Hydrogel in Bone/Cartilage Regeneration

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Contributor: Anchun Mo

Hydrogel is a polymer matrix containing a large amount of water. It is similar to extracellular matrix components. It comes into contact with blood, body fluids, and human tissues without affecting the metabolism of organisms. It can be applied to bone and cartilage tissues.

bone regeneration mechanical property biocompatibility biodegradability

1. Introduction

Hydrogel is a kind of polymer network system with water as dispersion medium and a lot of water in the matrix. It is insoluble in water due to its special cross-linked structure[1]. At the same time, hydrogels are very similar in physical and chemical properties to most human tissues and consist of polysaccharides and proteins[2][3]. Hydrogels usually not only do not affect the body's metabolic processes, but also allow metabolites to pass through them to be excreted from the body[4]. They play an important role in regulating cell functions, including cell migration and binding to cell membrane receptors to transmit signals[5]. In addition, hydrogels absorb water and reduce friction and mechanical effects on surrounding tissues[6]. Therefore, hydrogels with controllable degradability, biocompatibility, and good mechanical properties have a broad application prospect[7]. The polymer system of hydrogels can be used for cell transplantation and differentiation, endogenous regeneration, and biological repair, wound healing, and continuous drug delivery providing a good matrix [8], and its three-dimensional network system can mimic the microstructure of the original extracellular matrix and provide living ecological conditions for cell survival [9]. In general, the mechanical properties of hydrogels are enhanced with the increase of polymer concentration, which indicates that the biocompatibility and degradation of hydrogels are low[10]. This contradiction limits the application of hydrogels in biomedicine. As we all know, the brittleness of hydrogels mainly comes from irregular structures. Designing a series of high-strength polymer hydrogels with different structures, such as structures with regular or special networks, has become a solution to this problem[11]. With the deepening of research, hydrogels with good physical properties have been developed, which have obtained new applications in the field of biomedicine and promoted the development of medicine (As shown in Table 1)[12]. This article describes the morphology and mechanical properties of hydrogels used in bone and cartilage engineering. The application of hydrogels with special physical properties prepared by different methods in osteochondral tissue engineering are discussed.

Table 1. Mechanical properties and examples of several hydrogels [12].

Materials	Tensile Strength	Tensile Modulus	Compressive Strength	Compressive Modulus
Traditional single network hydrogel[13][14]	1–100 kPa	<100 kPa	10–100 kPa	1–100 kPa
Double network hydrogel[15]	10 MPa	1 MPa	60 MPa	100 kPa
Tetra-PEG hydrogel[16][17]	200 kPa	90 kPa	27 MPa	100 kPa
Topological[18]	20 kPa	-	-	350 kPa
Macromololecular microsphere composite hydrogel [19][20]	540 kPa	270 kPa	78.6 MPa	-
Nanocomposite hydrogel [21]	255 kPa	16 kPa	3.7 MPa	38 kPa

With the rapid development of hydrogels in the field of bone and cartilage tissue engineering, the objective of this review is to cover the current emerging design development of hydrogels for repairing bone and cartilage defects. This report is not comprehensive, but it considers the outstanding representatives of this field in recent years, especially focusing on the water gel changes in the design and processing performance, what makes it have strong mechanical properties, and the fact that it can adapt to the bone and cartilage tissue engineering high mechanical performance requirements.

2. Hydrogel in Bone/Cartilage Regeneration

Hydrogels can be defined by swelling in the water and maintaining large amounts of water without being dissolved; it is a three-dimensional crosslinked polymer network structure. It can not only have strength in shape and softness to allow small molecules through, but because of similar features and human body tissue hydrogels are widely used in bone and cartilage tissue engineering. However, due to the dispersion of a large number of aqueous media in the gel system and the heterogeneity of the network, the mechanical properties of the gel are poor, which greatly limits the application of gel. Many researchers have proposed innovative systems to enhance the strength of gels, which have greatly improved the tensile and compression properties of gels, such as tear energy, Young's modulus, elongation, and so on. In recent years, many methods have been developed to enhance gel strength, such as new double-network hydrogels and chemical/ionic double-crosslinked hydrogels.

In practical clinical use, it is hoped that the hydrogel will have a low strength before being implanted into the bone or cartilage defect, so that it will have good fluidity. After being implanted into the defect, the hydrogel will be in a higher-strength state. Injectable stimulation-responsive hydrogels provide an important platform for this goal. Injectable hydrogels encapsulate, manipulate, and transfer their cells and drugs to surrounding tissues in a minimally invasive manner. Although injectable hydrogels are easy to produce and have low cytotoxicity, generally they have slow response times and low stability. Over the past few years, many studies have focused on the synthesis of new injectable hydrogels for repairing cartilage and bone tissue. The main challenges are the injectable hydrogel bioactive scaffold required for cartilage and bone tissue engineering, full biocompatibility,

References

1. Branden, C.I.; Tooze, J. Introduction to Protein Structure; Garland Science: New York, NY, USA, 2012.
2. Lesk, A.M. Introduction to Protein Architecture: The Structural Biology of Proteins; Oxford University Press: New York, NY, USA, 2001.
3. Lesk, A. Introduction to Protein Science: Architecture, Function, and Genomics; Oxford University Press: New York, NY, USA, 2010.
4. Leader, B.; Baca, Q.J.; Golan, D.E. Protein therapeutics: A summary and pharmacological classification. Nat. Rev. Drug Discov. 2008, 7, 21–39.
5. Dimitrov, D. Therapeutic Proteins. In Methods in Molecular Biology; Voynov, V., Caravella, J.A., Eds.; Humana Press: Totowa, NJ, USA, 2012; pp. 1–26.
6. Shoichet, B.K.; Baase, W.A.; Kuroki, R.; Matthews, B.W. A relationship between protein stability and protein function. Proc. Natl. Acad. Sci. USA 1995, 92, 452–456.
7. Waldron, K.J.; Rutherford, J.C.; Ford, D.; Robinson, N.J. Metalloproteins and metal sensing. Nature 2009, 460, 823–830.
8. Lu, Y.; Yeung, N.; Sieracki, N.; Marshall, N.M. Design of functional metalloproteins. Nature 2009, 460, 855.
9. Karlin, K.D. Metalloenzymes, structural motifs, and inorganic models. Science 1993, 261, 701–708.
10. Kaltashov, I.A.; Zhang, M.; Eyles, S.J.; Abzalimov, R.R. Investigation of structure, dynamics and function of metalloproteins with electrospray ionization mass spectrometry. Anal. Bioanal. Chem. 2006, 386, 472–481.

biodegradability and stability, excellent mechanical properties for culturing three-dimensional cells, and how to design the proper amount of nutrients and growth factors. To address this challenge, in the first place, new injectable hydrogels can be developed using bioactive materials. Second, more advanced manufacturing methods need to be developed, primarily to improve mechanical properties and physiological stability and reduce cytotoxicity.

The incompatibility of some hydrogels may also affect the application of hydrogels in bone and cartilage tissue engineering. For example, polymethacrylate hydrogels, which are generally non-toxic in their own right, cause inflammation and tissue reactions mainly due to soluble substances in the polymer, which generally include residual monomers, low molecular weight polymers, catalysts, and other additives. Other hydrogels, which polymerize with ultraviolet light, can also cause cell death if the amount of photoinitiator is too high.

Previous studies on the mechanical properties of hydrogels mainly focused on the macroscopic level to ensure the mechanical strength of hydrogels to ensure that hydrogels can withstand the compression force from bone and cartilage tissue during movement. In recent years, more and more studies have focused on the mechanical effects of hydrogels at the cellular level. Viscoelastic hydrogels have been used for three-dimensional cell culture. How to precisely regulate the viscoelasticity of hydrogels may have a great influence on the physiological activities of cells. Hydrogels have several mechanics that play a key role in cellular activity, including cell proliferation and stem cell differentiation. These early results suggest that time-varying mechanics may be a unique and key parameter for regulating cell biology. In addition, depending on the viscoelastic mechanism of hydrogels, the importance of viscoelasticity and viscoplasticity affecting cellular behavior remains to be elucidated.

In order to construct complex three-dimensional physiological microenvironments, bio-inks based on shear thinning and self-healing hydrogels have been developed. For extruding-based bio-printing, it is a challenge to support high-reliability and high-resolution printing structures while ensuring that the cells are not subjected to shear forces during printing.

Although in recent years much correlation research has been carried out for high strength hydrogel, most studies focused on the simple increase gel strength; increasing polymer concentration can improve the mechanical strength, but result in poor biocompatibility and low degradability. This is the principal contradiction in the mechanical properties of the hydrogel in the field of biomedical applications. In previous studies, the introduction of non-chemical bonds has become an effective method to improve the strength of hydrogels, but the synergistic effect between chemical bonds and non-chemical bonds needs to be further studied. How to guarantee the mechanical strength; to further improve the biocompatibility of the hydrogel; how to maintain the stability of the hydrogels in the process of permanent replacement; how to implement gel in the temporary support process controllable degradation; how to better simulate the human body physiological environment; and realize the structure and function of bone and cartilage regeneration, while ensuring good biocompatibility and biodegradability, under the premise of development have special physical properties of water gel, is yet to be explored.

11. Nastri, F.; D'Alonzo, D.; Leone, L.; Zambrano, G.; Pavone, V.; Lombardi, A. Engineering Metalloprotein Functions in Designed and Native Scaffolds. Trends Biochem. Sci. 2019, 44, 1022–1040.
12. Wittenberg, J.B. Myoglobin-facilitated oxygen diffusion: Role of myoglobin in oxygen entry into muscle. Physiol. Rev. 1970, 50, 559–636.
13. Vergalli, J.; Bodrenko, I.V.; Masi, M.; Moynié, L.; Acosta-Gutiérrez, S.; Naismith, J.H.; Davin-Regli, A.; Ceccarelli, M.; Van den Berg, B.; Winterhalter, M.; Porins and small-molecule translocation across the outer membrane of Gram-negative bacteria. Nat. Rev. Microbiol. 2020, 18, 164–176.
14. Liu, C.; Xu, H. The metal site as a template for the metalloprotein structure formation. J. Inorg. Biochem. 2002, 88, 77–86.
15. Quesada-Perez, M.; Gonzalez-Tovar, E.; Martin-Molina, A.; Lozada-Cassou, M.; Hidalgo-Alvarez, R. Overcharging in colloids: Beyond the Poisson-Boltzmann approach. Chemphyschem Eur. J. Chem. Phys. Phys. Chem. 2003, 4, 234–248.
16. Kumar, S.; Pal, D. Protein Bioinformatics: From Sequence to Function; Academic Press: Cambridge, MA, USA, 2010.
17. Mittal, J.; Best, R.B. Thermodynamics and kinetics of protein folding under confinement. Proc. Natl. Acad. Sci. USA 2008, 105, 20233–20238.
18. Meersman, F.; Smeller, L.; Heremans, K. Protein stability and dynamics in the pressure–temperature plane. Biochim. Biophys. Acta (BBA) Proteins Proteom. 2006, 1764, 346–354.
19. Baker, D. What has de novo protein design taught us about protein folding and biophysics? Protein Sci. 2019, 28, 678–683.
20. Monera, O.D.; Kay, C.M.; Hodges, R.S. Protein denaturation with guanidine hydrochloride or urea provides a different estimate of stability depending on the contributions of electrostatic interactions. Protein Sci. 1994, 3, 1984–1991.
21. Huerta-Viga, A.; Woutersen, S. Protein denaturation with guanidinium: A 2D-IR study. J. Phys. Chem. Lett. 2013, 4, 3397–3401.

However, as a biomedical material, it only has high strength and activity, and its biological safety and biodegradability are far from meeting the actual requirements. Therefore, its biological function is an important index for the evaluation of biomedical materials. Many researchers have tried their hand at related fields. For example, 3D printing could be used to create defects specific to bone and cartilage to speed up tissue healing. Simultaneous defect of bone and cartilage is a common disease in clinical practice. The design of a hydrogel that can repair bone and cartilage defects at the same time is a research direction. Artificial grafts of bone and cartilage are often difficult to vascularize after implantation, so hydrogels that guide blood vessels could be a solution. At the same time, bone and cartilage are easy to be complicated with bacterial infection during wound healing, so it may have a good clinical application prospect to endow hydrogel with antibacterial properties. Although adhesion hydrogels have been applied in biomedical applications, most hydrogels show good adhesion only in dry environments, and adhesion can be significantly reduced or even lost in humid environment or underwater environment due to swelling and the formation of water molecular layer on the surface of hydrogels. Therefore, underwater high adhesion hydrogels have always been a hotspot and difficulty in this field. The surface modification on the macro and dynamic key water gel, the combination of regulation and control of dynamic water gel super molecular functional groups on the surface of the water gel, arrangement, so that it can rapidly with the substrate surface hydrophobic forces, thus successfully gives rapid and reversible hydrogels underwater strong adhesion, solved the difficult problem underwater adhesive. Especially in bone and cartilage tissue repair, in the context of fluid or blood containing potential applications.