Bioadhesion of injectable stem cell-laden hydrogels designed for cartilage repair: A mini-review

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Summary
Injectable bioadhesive hydrogels, known for their ability to transport substances and adaptability in processing, offer great potential in a variety of biomedical applications. They are particularly promising in minimally invasive stem cell-based therapies for the treatment of cartilage damage. This approach uses readily available mesenchymal stem cells (MSCs) to differentiate into chondrocytes for cartilage regeneration. In this review, we explore the relationship between the bioadhesion of an injectable MSC-laden hydrogel and tissue and how MSC stem cells contribute to this. We summarize the basic principles of bioadhesion and discuss recent trends in bioadhesive hydrogels. In addition, we highlight their specific applications in conjunction with stem cells, particularly in the context of cartilage repair. The review also includes a discussion of methods for testing bioadhesive hydrogels. Although this review offers valuable insights into the interrelated aspects of these topics, it highlights the need for further research to understand the complexity of their relationship fully.

Keywords: bioadhesive, injectable, hydrogel, stem cell, cartilage

Bioadhézia injekovateľných hydrogélov s kmeňovými bunkami navrhnutých na opravu chrupavky: mini-prehľad

Súhrn
Injekovateňé bioadhezívne hydrogély, známe svojou schopnosťou transportovať látky a prispôsobivosťou pri spracovaní, ponúkajú veľký potenciál v rôznych biomedicínskych aplikáciách. Sú obzvlášť sľubné v minimálne invazívnych terapiách založených na kmeňových bunkách na liečbu poškodenia chrupavky. Tento prístup využíva ľahko dostupné mezenchymálne kmeňové bunky (MSCs) na diferenciáciu na chondrocyty a na regeneráciu chrupavky. V tomto prehľade skúmame vzťah medzi bioadhéziou injektovateľného hydrogélu s obsahom MSCs a tkaniva a tým, ako k tomu prispievajú kmeňové bunky. Zhrnieme základné princípy bioadhézie a diskutujeme súčasné trendy v bioadhezívnych hydrogéloch. Okrem toho zdôrazňujeme ich špecifické aplikácie v spojení s kmeňovými bunkami, najmä v kontexte opravy chrupavky. Prehľad zahŕňa aj diskusiu o metódach testovania bioadhezívnych hydrogélov. Hoci tento prehľad ponúka cenné poznatky o vzájomne súvisiacich aspektoch týchto tém, zdôrazňuje potrebu ďalšieho výskumu, aby sa plne porozumelo zložitosti ich vzťahu.

Kľúčové slová: bioadhezívny, injekovateľný, hydrogél, kmeňová bunka, chrupavka

Introduction

Hydrogels, which are 3D cross-linked natural or synthetic polymer networks with high water-absorbing capacity and versatile fabrication characteristics, have wide-ranging applications, particularly in the fields of tissue engineering (TE) and regenerative medicine [1].

Injectable hydrogels, in particular, present potential advantages for minimally invasive local drug delivery, precise and site-specific implantation, as well as targeted delivery to challenging tissue sites and interface tissues. The phase transition in a polymer solution, transitioning from liquid to solid at a critical point, is referred to as the sol–gel transition state. Injectable hydrogels, encompassing in situ forming and shear-thinning hydrogels, undergo a swift sol–gel phase transition, facilitating the matrix to readily conform to the cavity's shape, ensuring a suitable fit and interface within tissues [2-4]. In this context, the adhesivity of the applied hydrogel stands out as one of the crucial properties for hydrogels in biomedicine.

Bioadhesive hydrogels have become essential materials in the field of cell therapy research due to their noteworthy attributes. These characteristics, which encompass desired biocompatibility, biodegradability, tissue and cellular adhesion capabilities, along with mechanical properties conducive to emulating the extracellular matrix (ECM), play a crucial role in supporting vital cellular processes such as proliferation, wound healing, and tissue regeneration [5-7]. Based on the presented information and observed experimental outcomes, one may cautiously infer that hydrogels demonstrate favorable attributes as potential materials for biomedical applications. Notably, there is a suggestion of their potential suitability as a conducive environment for the proliferation of stem cells [8,9].

Articular cartilage, also referred to as hyaline cartilage, is a porous viscoelastic connective tissue that serves as a surface allowing smooth bone motion and resistance to compressive loads. It is characterized as avascular, lacking a nerve system or lymphatics [10] Addressing the challenges associated with cartilage regeneration involves overcoming several significant hurdles. Firstly, there is a need to address the mechanical disparities between artificial implants and the native tissue. Secondly, it is crucial to surpass the limitations of stem cell products derived from cartilage. Thirdly, alternative approaches to invasive surgical procedures must be explored. Lastly, the ultimate goal is to achieve complete functional restoration in compromised articular cartilage [11].

In the current scientific environment, it is noteworthy that there are fewer reviews focused specifically on the adhesion of an injectable bioadhesive stem cell-laden hydrogel to tissue. This absence of literature motivates our study on this important correlation that deserves attention. Although the existing literature contains several reviews that discuss hydrogels in the context of stem cells [12,13], describing in particular the correlation of stem cell bioadhesion with hydrogel [14], few describe the relationship we explore in this review. Our aim is to review the existing knowledge regarding tissue bioadhesion with injectable hydrogels in conjunction with stem cells. This work should help to further elucidate the bioadhesion of tissue with stem cell-laden hydrogels.

Bioadhesion as a property of hydrogel

Bioadhesion is defined as the phenomenon in which natural and synthetic materials adhere to biological surfaces, with or without the use of adhesives to bond the material to the biological surface. It can also refer to the incorporation of a biomaterial into the body, leading to the formation of a biofilm on the biomaterial. Xiong et al. classified bioadhesion into three aspects: mucosal adhesion, cell adhesion, and bioadhesives [7]. Mucoadhesion, a specific type of bioadhesion, involves the formation of a mucus gel layer on the biological surface during the adhesion process [15]. Cell adhesion is a complex phenomenon where, in addition to

morphology, the chemical composition of the biomaterial surface interacts with surface molecules on cells [16]. Bioadhesives, whether synthetic or biological, are composed of highly biocompatible and biodegradable polymers, serving to join two surfaces, with at least one being a living tissue [17]. Another classification proposed by Chopra et al. identifies three types of bioadhesion: Type 1, adhesion between two biological phases; Type 2, adhesion of a biological phase to an artificial substrate; Type 3, adhesion of an artificial material to a biological substrate [18]. The adhesion of hydrogels involves a complex interplay of chemistry, topology, and mechanics, with various types of bonds introduced (refer to Table 1 or Figure 1). Hydrogels can achieve robust adhesion through both covalent and noncovalent bonds. Covalent bonds contribute individual inherent strength, while noncovalent bonds, facilitated by the synergistic interplay of polymer chains, collectively impart substantial adhesive properties [19,20,7]. The nature of bonds within hydrogels significantly influences the crosslinking process, which in turn affects their adhesive properties. Notably, increased crosslinking levels tend to diminish the adhesive capacity of hydrogels due to constrained mobility, impeding functional groups along polymer chains from accessing the hydrogel surface and establishing interactions with the substrate for adhesion [21].

Table 1. Overview of representative chemistry bonds that linked hydrogel to biological surfaces known as bioadhesivness [19].

Type of Bond	**Representative bond types**
Non-covalent bonds	Ionic interactions, Hydrogen bonds, Hydrophobic interaction, Dipole-dipole interaction, π-π interaction
Permanent covalent bonds	Carbon-carbon, Siloxane, Amide, Carbon-nitrogen
Dynamic covalent bonds	Disulfide, Imine, boronate ester complexations

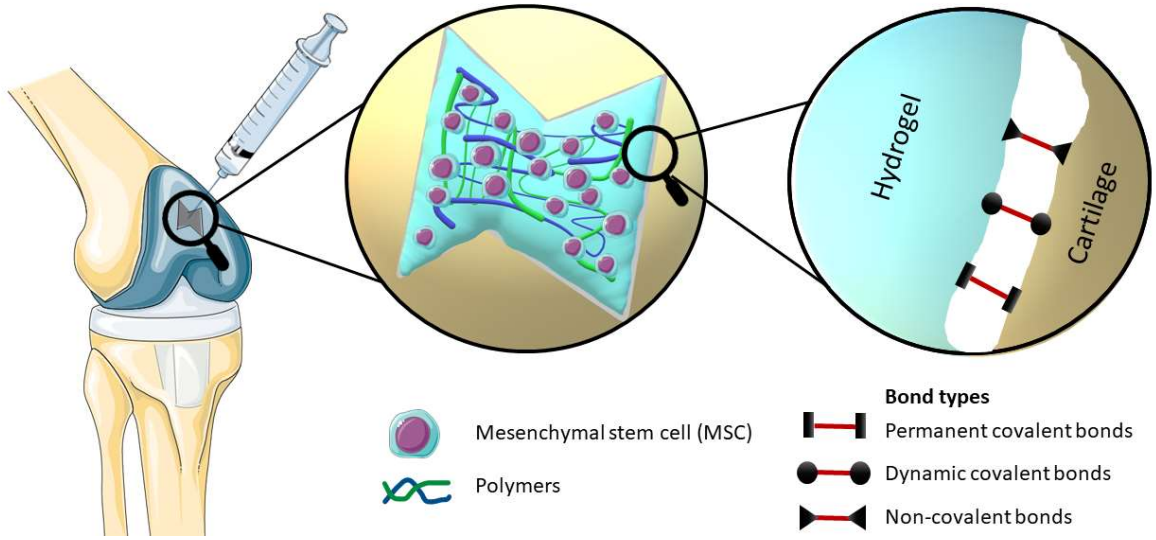

Figure 1. The text illustrates the injection of bioadhesive hydrogel containing incorporated stem cells, effectively occupying the defect in the cartilage structure. It visually represents the various types of bonds associated with bioadhesion, namely permanent covalent bonds, dynamic covalent bonds, and non-covalent bonds [22].

Bioadhesives are generally categorized into three fundamental types: I. wound closure, II. sealing leakage, III. Immobilization [23]. An ideal bioadhesive polymer is distinguished by the following criteria [18]:

1. The polymer and its degradation products must be non-toxic, biodegradable, and non-absorbable.
2. It should have the capacity to form strong bonds with mucus or other biological surfaces.
3. Achieving rapid and robust adhesion to surfaces should be possible.
4. It should facilitate easy formulation with drugs without affecting drug release patterns.

Testing of bioadhesion

Adhesion is a complex phenomenon influenced by intricate interactions among chemical, topological, and mechanical factors. A thorough assessment of adhesion usually involves four distinct mechanical tests. Among these, the probe-pull and lap-shear methodologies are employed to quantitatively measure adhesion strength by specifically determining the maximum force per unit area. Simultaneously, the peel and bilayer-stretch tests are utilized to evaluate adhesion toughness, measuring the energy required for separation per unit area. These four tests are instrumental in investigating and distinguishing various aspects of adhesion properties [19,24].

The majority of adhesion and bioadhesion tests are commonly mechanical tests typically conducted ex vivo. Peel tests, a type of mechanical test, are employed to evaluate the strength of adhesive bonds, especially for flexible adherents [25]. Various variants based on peeling angle exist, and standardized protocols are often followed. For instance, Wei et al. adhered to the standard protocol for peeling adhesion test ASTM F2256-05 [26], occasionally with minor modifications by research teams; for example, Jeon et al. utilized a 90° peel test with a porcine skin substrate [27]. While peeling is typically a straightforward experiment, the analysis method significantly relies on the materials, geometry, and loading conditions involved in the experiment. Consequently, the selection of the analysis method must be meticulous, and its application must be accurate to extract the pertinent adhesion and material properties of interest [28].

The bilayer stretch test methodology is applicable to assess extensional adhesion, measuring the adhesion energy when hydrogels are either in their unextended or extended state [29]. Additionally, innovative approaches to adhesion measurement are emerging; for instance, Dehene et al. recently introduced a straightforward and replicable supplementary method in viable tissues [30] Ultimately, scientific teams often quantify adhesion in a straightforward manner by using weights and gradually increasing tensile loading until adhesion failure [31], [32].

The evaluation of adhesive characteristics in bioadhesive hydrogels commonly relies on the lap-shear test, also known as bulk adhesion testing. This test examines shear strength, where cohesive failure occurs within the adhesive. Adhesive failure, on the other hand, is contingent upon the interface properties of the adherend [33]. The method adheres to a standardized protocol (ASTM F2255:2005), which research teams may adapt [34], Typically, the test is conducted ex vivo using porcine skin [35], [36], although it can also be performed in vitro [37].

Also, Villanueva et. al. tested bioadhesion of chitosan-based bone bioadhesive utilising texture analyser, adhesion properties were determined by a double compression test such as cohesiveness, adhesiveness, hardness, and resilience [38].

In addition to mechanical tests, biocompatibility tests are an important part of hydrogel bioadhesiveness tests. One such test is the ISO-10993-11 medical device rules and standards. Thanusha at al. evaluated biocompatibility tests for the developed hydrogel wound dressing, they've performed six different biocompatibility tests: (I) skin sensitization test, (II) acute

systemic toxicity test, (III) implantation study, (IV) intracutaneous reactivity test, (V) In vitro cytotoxicity test and Bacterial reverse mutation test [39].

The assessment of bioadhesive hydrogels encompasses clinical trials. For example, as outlined in the research conducted by Øvrebø et al., the progression of hydrogels from laboratory development to clinical application requires compliance with a comprehensive range of protocols and regulatory standards, along with the implementation of post-market surveillance measures [40].

Application of bioadhesive injectable stem cell-laden hydrogels in cartilage regeneration

Bioadhesive injectable hydrogels have attracted considerable attention in recent years due to their notable properties. This text discusses the diverse applications of these hydrogels, encompassing areas such as wound healing, tissue repair, cell adhesion, and wearable sensors. Emphasizing their promising role in biomedicine, the text provides insights for future research [7]. To illustrate the increasing prominence of bioadhesive injectable hydrogels in medicine, several notable studies are highlighted. These studies include the use of adhesive hydrogels for delivering mesenchymal stem cell-derived exosomes to treat spinal cord injuries [41], an innovative approach utilizing hypoxia-stimulated exosomes within a peptide-modified adhesive hydrogel for spinal cord injury treatment [42], and GelMA-dopamine-EV hydrogel for enhanced MSC-EV function in diabetic wound healing [43], Additionally, there is mention of an adhesive hydrogel integrated with placental mesenchymal stem cell conditioned medium (CM) to prevent uterine adhesions and improve patient outcomes [44]. Other applications discussed include a PEG-based hydrogel for muscle regeneration [45], Col/APG hydrogels incorporating umbilical cord stem cell factor (SCF) for therapeutic treatment of diabetic wounds [12] and diabetic ulcers [46]. The bioadhesive injectable hydrogel with a phenolic nanozyme (SAN) and CpGODN adjuvant is noted for its potential in localized immunomodulation and catalytic immunotherapy in the tumor microenvironment [47]. Inspired by mussel adhesive proteins, a dopamine-modified poly(α,β-aspartic acid) derivative (PDAEA) forms an injectable bioadhesive hydrogel with strong adhesion and drug delivery potential [48]. An innovative dynamic cross-linked photothermal hydrogel adhesive is mentioned for its photothermal effects and on-demand removability, suitable for wound closure and healing, including MRSA-infected wounds [49]. A novel injectable acacia gum (AG) hydrogel with rapid gelation, self-healing, and effective bioadhesion is discussed as holding promise for future biomedical applications as a carrier for wound-healing agents [50]. Finally, a composite hydrogel designed for bladder injuries is noted for its potential in tissue engineering and bladder tissue regeneration [37], and a Tetra-PEG hydrogel bioadhesive (SS) is highlighted for its sutureless repair of GI defects with controlled inflammation and tissue regeneration [51].

Articular cartilage possesses limited regenerative capacity, prompting the exploration of MSC-based approaches as a promising alternative for treating cartilage defects and osteoarthritis. MSCs are considered a valuable source of cells for hyaline cartilage regeneration due to their ability to differentiate into the chondrogenic lineage. However, experimental findings indicate that intra-articularly injected MSCs tend to undergo differentiation into transient cartilage, which subsequently transforms into bone through endochondral ossification, rather than forming hyaline articular cartilage. This phenomenon results in reduced treatment effectiveness, accompanied by the loss of the stratified ultrastructure and spatial organization characteristic of native hyaline cartilage [52]. Moreover, a significant portion of intra-articularly injected MSCs fails to adhere to the damaged cartilage layer, potentially leading to their quick dissemination into the systemic circulation due to the rapid turnover of synovial capillaries and lymphatic vessels [53]. To optimize clinical strategies in the field of cell-based

cartilage engineering, it becomes crucial to establish a conducive 3D microenvironment. This microenvironment should involve a tailored combination of biomaterials and bioactive factors aimed at enhancing the differentiation of MSCs into chondrocytes. Xu et al highlighted various examples of MSCs used in stem-laden hydrogels with biomimetic microenvironments for osteochondral tissue engineering application, such as Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs), Adipose-Derived Stem Cells (ADSCs), Umbilical Cord Blood-Derived Mesenchymal Stem Cells (UCB-MSCs), Autologous Peripheral Blood Stem Cells (AAPBSCs) [54].

Mesenchymal stem cells (MSCs) present a promising source of cells for therapeutically relevant hyaline cartilage regeneration, given their ability to differentiate into the chondrogenic lineage. The targeted differentiation aims to yield artificial cartilage tissue with biomechanical properties akin to native hyaline cartilage, including hyperelastic and dissipative properties, smoothness, toughness, wear resistance, and resistance to compressive, tensile, and shear forces. In addition to MSC differentiation into chondrocytes, it is essential to enhance the synthesis of proteins constituting the hyaline cartilage extracellular matrix, such as fibronectin, collagens, glycosaminoglycans, proteoglycans, cytokines, and growth factors crucial for cartilage function [55] [56]. MSCs can be applied to a suitable scaffold, constituting the so-called indirect method of differentiation, with success contingent on scaffold properties. An alternative approach involves the in vitro targeted direct differentiation of MSCs into chondrocytes, which are subsequently applied to the scaffold. Carneiro et al. summarize clinical trials employing MSC therapies for hyaline cartilage regeneration [57]. Most experimental methods for hyaline cartilage regeneration introduced into clinical practice utilise direct modification techniques.

Conclusion

Stem cell-laden injectable hydrogels have demonstrated excellent cell viability and osteogenic properties in both in vivo and in vitro experiments, however Wang et. al. pointed out that most of the studies have not analysed the mechanical properties of the regenerated tissue and they propose for future use of novel hydrogel combined with mechanical stimuli, to ensure regenerated tissue is well reshaped [58]. Thus, very good bioadhesion of stem cell-laden injectable hydrogels is required. Strategies to enhance stem cell bioadhesion, such as introducing conjugates into hydrogels, show significant improvements, suggesting the potential of stem cell-laden injectable hydrogels in enhancing regenerative capacity for cartilage tissue repair [59]. In conclusion, our comprehensive review highlights the potential correlation between bioadhesion of MSC-containing injectable hydrogels and tissue in the context of cartilage repair. The reviewed literature suggests that these stem cell-laden injectable hydrogels in combination with MCS are a very promising platform to enhance bioadhesion, and thus the regenerative capacity in cartilage tissue repair. However, this topic requires further investigation, and further research and clinical studies are necessary to validate and optimize it.

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