairs. This paper aims to revolutionize the treatment of severe bone abnormalities by providing a comprehensive examination of hydrogels capable of morphological adaptation to environmental changes. It delineates their classification, manufacturing principles, and current research status within the field of bone defect regeneration.

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1. INTRODUCTION

Stimuli-responsive hydrogels have emerged as promising biomaterials for bone tissue engineering, offering dynamic properties that respond to various environmental cues present in the physiological microenvironment. These hydrogels can adapt their physical, chemical, and mechanical characteristics in response to external stimuli, providing tailored solutions for bone regeneration and repair. In this section, we explore recent advancements and applications of stimuli-responsive hydrogels in bone tissue engineering [1]–[4].

Temperature-responsive hydrogels exhibit reversible phase transitions in response to changes in temperature, making them suitable for minimally invasive applications in bone tissue engineering. These hydrogels can undergo gel-sol transitions at physiological temperatures, enabling injectable delivery and in situ formation within bone defects [5]. Light-responsive hydrogels offer precise spatiotemporal control over their properties through exposure to light of specific wavelengths. By incorporating photochromic molecules or photoinitiators, these hydrogels can undergo rapid changes in crosslinking density, stiffness, and degradation rates, facilitating on-demand manipulation of their mechanical properties for bone tissue engineering applications [6]. Chemical-responsive hydrogels can sense and respond to specific chemical cues present in the bone microenvironment, such as pH variations, enzyme activity, or ion concentrations. These hydrogels enable controlled drug release, modulation of cellular behavior, and dynamic interactions with the surrounding tissue, promoting enhanced tissue regeneration and repair [7], [8]. Magnetic-responsive hydrogels leverage the application of external magnetic fields to manipulate their physical, biochemical, and mechanical properties. By incorporating magnetic nanoparticles, these hydrogels can undergo controlled deformation, alignment, and drug release in response to magnetic stimuli, offering opportunities for targeted drug delivery and cellular manipulation in bone tissue engineering [9], [10]. This review will begin by introducing the concept of classifying and designing smart hydrogels in response to various environmental stimuli and will then go on to discuss exemplary instances that illustrate how these stimuli-responsive hydrogels have been put to use, with a primary focus on, but not exclusive to, bone restoration applications. Figure 1 shows a schematic representation of various smart hydrogels for bone regeneration.

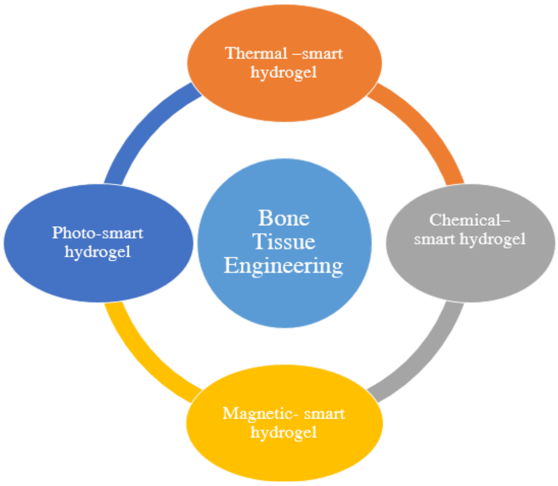

Figure 1. A schematic representation of various smart hydrogels for bone regeneration

2. TEMPERATURE-RESPONSIVE HYDROGELS

Temperature-responsive hydrogels have garnered significant attention in the field of bone tissue engineering due to their unique properties and potential applications. These hydrogels undergo mechanical and biochemical transformations in response to changes in temperature, offering precise control over their structure, porosity, and degradation rates. Here, we review recent advancements and key findings in the development and utilization of temperature-responsive hydrogels for bone tissue engineering [1], [5].

Poly N-isopropyl acrylamide (NIPAAm) and its derivatives have gained significant attention as temperature-responsive hydrogels for bone healing applications. Subhash *et al.* [11] synthesized poly (NIPAAm-co-AAm) copolymers through radical polymerization, resulting in temperature-sensitive nanogels with volume phase transition temperatures ranging from 37 °C to 43 °C. These nanogels exhibited controlled LCST and tissue heating processes, enabling targeted gel administration in animal studies using near-infrared fluorophores. Nafee *et al.* [12] explored the use of a temperature-responsive chitosan/glycerol phosphate hydrogel for treating various bone disorders, including Paget's disease and osteoporosis. This hydrogel exhibited temperature-reversible gelation behavior, ensuring controlled release of therapeutic agents over an extended period. The encapsulation of bone resorption inhibitors, such as alendronate, within this hydrogel system showed promising results in reducing inflammatory responses and promoting tissue regeneration.

Polyethylene glycol (PEG) and polycaprolactone (PCL) copolymers represent another category of temperature-responsive hydrogels investigated for bone tissue engineering Ni *et al.* [13] investigated an injectable PEG-PCL-PEG hydrogel as a thermally induced material for bone regeneration. The reversible transition from sol to gel upon exposure to heat makes this hydrogel system suitable for minimally invasive surgical procedures and filling irregular bone defects. Fu *et al.* [14] synthesized a hydrogel by combining collagen and hydroxyapatite (HAP) in a PEG-PCL-PEG copolymer matrix. This composite hydrogel leverages the biocompatibility and enhanced biomimetic microstructure of collagen and HAP for treating bone defects. The incorporation of HAP particles into the hydrogel scaffold promotes osteoconduction and enhances bone regeneration processes. Cai *et al.* [15] developed a dual-network hydrogel (SHIELD) capable of facilitating the direct injection of transplanted stem cells for bone healing. This hydrogel system offers enhanced cell retention and creates a conducive environment for cell proliferation and differentiation at physiological temperatures. The synergistic combination of multiple networks in the hydrogel structure enhances its mechanical strength and stability, making it suitable for load-bearing bone defects.

3. PHOTO-RESPONSIVE HYDROGELS

Photo-responsive hydrogels have garnered significant interest in bone tissue engineering due to their ability to undergo structural and biochemical changes upon exposure to light stimuli. This section reviews recent studies focusing on the application of photo-responsive hydrogels in bone tissue engineering [16]. Photo-responsive hydrogels incorporate photochromic groups within their polymer network, allowing them to undergo reversible changes in structure or properties upon exposure to light of specific wavelengths [17]. These changes can include alterations in stiffness, porosity, and degradation rate, which are crucial for modulating cell behavior and tissue regeneration in bone repair processes.

Photo-responsive hydrogels have been investigated as carriers for controlled drug delivery in bone tissue engineering. By incorporating light-sensitive molecules or nanoparticles into the hydrogel matrix, researchers have demonstrated the ability to spatially and temporally control the release of therapeutic agents, such as growth factors or antibiotics, to promote bone healing [18]. Photo-responsive hydrogels offer precise control over cell behavior and function in bone tissue engineering applications. Through spatial and temporal modulation of light exposure, researchers can manipulate cell adhesion, migration, proliferation, and differentiation within the hydrogel matrix [19]. This capability enables the creation of dynamic microenvironments that mimic the complex signaling cues present in native bone tissue.

Advances in three-dimensional (3D) bioprinting technology have enabled the fabrication of complex scaffolds using photo-responsive hydrogels. By utilizing light-based patterning techniques, researchers can precisely deposit hydrogel layers and incorporate cells and bioactive molecules to create biomimetic structures that support bone regeneration [20]. Recent studies have explored the in vivo application of photo-responsive hydrogels for bone tissue engineering. By implanting photo-responsive hydrogel scaffolds into animal models of bone defects, researchers have demonstrated enhanced bone regeneration and integration compared to traditional scaffold materials [21].

4. CHEMICAL-RESPONSIVE HYDROGELS

Chemical-responsive hydrogels have emerged as promising biomaterials for bone tissue engineering, offering the ability to sense and respond to specific chemical cues present in the physiological environment. This section provides an overview of recent research efforts focused on the application of chemical-responsive hydrogels in bone tissue engineering [6]. Enzyme-responsive hydrogels have gained attention for their ability to undergo controlled degradation in response to enzymatic activity commonly found in the bone microenvironment. Matrix metalloproteinases (MMPs), phosphatases, and other enzymes present in bone tissue can trigger the degradation of these hydrogels, facilitating the release of encapsulated therapeutic agents or promoting cell infiltration and tissue regeneration [22], [23].

pH-responsive hydrogels exhibit changes in swelling behavior and mechanical properties in response to variations in pH levels. By incorporating acidic or basic functional groups into the polymer network, these hydrogels can respond to the acidic microenvironment of bone defects or the alkaline environment during bone formation [24]. pH-responsive hydrogels offer opportunities for controlled drug delivery and modulation of cellular behavior in bone tissue engineering applications.

Redox-responsive hydrogels undergo structural changes in response to variations in the redox potential of the surrounding environment. By incorporating redox-active moieties such as disulfide bonds or metal ions, these hydrogels can be designed to undergo reversible crosslinking or degradation, enabling dynamic control over their mechanical properties and degradation kinetics [25]. Ion-responsive hydrogels are designed to interact with specific ions present in the bone microenvironment, such as calcium, phosphate, and magnesium ions. These hydrogels can sequester ions from the surrounding tissue or release ions to modulate cellular responses and promote tissue regeneration [26].

5. MAGNETIC FIELD-RESPONSIVE HYDROGELS

Magnetic-responsive hydrogels have emerged as promising biomaterials for bone tissue engineering, offering the capability to respond to external magnetic fields and thereby modulate their mechanical and biochemical properties. In recent years, researchers have explored various strategies to harness the potential of magnetic-responsive hydrogels for promoting bone regeneration and repair. Anisotropic magnetic hydrogels: anisotropic magnetic hydrogels, incorporating magnetic nanoparticles or microparticles within a hydrogel matrix, have garnered significant interest due to their ability to align in response to external magnetic fields. By manipulating the orientation of magnetic particles, these hydrogels can mimic the anisotropic architecture of native bone tissue, promoting cell alignment and tissue regeneration [27], [28].

Magnetic-responsive hydrogels enable precise control over drug delivery through the application of external magnetic fields. Magnetic nanoparticles embedded within the hydrogel can be loaded with therapeutic agents and targeted to specific sites of bone injury or inflammation. Upon exposure to a magnetic field, the hydrogel releases therapeutic payloads, facilitating localized drug delivery and enhancing therapeutic efficacy while minimizing systemic side effects [29], [30]. Magnetic-responsive hydrogels can undergo reversible changes in mechanical properties in response to magnetic fields. By tuning the alignment and distribution of magnetic particles within the hydrogel matrix, researchers can dynamically adjust its stiffness, elasticity, and viscoelastic properties. These mechanical adaptations enable the hydrogel to better mimic the mechanical cues present in the native bone microenvironment, promoting cellular adhesion, proliferation, and differentiation [31], [32].

Magnetic-responsive hydrogels offer the ability to remotely manipulate cellular behavior within tissue-engineered constructs. Magnetic nanoparticles incorporated into the hydrogel can act as mechanical actuators, exerting forces on encapsulated cells in response to external magnetic fields. This mechanical stimulation can promote cell migration, alignment, and tissue morphogenesis, facilitating the development of functional bone tissue constructs [33], [34]. Recent advancements in magnetic-responsive hydrogel technology have facilitated their translation from bench to bedside for bone tissue engineering applications. Biocompatible formulations and scalable manufacturing processes have enabled the development of magnetic-responsive hydrogels suitable for clinical use. Preclinical studies have demonstrated the safety and efficacy of these hydrogels in promoting bone regeneration and repair in animal models, paving the way for future clinical trials and translational research efforts [35], [36].

6. CONCLUSION

The development of hydrogels responsive to diverse environmental stimuli, encompassing light, temperature, pressure, electric fields, and magnetic fields, signifies a burgeoning domain of intelligent biomaterials. These controlled stimulus-sensitive hydrogels hold considerable promise as scaffold materials for tissue repair following bone injuries, offering characteristics such as high hydrophilicity, excellent biocompatibility, and sensitivity to environmental cues. While substantial progress has been made in tissue engineering for bone regeneration, achieving artificially generated healthy tissue and organ replacements that closely mimic native bone remains a critical goal with profound implications for medical practice. Challenges persist in attaining optimal therapeutic efficacy due to the varied biological contexts and environmental factors present at defect sites during the construction of tissue-engineered scaffolds using biocompatible hydrogels with stimulus-responsive properties. Addressing this challenge necessitates the integration of a novel type of smart nanofiller-loaded hydrogel into the same carrier, enabling adaptive responses based on specific environmental conditions.

Advancements in individualized medicine and precision fabrication are poised to make biomaterials with tailored structures and functions increasingly accessible. The role of additive manufacturing in providing personalized treatments underscores the importance of thoroughly investigating processing technologies and biological applications, particularly in the realm of biofabrication. The synergy between additive manufacturing and tissue engineering has facilitated the development of individualized constructs and hierarchical structures resembling tissues, paving the way for innovative solutions in patient care. Bioinks, which exemplify a blend of cytocompatibility and high-resolution printability, represent ideal scaffold materials produced using 3D bioprinting technology, ready for clinical translation. These bioinks, by regulating distribution rate and effectiveness, play a critical role in bone repair. Co-culture 3D-printed models of osteoblasts and osteoclasts are essential for better understanding cell-cell interactions and advancing studies on bone regeneration.

The primary challenge in bone lesion healing lies in hydrogel matrices with appropriate mechanical properties, capillary bioactivity, and degradation efficiency. Highly sensitive hydrogels responsive to weak external signals post-implantation could mitigate risks associated with native implants. Real-time monitoring of material changes within the body is crucial due to the significant influence of microenvironments on bone growth following biomaterial implantation. The adaptability of stimulus-responsive hydrogels opens new avenues for patient-specific personalized treatment. By modulating sensitivity to different stimuli, these hydrogels can be tailored to meet the unique needs of each patient, enabling more effective treatment with fewer side effects across various clinical settings.

Moreover, stimulus-responsive hydrogels find versatile applications in advanced biomedical fields, serving as scaffolds for tissue engineering, drug delivery systems, and implantable devices. Researchers and clinicians can leverage these hydrogels' unique properties to enhance patients' quality of life, promote bone healing, and restore tissue function through innovative approaches. In essence, stimulus-responsive hydrogels represent a new and promising frontier in bone tissue engineering, holding the potential to revolutionize medical interventions, improve treatment outcomes, and advance regenerative medicine practices.

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