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REVIEW

Interdisciplinary MEDICINE

Application of adhesives in the treatment of cartilage repair

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Abstract

From degeneration causing intervertebral disc issues to trauma-induced meniscus tears, diverse factors can injure the different types of cartilage. This review highlights adhesives as a promising and rapidly implemented repair strategy. Compared to traditional techniques such as sutures and wires, adhesives offer several advantages. Importantly, they seamlessly connect with the injured tissue, deliver bioactive substances directly to the repair site, and potentially alleviate secondary problems like inflammation or degeneration. This review delves into the cutting-edge advancements in adhesive technology, specifically focusing on their effectiveness in cartilage injury treatment and their underlying mechanisms. We begin by exploring the material characteristics of adhesives used in cartilage tissue, focusing on essential aspects like adhesion, biocompatibility, and degradability. Subsequently, we investigate the various types of adhesives currently employed in this context. Our discussion then moves to the unique role adhesives play in addressing different

Abbreviations: ACI, autologous chondrocyte implantation; AD, alginate-dopamine; AF, annulus fibrosus; AHAMA, hyaluronic acid hydrogel modified by aldehyde groups and methacrylate; BMSCs, bone marrow mesenchymal stem cells; CAMs, cell adhesion molecules; ChABC, chondroitinase ABC; CS, chondroitin; CS-BM, hydrogels containing chondroitin sulfate adhesive and bone marrow; DST, disuccinimidyl tartrate; DST/HAS, adhesive composed of disuccinimidyl tartrate and human serum albumin; ECM, extracellular matrix; EDC, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; EGF, epidermal growth factor; Exo, exosome; FibGen, genipin-cross-linked fibrin; Fib-T-G, adhesive hydrogel of fibrinogen, thrombin and genipin mixture; GAGs, glycosaminoglycans; GelMA, gelatin methacryloyl; GelNB, gelatin modified with o-nitrobenzaldehyde groups; HA, hyaluronic acid; HA-CDH, hyaluronic acid combined with carbohydrazide; HAMA, methacrylated hyaluronic acid; HANB, hyaluronic acid grafted with o-nitrobenzyl; HMW-HA, high molecular weight hyaluronic acid; HPC, hybrid photocrosslinkable; HSA, human serum albumin; IVD, intervertebral disc; LCST, lower critical solution temperature; L-DOPA, 3,4-dihydroxyphenylalanine; MAP, mussel adhesion protein; MHHS, modified Harris Hip Score; MSCs, mesenchymal stem cells; NHS, N-hydroxysuccinimide; NP, nucleus pulposus; OCS, aldehyde-functionalized chondroitin sulfate; OHA, oxidized hyaluronic acid; OHA/HTCCMA, dually cross-linked hydrogels using oxidized hyaluronic acid and N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride methacrylate; oNB, o-nitrobenzyl; PAA, polyacrylic acid; PCL, polycaprolactone; PDMS, polydimethylsiloxane; PEG, polyethylene glycol; PEGDA, poly (ethylene glycol) diacrylate; PEO, polyethylene oxide; PIL, phenylboronic acid-ionic liquid; PLGA, poly(lactic acid-co-glycolic acid); PNIPAAm, poly(N-isopropylacryIamide); PNIPAAm-g-CS, poly(N-isopropylacryIamide) grafted with chondroitin sulfate; PNIPAM, poly (n-isopropylacrylamide); PRP, platelet-rich plasma; PTH, parathyroid hormone; RF, riboflavin; ROS, reactive oxygen species; RSF, regenerated silk fibroin; SFMA, methacrylated silk fibroin; TA, tannic acid; UV, ultraviolet; VEGF, vascular endothelial growth factor.

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cartilage injuries. Finally, we acknowledge the challenges currently faced by this promising technology.

KEYWORDS
adhesive, cartilage injury, cartilage repair

1 | INTRODUCTION

Cartilage, a translucent avascular and aneural tissue, exhibits limited intrinsic regenerative potential due to the absence of vasculature, lymphatics, and nerves. This inherent deficiency in self-repair mechanisms poses a significant challenge in orthopedic practice, as cartilage injuries from various causes are often difficult to manage effectively.[1,2] Most of the currently available treatment methods involve traditional invasive surgeries. For instance, treatments for disc disease include spinal fusion, total disc replacement, and discectomy. Meniscal tears are typically treated with sutures, while small cartilage defects may be addressed through procedures such as autologous chondrocyte implantation, grafting, arthroplasty, and microfracture. Despite these options, these treatments offer limited benefits for cartilage repair and face various challenges. These challenges include the risk of adjacent disc degeneration,[3] a higher risk of progressive joint degeneration and early-onset osteoarthritis,[4–6] limited donor availability, intricate surgical manipulations carrying substantial financial burden, and the undesirable formation of mechanically inferior fibrocartilage instead of robust hyaline cartilage.[7] Therefore, a new cartilage repair scheme is urgently needed to solve these thorny problems.

As tissue engineering evolves, adhesives emerge as an interesting solution for cartilage repair, offering distinct advantages over traditional techniques. Their facile application simplifies intricate surgical procedures, potentially reducing both cost and operative time.[8] In an ideal scenario, they offer multifaceted physical support including adhesion, filling, sealing, lubrication, or moisturization, among others, thus establishing a stable reparative milieu for cartilage injuries.[9–12] In conjunction with provisioning this physical sustenance, such modalities are expansively employed as conveyance vehicles for bioactive signals and cellular entities, thereby administering them in situ to the locus of lesion.[13,14] This dual action paves the way for enhanced tissue regeneration and therapeutic potential in the realm of regenerative medicine.[11,13–19] Optimal tissue adhesives should embody a multitude of attributes to aptly navigate the myriad and intricate clinical utilization scenarios. These incorporate (1) biocompatibility and non-toxicity, acting as the cornerstone for the safe deployment of adhesives; (2) chemical attributes conducive to the generation of robust tissue adhesion; (3) mechanical congruence with the underlying tissue, exhibiting resilience against recurring dynamic forces imparted by cartilage tissue; (4) the trait of biodegradability at a pace that is harmonious with tissue recuperation; and (5) the curative form of the adhesive, which should be modifiable to suit complex cavities, such as joint cavities.[20–23]

To fulfill the criteria delineated for the aforementioned ideal adhesives, engineers have embarked upon an exploratory trajectory to engineer, refine, and subsequently introduce to the market an array of adhesive formulations. These sundry adhesives have been systematically categorized based on disparate evaluative parameters. Depending on the chemical composition and source, it can be roughly divided into natural adhesives (including protein-based and polysaccharide-based adhesives, etc.), synthetic adhesives, etc.[23–25] Disparate activation response conditions further bifurcate these adhesives into pH-reactive and thermoresponsive subcategories.[26–29] Additionally, adhesives may be classified grounded on the genesis of their design ethos into non-biomimetic hydrogels and bioinspired hydrogels, the latter comprising amphibian-secreted glues and mussel-inspired adhesives, inter alia.[8,30]

At present, these adhesives play an important application value in their specific clinical scenarios. Prevailing adhesive technologies manage to satisfy a portion of these stipulated requisites, thereby securing a pivotal role within designated application environments. On one hand, certain adhesives are anticipated to offer significant contributions to postoperative care following conventional cartilage repair procedures. For instance, fibrin-based adhesives have been explored for their hemostatic properties to arrest bleeding subsequent to surgical incisions.[31–33] Cyanoacrylate-based adhesives serve the function of creating an impermeable seal, thus potentially preventing postoperative cavity fluid leakage.[34,35] Furthermore, selected adhesive formulations may serve as wound dressings applied at the site of cartilage injury, aiding in the prompt stabilization of adjacent wounds and fostering an environment conducive to tissue regeneration.[36] On the other hand, in addition to being a complementary solution to traditional repair method, some

scholars have developed promising alternatives based on specific application requirements and the type of cartilage involved, such as the outcomes of an investigation reveal that a photocrosslinked hydrogel demonstrates considerable potential for utilization in arthroscopic surgical interventions.[37]

Nonetheless, the adhesives presently available on the market do not epitomize "ideal adhesives" that satisfy all exigencies, as they possess varying degrees of drawbacks. These limitations continue to curtail their utilization across a spectrum of clinical settings. For instance, alginate exhibits biological inertness and typically presents difficulties in degradation within the human body, potentially eliciting sustained foreign body responses in patients.[23,38,39] Concurrently, the adhesive prowess of gelatin-based adhesives necessitates enhancement to more adequately conform to the mechanical stresses inherent in bone-cartilage tissues.[40,41] The fruition of ideal adhesives and their efficacious application in the realm of cartilage repair is contingent upon collaborative endeavors spanning the disciplines of chemistry, biomechanics, and biology.

Here, we furnish an exhaustive review of adhesives implemented in cartilage repair procedures. Commencing with a succinct delineation of the specifications and hurdles that must be addressed and surmounted by adhesives poised for clinical deployment, we adopt a tissue engineering-accented perspective. Subsequently, we proffer instances of the aforementioned adhesives encompassing but not restricted to their taxonomic classification, structural configuration, inherent advantages and disadvantages as well as prevalent variants. In the subsequent sections, we deliberate on their merit as ancillary or substitute methodologies in the realm of cartilage restoration, and survey the advancements in research pertaining to adhesives employed in the repair of a diverse array of cartilaginous structures, encompassing intervertebral discs (IVDs), articular cartilage, meniscus, growth plates, and nasal cartilage (Figure 1). In the concluding remarks, a foresight is provided into the prevailing unfulfilled as well as prospective clinical demands that future iterations of adhesives could potentially pander to.

2 | TISSUE ENGINEERING OF ADHESIVES

Tissue adhesives, according to DIN 16920, are glue-like substances that bind tissues together without changing their chemical configuration significantly.[8,42] In order to achieve a reproducible therapeutic effect, several key properties and mechanisms of adhesives should be paid attention to. (1) Suitable mechanical properties, such as adhesion, filling, plasticity, lubrication and moisture retention. (2) Regenerative medicine, such as the loading and release of bioactive factors, the ability to act as a scaffold for cell regeneration. (3) Biosafety, such as

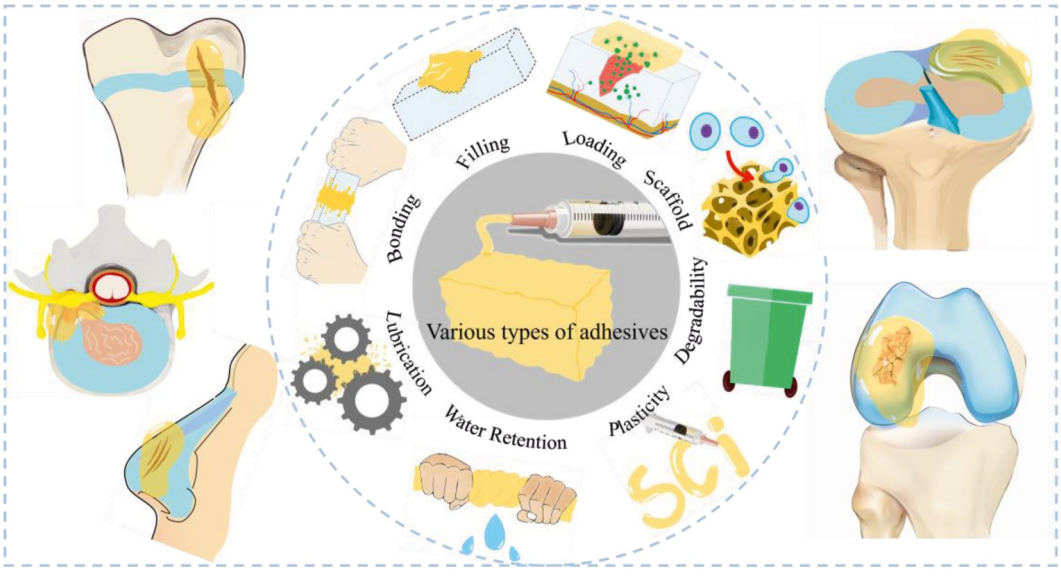

FIGURE 1 Adhesives can be categorized into various types, each with distinct functionalities. These functionalities may encompass adhesion to fractured surfaces, defect site filling, incorporation of bioactive agents, facilitation of cell growth scaffolding, biodegradability, plasticity, moisture retention, and lubrication. Adhesives find applicability in addressing cartilage injuries affecting a spectrum of cartilaginous tissues, such as the epiphyseal plate, intervertebral disc, nasal cartilage, meniscus, and articular cartilage.

biocompatibility and degradability. In this section, we endeavor to explicate the foundational design tenets undergirding the formulation of adhesives derived from chemical, biological, and physical premises. Synthesis of a single material that capitulates to the entirety of these stipulations represents a formidable challenge. Thus, it necessitates that both creators and practitioners exercise judicious prioritization of requisite attributes in alignment with the specificities of the target tissue and the exigencies of the clinical landscape.

2.1 | Mechanical properties of adhesives

2.1.1 | Design of adhesion mechanism

The adhesive exhibits a mechanical force that facilitates its adherence to the targeted tissue, ensuring the cohesive maintenance of the tissue sections without separation. This mechanical force, referred to as "adhesion," constitutes the fundamental mechanical characteristics of the adhesive material. It plays a crucial role in guaranteeing the stability and functional restoration of the repaired cartilage tissue.[8,43,44]

The efficacy of adhesive hinges on its combined adhesive and cohesive strength. At the microscopic level, the total bond strength arises from the synergistic interplay of these two fundamental forces.[8] Adhesive force describes the interfacial bond forged between the adhesive and the tissue surface upon application. Cohesive force, on the other hand, represents the intramolecular binding within the adhesive itself, enabling it to resist external stresses on the bond (Figure 2).[43–46] In this section, our focus lies on reviewing the principles underlying adhesion formation, while briefly introducing associated design concepts. Subsequently, a concise overview of cohesion is provided.

Formation of adhesion

According to the classical adhesion mechanism theory, the formation of adhesion force depends on the covalent chemical bonds and noncovalent interaction (mechanical nesting, electrostatic action, surface miscibility, intermolecular force) formed between the two surfaces. Covalent chemical bonds formed on the surface (Figure 3).[23,47]

Covalent linkage

Covalent linkage refers to the process of connecting two surfaces together through covalent chemical bonds.[8,48] This process represents a pivotal mechanism for facilitating adhesion, possessing the capability to surmount the challenges posed by the formation of a moist environment within the physiological setting. Typically, this linkage emerges from the interactions between the functional groups present in the cartilage tissue and those inherent to the adhesive compound.[9,10,23]

Tissue functional groups

The interface of cartilage tissue and its adjacent tissues can provide binding sites that contribute to adhesive moieties present on the tissue interface, allowing for chemical bonds with adhesives. Reactive moieties originating from protein building blocks in proteins are particularly prominent binding sites. While basic amino acids containing positively charged residues such as lysine supply primary amines (ε-amines), acidic amino acids such as glutamic acid contribute carboxylic acids. Further, primary amines (α-amines) and carboxylic acids located at the C- and N-terminus of a polypeptide, histidine-derived imidazole, and cysteine-derived thiols also add to the pool of available functional groups in the tissue.[49] Due to their inherent reactivity and widespread availability, primary amines are utilized extensively in the development of adhesives.[50] Due to their nucleophilic

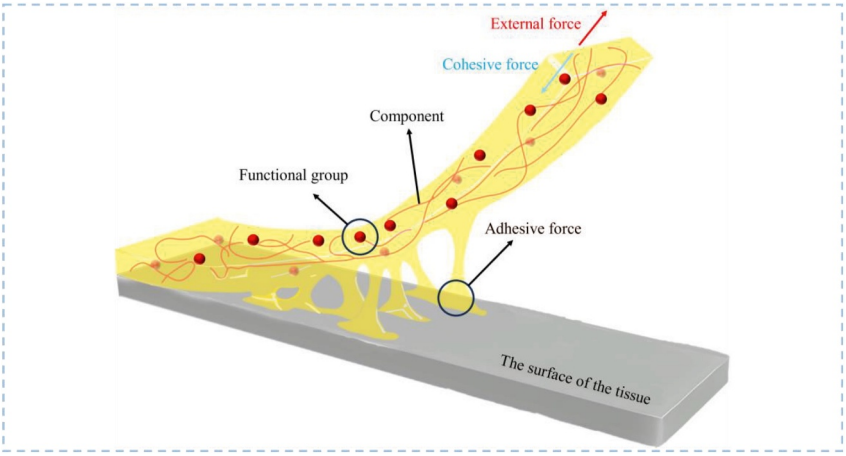

FIGURE 2 Adhesive force refers to the force formed between two different surfaces; Cohesion refers to the attraction between molecules within a material. Reproduced with permission.[45] Copyright 2012, Royal Society of Chemistry.

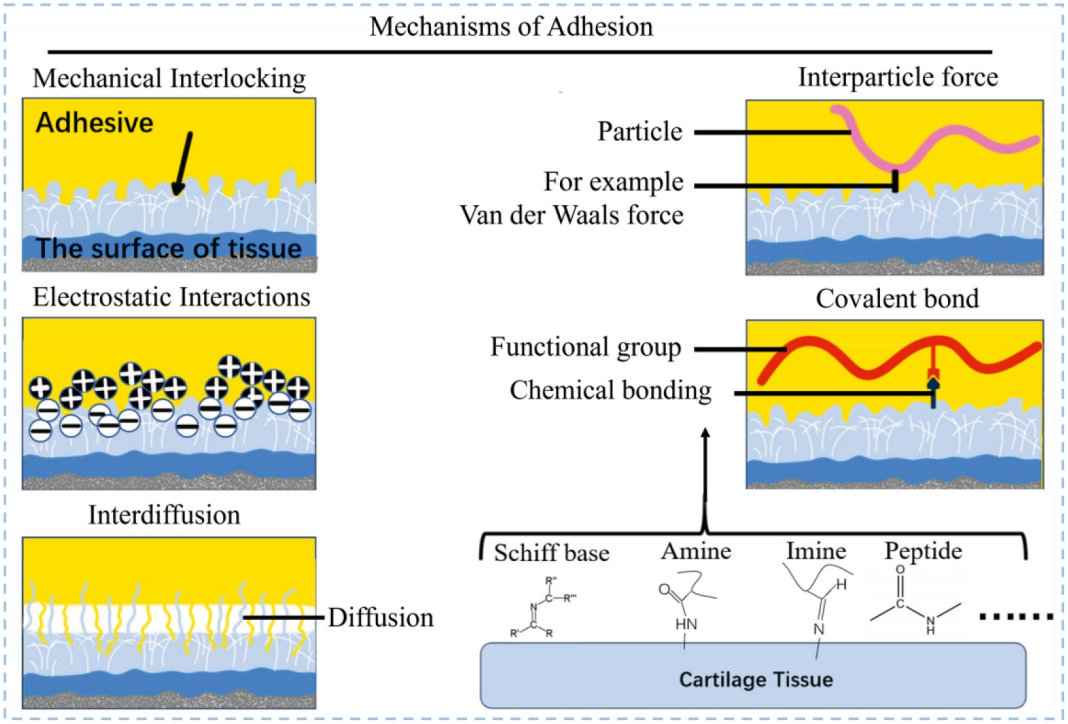

FIGURE 3 Classical adhesion mechanisms include mechanical nesting, electrostatic action, surface miscibility, intermolecular force, and covalent bond (the first four are summarized as non-covalent effects). Reproduced with permission.[23] Copyright 2020, American Chemical Society.

nature, primary amines serve as the catalyst for diverse chemical transformations within tissue adhesives, readily donating an electron pair to engage with the reactive components.[51]

Covalent functional groups in adhesives

Most present and future adhesives for cartilage repair rely on different reactive molecules to form strong, permanent bonds with the tissue's building blocks. These reactive molecules, like N-hydroxysuccinimide (NHS) esters, cyanoacrylates, and aldehydes, typically bond through chemical reactions outlined in Table 1.

Non-covalent interaction connection

Beyond the key covalent bonds, secondary or non-covalent bonds also play a contributory role in the formation of adhesion. These non-covalent interactions typically manifest through various mechanisms, including mechanical interlocking, electrostatic attraction, surface compatibility, hydrogen bonding, and hydrophobic forces.[8] Although such interactions are multifaceted, they generally do not yield the same level of robust adhesion characteristic of covalent bonds. Frequently, these bonds perform an auxiliary function, resulting in a concerted action with covalent bonds to establish a significantly strong adherence between disparate surfaces.[10,23,25]

Mechanical nesting. The concept of mechanical nesting in adhesive agents, alternatively denoted as physical entanglement or interlocking, is indicative of a physical mechanism warranting the strong interconnection of two surfaces. This process transpires independent of the formation of chemical or covalent bonds. In alignment with its denotation, the emergence of such a cohesive force may transpire in dual modalities: (1) physical entanglement. The term "physical entanglement" encapsulates a phenomenon where microstructures from juxtaposed surfaces are interwoven or ensnared with one another to forge a steadfast union.[67,68] This intertwining is attributable to disparities in roughness, texture, or structural congruity between the two interfacing entities. Contact between these surfaces facilitates the interlocking of minute protuberances or configurations, akin to the manner in which two puzzle pieces intermesh, culminating in an expanded contact domain and an enhancement in adhesive strength.[69] A prototypical exemplification of binders deploying this mechanism of physical entanglement is evident in the polymerization of acrylates contingent upon the activation by free radical initiators. Photoinitiators are frequently employed to furnish free radicals on a requisite basis, thereby facilitating in situ polymerization.[23,70] Prior to the process of cross-linking, the acrylate-enriched prepolymer is permitted to permeate the tissue, subsequently undergoing cross-linking to culminate in the formation of

TABLE 1 Mechanisms of covalent cross-linking between functional groups in adhesives and cartilage tissue.

Functional groups on tissues	Functional groups in adhesives	Chemical reaction/ product	Adhesives that can interact with it	Refs
Amine thiol 1,2-aminothiol	Aldehydes	1) Amine 2) Schiff-base reaction (imine group) thiol 3) Hemithioacetal formation 1,2-aminothiol 4) Thiazolidine formation	Chondroitin sulfate gelatin	52–57
Amine	Cyanoacrylates	Michael-type addition	Cyanoacrylates	58, 59
Amine thiol	NHS esters	Amide bond and thioester (amide bond and thioester)	1) PEG 2) Most the protein-based adhesives	60–63
Amine thiol imidazole	Catechol	Quinone formation by oxidation, and subsequent Michael addition or Schiff-base reaction	1) Most of the bionic adhesives 2) DOPA	49, 50, 64
Amine	Aryl azides	UV irradiation to *p*-azidobenzonic acid to generate nitrene	Chitosan	64, 65
Glutamine and lysine	Transglutaminases	Michael-type addition	Fibrin glue	65, 66

Abbreviations: DOPA, 3,4-dihydroxyphenylalanine; NHS, N-hydroxysuccinimide; PEG, polyethylene glycol; UV, ultraviolet.

a polymer matrix intricately entangled with the tissue structure. For instance, the macromolecular monomer comprising poly(ethylene glycol)-co-poly(α-hydroxy acid) diacrylate undergoes polymerization under the influence of ultraviolet illumination, ensuring direct engagement with the tissue to yield a hydrogel distinguished by its tissue adhesive properties.[23] (2) Interlocking. Interlocking delineates the genesis of a concordantly cogging structure among two surfaces, analogously to the meshing of gears or the intertwining in collusion. This interlinkage is potentially attributable to the purposeful configuration of the surface contour, texture, or architecture. The adhesive interface can be architecturally configured to present a serrated or capillary formation, intermeshing with the target substrate to engender a gear-mimetic effect, thereby augmenting the robustness of the conjunction.[71,72] An illustrative case in point is an adhesive patch endowed with a micro-structured apex. Said apex is composed of a polystyrene core resistant to swelling, encased within a poly(styrene)-block-poly(acrylic acid) swellable exterior. Upon application to biological tissue, the microneedles perforate the tissue, whereupon the apex experiences volumetric expansion upon interaction with aqueous media and physiologic fluids. This expansion instigates localized deformation of the tissue, culminating in mechanical entrapment with the tissue matrix. Empirical evidence posits that the microneedle-patched design secures formidable tissue adhesion, which is efficacious even in the context of cutaneous sutured closures.[73,74]

Electrostatic interaction. The adhesive's surface may exhibit diverse charge characteristics, encompassing both positive and negative charges. This differentiation leads to either electrostatic attraction or repulsion amongst them.[75,76] Such electrostatic phenomena can significantly influence the adsorption kinetics and diffusion behavior of the adhesive on the interface, thereby impacting the adhesive's ultimate bond strength to cartilage or tissue substrates. Frequently, gelatin is cited to exemplify this idea. The natural protein Gelatin is rich in various functional groups, prominently including carboxyl and amino groups. When submerged in water, gelatin's carboxyl groups discard their hydrogen atoms, resulting in negative charge inheritance, and its amino groups give

up protons to produce positive ions. Consequently, gelatin presents a dual character in its anionic and cationic attributes, allowing it to interact with surfaces carrying opposing charges via electrostatic forces. Such interplay markedly enhances both the bond to and the connection with tissue boundaries.[41,77,78] Likewise, polycarboxylate adhesives are a prime example of this concept. Commonly, these adhesives are distinguished by a profusion of carboxyl functional groups. In a damp, corporal environment, these entities undergo separation to produce negatively charged ions. When the polycarboxylate adhesive reaches the soft tissue boundary, its negative charge interacts with the cations on the tissue's surface, leading to the initiation of electrostatic forces.[79] This electrostatic convergence critically bolsters both the adhesion to and cohesion with the tissue surface.

Surface miscibility. Certain adhesives incorporate constituents analogous to those typically identified in the matrices of cartilaginous tissue, such as gelatin, hyaluronic acid (HA), and polysaccharide-derived adhesives.[24,80–84] Upon interface with the tissue's components, the molecular structures of the adhesive and the tissue constituents may facilitate mutual mobility, allowing for potential penetration into each other's architectural framework. This interstitial migration culminates in the establishment of an adhesive force.

Hydrogen bonding. Hydrogen bonding arises from a dipole-dipole intermolecular interaction involving a hydrogen atom covalently bonded to a strongly electronegative atom, and another electronegative atom in possession of a lone electron pair. The tissue surface presents a variety of chemical groups such as hydroxyl groups, carboxylic acids, and primary amines, which are conducive to the formation of hydrogen bonds with tissue adhesives.[85–87] Prototypical representatives of adhesives that engage in hydrogen bonding with tissue include those based on proteinaceous materials, acrylates, HA, and chitosan. Protein constituents inherent within protein-based binders can establish hydrogen bonds with protein molecules present within tissue structures.[60,88] Such bonds typically form between amino groups (NH) and carboxyl groups (COOH) or between hydroxyl groups (–OH), amino groups ($–NH_2$), and carboxyl groups (–COOH) located in the side chain. Furthermore, acrylic acid-based adhesives exhibit the capability to form high-density hydrogen bonds with tissues via the repetition of carboxylic acids, thus facilitating adhesion. Moreover, HA, rich in hydroxyl functional groups, and chitosan, bearing hydroxyl and amino functional groups, can also form a substantial quantity of hydrogen bonds with tissues.[88] Whilst an individual hydrogen bond may display relative weakness, the cumulative strength of numerous bonds can yield considerable adhesive integrity.[85]

However, that hydrogen bonds are susceptible to neutralization in aqueous environments, precipitating their subsequent dissociation.[87] For hydrogen bonds to form efficaciously, it is imperative that the tissue surface is desiccated prior to the application of the adhesive. Nonetheless, the intrinsic presence of blood and bodily fluids will ultimately induce the dissociation of these hydrogen bonds.[23] Consequentially, hydrogen bonds are frequently employed in conjunction with alternative chemical methodologies to cultivate a robust and stable adhesiveness.

Hydrophobic interaction. Hydrophobic interaction refers to the force that arises between nonpolar molecules or groups, predominantly attributed to their inherent propensity to repel water. Within the context of the hydrophobic effect, polar molecules or groups situated on the adhesive's surface coalesce, thereby augmenting the effective contact zone between the adhesive and the tissue surface. Concurrently, the nonpolar domains engendered through hydrophobic interactions exhibit water-repellent properties, which serve to mitigate the ingress of water molecules at the interface between the adhesive and tissue surface. This attenuation of water molecule-induced impediments at the interface is critical. Moreover, hydrophobic interactions facilitate the adhesive in forming a stable colloidal framework, ensuring the maintenance of a stable dispersion state throughout the period of contact.[89–91]

Research has demonstrated that augmenting the hydrophobicity of binder prepolymers can substantively enhance tissue adhesion. In the referenced study, the introduction of cholesterol groups to modify gelatin facilitated hydrophobic interactions with the tissue, thereby augmenting the tissue permeability of the prepolymer. Notably, the adhesive strength of gelatin, post-cholesterol group modification, was markedly superior compared to its unmodified counterpart. This observation underscores the potential role of hydrophobic interactions in facilitating tissue adhesion. Nonetheless, it is acknowledged that hydrophobic interactions typically display limited binding strength, which may not profoundly influence the formation of tissue adhesion. Drawing inspiration from the adhesive secretions observable in the foot pads of insects, mussels, worms, or spiders, subsequent research endeavors have led to the synthesis of hydrophobic adhesives based on glycerol and sebacic acid, specifically poly(glycerol sebacate acrylate). The inherent long-chain alkyl groups and high viscosity attribute to the binder's prepolymer being hydrophobically immiscible with water, rendering it challenging to dislodge post-

deposition. Subsequent to ultraviolet (UV) irradiation, the prepolymer undergoes solidification into an elastic gel. This transformation is instrumental in sustaining adhesion to tissue, attributable to enhanced tissue surface contact and improved tissue penetration.[89–92]

Force of cohesion

Cohesion, also known as cohesion, is the mutual attraction between adjacent parts of the same substance. This mutual attraction is the expression of the molecular force between the same substance molecules. In the case of effective stress, the total shear strength is deducted from the friction strength to obtain the cohesion. From another point of view, cohesion is the shear strength of the failure surface without any normal stress.[8,23]

The adhesive's cohesion, if too low, may inadequately establish fixation strength when utilized in cartilage injury repair. Conversely, an excessively high cohesive force in the adhesive could potentially result in localized tension and bone atrophy at the fixation site due to disparities in elastic modulus between the material and tissue. Consequently, clinicians are advised to comprehensively assess factors such as the growth rate of diseased cartilage tissue, patient age, and nutritional status when selecting adhesive materials with suitable cohesion for optimal clinical outcomes.[8]

2.1.2 | Filling property

The filling efficacy of an adhesive delineates its aptitude to occupy and reconstruct the compromised region. Within the context of cartilaginous restoration, this aspect is paramount as it significantly influences the structural and functional restitution of the treated locale. Upon application, the adhesive ought to seamlessly integrate with adjacent tissue, fostering a cohesive and stable configuration that precludes further dislocation and exacerbation of injury. However, the objective of the filling performance transcends mere spatial occupation; it extends to the provision of an optimal microhabitat that augments chondrocytic proliferation, maturation, and rejuvenation. Therefore, the complex design and makeup of the adhesive must be customized to facilitate cell attachment, movement, and diversification, thus hastening the recovery process of cartilage tissue.[93,94]

Joint surgeons might find this performance to be a thrilling development. The crucial role of joint cartilage, a key connective tissue that connects bone segments, in the movement and operation of joints is attributed to its sturdy but flexible structure and smooth surface.[95,96] Aberrations like trauma and arthritis, which harm the articular cartilage, frequently lead to joint pain, unease, and functional deficits in patients. Under these circumstances, healthcare professionals use adhesives to fill the impacted area, offering safeguarding, preventing additional risks and wear, and alleviating joint discomfort and pain. Typical instances of this method include the use of HA fillers and adhesive materials based on gelatin.[97–100]

2.1.3 | Plasticity

The flexibility of the adhesive implies its ability to be pliable, characterized by features like shape flexibility, stretchability, malleability, compressibility, and pliability.[100–103] Such characteristics enable the adhesive to adapt to lesions with varied shapes and sizes, including complex connections and porous edges surrounding IVDs, while maintaining praiseworthy integration with the surrounding tissue matrix. The flexibility of the adhesive material naturally enhances the surgeon's procedural effectiveness, supporting a method that is both quick and simple to implement.[104]

The foundational concepts and processes of plasticity in adhesives primarily encompass the choice of materials, designing molecular structures, and the application of additive regulation and processing techniques. Initially, choosing materials that exhibit high plasticity is crucial for understanding the adaptability of adhesives. Essentially, obtaining inherently flexible materials is a key factor in realizing the adaptability of adhesives. Commonly used components encompass biodegradable polymers, collagen from animals, and HA. Following this, altering the plastic characteristics of the material is achievable by shaping its molecular structure, demonstrated through methods that modify the length of the polymer chain, the degree of crosslinking, and the architecture of the side chain. Finally, introducing a suitable proportion of plasticity regulators or plasticizers can lead to changes in the adhesive's physical properties, directly affecting its flexibility. The execution of this alteration may include incorporating surfactants, plasticizers, or solvents.[8,23]

2.1.4 | Water retention

The water content in cartilage usually varies between 60% and 80% by weight. The water-based component plays a crucial role in the function of cartilage, acting both as a lubricant and a shock absorber, maintaining flexibility and adaptability of the tissue, and aiding in the absorption and dispersal of mechanical forces during joint movement.[104,105] Moisture content in cartilage plays a pivotal role in maintaining its functional integrity and general health. In the realm of cartilage repair, the ability of adhesives to hold water is crucial, supporting the

survival of chondrocytes and encouraging the natural regeneration of cartilage tissue.[106–108]

The adhesive's capacity to absorption, retain, and release water is known as its water-holding capacity.

Water absorption

The term "water absorption" in an adhesive denotes its capacity for water uptake. Within the realm of cartilage restoration, this characteristic plays a crucial role in maintaining the moisture balance of the surrounding environment, thereby aiding in cell growth and the differentiation of physical traits. Materials with enhanced water-attracting qualities can absorb water from adjacent tissues, creating a moisture-rich environment conducive to the survival and functionality of chondrocytes.

Water retention

The term "water retention" denotes the capacity of an adhesive to hold onto water post-absorption. High-quality adhesive stands out for its prolonged hydration preservation, avoiding quick drying out to maintain moisture over time.

Water release

To be effectively applied, the adhesive needs to show the ability to regulate water flow while maintaining the necessary level of moisture. Excessive buildup of moisture can lead to localized swelling in tissues and trigger a series of inflammatory responses, consequently impairing the function of chondrocytes. As a result, the ideal adhesive is distinguished by its capacity to release moisture wisely, thus maintaining an advantageous hydrostatic balance.[109,110]

Enhancing the adhesive's ability to retain water can be achieved by strategically altering its structural and compositional characteristics. Adding moisture-absorbing components like hydroxyethyl cellulose or gelatin can enhance the adhesive's water-attracting and water-maintaining qualities.[23,77] Furthermore, the engineering of porous configuration or micro-nano scale surface topography serves to amplify the adhesive's surface area, thereby bolstering its capacities for water uptake and retention.

2.2 | Regenerative medicine of adhesives

2.2.1 | Performance of loaded bioactive substances

The adhesive holds potential as a potent vehicular platform for the conveyance and subsequent deployment of diverse bioactive agents to targeted tissue sites. This capability can be strategically deployed to modulate the pathological conditions at sites of injury and foster the restoration process of the afflicted tissue.[111,112] These bioactive factors include drugs (such as analgesics, anti-inflammatory agents or monoclonal antibodies), exosomes, etc. (Table 2). The salient advantage of this approach resides in its capacity to permit clinicians to precisely target and modulate the activity of bioactive agents within the cartilage region of interest or the surrounding tissue, both temporally and quantitatively. This precision localization significantly negates systemic side effects and reduces the necessitated dosage of pharmaceuticals, concurrently preempting the degradation of active components by the digestive or circulatory systems. Currently, a myriad of approaches is available for facilitating the localized and sustained dispensation of bioactive agents via biomaterials. A prevalent technique involves the incorporation of bioactive molecules into premade or injectable hydrogels, which are subsequently applied to or near the targeted tissue. These bioactive entities are capable of binding to the hydrogels through the formation of either covalent bonds, non-covalent bonds, or a combination thereof with the adhesive substrates. Moreover, the release dynamics of the bioactive factors can be meticulously regulated by manipulating the hydrogel's physical characteristics—such as pore size, biodegradability, and degree of swelling—in conjunction with the chemical interactions occurring between the hydrogel and the bioactive agent.[120–122]

2.2.2 | Ability of the adhesive to act as a scaffold for cell regeneration

In the wake of progressions in developmental biology, stem cell research, and bioengineering, adhesives have garnered significant attention across numerous clinical disciplines as vehicles for cell regeneration and as scaffolding for delivery mechanisms. Adhesives characterized by their high biocompatibility are capable of emulating the physical and chemical attributes akin to natural extracellular matrices, encompassing their mechanical strength and substantial water retention capabilities.[123–125]

During the course of cartilage regeneration, it is observed that certain adhesives can emulate a scaffold that parallels the three-dimensional architecture of the extracellular matrix (ECM).[124–126] This scaffold affords an environment conducive to the proliferation and adhesion of chondrocytes, thus fostering the formation of nascent cartilage tissue and preserving its structural integrity. Notable examples include adhesives derived from fibrin

TABLE 2 Bioactive substances loaded in adhesives.

Type	Name	Adhesive	Function	Refs
Drug	Ibuprofen	Cyanoacrylate	Anti-inflammatory analgesia of incision	113
	Acetaminophen	Cyanoacrylate	Anti-inflammatory analgesia of incision	113
	Benzocaine	Cyanoacrylate	Anti-inflammatory analgesia of incision	113
	Bevacizumab	Gelatin methacryloyl hydrogel	Preventing the formation of bone bridge	114
Exosome	Exosome derived from BMSCs	GMOCS	Recruitment of endogenous cells and repair of cartilage defects	115
	Exosome derived from BMSCs	AD/CS/RSF	Recruitment of endogenous cells and repair of cartilage defects	13
Cytokine	TGF-β1	S-PIL10	Promoting cell recruitment and bridging of the defect edge	116
	IGF-1	Gelatin methacryloyl hydrogel	Promote chondrogenic differentiation, chondrocyte proliferation, and matrix synthesis	114
Other	Cell adhesion molecules	Genipin-cross-linked fibrin hydrogel	Increasing cell adhesion	117
	PTH (1–34)	Gelatin methacryloyl hydrogel	Inhibit chondrocyte hypertrophy, facilitate transparent chondrocyte matrix formation	118
	Platelet-rich plasma	Gelatin	Promoting chondrocyte proliferation and maintaining cartilage phenotype	119

and gelatin. As the repair progresses, the inherent biodegradable and malleable nature of these adhesives permits the original scaffold to be incrementally substituted by emerging cartilage tissue, culminating in the establishment of a fully functional cartilaginous structure. In a different scenario, certain adhesives also serve as vectors for the delivery of therapeutic cells, offering a potent instrument within the sphere of cell therapy. A pivotal aspect of adhesive design involves ensuring that the reactive functional groups of the binder are cell-compatible to sustain cell viability and functionality.[124,126,127] This criterion may constrict the range of chemical entities available for the formulation of adhesives. Investigations into these approaches have been active and have corroborated the curative outcomes of adhesives laden with cells across multiple scenarios.[23,126,127] For instance, the utilization of genipin-cross-linked fibrin (FibGen) hydrogel containing annulus fibrosus (AF) cells has been evidenced to facilitate the repair of AF defects.[128] Additionally, in another inquiry, the employment of gelatin methacryloyl (GM) hydrogel impregnated with bone marrow mesenchymal stem cells (BMSCs) has demonstrated therapeutic benefits in addressing injuries to the growth plate.[129]

2.3 | Biological performance

Ensuring biocompatibility and non-toxicity at all levels, from the microscopic realm of individual cells to the broader scope of the organism, stands as the foundational principle guiding the development of cartilage repair adhesives. Furthermore, minimal inflammatory reactions, negligible susceptibility to microbial colonization, and an absence of carcinogenic potential are essential requisites for these materials.[43] Biocompatibility is fundamentally dictated by the interplay of an adhesive's chemical, biological, and physical characteristics, and its evaluation typically relies on empirical approaches.

Here is a brief introduction to the biocompatibility of the most commonly used adhesives. (1) A common

problem in the synthesis of adhesives, such as cyanoacrylates, is that because most of them have a large molecular weight, they are usually difficult to degrade in tissues and may cause persistent foreign body reactions.[130,131] In addition, synthetic chemical crosslinkers, initiators, accelerators, stabilizers, etc., are usually used in the production of these polymers. The persistence of specific chemical constituents within the polymeric material raises concerns regarding their potential biocompatibility. These constituents retain the ability to undergo metabolic transformations leading to the formation of cytotoxic and histotoxic byproducts, which may ultimately elicit inflammatory responses.[132–134] (2) The protein-based adhesives are usually made from naturally derived proteins. Such adhesives are generally considered to have a good biocompatibility. However, if improperly purified, these adhesives may carry viruses, bacteria, or other pyrogens, which can cause incalculable damage to cartilage tissue and even the whole body.[134] (3) Analogously, adhesives formulated with naturally derived polysaccharides, like alginate and chitosan, carry the inherent risk of harboring endotoxins unless adequately purified.[135] (4) A major concern surrounding nonmammalian-derived adhesives lies in their potential to elicit antigenic and immunogenic responses within the recipient, posing a risk of immunological rejection.[8,17] Given that other less commonly used adhesives are thoroughly discussed in some reviews,[8,136–138] this section will briefly highlight the essential factors to ponder when employing these less-common approaches. A more in-depth exploration of this topic will be provided in the third part of this article.

2.4 | Degradability

The controlled degradation of an adhesive following placement can present a significant advantage. In scenarios of cartilage repair, the ideal adhesive would undergo gradual degradation post-intervention without generating any toxic byproducts.[139] This characteristic is particularly valuable in applications where adhesive removal would be undesirable or impractical, eliminating the need for additional procedures after surgery.[58] Notably, the degradation rate of these adhesives should be meticulously tailored to match the expected tissue regeneration timeline of the treated cartilage. The rapid degradation of the adhesive may not be conducive to the complete repair of cartilage tissue. Conversely, excessively slow degradation can result in the undesirable retention of the hydrogel as a foreign body, potentially instigating a prolonged immune inflammatory response. Extensive in vitro degradation studies, as documented in relevant research, demonstrate the hydrogel's remarkable persistence for a minimum of 2 weeks within a simulated physiological environment. This timeframe aligns with the estimated duration necessary for mechanical support or drug release to exert a therapeutic effect on cartilage tissue repair.[115,140] Most of the diseased cartilage is filled with healthy cartilage or other tissues, which generally takes 6–8 months.[141] Indeed, the precise degradation time is likely to vary, influenced by numerous factors such as the type of cartilage (thickened or dense), cartilage thickness, age, vitamin D levels in the body, the severity of the injury, and the therapeutic outcome, among others.[142]

The current binder degradation strategy mainly relies on incorporating degradable polymers into the binder and adjusting the sensitivity to hydrolysis and enzymatic degradation. A strategy may involve photocleavable functional groups that can be achieved by partially modifying the polymer backbone with azobenzene, spirobenzopyran, coumarin, and nitrobenzyl groups. For example, o-nitrobenzyl (oNB) is used to synthesize photolyzable connectors. It is then used to form a hydrogel network with acrylate monomers (such as acrylamide). When exposed to UV light (365 nm), the oNB joint in the hydrogel is cracked, resulting in a decrease in mechanical properties over time. The degree of degradation can be adjusted by adjusting the ratio of oNB linker to acrylate monomer.[143–145]

3 | TYPES OF ADHESIVES AND THEIR APPLICATION IN DIFFERENT CARTILAGES

3.1 | Types of adhesives

Adhesives can be categorized based on a multitude of criteria, tailored to meet diverse medical requisites and application contexts. Common classification parameters include but are not limited to chemical composition, origin, responsiveness to specific conditions, and conceptual design inspiration. This chapter endeavors to explore representative instances within each classification, delving into their chemical structures, adhesion mechanisms, and performance attributes. Subsequently, a comprehensive list and an overview of the featured adhesives will be provided.

3.1.1 | Adhesives with different main components and sources

Natural adhesives

The primary constituents of these adhesives predominantly consist of natural biological macromolecules. These macromolecules are typically derived or

synthesized from natural reservoirs and can be procured through direct extraction and isolation from human blood, animal tissues (including but not limited to cattle, sheep, and pigs), or plant tissues.[146] Based on their distinct chemical compositions, these adhesives are broadly categorized into protein-based and polysaccharide-based variants.

The majority of these glues display structural and chemical characteristics similar to those of human tissues, making them highly compatible with biological systems. These provoke comparatively gentle inflammatory reactions and are notable for their excellent biocompatibility. Furthermore, endogenous enzymes easily identify their structural patterns, facilitating effective breakdown and metabolism, thus demonstrating significant biodegradability. When applied, natural adhesives are considered secure and effective, frequently eliminating the necessity for additional surgeries after wound recovery, thus reducing patient pain and related dangers. As a result, their broad applicability spans cartilage repair and multiple medical fields, highlighting their crucial function as a notable subclass of adhesives. However, they also present similar disadvantages. As an example, adhesives based on proteins come from different proteins, in contrast to polysaccharide-based adhesives that come from varied plants, making them susceptible to triggering allergies in specific groups. The intensity of these responses fluctuates and presents difficulties in forecasting. Furthermore, due to their sticky characteristics, additional improvements are required to endure significant mechanical strains during joint movements, like movement of the hip joint.[14,23,26,147]

Protein-based adhesives are exemplified by gelatin-based adhesives and fibrin glue, whereas polysaccharide-based adhesives are exemplified by HA, chitosan, alginate, and chondroitin sulfate (CS). This part offers a concise summary of the common nature, molecular structure, key characteristics, and constraints of adhesives based on these elements. Following this, we introduce a summary of the dominant commercial options in this field.

Protein based adhesives

Gelatin. Gelatin-based adhesives are a form of macromolecular hydrophilic colloid, mainly originating from the partial alteration of collagen derived from animal skin, bone, or cartilage. This entity has a lustrous look and is distinguished by its lack of smell and flavor.[146] Generally, the molecular mass varies from 50,000 to 100,000, and its relative density spans from 1.3 to 1.4.

Collagen, a polypeptide protein mainly made up of glycine, proline, and hydroxyproline, serves as the main component in gelatin-based adhesives. Around one-third of collagen molecules are made up of glycine, while proline and hydroxyproline play a role in creating the triple helical configuration found in collagen molecules. The collagen's tertiary structure features tripeptide chains organized in a left-handed spiral pattern, creating a triple helix referred to as the collagen helix. The stability and malleability of this collagen helix significantly contribute to its strong mechanical characteristics.[148] In collagen, the processes of hydroxylation and acetylation are crucial for creating cross-linked structures. Agents for cross-linking, like formaldehyde and glutaraldehyde, are utilized to aid in these chemical reactions. Formaldehyde facilitates swift interlinking of gelatinous structures, whereas glutaraldehyde guarantees prolonged stability.[23,25,149]

These structures of collagen endow it with a variety of biomechanical properties: (1) Viscosity and elasticity. The primary source of these two characteristics lies in the intricate tripeptide helical configuration of the collagen chain, characterized by numerous amino acid residues. The residues engage amongst themselves or with protein residues on the tissue's surface via hydrogen bonds and van der Waals forces, creating a molecular network with specific elasticity and viscosity characteristics.[41,148] Elasticity gives the adhesive a certain ductility, so that it can adapt to the morphological changes of the tissue surface. At the same time, this viscosity enables gelatin-based adhesives to effectively adhere to and wrap the tissue surface. (2) Gelation. Gelatin-based adhesives have the characteristics of forming a gel state in water, which is due to the special structure of collagen and the formation of hydrogen bonds, making it possible to form a protective gel layer in water. This hydrogel morphology helps to maintain the wet environment of the tissue. (3) Reversibility. When the warm colloidal aqueous solution is cooled, its viscosity gradually increases. If the concentration is large enough and the temperature is low enough, the gelatin aqueous solution is transformed into a gel. It can be reversibly transformed into a solution state after being heated. This is its incomparable characteristics.[23,147,148,150]

Despite the advantages of gelatin-based adhesives in tissue adhesion and repair, several disadvantages exist. These encompass their rapid and challenging-to-control degradation rate, which may result in complete degradation before tissue healing is achieved. Additionally, issues such as high production costs and the necessity for refrigeration pose further challenges. These shortcomings may constrain the effectiveness of gelatin-based adhesives in certain specific applications.[23,25]

At present, the main commercial gelatin-based adhesives used in commercial applications include, but are not limited to: (1) LifeSeal.[151] LifeBond is its

manufacturer. Gelatin and microbial transaminase are its main components. Its main function is to provide reinforcement and minimize the leakage of stitches. (2) GRF Biological Glue.[152] Microval is its manufacturer. Gelatin, resorcinol, and formaline are its main components. It is mainly used for surgical hemostasis.

Fibrin. Fibrin glue was first introduced in 1940s and is a biological product extracted from human plasma.

This system comprises two principal components: fibrinogen with factor XIII and thrombin with Ca^{2+}. Thrombin enzymatically cleaves fibrinopeptides A and B from the α and β chains of fibrinogen, resulting in the formation of fibrin monomers. These monomers polymerize into an unstable clot via physical cross-linking mediated by hydrogen bonds. Factor XIII serves as a fibrin-stabilizing factor, which, upon activation by thrombin and in the presence of cofactor Ca^{2+}, transforms into factor XIIIa. Subsequently, factor XIIIa catalyzes the cross-linking of blood fibrin monomers or unstable clots via amide bonds between glutamine and lysine residues, yielding insoluble blood clots resistant to proteolytic cleavage.[153–155]

Based on the findings, fibrin glue ultimately assumes a stable, non-brittle structure akin to that of blood clots. Consequently, it shares several characteristics with blood clots: (1) Superior Hemostatic Properties. Fibrin glue swiftly and effectively controls blood loss during surgery, particularly in managing slow bleeding, body fluid exudation, needle bleeding, lymph exudation, and substantive organ bleeding. During the surgical procedure, the uniform application of fibrin glue onto the wound surface expeditiously generates a protective barrier, preventing the leakage of proteases from necrotic tissue cells. This facilitates rapid scab formation, cessation of bleeding, and prevention of further tissue damage. (2) Outstanding Biocompatibility. It is noteworthy that fibrin glue surpasses most biological or synthetic topical hemostatic adhesives in terms of histocompatibility and non-toxicity, underscoring its excellent biocompatibility.[156–158]

Nevertheless, the inclusion of a human component in fibrin glue poses a potential risk of viral transmission (e.g., HIV, hepatitis, etc.), thereby restricting its clinical application to some extent. Besides the potential spread of pathogens, there exists a rare but plausible risk of inadvertent injection of fibrin glue into blood vessels during surgical procedures, leading to thrombosis.[156,159]

At present, the main application of commercial fibrin glue is: (1) Tisseel.[160] Its manufacturer is Baxter. Its main components are human fibrinogen, thrombin, fibronectin, bovine aprotinin. (2) Evicel.[161] Its manufacturer is Ethicon. Its main components are human fibrinogen, thrombin. (3) Hemaseel.[162] Its manufacturer is Haemacure. Its main components are human fibrinogen, fibronectin, bovine thrombin. Their application in the medical field is mainly that it can assist surgeons to stop bleeding at the incision site during surgery.

Polysaccharide based adhesives

Hyaluronic acid. HA, alternatively referred to as hyaluronan, is an anionic, non-sulfated polysaccharide belonging to the glycosaminoglycan (GAG) family. This substance is commonly found in mammalian tissues, encompassing connective tissue, epithelial tissue, and nerve tissue. As a constituent of the ECM, HA exhibits a natural affinity with cells.[82,163]

HA, a high molecular weight polymer, is a polysaccharide composed of repeating units of D-glucuronic acid and N-acetylglucosamine. Its molecular formula is $(C_{14}H_{21}NO_{11})_n$. D-glucuronic acid and N-acetylglucosamine are connected via β-1,3-glycosidic bonds, while disaccharide units are linked by β-1,4-glycosidic bonds. The disaccharide unit can extend up to 25,000 repetitions. The molecular weight of HA in the body ranges from 50 to 20 million daltons.[82,163,164]

The principal biological functions of HA encompass its role in regulating the viscoelasticity of biological fluids, such as serving as joint synovial fluid or being employed at active growth sites (e.g., the epiphyseal plate). Its hydrophilicity, along with biocompatibility and non-immunogenicity, has rendered it indispensable in a diverse array of clinical applications. These include its use as adhesive supplements for arthritis and wound dressings aimed at enhancing pain relief and functional improvement. Additionally, as a major constituent of the ECM in tissues, HA actively participates in cell-matrix interactions and provides guidance cues for a wide spectrum of cellular behaviors, including proliferation and migration.[164,165]

The primary drawback of HA biomaterials typically lies in their poor mechanical properties attributed to excessive swelling and rapid degradation. HA degradation proceeds via enzymatic and non-enzymatic pathways, including hydrolysis, thermal decomposition, and oxidant-induced degradation, primarily facilitated by the hyaluronidase family. In certain instances, these degradation byproducts may elicit inflammatory responses in macrophages and dendritic cells. Consequently, in most applications, HA undergoes chemical modification and is combined with cross-linking agents to modulate the mechanical properties, swelling behavior, and degradation kinetics of the resultant gel. Chemical alteration of HA mainly affects its carboxylic acid and hydroxyl groups. Utilizing carbodiimide chemistry techniques, HA's carboxylic acid groups are linked with tissue-reactive groups like pyrogallol, dopamine, serotonin, and o-nitrosobenzaldehyde. Following this,

the reactive groups undergo cross-linking with tissue functional groups via catechol chemistry or the creation of imine. Additionally, HA's hydroxyl groups are commonly altered through methacrylic anhydride transesterification to attain in situ crosslinking and tissue bonding characteristics.[166–171]

Commercially available tissue adhesive based on HA grafted with N-(2-aminoethyl)-4-(4-(hydroxymethyl)-2-methoxy-5-nitrophenoxy) butanamide (NB) can generate aldehyde groups at the termini following ultraviolet irradiation.[170] This characteristic aid in the in situ gel formation and adherence to tissues by facilitating cross-linking with agents and tissue amines. GelMA, also known as methacrylate-modified gelatin, or HA combined with carbohydrazide (HA-CDH), functions as agents for cross-linking. The two types of adhesives show enhanced adherence to tissues over fibrin glue found in the market, yet they exhibit lesser cytotoxic effects. Furthermore, their effectiveness in serving as post-surgery wound adhesives, fillers, and hemostatic agents has been confirmed. The use of HA-CDH adhesives on rats' wounds after surgery led to smooth adherence at the site and hastened the healing process.[23,170,171]

Chondroitin sulfate. Adhesive made of CS is commonly used as a biomaterial for repairing and regenerating cartilage. CS, its main component, forms a GAG that is tightly attached to proteins, leading to the creation of proteoglycans. CS, commonly obtained from sea creatures like sharks, fish, and mussels, is crucial in the makeup of adhesives, aiding in their effectiveness for cartilage restoration and regeneration.[172–175]

CS fundamentally consists of a chondroitin unit (N-acetylgalactosamine), an N-sulfate group, and possibly a glucosamine unit. Commonly, the chondroitin unit is connected through a 1–4 bond, creating a polymer chain, and then linked with a sulfate group to produce an N-sulfate group.[174,175]

The main use of this substance is as a bonding agent in treating joint disorders, frequently used together with glucosamine. The combined treatment shows effectiveness in reducing pain and promoting cartilage repair, thus tackling root joint problems. Rigorous, randomized, placebo-controlled clinical studies have confirmed the effectiveness of CS in alleviating osteoarthritis-related pain, improving joint performance, diminishing joint swelling and effusion, and averting gap stenosis in knee and hand joints. Additionally, CS serves as a buffer to reduce the effects of impact and friction during motion. This enhances the absorption of water into proteoglycan molecules, which in turn increases the thickness of cartilage and augments the volume of synovial fluid in the joint area. Significantly, chondroitin plays a crucial role by serving as a channel for delivering vital oxygen and nutrients to joints, simultaneously aiding in the removal of waste and carbon dioxide. Due to the lack of blood vessels in articular cartilage, synovial fluid is the exclusive provider of joint oxygen, nutrition, and lubrication.[176,177]

Chitosan. Chitosan arises from the partial deacetylation of the natural polysaccharide chitin, which exhibits wide distribution in nature. Abundant in the exoskeletons of marine arthropods like shrimps and crabs, as well as in insect and mollusk shells, chitin stands as the second-largest natural polymer.[8]

Chitin represents an insoluble linear mucopolysaccharide composed of β-(1,4)-linked N-acetyl-D-glucosamine repeat units, interconnected by β-(1,4) glycosidic bonds. In addition to each monomer featuring a hydroxyl group substituted by an acetylamino group, chitin exhibits chemical properties akin to cellulose. Complete deacetylation of chitin can be achieved at elevated temperatures using alkaline substances such as sodium hydroxide, yielding chitosan. In the context of tissue adhesion applications, chitosan is commonly utilized alongside a cross-linking agent, typically based on a diester or diisocyanate, which reacts with an amine moiety on the chitosan backbone. Throughout the curing process, tissue adhesion is attained via the reaction between aldehyde and histamine.[178]

Chitosan exhibits noteworthy antimicrobial activity against a broad spectrum of microorganisms, encompassing algae, bacteria, yeasts, and fungi. Notably, when subjected to incubation with the adhesive, both Gram-negative bacteria such as *Escherichia coli* and Gram-positive bacteria like *Staphylococcus aureus* were predominantly eradicated in 1 day.[179] Nevertheless, the precise sterilization mechanism remains elusive. Furthermore, in a rat model of postoperative skin defects, the adhesive demonstrated pronounced enhancements in wound healing processes, characterized by accelerated wound closure and augmented collagen deposition. These beneficial effects were attributed to the up-regulation of growth factors, including vascular endothelial growth factor, epidermal growth factor, and TGF-β. Additionally, chitosan finds utility as a hemostatic agent, effectively curbing bleeding and facilitating wound regeneration.[180,181]

In the commercialization of chitosan, the more representative example is HemCon Bandage Pro.[182] Its manufacturer is HemCon Medical Technologies Inc. The product is used to temporarily control severe bleeding wounds in emergency situations.

Synthetic polymer based adhesives

This type of adhesive comprises synthetic polymers, initially investigated and employed in biomedical applications. Their production can be scaled up efficiently and

cost-effectively, offering economic advantages. Furthermore, they feature well-defined structures and typically afford a high degree of tunability concerning chemical and mechanical properties. Nonetheless, synthetic polymers often consist of polymeric macromolecules, potentially leading to inadequate degradability and eliciting persistent foreign body reactions in patients. Additionally, the biocompatibility of synthetic polymers varies, necessitating further investigation.[183]

Due to the diversity within this category, our focus here is primarily on introducing representative examples, namely polyethylene glycol (PEG) and cyanoacrylate adhesives. In this section, we provide a succinct overview of their status, molecular composition, key attributes, limitations, and subsequently highlight prevalent products in the market.

Polyethylene glycol. Polyethylene glycol, commonly abbreviated as "PEG," results from the addition reaction between polyethylene oxide (PEO) and water. At a molecular weight below 700, it exists as a colorless, odorless, and non-volatile viscous liquid at 20°C, with minimal water absorption. Molecular weights ranging between 700 and 900 render it semi-solid, while molecular weights exceeding 1000 manifest as light white waxy solids or flocculent flake paraffins, or even as flowing powders.[23,184]

The molecular structure of PEG is remarkably straightforward, consisting of repetitive linkages of ethylene glycol units (-CH_2-CH_2-OH). Oxygen atoms within this structure bridge adjacent ethane units, yielding a linear polymer chain. Typically expressed as HO-(CH_2-CH_2-O)$_n$-H, where "n" denotes the number of ethylene glycol unit repetitions, the chemical formula of PEG reflects its linear configuration. In PEG adhesives, cross-linking and tissue binding are commonly achieved through NHS esters. These PEG formulations typically comprise two constituents: a four-arm star-shaped PEG, functionalized with an NHS ester terminus, and a tetramine cross-linking agent such as trilysine. Upon mixing and application onto tissues, the NHS ester of PEG undergoes cross-linking with the amines of both the cross-linking agent and those within the tissue, culminating in the formation of a hydrogel adhesive.[23,85]

PEG stands out as a synthetic adhesive renowned for its exceptional biocompatibility. Moreover, the inherent modifiability of the PEG architecture facilitates the convenient design of adhesives featuring adjustable physical properties such as degradation rate and cross-linking density. Despite these advantages, the utilization of PEG is constrained by several limitations. Primarily, most PEG adhesives exhibit poor mechanical properties and high brittleness, rendering them suitable primarily for regions with minimal expected tension or as adjuncts to conventional tissue closure methods. Despite numerous strategies aimed at mitigating their swelling, the inherent hydrophilicity of PEG often results in significant swelling. Additionally, adhesives based on NHS esters necessitate dry storage due to the hydrolytic instability of NHS esters. Consequently, their application typically entails multiple preparatory steps, including polymer dissolution, which may prolong the application duration.[23,185]

At present, the main applications of PEG include: (1) FocalSeal.[186] Its manufacturer is Genzyme Corp. Its main components are PEG-co-poly (lactic acid) diacrylate, and PEG-co-poly(trimethylene carbonate) diacrylate. It is mainly used to provide watertight closure for the surgical area after surgery. (2) CoSeal.[187] Its manufacturer is Angiotech. Its main components are PEG NHS ester and PEG thiol. It is mainly used to assist hemostasis during surgery. (3) The others, such as Adherus, SprayGel, and OcuSeal, also commonly use PEG adhesives.[188–190]

Cyanoacrylate. Cyanoacrylate adhesive, categorized as a resin within the acrylate group, is commonly referred to as an "instant adhesive" due to its rapid curing properties, allowing for instantaneous solidification upon application.[191]

The molecular structure of cyanoacrylate adhesive encompasses an acrylate group and a cyano (–CN) group. Typically denoted by the chemical formula R-CH_2-CH (CN)-COOR', where R and R′ represent distinct organic groups, respectively, the acrylate group serves as a primary structural unit within cyanoacrylate, featuring a double bond and a carboxyl group. Acrylate groups commonly engage in copolymerization with other functional groups, contributing to the formation of polymer materials. Within synthetic binders, the acrylate group enhances adhesion and water resistance. Conversely, the cyano group, housing a carbon-nitrogen triple bond, exhibits heightened polarity and reactivity.[23] Within cyanoacrylate, it's common for the cyano group to be linked with the acrylate group, enhancing the molecule's polarity and thus improving its adhesive efficacy and chemical steadiness. Organic entities R and R′ can differ, including methyl, ethyl, propyl, phenyl, among other organic components. Choosing these specific organic groups significantly affects the characteristics and uses of cyanoacrylates, encompassing their solubility, fluidity, and bonding properties.[34,35,59,192]

The use of cyanoacrylate adhesive comes with its own set of pros and cons. Benefits include: (1) Instant bonding: Swift tissue fusion is attained through the use of small amounts of water and gas, enabling quick adhesion in a remarkably brief period. Its characteristic makes it an

essential instrument for urgent surgeries, especially for severe bleeding due to pelvic-hip fractures.[193–195] (2) Hardening at room temperature: This process solidifies at room temperature, eliminating the need for extra heating steps. (3) Composition of a single component: Without solvents, it simplifies application.[192] (4) Elevated viscosity: Some altered versions of cyanoacrylate, like α-cyanoacrylate adhesives, include small quantities of thickening agents and stabilizers.[196] α-cyanoacrylate adhesive, rich in polar cyano and ester bonds, exhibits robust adhesion to polar substrates, resulting in formidable bonding strength. Interface adhesion strength can reach levels as high as 17–22 MPa.[197,198] However, the drawbacks of cyanoacrylate adhesives are notable. The primary issue with cyanoacrylate-based adhesives lies in their cytotoxicity, which has been associated with acute and chronic inflammation as well as the toxicity of their degradation products, particularly formaldehyde. Additionally, they exhibit poor biocompatibility with repaired tissues and degrade slowly in vivo with a degradation rate exceeding 3 years. Consequently, most cyanoacrylate adhesives are primarily employed for external local applications such as sealing incisions and serving as hemostatic agents following orthopedic surgeries. Furthermore, challenges related to stringent storage conditions and the imperative to avoid exposure to atmospheric moisture further constrain their usage.[23,198]

The main cyanoacrylate adhesives currently used include: (1) Dermabond.[199] Its manufacturer is Ethicon. Its main component is 2-octyl. It is mainly used for local application to keep the skin edge of the surgical incision and trauma-induced laceration closed and easy to fit. (2) Indermil.[200] Its manufacturer is Covidien LP. Its main component is n-butyl cyanoacrylate. It is mainly used to close local skin incisions, including laparoscopic incisions, and traumatic lacerations in low skin tension areas. (3) Omnex.[201] Its manufacturer is Ethicon. Its main components are 2-octyl cyanoacrylate and butyl lactoyl cyanoacrylate. It is mainly used for vascular reconstruction, and continuous hemostasis is achieved by mechanically sealing the leakage area. (4) Others such as Glubran2, Derma + Flex, LiquiBand Exceed are also used in the field of surgical medicine.[201–203]

Active multifunctional tissue adhesives

Active multifunctional biomedical adhesives exhibit the capability to respond to environmental variations, thereby instigating chemical or structural alterations within the adhesive network, and consequently initiating their designated functions. These bioadhesives can modulate their properties in reaction to external stimuli, such as alterations in pH, electricity, temperature, and light, or fluctuations in the concentration of biomolecules, including glucose and enzymes, in their surroundings. In this context, our focus is primarily on pH and temperature-responsive active multifunctional tissue adhesives.[204]

pH-responsive adhesives. pH-responsive adhesives represent a distinct category of hydrogel materials, characterized by their gelation properties being influenced by the pH level of the solution. The gelation mechanism of these hydrogels hinges on the presence of ionizable groups within their molecular structure, such as carboxyl (–COOH) or amino ($–NH_2$) groups. Under varying pH conditions, these groups undergo ionization or protonation reactions, leading to structural alterations and subsequent gelation of the hydrogels.[205]

Common pH-responsive adhesives include, but are not limited to (1) Polyacrylic acid (PAA) adhesives. These adhesives exhibit negative charge in low pH environment and positive charge in high pH environment. As a result, pH variations can induce swelling or gelation of PAA adhesives within different ranges.[206,207] (2) Gelatin-chitosan composite adhesives. By adjusting the ratio of gelatin to chitosan, this composite adhesive can respond to changes in pH values, thereby modifying its gelation properties.[208,209]

Temperature-responsive adhesives. Temperature-responsive adhesives undergo swelling and gelation within specific temperature ranges. The gelation mechanism typically relies on inherent properties within their molecular structure, such as alterations in hydrophobic interactions, hydrogen bonds, or covalent bonds. Within these temperature ranges, these molecular structures undergo changes, transitioning the adhesive structure from a swollen state to a gel state, or vice versa. There are two main types of temperature-responsive adhesives: cold-induced gels and heat-induced gels. Cold-induced gelation occurs upon cooling, whereas heat-induced gelation occurs with increasing temperature. Some heat-induced gels demonstrate gelation properties close to human body temperature (approximately 37°C), making them suitable for in vivo applications.[204,210]

Common temperature-dependent adhesives include but are not limited to: (1) Poly (N-isopropylacrylamide) (PNIPAM) hydrogels. The PNIPAM hydrogel exhibits a gel state below its lower critical solution temperature (LCST) and dissolves above LCST. Its LCST is usually between 30°C and 40°C, so it can achieve gelation properties near human body temperature. PNIPAM hydrogels have a wide range of applications in drug delivery, tissue engineering and biosensors.[211] (2) Poly (ethylene glycol)-polypropylene ether copolymer (PEG-PPO-PEG) adhesive. The gelation properties depend on

the hydrophilicity and hydrophobicity of the PPO segment. The PPO segment is hydrophilic at low temperature, while it is hydrophobic at high temperature, resulting in swelling and gelation of the adhesive. PEG-PPO-PEG adhesives are widely used in drug-controlled release and tissue engineering.[212,213]

Bionic adhesives

Biomimetic adhesives represent a category of adhesives inspired by the structural and functional attributes observed in organisms, aimed at tissue binding and promoting healing. These adhesives draw inspiration from a variety of organisms, including but not limited to frogs, mussels, and others.

Frog glue. Frog glue, mainly derived from frog skin and especially from species rich in adhesives such as tree frogs in tropical rainforests, is predominantly made up of collagen. The chemical makeup of this substance is strikingly similar to that of human collagen, showing advantageous biocompatibility. Additionally, it might include naturally occurring bioactive elements like polysaccharides, amino acids, and growth factors.[8]

Presently, foundational in vivo research shows frog adhesive to be exceptionally adhesive, biocompatible, and biologically active, suggesting its potential for various medical uses, thus opening up new opportunities in the medical field.[8,214]

Mussel. The adhesive properties of mussels have been studied for decades, and have attracted much attention due to their ability to attach to almost any surface through a thread secreted by the soles of the feet.[215]

The mussel foot typically comprises four primary components: an acidic mucopolysaccharide serving as a primer, a sticky protein primarily composed of polyphenolic proteins abundant in 3,4-dihydroxyphenylalanine (L-DOPA) and lysine, fibrin acting as a linker between mussels and substrates, and polyphenol oxidase facilitating intermolecular cross-linking.[8]

Immunological investigations have demonstrated the low antigenicity of mussel adhesive proteins, making them suitable for biomedical applications, particularly as biological tissue adhesives. Research indicates that mussel adhesion protein extracted from mussels exhibits promising adhesive properties in fundamental studies related to bone and cartilage. Moreover, this adhesion is reversible and exhibits resilience against water exposure, temperature fluctuations, and variations in salt concentration.[8,216]

3.2 | Adhesives used in different kinds of cartilages

At present, adhesives are mainly applied to the cartilage tissue, including IVDs, articular cartilage, meniscus, growth plates, and nasal cartilage.

3.2.1 | Adhesives used in the IVD

Currently, discectomy is considered the preferred surgical intervention for alleviating low back pain and sciatica due to lumbar disc herniation. However, the loss of AF integrity and nucleus pulposus (NP) following discectomy can significantly impact spinal biomechanics, leading to discogenic back pain.[217] Therefore, we have the option to select certain adhesives with potential applications to address this issue.

Proteinaceous adhesives

FibGen hydrogels. Fibrin can be used as a scaffold for chondrocytes because it can adapt to the migration, differentiation and proliferation of chondrocytes.[218] Extracted from plants, Genipin serves as a crosslinking agent, capable of enhancing the mechanical rigidity of fibrin to closely approximate the characteristics of the AF. DiStefano et al. employed genipin to cross-link fibrin, generating FibGen hydrogels. This process involves the injection of FibGen into the AF defect, where thrombin catalyzes the polymerization of fibrinogen monomers into the primary fibrin network. Transglutaminase 2 then facilitates the covalent attachment of this network to the AF tissue. Concurrently, genipin molecules form additional cross-links within the hydrogel backbone by reacting with primary amine groups on fibrin and subsequently dimerizing. FibGen is covalently attached to AF tissue via genipin dimerization, which is accomplished by the same process as hydrogel crosslinking.[47] This hydrogel exhibits huge potential as a biomaterial adhesive for gap filling, offering adjustable material properties. They could prove particularly suitable as a sealing agent for small AF defects or as an adhesive to enhance the repair of larger AF, thus presenting valuable applications in addressing tissue damage.[219] Moreover, compared to fibrin alone, FibGen, with the addition of cell adhesion molecules, exhibits enhanced material behavior and can be adjusted to higher shear stiffness values that closely resemble human annulus tissue. Additionally, it demonstrated improved stability in size and a slower degradation rate in vitro.[117] In a subsequent large animal study, it was demonstrated that FibGen effectively closed significant AF defects and facilitated

functional recovery by enhancing the biomechanics of the moving segment. This superiority over fibrin alone as an AF repair material stemmed from its ability to augment mechanical stiffness, decelerate degradation rate, and exhibit excellent in vivo biocompatibility.[220] In recent years, a series of successful in vitro biomechanical studies conducted on small animals have demonstrated the efficacy of FibGen in effectively sealing IVD defects and partially restoring various biomechanical properties altered by injury.[221] Furthermore, the study conducted by Cruz et al. provided compelling evidence that Cell-Seeded FibGen exhibits promising potential as an adjustable AF sealer, capable of delivering cells to effectively facilitate AF repair following microdiscectomy or during intradiscal injection.[128] Wang et al. discovered that Genipin cross-linked hydrogels could effectively adhere to the interface of the AF lesion, facilitate strain transmission, and enhance AF healing through sustained stress stimulation.[222]

Other investigations have been conducted on FibGen hydrogel-based materials for IVD diseases. Frauchiger et al. substantiated that the integration of genipin-reinforced fibrin hydrogel and engineered silk scaffold (as a filling material) exhibits suitability and holds promise as an approach to repair AF.[223] Alexeev et al. showed that a composite material comprising an electrospun polycaprolactone (PCL) scaffold integrated with FibGen exhibited robust adhesion to the injury site throughout the experimental procedure, thereby holding promising potential for restoring mechanical properties comparable to those of the intact IVD.[224]

FibGen hydrogels are biocompatible with human cells and can have a modulus in the range of native annular tissues.[137] Furthermore, the presence of FibGen has been associated with the upregulation of chondrogenic differentiation markers.[225] These advantages make it a potential adhesive for repairing IVD injuries. However, there are still some limitations, such as the possibility that cell proliferation may be slower in FibGen gels, which could potentially limit the rate of tissue repair.[219] Additionally, the mechanical properties and the biocompatibility of the hydrogels depend on the correct concentration of fibrin and genipin, which necessitates precise control during preparation.[226] More long-term studies are required to better define their benefits in surgery.

RF cross-linked collagen gels. Type I collagen is one of the main components of ECM, which provides a bionic growth environment for implanted cells and shows good cell adhesion and proliferation promotion. In addition, type I collagen gel can effectively assist cartilage repair and maintain the regenerated cartilage type as hyaline cartilage.[227] Prior research has explored the potential of riboflavin (RF) in the context of tissue engineering, demonstrating its ability to stiffen collagen scaffolds and promote the survival of chondrocytes and fibroblasts.[228,229] In the context of IVD repair, RF plays a crucial role in the cross-linking of collagen macromers, specifically rat-tail type I collagen, to both the native AF collagen and other collagenous components within the scaffold through photochemical mechanisms. One notable example of this approach is the rat-tail type I collagen hydrogel developed by Borde et al.[230] This hydrogel utilizes RF-mediated photochemical cross-linking for enhanced stability and mechanical properties, making it a promising candidate for AF repair application. The efficacy of AF repair is positively associated with RF cross-linking.[231] After undergoing repair, the IVD effectively retains a substantial portion of its NP tissue, thereby exerting inhibitory or partially reversing effects on degenerative changes. Collagen gel integration demonstrably augments AF healing by fibroblast recruitment and subsequent tissue remodeling. RF crosslinking is empirically essential for this reparative process.[232] In subsequent experiments using animal models, the efficacy of RF cross-linked collagen gels was further validated.[233–235]

In addition, Jiang et al. investigated the feasibility of promoting AF repair by using chondroitinase ABC (ChABC) to improve the adhesion of RF cross-linked collagen gels to AF. Implementation of ChABC digestion yielded a time-dependent decrease in proteoglycan content within the AF, subsequently enabling a notable improvement in gel adhesion, characterized by an 88% increase in elastic toughness and a 46% increase in total shear energy at the interface. Notably, this enhancement in adhesion was achieved without significant compromise to the viability of AF cells.[236] Additionally, the investigation encompassed incorporating AF cells into RF cross-linked collagen gels. This cell seeding strategy aims to amplify the restorative potential of these injectable scaffolds through augmented ECM production. The results showed that compared with the acellular gel, the gel loaded with AF cells demonstrated a faster reparative sealing rate.[237]

RF cross-linked collagen gels are generally biocompatible with human cells and can control the mechanical properties of collagen gels, making them suitable for mimicking soft tissues such as the IVD.[238] These advantages make it a potential adhesive for repairing IVD injuries. However, there are still some limitations. The photoactivation process requires exposure to UV light, which needs to be carefully controlled to prevent potential damage to the surrounding tissues or cells.[239]

Therefore, more studies, especially long-term ones, are necessary to better define the surgical benefits and any potential long-term complications.

Polysaccharide based adhesives

Alginate based adhesives. Alginates have been studied as adhesives since they form ions and/or hydrogen bonds with matrix components in tissues.[240] Collagen can assist cartilage regeneration, and alginate has a strong ability to retain collagen. The ECM in alginate is rich in collagen fibers. Alginate not only helps to maintain the differentiated phenotype of chondrocytes, but also helps to restore the normal phenotype of dedifferentiated chondrocytes, and even restore the normal phenotype from damaged cartilage.[241] Besides, alginates have been extensively documented to be a promising scaffold for IVD repair due to their remarkable resemblance to the mechanical and cell adhesive properties of the IVD NP. Bron et. al discovered that alginate effectively emulates the viscoelastic characteristics of NP while simultaneously preserving the biosynthetic phenotype of NP cells.[242] In Wiltsey et al.'s study, poly(N-isopropylacryIamide) (PNIPAAm) was grafted with CS. PNIPAAm-g-CS adhesive containing alginate microbeads demonstrated superior potential compared to PNIPAAm-g-CS adhesive containing CS aldehyde, as it exhibited enhanced adhesive performance and improved cell compatibility.[243–245] Hence, alginate exhibits promising potential as a tissue engineering scaffold adhesive for addressing IVD NP defects.

Alginates are well tolerated when in contact with human cells, which makes them suitable for implantation.[246] Moreover, Tsujimoto et al. have shown that alginate gels possess appropriate biomechanical properties under loads that are relevant in a clinical context for IVD repair.[247] Furthermore, these materials are capable of retaining water, a critical aspect for the disc environment, given that hydration of the NP is vital to its normal function.[248] In addition, alginate can be utilized in minimally invasive procedures, allowing the gel to be injected directly into the disc space.[249] However, although alginate can simulate the biomechanical properties of IVDs to a certain degree, it may require modification to provide the strength necessary for the spine's load-bearing functions.[250] Lastly, it is essential that the rate of degradation for alginate materials is calibrated to match the tissue healing rates, as inappropriate degradation can lead to repair failure,[251] and it's important to note that alginates typically exhibit poor cell adhesion properties, which can hinder integration and tissue regeneration processes within the IVD.[252]

Synthetic polymer based adhesives

Cyanoacrylate. Cyanoacrylate is synthesized by condensation of cyanoacetate and formaldehyde in the presence of heat and vacuum.[253] The resulting basic monomeric form of cyanoacrylate exhibits a low viscosity appearing as a fluid. Upon exposure to various anionic species, a remarkable transformation occurs. The cyanoacrylate monomer undergoes rapid polymerization, transitioning from a liquid to a solid film with a chain-like structure. This phenomenon serves as the basis for the adhesive properties of cyanoacrylate, enabling it to join tissues by effectively fixing and connecting their corresponding edges.[254] Kang et al. demonstrated that the use of cyanoacrylate glue improved the closure effectiveness following scaffold implantation and suture fixation. It promptly sealed the IVD, preserving its physiological stress and mechanical properties in vitro. Both in vitro cell culture and in vivo implantation showed no significant toxic effects.[255]

Cyanoacrylate is relatively easy to apply and can be delivered precisely to the site of injury. Moreover, cyanoacrylate forms an impermeable barrier to microorganisms, potentially diminishing the likelihood of postoperative infections, particularly in surface applications where microbial invasion poses a significant risk. The bacteriostatic properties inherent in this adhesive may contribute to a reduction in post-surgical complications, streamlining patient recovery.[35] Despite these benefits, cyanoacrylates present certain limitations that cannot be overlooked. Of particular concern is the question of biocompatibility. There is evidence to suggest that these adhesives may provoke an inflammatory reaction or manifest toxicity in adjacent tissues, which undermines their overall therapeutic value. Furthermore, the degradation of cyanoacrylate can result in the release of breakdown products that have the potential for cytotoxicity over extended periods, thereby posing a long-term risk to cellular health.[256]

Hybrid adhesive

DiStefano et al. conducted a study on a two-step biomaterial adhesive strategy to develop a hybrid adhesive. They devised a repair strategy in two parts, involving the utilization of a dual-modified GAG (oxidized and methacrylated) capable of chemically adsorbing an injectable interpenetrating network hydrogel composed of fibronectin-conjugated fibrin and poly (ethylene glycol) diacrylate (PEGDA). A cohesive interaction mediated by GAGs establishes covalent bonds between the tissue and the biomaterial. This approach involves the integration of injectable hydrogels with IVD ECM proteins, which has been meticulously optimized to effectively seal AF defects and exhibit promising potential for IVD repair. However, in this study, systemic immune response, changes in pain behavior, in vivo degradation kinetics, and endogenous cellular repair processes have not been evaluated.[257]

Li et al. fabricated tissue-mimetic hybrid bioadhesives. The hybrid bioadhesive consists of two components: an injectable glue for the NP cavity filling and a tough sealant for the AF defect sealing. The NP adhesive is composed of an ionically cross-linked alginate hydrogel and an adhesion primer containing Chitosan/EDC/NHS. The alginate hydrogel is prepared by mixing a sodium alginate solution with a calcium sulfate solution. To enhance adhesion to tissues, an adhesion primer containing EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride) and NHS was employed. These primers enhance adhesion by forming covalent amide bonds with the proteins of the tissue and the carboxyl groups of the alginate. The AF sealant is fabricated from a tough alginate-polyacrylamide hydrogel, which is further modified on its surface with the same adhesion primers to achieve strong adhesion with the tissue. The design of this sealant is aimed at maintaining the position of the NP adhesive in the presence of extreme mechanical loads, thereby preventing its displacement and extrusion. The NP glue demonstrated viscoelastic properties akin to those of the native human NP, essential for sustaining load-bearing capacities and hydrodynamic balance, while the AF sealant exhibited formidable adhesion and resilience against extrusion, even when subjected to physiological spinal loads. In terms of biocompatibility, the NP glue supported the survival and function of both indigenous IVD cells and introduced cells such as human primary NP cells and mesenchymal stem cells (MSCs), with encapsulated cells within the adhesive manifesting high viability and metabolic function, evidenced by the synthesis of key NP matrix constituents like collagen type II and aggrecan. The findings suggest that the hybrid bioadhesive strategy effectively integrates bioadhesive and tissue-engineering approaches, offering a promising solution for IVD repair and regeneration.[258]

3.2.2 | Adhesives used in the articular cartilage

The occurrence of articular cartilage degeneration is commonly observed during clinical practice and typically results from aging, trauma, or inflammation.[259–261] These injuries last for many years and eventually lead to arthritis.[262] Repairing the damaged cartilage is crucial in addressing traumatic arthritis.[263,264] Promising adhesives have been developed in recent years to solve this problem.

Proteinaceous adhesives

Fibrin glue. Fibrin glue is a mixture of fibrinogen and thrombin.[265] Fibrin glue exhibits excellent in vivo tolerability owing to its exceptional biocompatibility and biodegradability. Moreover, this versatile biomaterial serves as an adhesive, sealant, and/or hemostatic agent, thereby offering a multifunctional approach.[266] Fibrin establishes a robust attachment with the underlying tissue through a multifaceted mechanism. This attachment involves the interplay of several distinct forces, including the formation of covalent bonds, the establishment of hydrogen and electrostatic interactions, and the intricate interlocking of fibrin fibers with the tissue matrix.[267] Stafford et al. studied the efficacy of fibrin adhesive in 43 patients with femoroacetabular impingement. The modified Harris Hip Score was employed to assess patient outcomes, demonstrating a significant improvement in both pain and functional parameters.[268]

Fibrin glue demonstrates biocompatibility and effectively integrates with the body's natural tissue structures, promoting healing through the establishment of an organic scaffold conducive to cellular migration and integration within tissues.[269] Its facile and swift application methodology facilitates surgical procedures, thereby diminishing operative duration.[270] Owing to its biodegradable nature, fibrin glue obviates the requirement for subsequent removal, a necessity in the case of alternate mechanical fastening devices.[271] Notwithstanding, the mechanical robustness offered by fibrin glue may not achieve the strength or endurance of conventional suturing materials, particularly in the biomechanically exigent regions of the meniscus which demands consideration.[272] Primitively, fibrin glue sourced from collective human plasma posed a plausible vector for infectious agents including viruses. Despite the advancements in safety protocols and manufacturing techniques that modern fibrin glue benefits from, a small yet significant risk of pathogen transmission persists, necessitating vigilant management.[273] Additionally, there exists a potential for allergic responses to constituents of the fibrin glue, notably aprotinin, a component previously employed in certain formulations to inhibit fibrinolysis.[274] The intricacies and financial implications associated with the manufacture of fibrin glue are substantial, reflective of the requirements for sourcing human or animal-derived components and implementing virus inactivation protocols.[275]

Gelatin based adhesives. Li et al. developed an injectable granular hydrogel composed of gelatin microspheres and tannic acid (TA) acting as a carrier for platelet-rich plasma (PRP). Gelatin Microspheres are created with a gelatin concentration of 10 wt% and a diameter distribution of 1–10 μm, which are used to form the granular hydrogel when combined with TA. TA acts as a cross-linking agent that binds to the gelatin microspheres

through abundant hydrogen bonding, forming the granular hydrogel structure. PRP is a suspension enriched with platelets, which is used for its various growth factors that promote cellular proliferation and tissue regeneration. The adhesion strength of granular hydrogels was stronger than that of the clinically used fibrin glue. In terms of biocompatibility, the granular hydrogel carrying PRP shows good cell compatibility, as evidenced by the promotion of chondrocyte proliferation and the maintenance of the chondrogenic phenotype, which is essential for the formation and maintenance of cartilage tissue. The hydrogel supports the expression of cartilage-specific genes such as aggrecan and COL II, indicating that it can facilitate the chondrogenic differentiation of cells. And the presence of TA in the hydrogel confers reactive oxygen species scavenging ability, which is important for reducing inflammation and oxidative stress. In vivo experiments showed that the Gel/TA-PRP group exhibited stronger cartilage repair capabilities compared to the groups without PRP, indicating the potential of this hydrogel as a therapeutic strategy for cartilage defects.[119]

Polysaccharide-based adhesives

CS-based adhesives. CS is a GAG mainly present in the ECM of biological tissues and possesses properties conducive to cartilage formation.[276] Aldehyde groups can be added to CS to enable its application to adhesive-forming chemistries. On the surface of the tissue, the Schiff base reaction occurs between the aldehyde of CS-aldehyde and the amines of the tissue. Then it forms the connection between adhesive and tissue.[51] In cartilage injury, CS has direct and/or indirect anti-inflammatory effects. In addition, CS can promote the synthesis of high molecular weight HA and collagen II. More importantly, CS has an anti-angiogenic effect.[277] Reyes et al. studied the treatment of chondral defects with CS functionalized with both methacrylate and aldehyde groups in goat femoral condyles. Through their investigation, it was ascertained that the cohesive strength of the CS adhesive surpassed that of the PEGDA hydrogels, reaching a remarkable 40 kPa. This adhesive capability demonstrably exceeded the minimum requirement for effective hydrogel fixation to the native cartilage interface. Moreover, following a 6-month period, cartilage regeneration within defects treated with the adhesive exhibited a statistically significant improvement compared to untreated, empty defects.[52]

Due to CS's endogenous presence within the cartilage, adhesives formulating with this molecule can seamlessly integrate with native tissue, mitigating the risk of adverse immune responses.[21] This compatibility advantageously positions CS-based adhesives as potential facilitators for the proliferation and maturation of chondrocytes, thereby establishing scaffolds that optimally support the cellular processes requisite for cartilaginous regeneration. Studies have indicated that adhesives incorporating CS not only foster an environment amenable to cartilage cell growth but also actively encourage the restitution of cartilage, which is paramount in the context of joint repair and rehabilitation.[278] Nevertheless, while the biological benefits of CS-based adhesives are clear, their mechanical properties present a formidable challenge. The tensile and compressive forces experienced in significant load-bearing joints necessitate adhesive materials that can withstand the considerable stresses imparted upon them. In this regard, CS adhesives may falter, as their mechanical fortitude may be insufficient for high-stress applications, thereby circumscribing their use to the repair of less demanding, smaller, or more quiescent cartilage defects.[279]

HA-based adhesives. HA has good biocompatibility and biodegradability[280]; it is one of the primary ingredients of synovial fluid, which is crucial for lubricating joints and preserving joint homeostasis.[281,282] The abundance of GAGs within the intricate architecture of cartilage plays a crucial role in anchoring engineered hydrogels. These GAGs offer several avenues for adhesion, including covalent bond formation with the aldehyde groups of oxidized hyaluronic acid (OHA) present in the hydrogel. Additionally, electrostatic interactions and hydrogen bonding across the interface further strengthen the attachment. HA can promote fibroblast proliferation and collagen synthesis as well as the synthesis of proteoglycans in degenerated chondrocytes. In vivo studies have shown that HA is involved in regulating cell movement and promoting cell migration, and interacts with the cell surface receptor CD44 to regulate the accumulation and formation of ECM.[283,284] Qiu et al. demonstrated this principle by designing dually cross-linked hydrogels composed of OHA and N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC) methacrylate (HTCCMA). These OHA/HTCCMA hydrogels exhibited desirable rheological properties and a unique self-healing capability due to their dual cross-linking strategy: dynamic cross-linking and subsequent photo-induced covalent cross-linking. The moderate yet stable tissue adhesion exhibited by these hydrogels stems from the formation of dynamic covalent bonds with the cartilage surface. Friction coefficients as low as 0.065 and 0.078 for dynamically and double-cross-linked hydrogels, respectively, showcase their superior lubrication properties. Moreover, in vitro studies revealed promising antibacterial properties and enhanced cell proliferation within these hydrogels, suggesting their potential for biomedical applications. Preclinical investigations conducted in live rabbit models successfully

validated the therapeutic potential of OHA/HTCCMA hydrogels for the repair of chondral lesions in the femoral trochlea. Over a 56-day treatment period, these hydrogels demonstrated superior efficacy compared to the control group. Notably, the hydrogels exhibited excellent biocompatibility and biodegradability while promoting robust regeneration of articular cartilage. These findings suggest that this lubricant-adhesive hydrogel system holds significant promise as a novel therapeutic approach for both alleviating joint injury symptoms and facilitating cartilage regeneration.[11] Chen et al. investigated a novel HA hydrogel modified by aldehyde groups and methacrylate (AHAMA) hydrogel, a modified HA methacrylate incorporating aldehyde groups. This innovative biomaterial exhibits multi-modal targeting of the cartilage surface facilitated by a dynamic Schiff base reaction forming amide bonds, robust hydrogen bonding, and physical interpenetration. Notably, AHAMA demonstrated excellent biocompatibility and tissue adhesion, making it a promising candidate for treating femoral trochlear defects in the knee joint.[285]

HA, a naturally occurring polysaccharide within the cartilage ECM, is recognized for its superior biocompatibility, which stems from its inherent presence in cartilaginous tissues. Adhesives developed from HA are less prone to elicit unfavorable biological responses, which is a substantial advantage when considering materials for tissue interfacing and repair.[286] The intrinsic lubricating attributes of HA contribute beneficially to joint functionality, particularly during the recovery phase, by reducing friction and maintaining ease of movement. Additionally, HA hydrogels can be rendered into an injectable form, facilitating a minimally invasive technique for administering treatment directly to sites of cartilage damage.[287] Further, the chemical versatility of HA permits modifications, such as methacrylation, which can be utilized to enhance the mechanical and physical properties of HA-based adhesives. This attribute renders them more adaptable and suitable for varying scenarios within cartilage tissue engineering.[288,289] Despite these considerable advantages, there remain notable drawbacks that restrict the application scope of HA adhesives. Primary among these is their intrinsic mechanical limitations. The required strength and durability to endure the high-load conditions associated with joint movement may exceed what HA adhesives can provide, thus limiting their use to less mechanically demanding environments.[290] Moreover, concerns exist regarding the longevity of the adhesive. Its capacity to maintain effective adhesion over extended periods may be compromised, particularly in joint areas subjected to constant motion and load, which could necessitate further intervention or supportive treatments as time progresses.[291]

Hybrid adhesive

Kazusa et al. assessed the adhesive strength and cytotoxicity of LYDEX, a combination of aldehyde dextran and polylysine when applied to articular cartilage. The mean adhesive strength of LYDEX was 1.5 ± 0.4 N/cm^2. Importantly, the adhesive strength of LYDEX was superior to that of fibrin glue, exhibiting values approximately 3.8 times greater. Furthermore, LYDEX does not pose a risk of transmitting infectious materials of human or animal origin, as only medical and food additive sources are selected as starting materials, rather than human plasma and animal derived ingredients. The use of LYDEX instead of fibrin glue for the treatment of cartilage repair has great potential.[292]

In a recent study, Hua et al. successfully developed a novel hybrid photocrosslinkable (HPC) hydrogel composed of HA and o-nitrobenzyl moieties. This innovative material exhibits the remarkable ability to adhere to surrounding cartilage tissue through the formation of imine bonds. The results of CCK-8 assays and LIVE/DEAD staining showed that HPC hydrogels had good cell compatibility, and furthermore, the results of hematoxylin and eosin staining and immunohistochemical staining indicated that HPC hydrogels elicited only a minimal inflammatory response in the host body. Notably, the researchers demonstrated that the HPC gels possess exceptional mechanical strength, requiring tensile and shear forces of 33.8 ± 4.6 and 47.4 ± 4.9 kPa, respectively, for dislodgement from the cartilage surface. Furthermore, preclinical experiments conducted on weight-bearing areas of swine models revealed the rapid gelation, impressive mechanical properties, and exceptional tissue adhesion exhibited by the HPC hydrogels. These promising findings suggest that HPC hydrogels hold significant potential as a therapeutic option for cartilage regeneration.[37]

Mussels have a remarkable ability to adhere firmly under water due to specific catechol groups from L-DOPA found in their foot proteins. An analog of DOPA, dopamine, which is derived from tyrosine, can confer similar wet adhesion properties when incorporated into dopamine-based hydrogels that contain catechol groups. Leveraging this natural mechanism, Zhang et al. have developed an adhesive hydrogel by creating a crosslinked network composed of alginate-dopamine (AD), CS, and regenerated silk fibroin (RSF). This novel hydrogel, named AD/CS/RSF, exhibited a strong bonding capacity to wet surfaces with a lap shear strength of 120 kPa. This strength is comparable to that of commercial tissue adhesives, and notably, the hydrogel's adhesive capability proved to be durable over time. Further innovations to the AD/CS/RSF hydrogel included the encapsulation of exosomes derived from bone marrow-derived mesenchymal stem cells (BMSCs). The modified

hydrogel, AD/CS/RSF/EXO, significantly enhanced the migration, proliferation, and differentiation of BMSCs—key factors in effective cartilage regeneration. When tested in vivo, the hydrogel not only expedited the repair of cartilage defects in rat patellar grooves but also actively promoted the remodeling of the ECM after being injected. At both 6 and 12 weeks post-surgery, histological analysis using H&E staining revealed that the AD/CS/RSF/EXO hydrogels were biocompatible with major organs. The mechanisms underlying the regenerative effects included the recruitment of BMSCs into the hydrogel and the newly formed cartilage driven by exosomes that signaled through chemokine pathways. Overall, this injectable and adhesive hydrogel is an innovative biomaterial with significant potential for minimally invasive treatments of cartilage defects, and it may be particularly effective when used in conjunction with arthroscopic techniques.[13]

3.2.3 | Adhesives used in the meniscus

The existing surgical interventions, such as the meniscus suture technique and meniscectomy, for meniscus injuries may lead to the development of degenerative changes and osteoarthritis.[293] Hence, the preferable approach is to prioritize meniscus repair to preserve its integrity rather than resorting to meniscectomy.[294] Importantly, adhesives present a promising solution for addressing meniscus injuries.

Proteinaceous adhesives

Fibrin glue. A recent study by Ishimura et al. investigated the efficacy of fibrin glue in meniscus tear repair. Among 40 participants who underwent the intervention, the subsequent monitoring period of up to 11.4 years revealed a re-tear incidence of <10% for tears located in the red-red or red-white zones. Notably, white-white zone tears demonstrated a higher re-tear incidence of 17%.[295] Another study investigated the use of fibrin adhesives alongside sutures for managing degenerative horizontal tears in a group of 18 patients. Among the 10 patients subsequently assessed, a promising 70% demonstrated satisfactory recovery.[296] The outcomes demonstrated the therapeutic efficacy of fibrin glue on meniscus tears.

Polysaccharide-based adhesives

CS-based adhesives. Simson et al. combined a modified CS tissue adhesive with bone marrow aspirate, resulting in a biocompatible scaffold that promotes MSCs migration, survival, and ECM production. Notably, the adhesive exhibits robust mechanical properties and strong meniscus-binding ability. After conducting research on the mechanics of hydrogels, it was discovered that the adhesive strength of CS-BM is comparable to what is required for withstanding forces in a suture-repaired human meniscus.[297]

CS, as an endogenous component of cartilage and the meniscus, offers a substantial biocompatibility advantage that potentially minimizes the likelihood of adverse biological responses when used in adhesive formulations.[298] Further, CS-based adhesives may facilitate meniscal healing by fostering an environment conducive to cellular adhesion and proliferation.[297] Despite these advantageous interactions at the biological level, the physical properties of CS adhesives present certain limitations.[21] Additionally, the temporal aspects of adhesive degradation warrant careful consideration. The rate at which the CS adhesive degrades must be synchronized with the tissue healing process.[298] An imbalance in these rates could lead to complications—either the premature disintegration of the adhesive before adequate healing or its prolonged presence, which could interfere with tissue remodeling and potentially provoke adverse clinical outcomes.

Synthetic polymer based adhesives

Shimomura et al. fabricated a nanofibrous scaffold composed of poly(ε-caprolactone) (PCL) and PEO. Their results showed that meniscal fibrochondrocytes incorporated into the nanofibrous scaffold significantly accelerated the meniscus's healing process by recruiting new cells, strengthening the interface at the location of the radial tear, and promoting the cells' differentiation into fibrocartilaginous tissue. The cell-seeded scaffold's strong adhesion to the meniscal tissue is expected to contribute positively towards repairing the meniscus through the stabilization of its fibers.[299]

Nayeb et al. demonstrated the potential of hyperbranched isocyanate-terminated oligomers based on citric acid, poly (ethylene glycol), and trimethylene carbonate as promising options for biocompatible resorbable tissue adhesives in the repair of meniscus tears. These materials exhibit a pronounced affinity for primary amines prevalent in tissue surface proteins, enabling the formation of robust covalent urea bonds, thus facilitating a secure and long-lasting adhesion.[300] They possess remarkable mechanical and adhesive characteristics modified by altering the copolymers' structures. They found that much higher rates of curing were achieved when a catalyst or a cross-linking composition was added to the hyper-branched adhesive component. This made it possible to resolve the problem of tissue adhesives needing an extended amount of time to cure. After undergoing the curing procedure, these adhesives exhibit

adequate adhesive strengths to meniscus tissue. In summary, the utilization of hyperbranched and isocyanate-functionalized tissue adhesives holds huge potential as effective materials for repairing meniscal tears.[301–304]

Hybrid adhesives

Inoue et al. prepared an adhesive composed of disuccinimidyl tartrate (DST) and human serum albumin (HSA). In their study, they found that suturing with a suture strand dipped in adhesive resulted in a far stronger binding than putting the glue directly on the surface of the lesion. It has been discovered that the adhesive DST/HSA is quite effective at encouraging the meniscus's avascular zone tears to adhere.[305]

Lei et al. created a GelNB/HAMA-hydrogel and polydimethylsiloxane elastomer composite material, which serves as an adhesive for repairing meniscus tears. Through the Schiff base reaction under UV light, GelNB could establish a connection with the tissue surface. This innovative hybrid material exhibits robust mechanical properties, compatibility with living tissues, and the ability to adhere to moist surfaces. During in vivo tests on rabbit meniscus tears, it demonstrated a positive repair effect.[306]

Karami et al. developed a double-network hydrogel composed of covalently cross-linked poly (ethylene glycol) dimethacrylate and ionically crosslinked alginate. This ingenious design, reinforced with nano-fibrillated cellulose, exhibits remarkable adhesive strength to load-bearing tissues like cartilage and meniscus.[307]

Pan et al. developed a novel bioadhesive hydrogel adhesive, designated as S-PIL10. The adhesive is composed of methacrylated silk fibroin (SFMA) cross-linked with phenylboronic acid-ionic liquid (PIL) and loaded with the growth factor TGF-β1. SFMA is derived from silkworm cocoons and is known for its superior mechanical properties and good biocompatibility. It is modified with glycidyl methacrylate to form photocurable hydrogels, which are essential for the adhesion and mechanical strength of the final adhesive. TGF-β1 is incorporated into the adhesive to promote cell recruitment and bridging of the defect edge, contributing to the regenerative aspect of the adhesive. It is continuously released from the hydrogel, aiding in the local meniscus tear repair by affecting the inflammatory microenvironment. In terms of biomechanical properties, the S-PIL10 adhesive demonstrated a significant increase in adhesive shear strength compared to neat silk fibroin gel, reaching up to 113.37 kPa with the addition of PIL. The storage modulus (G′) of the adhesive increased with the addition of PIL, indicating improved mechanical strength and resistance to deformation. S-PIL10 showed excellent anti-swelling properties, retaining its original shape and volume after 14 days, which is essential for maintaining adhesion over time. At the same time, The S-PIL 10 maintained good cell viability and proliferation when co-cultured with rabbit meniscus cells, indicating that the adhesive is safe for use in a biological environment. The S-PIL10 adhesive successfully repaired meniscus tears in in vivo rabbit models, demonstrating seamless and dense reconstruction of the torn meniscus without joint wear. The adhesive's integration of chemo-mechanical restoration with inner meniscal regeneration makes it a promising strategy for preclinical research and a potential revolutionary approach for clinical meniscus tear repair management.[116]

Biological adhesives

Szomor et al. studied a novel biological adhesive (frog glue) produced by an Australian species of frogs (genus Notaden). Through mechanical testing on freshly harvested sheep menisci, it was found that this specific adhesive outperformed two other adhesives in terms of mechanical strength (fibrin and gelatin).[308]

3.2.4 | Adhesives used in the growth plate

Addressing growth plate injuries presents a significant challenge due to the inherent limitations of conventional surgical techniques. Their invasive nature often yields modest benefits, highlighting the critical need for innovative approaches. Such advancements should prioritize the dual objectives of effectively preventing the undesirable formation of bone bars and actively promoting the regeneration of the growth plate cartilage.[309] In this context, exploring the potential application of biocompatible adhesives emerges as a promising avenue for tackling this issue.

Proteinaceous adhesives

Gelatin based adhesives. GM, a biocompatible hydrogel with highly tailorable physical properties, finds extensive application in the field of tissue engineering, particularly for bone, cartilage, and heart regeneration.[41] Guan et al. proposed a novel exosome-laden ECM-mimicking hydrogel comprising GM and aldehyde-functionalized chondroitin sulfate (OCS). This biomaterial was strategically applied to the site of growth plate injury to encourage repair. Their study successfully demonstrated the efficacy of GMOCS-Exos hydrogels in promoting cartilage regeneration and suppressing the formation of undesirable bone bridges by stimulating

ECM synthesis and curtailing inflammatory responses.[115] Building upon this success, subsequent research involved photoencapsulation of BMSCs within GMOCS hydrogels for growth plate injury repair. These hydrogels possess tuneable mechanical properties, facilitating optimal support for cell growth and function. In vivo studies confirmed that the adhesion of GMOCS/BMSC constructs to the injured growth plate significantly reduces bone bridge formation and fosters cartilage regeneration. This innovative approach presents promising avenues to facilitate the treatment of growth plate injuries.[129]

Qiang et al. developed a GM hydrogel loaded with Bevacizumab, IGF-1, and BMSCs to adhere to the growth plate injury area and play a repairing role. Rigorous experimentation across both in vitro and in vivo models, encompassing a spectrum of laboratory and living organism studies, consistently demonstrated the remarkable efficacy of the composite hydrogel in impeding bone bridge formation and promoting cartilage regeneration.[114] Subsequently, they designed the PTH (1–34) @PLGA/BMSCs/GelMA-PCL scaffold with commendable mechanical properties, biocompatibility, and suitability for cell chondrogenic differentiation. When compared to directly injected hydrogel, this scaffold significantly reduced limb deformities after growth plate injuries.[118]

Gelatin-based adhesives offer potential benefits as biocompatible and biodegradable options, significantly reducing the risks of long-term complications customarily associated with non-biodegradable materials.[310] Additionally, these adhesives can be chemically modified to achieve controlled degradation rates, such that the adhesive material resorbs in synchronization with the natural healing process of the growth plate, avoiding interference with tissue development and recovery.[311] The customization of gelatin adhesives does not stop at degradation rates; they can also be functionalized to release therapeutic agents like exosome, enhancing the healing process and promoting tissue regeneration.[312] On the other hand, their strength might not compete with that of synthetic adhesives or metallic fixtures, which could limit their application in areas that experience significant mechanical load and require robust structural support.[85] Variability in the adhesive's degradation process further complicates their application, as inconsistent degradation rates could lead to an uneven healing process, with possible consequences for tissue regeneration and functionality.[313] Moreover, the animal-derived nature of gelatin raises concerns regarding immunogenicity; there is a potential for immune responses which could complicate the clinical outcomes and patient recovery.[314]

3.2.5 | Adhesives used in the nose

2-octyl cyanoacrylate

The process of suturing graft segments in reconstructive rhinoplasty is challenging and requires a significant amount of time. Dabb et al. investigated the use of 2-octyl cyanoacrylate in the preformation and stability of nasal cartilage grafts in order to address this issue. After therapy, none of the nine patients experienced any problems, and the curative outcome was satisfactory. According to their findings, the prefabrication and fixation of cartilage transplants can be accomplished quickly, safely, and effectively with the use of 2-octyl cyanoacrylate.[315]

4 | CONCLUSION

This article reviews the research progress of cartilage repair adhesives, exploring their potential for treating diverse anatomical structures such as IVDs, articular cartilage, menisci, growth plates, and nasal cartilage. Each of these tissues necessitates unique adhesive properties tailored to their specific biomechanical functions and healing demands. For IVD repair, the focus lies on sealability, tensile strength, and compressive resilience to effectively restore disc integrity. Adhesives employed in articular cartilage and meniscus interventions prioritize strong adhesion, surface lubrication, and wear resistance, critical factors for joint mobility and load distribution. In growth plate restoration, the ability to deliver bioactive agents takes center stage, promoting optimal tissue regeneration. Nasal cartilage repair adhesives, on the other hand, emphasize user-friendliness and swift application. Despite the significant strides made in adhesive research, clinical translation remains limited. A handful of adhesives, such as protein glue for articular cartilage and menisci and cyanoacrylates for nasal cartilage rhinoplasty, have garnered clinical adoption. However, the majority of these innovative materials reside in the preclinical realm, validated primarily through in vitro experiments (Table 3). While these studies showcase their remarkable potential for cartilage repair, bridging the gap from bench to bedside remains a crucial challenge. To propel this field forward, future research should prioritize robust large animal studies that closely mimic human anatomy and biomechanics. By simulating clinical scenarios, researchers can refine adhesive formulations and optimize surgical techniques, paving the way for their safe and effective integration into routine surgical practice. In conclusion, the burgeoning field of cartilage repair adhesives holds immense promise for revolutionizing the treatment of musculoskeletal injuries. With continued research and advancement, these innovative materials

TABLE 3 Overview of the application of adhesives in cartilage repair.

Adhesive	Test method of application (species)	Application	Refs	Adhesive	Test method of application (species)	Application	Refs
FibGen	Ex vivo (human and bovine) In vivo (rat)	Repair AF defects	219–221	OHA/HTCCMA	Ex vivo (rabbit) In vivo (rabbit)	Repair in cartilage defects	11
FibGen/CAMs	Ex vivo (bovine)	Repair AF defects	117	HANB	Ex vivo (hog) In vivo (rat and swine)	Repair in cartilage defects	37
Cell-seeded FibGen	Ex vivo (bovine)	Repair AF defects	128	AD/CS/RSF	Ex vivo (rat) In vivo (rat)	Repair in cartilage defects	13
Fib-T-G	Ex vivo (bovine) In vivo (rat)	Repair AF defects	222	Fibrin	In vivo (human)	Repair meniscal tears	295, 296
FibGen and an engineered silk scaffold	Ex vivo (bovine)	Repair AF defects	223	CS-BM hydrogels	Ex vivo (bovine) In vivo (rat)	Repair meniscal tears	297
FibGen and PCL scaffold	Ex vivo (bovine)	Repair AF defects	224	The composite electrospun mat consisting of PCL and PEO fibers	Ex vivo (bovine)	Repair meniscal tears	299
Riboflavin cross-linked collagen gels	Ex vivo (rat and ovine) In vivo (rat and ovine)	Repair AF defects	230–233	Hyper-branched isocyanate-terminated oligomers	Ex vivo (bovine)	Repair meniscal tears	301
Mesenchymal stem cell-seeded riboflavin cross-linked collagen gels	In vivo (ovine)	Repair AF defects	234	Reactive three-armed- and hyper-branched adhesive block copolymers	Ex vivo (cow and bovine) In vivo (rat)	Repair meniscal tears	303, 304
Riboflavin cross-linked collagen gels and hyaluronic acid	Ex vivo (ovine)	Repair AF defects	235	DST/HSA	Ex vivo (porcine) In vivo (rabbit)	Repair meniscal tears	305
Alginate	Ex vivo (goat)	As a scaffold material for IVD engineering	242	GelNB/HAMA	Ex vivo (porcine) In vivo (rat)	Repair meniscal tears	306
Alginate and PNIPAAm-g-CS gel	Ex vivo (pig and human)	As a scaffold material for IVD engineering	244	A composite double-network hydrogel covalently crosslinked poly (ethylene glycol) dimethacrylate and ionically crosslinked alginate	Ex vivo (bovine)	Repair meniscal tears	307
Cyanoacrylate glue	Ex vivo (pig) In vivo (pig)	Repair AF defects	254	SFMA and PIL	Ex vivo (rabbit) In vivo (rabbit)	Repair meniscal tears	116
Synthetic (PEGDA) and natural (fibronectin-conjugated fibrin/	Ex vivo (bovine) In vivo (ovine)	Repair AF defects	257	Frog glue	Ex vivo (sheep)	Repair meniscal tears	308

TABLE 3 (Continued)

Adhesive	Test method of application (species)	Application	Refs	Adhesive	Test method of application (species)	Application	Refs
FN-fibrin) polymer networks and a dual-modified (oxidized and methacrylated) GAG							
Chitosan/EDC/NHS and alginate-polyacrylamide hydrogel	Ex vivo (bovine) Ex vivo (human)	Repair AF defects	258	2-octyl cyanoacrylate	In vivo (human)	Rhinoplasty	315
Fibrin	In vivo (human)	Repair in cartilage defects	268	GMOCS-Exos	Ex vivo In vivo (rat)	Repair growth plate injury	115
Gelatin microspheres and tannic acid	Ex vivo (rat) In vivo (rabbit)	Repair in cartilage defects	119	GMOCS/BMSC	Ex vivo In vivo (rat)	Repair growth plate injury	129
LYDEX	Ex vivo (pig) In vivo (rat)	Repair in cartilage defects	292	GelMA	Ex vivo In vivo (rabbit)	Repair growth plate injury	114
AHAMA	Ex vivo (pig) In vivo (rat)	Repair in cartilage defects	285	PTH (1–34) @PLGA/BMSCs/GelMA-PCL scaffold	Ex vivo In vivo (rabbit)	Repair growth plate injury	118
Multifunctional CS	Ex vivo In vivo (mouse, rabbit and goat)	Repair in cartilage defects	53				

Abbreviations: AD, alginate-dopamine; AF, annulus fibrosus; AHAMA, hyaluronic acid hydrogel modified by aldehyde groups and methacrylate; CAMs, adhesion molecules; CS, chondroitin sulfate; EDC, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; GAG, glycosaminoglycan; HANB, hyaluronic acid grafted with o-nitrobenzyl; HSA, human serum albumin; IVD, intervertebral disc; NHS, N-hydroxysuccinimide; OHA, oxidized hyaluronic acid; PCL, polycaprolactone; PEGDA, poly (ethylene glycol) diacrylate; PEO, polyethylene oxide; PIL, phenylboronic acid-ionic liquid; PTH, parathyroid hormone; RSF, regenerated silk fibroin; SFMA, methacrylated silk fibroin.

offer the potential to address a significant unmet clinical need, ushering in a new era for the personalized and minimally invasive management of cartilage damage.

5 | PERSPECTIVES

In recent decades, significant strides in tissue engineering and industrial research have culminated in the successful synthesis of diverse adhesive varieties. These adhesives exhibit promising prospects within biomedical realms. Nevertheless, notwithstanding these achievements, ample scope for further enhancement persists.

With regard to fundamental mechanical attributes, a primary challenge persists: extant adhesives inadequately meet the requisite bonding strength necessary for a complete substitution of orthopedic metal screw-rod systems, sutures, and staples. Consequently, they are predominantly relegated to ancillary roles, aiding in the fixation of minor fragments or serving as adjunctive postoperative management tools. A seminal advancement in adhesive design holds the potential to bolster bonding strength, thus mitigating this disparity.

In terms of biosafety assessment, a comprehensive evaluation of the biocompatibility of bioadhesives is imperative, ideally validated in large animal models or human subjects. Such assessments should encompass vital parameters including but not limited to cell viability, migration, and proliferation as well as tissue growth, remodeling, and angiogenesis within target tissues. Moreover, meticulous scrutiny of cytotoxicity is warranted, encompassing both in vitro assays involving direct cell contact and long-term in vivo follow-up to ascertain potential deleterious effects of any degraded

byproducts. Notably, the in vivo degradation rate of bioadhesives has been inadequately addressed in prior investigations, underscoring the necessity for heightened attention in this domain. Encouragingly, the integration of advanced imaging modalities into diverse biomaterial platforms facilitates real-time monitoring of degradation kinetics within the physiological milieu.

In the field of regenerative medicine, most of the research on adhesives and their loading components is limited to the simple therapeutic effect of hydrogels without in-depth exploration of their therapeutic mechanisms. These endeavors typically lack exhaustive scrutiny of hydrogels' molecular-level impact on diseases and their intricate interplay with cellular constituents, thus constraining a comprehensive comprehension of their therapeutic efficacy. To engender a more profound and comprehensive understanding of hydrogel mechanisms in addressing cartilage injuries, future investigations could contemplate broadening the spectrum of experimental cell lines, integrating additional pertinent biological and molecular methodologies, and delving deeper into mechanistic inquiries. Such endeavors aim to augment the scientific rigor and applicability of experimental findings. Furthermore, it's essential to acknowledge potential limitations inherent in the study, such as relatively modest sample sizes and potential design flaws, which could impinge upon the reliability and generalizability of findings. Additionally, while preliminary experimental findings hint at the therapeutic potential of hydrogels in cartilage injury management or postoperative care, the dearth of compelling clinical trials or application case studies underscores the necessity for further comprehensive research and evaluation to elucidate their clinical utility effectively.

AUTHOR CONTRIBUTIONS

Haoyang Feng: Methodology; formal analysis; investigation; writing – original draft. **Kai Ang**: Methodology; formal analysis. **Pengfei Guan**: Methodology; formal analysis. **Junji Li**: Methodology; formal analysis. **Huan Meng**: Formal analysis; visualization. **Jian Yang**: Resources. **Lei Fan**: Methodology; supervision. **Yongjian Sun**: Conceptualization; methodology; supervision; data curation; project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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