Potentials of Hydrogel in Tissue Engineering: An Overview

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Abstract

Over the years, the demand for tissue and organs has grown due to accidents and other disease conditions. Tissue repair and restoration are vital for maintaining the body's integrity. However, the biggest challenge in tissue damage and repair has been finding an alternative cell/tissue for damage repair. Tissue engineering has proven successful in this field. Its primary objective lies in the creation of synthetic alternatives that bear close resemblance to natural tissues. Today, tissue regeneration from synthetic alternatives is successfully considered for treating several types of tissue damage and repair, including chronic kidney disease. This paper aims to give an overview of tissue engineering, emphasising hydrogel as a potential biomaterial for tissue engineering.

Key words: Hydrogel, regenerative medicine, tissue engineering, tissue repair

INTRODUCTION

Tissue engineering is a multidisciplinary field that amalgamates life science, biochemistry, and engineering, aiming to comprehend mammalian tissue's intricate framework and dynamic functionality. Tissue engineering requires cells, scaffolds/biomaterials, and growth-stimulating signals. The primary objective lies in creating synthetic alternatives that resemble the authentic tissue, thereby enabling their efficacious implementation in the restorative or restitutive procedures for impaired or absent tissue resulting from adversities such as injuries or pathological conditions.[1] Over the years, tissue engineering has gained vast acceptance and recognition as a transformative field of research and application.

Although significant progress has been made in tissue engineering, it is evident that the restoration of soft tissue, particularly in terms of its three-dimensional (3D) structure, poses challenges due to its inherent characteristics, such as viscosity, flexibility, and high elasticity. Traditional methodologies such as electrospinning or injection molding exhibit limited control over scaffolds' composition, architectural design, and pore morphology, creating a need for alternative approaches. The emergence of 3D-(bio) printing has shown promising techniques to eliminate this limitation.[2]

Tissue engineering has emerged as a promising field dedicated to addressing the challenges posed by chronic kidney disease (CKD), a progressive condition affecting more than 10% of the global population, which amounts to over 800 million individuals.[3] CKD exhibits a higher prevalence among specific demographics, including older individuals, women, racial minorities, and those with comorbidities such as diabetes mellitus and hypertension.[3]

While kidney transplantation has been considered a viable treatment option in the past, the scarcity of suitable donors has posed a significant constraint. The presence of long waiting periods, coupled with strict medical eligibility criteria such as advanced age and pre-existing medical conditions (including cardiac ailments, infections, and cancer), has limited the feasibility of transplantation as the optimal treatment choice.

Over the past decade, biomaterials have witnessed remarkable growth, offering novel approaches for therapies focused on central nervous system regeneration. One notable advancement lies in utilizing multifunctional scaffolds capable of carrying therapeutic molecules and cells, addressing the specific challenges associated with neural tissue engineering. Hydrogels, characterized by their hydrophilic polymer

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structures capable of retaining a substantial amount of water, have proven valuable tools for transporting cells, medications, and proteins. In addition, hydrogels hold promise for repairing damaged spinal cord and brain tissues, offering potential solutions for overcoming injuries in these regions.[4]

Hydrogel has garnered increasing attention recently due to its remarkable flexibility and biofriendly characteristics. Notably, hydrogels exhibit a high water content, demonstrate biocompatibility, and possess the capacity to mimic the extracellular matrix (ECM). Within the field of tissue engineering, hydrogels assume a pivotal role as scaffolds that facilitate cellular growth, furnish a 3D milieu for tissue formation, and enable the controlled delivery of bioactive molecules to expedite tissue regeneration.

At present, hydrogel research primarily focuses on two prominent directions: Stimulus-responsive hydrogels and conductive hydrogels. The former, also recognized as intelligent hydrogels, are characterized by their ability to undergo changes in shape or color in response to external stimuli. Several examples of stimulus-responsive hydrogels include photosensitive hydrogels, pH-sensitive hydrogels, and temperature-sensitive hydrogels.[5]

Hydrogel polymer structures can be cross-linked physically or chemically, depending on the fabrication method employed. Chemically cross-linked hydrogels are characterized by solid and enduring interactions among their polymer chains, achieved through the formation of covalent bonds. Typical fabrication methods for chemically cross-linked hydrogels include grafting, radical polymerization, click chemistry, enzymatic reactions, dehydrothermal treatment, and radiation cross-linking.[6]

On the other hand, physically cross-linked hydrogels exhibit temporary and weaker interactions, such as hydrogen bonds, molecular entanglements, ionic bonds, or hydrophobic forces. These interactions can be reversible in response to environmental changes such as variations in pH, ionic strength, or temperature.[6] Fabrication techniques utilized to produce physically cross-linked hydrogels encompass freeze-thawing, stereo-complex formation, ionic interaction, and hydrogen bonding.[6]

NATURAL HYDROGELS

Natural protein hydrogels refer to hydrogels constructed primarily from natural proteins. These hydrogels demonstrate remarkable biocompatibility, rendering them promising candidates for various applications, including tissue engineering, tissue repair, and drug delivery. The poor mechanical properties of natural protein hydrogels often present limitations,[7] particularly in scenarios where robust hydrogels are required. Consequently, various strategies have been developed in recent years to enhance the mechanical properties of these hydrogels.[8] Noteworthy, approaches include solvent induction, hybrid cross-linking, dual-physical cross-linking, and the implementation of double network structures. These advancements aim to overcome the mechanical shortcomings of natural protein hydrogels and broaden their potential applications in the scientific field.[9]

CKD continues to pose a significant global public health challenge, as conventional organ transplantation and dialysis face limitations in providing effective therapeutic interventions. Renal tissue engineering presents a promising alternative for addressing this issue by offering therapeutic or regenerative options beyond traditional donor organs. However, despite the notable advancements in decellularized ECM-based scaffolds for renal tissue revival, several issues regarding safety and the intricate composition of these scaffolds persist.

CKD is characterized by a progressive decline in renal function and/or structural damage, with a prevalence of approximately 8−16% worldwide. Dialysis serves as a partial substitute for renal filtration by eliminating specific metabolic wastes from the bloodstream. However, long-term reliance on dialysis often leads to a diminished quality of life for patients. When CKD progresses to end-stage renal disease, kidney transplantation becomes the only option. Nevertheless, the scarcity of organ transplantation and the adverse effects associated with prolonged use of immunosuppressants significantly limit its widespread clinical application.[10]

Several natural hydrogels have been employed in various tissue engineering projects, including alginate hydrogel, alginate/gelatin hydrogel, alginate/hyaluronic acid, and gelatin/hyaluronic acid.[11] Natural polymers possess several advantageous characteristics for biomedical applications, including biocompatibility, biodegradability, and the presence of biologically recognizable components. However, their mechanical properties often fall short of meeting the requirements of the specific application site. Moreover, introducing natural polymers into the human body may elicit immune or inflammatory responses.

On the other hand, synthetic polymer hydrogels offer the advantage of being tailored to exhibit desired mechanical properties and other favorable attributes. Although they lack inherent bioactivity, synthetic polymer hydrogels can be engineered to meet specific needs and requirements in biomedical applications.[12]

The physical specifications of hydrogel constructs, including their mechanical properties and electric conductivity, are crucial factors that contribute to maintaining their 3D architecture.[13] These properties also influence the mechanical interaction between the hydrogels and cells and their ability to induce cell-to-cell signaling.[13]

The mechanical properties of hydrogel constructs, such as stiffness and elasticity, determine their ability to provide structural support and mimic the mechanical cues of the native tissue. Hydrogels can promote cell adhesion, migration, and proliferation by possessing mechanical properties similar to the surrounding tissue.

Electric conductivity is another essential characteristic of hydrogels, especially in the context of bioelectrical signaling and electrical stimulation therapies. Electrically, conductive hydrogels can facilitate the transfer of electrical signals within the constructs, enabling communication between cells and promoting cellular behaviors, such as differentiation or tissue regeneration.

Therefore, careful consideration and control of the mechanical properties and electric conductivity of hydrogel constructs are vital for their successful application in tissue engineering, as they significantly influence the overall performance and functionality of the constructs in supporting cellular processes and tissue regeneration.[14]

Despite their inherent advantages, natural hydrogel systems often lack the necessary factors to initiate and facilitate physiological and biological processes vital for tissue formation and maturation.[13] Consequently, extensive research has been focused on modulating the properties of these hydrogels to enhance their biomimetic nature. By incorporating biomimetic cues and functionalities into natural hydrogel systems, researchers aim to create platforms that more closely resemble the complex microenvironment of native tissues. This approach holds great promise for advancing tissue engineering and regenerative medicine, as it seeks to replicate better the intricate biological processes necessary for successful tissue formation and maturation.

SYNTHETIC HYDROGELS

The key quality enabling biological tissues to perform sophisticated functions lies in their ability to maintain a suitable level of water content for molecular mobility while simultaneously possessing intricate structures. In contrast, synthetic hydrogels typically exhibit amorphous and isotropic structures, lacking the complexity observed in biological soft tissues. However, recent advancements in the field of synthetic hydrogels have focused on enhancing their structural properties to mimic the architecture found in biological systems. These developments aim to bridge the gap between the structural sophistication of natural tissues and the synthetic hydrogels' elastic mechanical properties, mesh sizes, and viscoelastic behavior. Researchers have successfully introduced time-dependent mechanical characteristics, including stress relaxation by incorporating dynamic cross-linking mechanisms into synthetic hydrogel networks, such as guest-host linkages, dynamic covalent chemistry, and hydrogen bonding groups.[15]

Synthetic hydrogels, such as polyethylene glycol (PEG), polyvinyl alcohol, and polyvinylpyrrolidone, have been widely employed in tissue engineering. These hydrogels offer several advantages, including the potential for patient-specific therapies, allowing for the precise development of scaffolds or constructs tailored to each patient's specific requirements. This level of customization ensures a meticulous and targeted approach to meet individual needs.

However, certain aspects need to be thoroughly addressed before the widespread implementation of synthetic hydrogels in long-term applications. Long-term degradation profiles of these hydrogels must be carefully studied to understand their stability and performance over extended periods. It is crucial to quantitatively determine the aging process of hydrogels to assess their durability and structural integrity over time.

In addition, comprehensive *in vivo* studies are necessary to evaluate the safety and longevity of synthetic hydrogels when used in longer-term applications. These studies will help assess any potential adverse effect, compatibility issues, and the overall biocompatibility of the hydrogel materials.

By conducting extensive research on the degradation profiles, quantitative aging determination, and comprehensive *in vivo* safety and longevity studies, we can better understand synthetic hydrogels' suitability and effectiveness for long-term tissue engineering applications. This knowledge is crucial for successfully translating these materials into clinical settings and providing patients with reliable and durable therapies.[16]

HYBRID HYDROGELS

Hybrid hydrogel systems offer a versatile platform incorporating natural and synthetic polymers and other functional biologics/fractions. This integration allows for controlled cell responses and release kinetics, making them highly desirable for diverse biomedical applications. Hydrogels, in general, possess functional groups with charges, making them hydrophilic and capable of absorbing water. This unique property enables them to swell in specific mediums and exhibit increased responsiveness to stimuli.

The concept of hybrid hydrogels is still under debate, with two main interpretations. One perspective describes them as complex structures composed of physically or chemically cross-linked nanogels, often numbering in the hundreds.

Incorporating synthetic components into hybrid hydrogels can introduce heterogeneity, improving cell adhesion, organization, and cell–cell interactions. This, in turn, facilitates the creation of tissue constructs with enhanced mechanical integrity, electroactivity, and improved cellular organization. Among the synthetic components used in hybrid hydrogels, those based on PEG have been extensively investigated in tissue engineering.[17] PEG-based hydrogels offer critical properties such as ease of structural modification and a proven track record of successful application in clinically-approved products.[17]

One prominent approach in developing hybrid hydrogels involves modifying synthetic networks with oligopeptides derived from natural ECM molecules.[17]

HYDROGEL-BASED SCAFFOLD IN TISSUE ENGINEERING

The utilization of hydrogel scaffolds in tissue regeneration emerged as a pioneering concept in the 1990s. Developing scaffolds exhibiting exceptional biocompatibility and biodegradability became crucial to restore the damaged ECM. Furthermore, the biomimetic properties inherent in these meticulously designed scaffolds have been recognized as pivotal factors in facilitating comprehensive and progressive tissue restoration processes.[18]

The implementation of collagen hydrogel, which constitutes a significant component of the ECM in the kidney, has exhibited potential in promoting repair processes, reducing local cell death, and mitigating glomeruli loss following injury. The introduction of collagen-based injections has been observed to elicit a host response, thereby facilitating renal tissue regeneration. This response activates various cell types, including inflammatory cells such as lymphocytes, macrophages (including dendritic cells), and neutrophils.[19]

A study conducted by Gilarska *et al*. focused on developing novel injectable hydrogels comprising collagen, chitosan, and modified hyaluronic acid. The researchers successfully incorporated lysine into the hyaluronic acid, thereby introducing free amine groups into the polymer chain.[20] By cross-linking all three biopolymers utilizing genipin (genipin is an aglycone derivative derived from fruits of *Gardenia jasminoides*), they successfully generated stable hydrogels with well-defined structures. The study demonstrated the ability to modulate the swelling, wettability, porosity, and degradation of the hydrogels by adjusting the content of modified hyaluronic acid and the concentration of genipin. The hydrogels exhibited a high degree of porosity, ranging from 85% to 95%, with increased porosity observed upon increasing the content of modified hyaluronic acid.[20]

This investigation highlighted the successful cross-linking of amine-functionalized hyaluronic acid with other biopolymers, forming stable hydrogels. The developed hydrogels hold promise for various biomedical applications, particularly in the field of tissue engineering and regenerative medicine.

Collagen, although a highly abundant fibrous protein found in the skin, bone, and connective tissues, has been widely employed in tissue engineering applications.[21] However, its usage is limited due to its inherently low mechanical strength.[21] To overcome this limitation, efforts have been made to enhance the mechanical properties of collagen-based materials by introducing cross-linking within the material. Recent studies have demonstrated the promising potential of using collagen and chitosan to create injectable hydrogels as scaffolds for tissue regeneration.

Chitosan, chosen as the polymer matrix in these hydrogels, offers several advantages, including biocompatibility, non-toxicity, and biodegradability.[21] The chemical composition of chitosan includes amino groups that promote cell adhesion, provide functional groups for chemical modifications, and contribute to the polymer's antibacterial activity. In addition, incorporating chitosan into the hydrogel structure can help reduce the risk of bacterial infections. By combining the unique properties of collagen and chitosan, these injectable hydrogels hold promise as effective scaffolds for tissue regeneration. The utilization of collagen and chitosan in tissue engineering applications represents a significant advancement in the field, providing improved mechanical strength and advantageous biological properties for enhanced tissue repair and regeneration.[21]

CONCLUSION

Cell sources, scaffold/biomaterials, and growth-stimulating factors are essential to tissue engineering. The success depends on the scaffold's ability to regenerate cell tissue without causing any toxic end product. A scaffold's effectiveness relies on possessing several essential biological properties, notably non-toxicity and biocompatibility. A desirable scaffold strives to replicate the target tissue's natural ECM, providing an environment conducive to cellular development and regeneration. The specific characteristics of a scaffold are determined by the type of tissue in which it is to be implanted. The hydrogel's potential as an effective scaffold holds promise in repairing and damaging cells and tissues.

REFERENCES

1. Chaudhary S, Chakraborty E. Hydrogel-based tissue engineering and its future applications in personalized disease modelling and regenerative therapy. In: Beni-Suef University Journal of Basic and Applied Sciences. Vol. 11. Issue 1. Berlin: Springer Science and Business Media Deutschland GmbH; 2022.
2. Karvinen J, Kellomäki M. Design aspects and characterization of hydrogel-based bioinks for extrusion-based bioprinting. Bioprinting 2023;32:e00274.
3. Kovesdy CP. Epidemiology of chronic kidney disease: An update 2022. Kidney Int Suppl 2022;12:7-11.
4. Hasanzadeh E, Seifalian A, Mellati A, Saremi J, Asadpour S, Enderami SE, *et al*. Injectable hydrogels in central nervous system: Unique and novel platforms for promoting extracellular matrix remodeling and tissue engineering. Mater Today Bio 2023;20:100614.

5. Zhang Y, Chen K, Li Y, Lan J, Yan B, Shi L, *et al*. High-strength, self-healable, temperature-sensitive, MXene-containing composite hydrogel as a smart compression sensor. ACS Appl Mater Interfaces 2019;11:47350-7.
6. Pita-López ML, Fletes-Vargas G, Espinosa-Andrews H, Rodríguez-Rodríguez R. Physically cross-linked chitosan-based hydrogels for tissue engineering applications: A state-of-the-art review. Eur Polym J 2021;145:110176.
7. Lu S, Zhu L, Wang Q, Liu Z, Tang C, Sun H, *et al*. High-strength albumin hydrogels with hybrid cross-linking. Front Chem 2020;8:106.
8. Huang G, Li F, Zhao X, Ma Y, Li Y, Lin M, *et al*. Functional and biomimetic materials for engineering of the three-dimensional cell microenvironment. Chem Rev 2017;117:12764-850.
9. Liu Z, Tang Z, Zhu L, Lu S, Chen F, Tang C, *et al*. Natural protein-based hydrogels with high strength and rapid self-recovery. Int J Biol Macromol 2019;141:108-16.
10. Wu H, Zhang R, Hu B, He Y, Zhang Y, Cai L, *et al*. A porous hydrogel scaffold is mimicking the extracellular matrix with swim bladder-derived collagen for renal tissue regeneration. Chin Chem Lett 2021;32:3940-7.
11. Serafin A, Culebras M, Collins MN. Synthesis and evaluation of alginate, gelatin, and hyaluronic acid hybrid hydrogels for tissue engineering applications. Int J Biol Macromol 2023;233:123438.
12. Madduma-Bandarage US, Madihally SV. Synthetic hydrogels: Synthesis, novel trends, and applications. J Appl Polym Sci 2021;138:50376.
13. Elkhoury K. Nanofunctionalization and Biofabrication of Natural Hydrogels for Tissue Engineering Applications. Biotechnology. Université de Lorraine; 2021. Available from: https://hal.univ-lorraine.fr/THESES-UL/tel-03285184 [Last assessed on 2024 Jul 08].
14. Gebeyehu EK, Sui X, Adamu BF, Beyene KA, Tadesse MG. Cellulosic-based conductive hydrogels for electro-active tissues: A review summary. Gels 2022;8:140.
15. Rausch MK, Parekh SH, Dortdivanlioglu B, Rosales AM. Synthetic hydrogels as blood clot-mimicking wound healing materials. Prog Biomed Eng (Bristol) 2021;3:042006.
16. Mantha S, Pillai S, Khayambashi P, Upadhyay A, Zhang Y, Tao O, *et al*. Smart hydrogels in tissue engineering and regenerative medicine. Materials (Basel) 2019;12:3323.
17. Lee HJ. Hybrid Hydrogels for Tissue Engineering. All Dissertations. 1775; 2015. Available from: https://tigerprints.clemson.edu/all_dissertations/1775 [Last assessed on 2024 Jul 08].
18. Kalai Selvan N, Shanmugarajan TS, Uppuluri VN. Hydrogel based scaffolding polymeric biomaterials: Approaches towards skin tissue regeneration. J Drug Deliv Sci Technol 2020;55:101456.
19. Lee SJ, Wang HJ, Kim TH, Choi JS, Kulkarni G, Jackson JD, *et al*. *In situ* tissue regeneration of renal tissue induced by collagen hydrogel injection. Stem Cells Transl Med 2018;7:241-50.
20. Gilarska A, Lewandowska-Łańcucka J, Guzdek-Zając K, Karewicz A, Horak W, Lach R, *et al*. Bioactive yet antimicrobial structurally stable collagen/chitosan/lysine functionalized hyaluronic acid - based injectable hydrogels for potential bone tissue engineering applications. Int J Biol Macromol 2020;155:938-50.
21. Nezhad-Mokhtari P, Akrami-Hasan-Kohal M, Ghorbani M. An injectable chitosan-based hydrogel scaffold containing gold nanoparticles for tissue engineering applications. Int J Biol Macromol 2020;154:198-205.

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