

Review

Advances Toward *In Vivo* Cartilage Repair: A Comprehensive Review of Current Strategies and Future Directions

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Abstract

The cartilage is avascular and has limited regenerative capacity, posing a significant clinical challenge. Conventional treatments often do not restore hyaline cartilage, leading to progressive osteoarthritis. Recent advances in tissue engineering have focused on integrating biomaterials, stem cells, growth factors, and gene-delivery approaches. In addition, *in vivo* models serve as critical platforms for translational validation. Biomaterial scaffolds, including polycaprolactone, silk fibroin, chitosan, and composite hydrogels, have demonstrated improved mechanical strength, biocompatibility, and cartilage-like matrix deposition. Functionalization with bioactive molecules, such as IGF-I, β FGF, exosomes, and Icaritin, further facilitated chondrogenic differentiation and immunomodulation. In long-term studies, scaffold-free organoid bio-assemblies, three-dimensional (3D) bioprinting, and multilayered scaffolds have shown promise in osteochondral regeneration. In contrast, artificial meniscus models and polyvinyl alcohol-hydrogel (PVA-H) have shown promise in reducing osteoarthritis



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progression. Although these advances have been made, significant challenges remain, including vascularization, long-term integration, and translation from large animals to humans. As part of this review, evidence from *in vivo* research has been synthesized, translational barriers highlighted, and future perspectives on cartilage repair discussed. The next-generation approaches may provide durable, clinically relevant solutions for cartilage regeneration and joint preservation by integrating advances in biomaterials, controlled delivery, and cell-based therapies.

Keywords

Cartilage repair; *in vivo* tissue engineering; regenerative medicine; biomaterials; 3D bioprinting; extracellular matrix (ECM) scaffolds

1. Introduction

Cartilage is characterized by the absence of blood and lymphatic vessels and nerves. Chondrocytes produce the extracellular matrix (ECM), which supports lubrication, shock absorption, and decompression. Because cartilage lacks blood vessels, lymphatic structures, and nerves, chondrocytes regenerate more slowly, limiting their self-repair capacity. Therefore, the cartilage can be injured or degenerate, leading to pain, dyskinesia, and loss of function. Over the past few years, the incidence of articular cartilage (AC) injuries has increased due to the aging of the population. Other risk factors include physical trauma, genetic predispositions, lifestyle habits, and certain metabolic diseases [1, 2]. Initial fracture formation and degenerative tissue changes are caused by mechanical stress on articular cartilage (AC), leading to osteoarthritis (OA) and adversely affecting joint mobility. Due to the complex mechanical effects and variable initial crack geometry, a comprehensive understanding of crack progression in cartilage damage remains elusive despite its clinical significance [3]. Osteoarthritis is a chronic (long-term) disease that affects millions of people worldwide, resulting in deterioration of cartilage, which is essential for joint function. Despite cartilage's essential role in bone cushioning, its limited self-repair capacity poses a significant therapeutic challenge [4]. Contemporary therapies, such as pain management and joint replacement, have limited efficacy and may lead to more difficulties, emphasizing the necessity for innovative therapeutic strategies [5]. Regenerative medicine has developed advanced treatment approaches, including gene editing, cell-based therapies, and bioengineered scaffolds, aiming to enhance cartilage regrowth and restore dysfunctional joints [6, 7]. To simulate articulating cartilage surfaces, *ex vivo* bioreactors have been employed, which offer regulated mechanical stimulation. In order to simulate continuous passive motion, bovine joints have been loaded, a type of rehabilitation treatment that primarily applies shear forces while minimizing weight bearing during the rehabilitation phase post-surgery [8]. As *in vitro* experiments become more complex, they will be able to more accurately replicate the intricate biomechanical and biological conditions encountered *in vivo*, thereby enhancing the translational relevance of cartilage regeneration therapies. In cartilaginous environments, cellular responses are highly context-dependent, making simplistic models ineffective at predicting therapeutic effects. Multiaxial loading bioreactors offer a potential way to mimic physiological joint mechanics. A thorough characterization and

standardization of the mechanical environment of encapsulated cells is essential to produce interpretable and comparable data. Accordingly, the purpose of this review is to critically evaluate the latest advances in cartilage repair strategies, with emphasis on *in vivo* evaluation of biomaterial-based therapies. To assess regenerative constructs' functional performance under near-clinical conditions, physiologically relevant animal models and mechanical stimulation paradigms are integrated. To assess functional performance under near-clinical conditions, this integration is important. Through synthesizing advances in scaffold design, delivery systems, cell therapies, and biomechanical modeling in translational cartilage repair, this review seeks to guide future efforts toward more effective, predictable, and durable clinical outcomes [9]. The purpose of this review is therefore to provide a summary of recent advances in the repair of cartilage *in vivo*. To provide a comprehensive overview of current advances in cartilage repair strategies, a literature search was conducted across major scientific databases, including PubMed, Scopus, and Web of Science, for articles published from 2000 to 2025. Studies with *in vivo* models, cartilage repair, tissue engineering, biomaterial scaffolds, stem cells, 3D bioprinting, and cartilage repair were included in the search. Research that reported *in vivo* experimental investigations or advanced therapeutic approaches relating to cartilage regeneration was considered. Moreover, the reference lists of relevant publications were screened in order to identify additional relevant studies and to ensure comprehensive coverage of the topic.

2. Cartilage Biology and Healing Mechanism

The articular cartilage (AC) structure is characterized by its complexity because of glycosaminoglycans (GAGs), chondrocytes, which represent only about 1-5% of the total cartilage volume, and collagen, which is randomly oriented and denser. Water is a primary component that makes up 60% to 85% of the cartilage composition, alongside collagen type II and proteoglycan (PG). The Articular cartilage (AC) is a nonlinear, anisotropic, viscoelastic, inhomogeneous biphasic tissue [10]. It possesses a thickness of approximately 1-3 mm in most joints, but it can reach up to about 4 mm in the patellofemoral joint and is avascular and soft. Its three depth-dependent zones are deep, transitional, and superficial. Each zone reduces load or sliding friction. The superficial zone (10-20% thickness) has horizontal collagen fibrils and flattened chondrocytes for strong tensile strength and stiffness. This layer resists tensile stresses, restricts the entry of interstitial fluid, and allows smooth sliding at low PG and high-water content. An acellular zone with fine collagen fibrils, elastic fibers, and the surface amorphous layer (SAL) contains proteins, PGs, hyaluronic acid, and lipids. The transition zone is the thickest (40-60% of AC) and has randomly arranged collagen and chondrocytes in a GAG-rich ECM. It has higher PG content than the superficial zone and helps distribute load. The vertically oriented deep zone of collagen fibers, low water content, PG, and cell content support the subchondral bone with collagen fibers perpendicular to the surface [11]. In addition to the calcified cartilage zone, which acts as the transition zone between the deep and subchondral bone zones, this zone contains hydroxyapatite (HAp) and type X collagen [10, 12]. Articular cartilage (AC) is characterized as non-vascular, aneural, and alymphatic tissue. The harsh external environment, characterized by exposure to shear compression pressures and limited access to nourishment and oxygen, may contribute to its impaired capability for intrinsic healing and repair [13]. Chondrocytes have a limited mitotic capacity, which subsequently diminishes cartilage's inherent regenerative capacity following injury [14]. Cartilage can repair itself and undergo

regeneration to a certain extent under specific internal and external conditions. Age is a crucial factor because younger people typically have a greater capacity for cartilage regeneration than older adults. How severe the harm is: Compared with more catastrophic injuries, minor or superficial injuries have a better chance of healing. The absence of blood vessels also makes it more difficult for the damaged area to acquire vital nutrients, oxygen, and immune cells, as was previously mentioned [12, 15]. Furthermore, mechanical stimulation is important since cartilage health and maintenance depend on it, maintained by controlled joint motion and regular physical activity. Additional notable components comprise inflammation, growth factors, and cytokines, among others [12]. The continuous mechanical pressures endured by the articular cartilage (AC) make it susceptible to mechanical wear, tearing, and injuries related to sports activities. Furthermore, the low cell density, absence of innervation, and avascular nature of mature articular cartilage (AC) limit its ability to self-renew and heal [16]. Unhealed articular cartilage (AC) lesions result in the development of degenerative osteoarthritis. Inflammatory conditions like osteoarthritis (OA) or trauma trigger a process of cartilage remodeling. Catabolic responses are promoted by inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- α) by suppressing cartilage-specific transcription factor (Sox9 mRNA) and protein expression through the NF- κ B signaling pathway. As a result, the expression of genes unique to cartilage that are necessary for the synthesis of extracellular matrix and chondrogenesis is significantly suppressed. However, a resident population of mesenchymal stem/progenitor cells (MSPCs) is found in almost all tissues. These cells live in stem-cell niches that maintain MSPCs' ability to quiesce, self-renew, or actively differentiate. To maintain tissue homeostasis and aid in the healing of injured tissues, they may undergo directed migration in response to appropriate stimuli. A unique subset of progenitor cells identified as cartilage-derived progenitor cells (CPCs) is found in both normal and degenerative articular cartilage (AC). Compared to healthy, uninjured cartilage, damaged cartilage has a noticeably higher percentage of cells that are positive for the MSPC marker. Moreover, MSPCs were more abundant in the synovial fluid following cartilage damage. All these data suggest that upon injury to the AC, MSPCs in various stem-cell niches adjacent to the affected area are activated by injury signals and migrate to the sites of injury to generate replacement cells. This process is referred to as the endogenous self-repair potential of AC [17]. Moreover, endogenous tissue self-healing is a complex biological process that requires cell migration and substantial interactions between the migrating cells and the surrounding tissue environment; therefore, it has limits. An overview of articular cartilage (AC) characteristics, repair limitations, and regeneration strategies is illustrated in Figure 1. The diagram illustrates the structural complexity, compositional elements, and limited healing potential of AC. It identifies factors such as age, avascularity, and mechanical stimulation as significant determinants of endogenous repair and biomedical interventions.

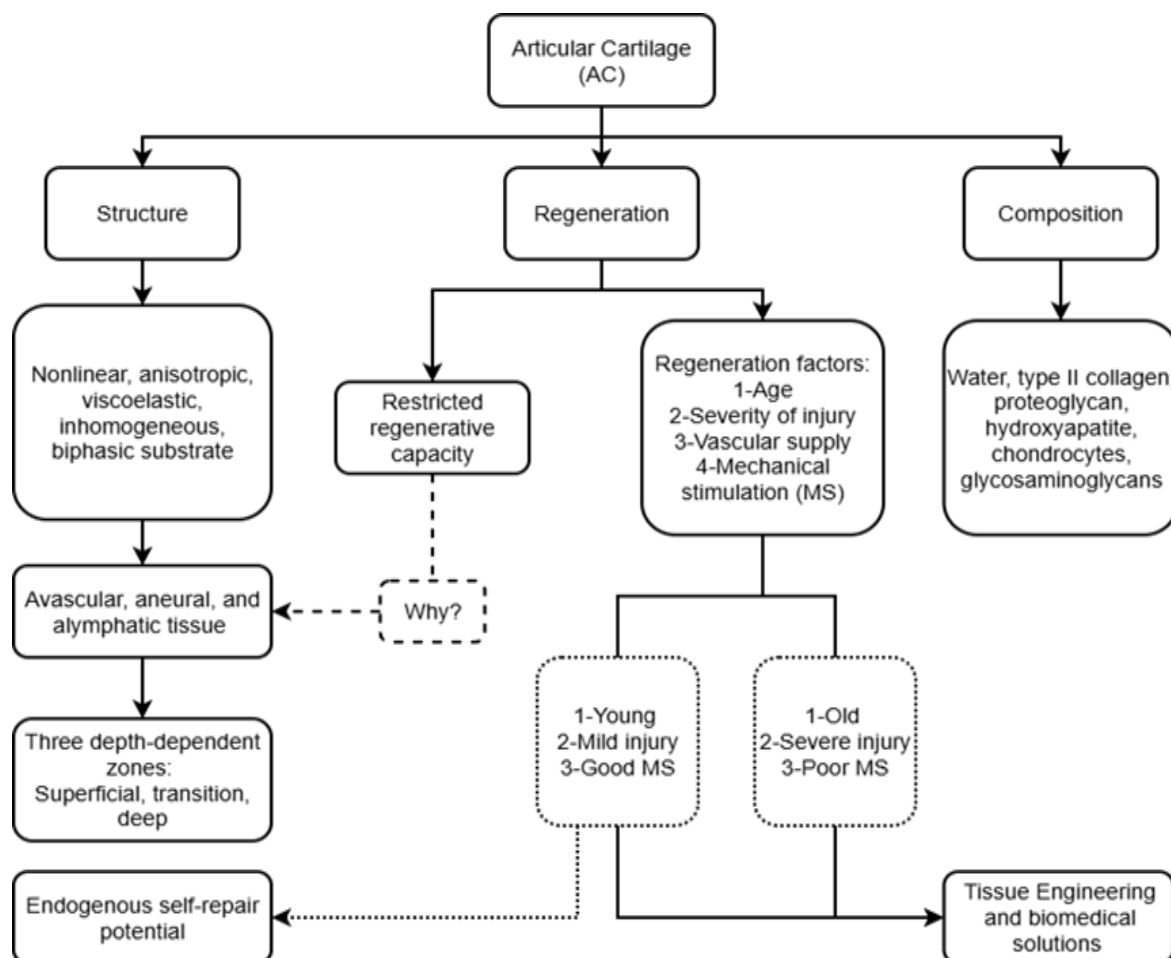


Figure 1 Challenges in articular cartilage (AC) regeneration from a biological and structural perspective.

3. Therapeutic Approaches in Cartilage Repair

Restoring injured cartilage function remains a significant task [18]. Previous treatments include bone marrow stimulation techniques, which involve exposing injured cartilage to bone marrow and nearby components, leading to spontaneous repair [19]. This section will review modern advanced strategies for repairing damaged cartilage.

3.1 Cell-Based Strategies

A wide range of cell types have been explored for treating injuries, like chondrocytes, embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), and others. Each cell type possesses inherent biological features [20]. Chondrocyte-based strategies include Autologous Chondrocyte Implantation (ACI) in both its 1st and 2nd generations, which involves extracting cartilage from the joint's low-weight-bearing region. This cartilage undergoes enzymatic digestion to extract chondrocytes, which are encapsulated in a collagen-based gel, placed on the site of defect, and closed up using a periosteal flap (1st gen) [21, 22], or collagen membranes (2nd gen) [23]. The 3rd generation of ACI, referred to as Matrix-Induced Autologous Chondrocyte Implantation (MACI), also uses chondrocytes, but embeds them in a scaffold to reduce hypertrophy associated with ACI, fits the scaffold to the defect, and fixes it with fibrin glue [24]. Another source is stem cells, which have

high proliferation rates and a greater capacity for chondrogenic differentiation compared to chondrocytes [25, 26]. Mesenchymal stem cells (MSCs) represent a heterogeneous population of stromal cells that may be obtained from a number of different tissues, including muscle, adipose tissue, synovium, and the marrow of bone (BMSCs) [25-27]. These cells require pretreatment with bioactive compounds, gene editing, and growth factors, as they lose their proliferative and multi-lineage differentiation properties [28, 29]. MSCs can be planted with or without a scaffold (scaffold-free), in which the implantation is similar to ACI [21, 26]. However, scaffolds are used for cell entrapment in cell-based tissue engineering due to their three-dimensional (3D) networks, tissue-like hydration, structural stability, and biocompatibility [20, 28]. Since MSCs in the living organism exist in a 3D environment, they can be delivered intravenously (IV), intra-arterially (IA), or intraperitoneally (IP) [30]. Reprogrammed differentiated somatic cells can be used to produce induced pluripotent stem cells (iPSCs), which exhibit pluripotency, proliferative capacity, and the potential for multi-lineage differentiation [31]. The differentiation of iPSCs into MSCs is accomplished via two methods: monolayer culture and embryonic body (EB) culture [32]. This method can effectively address the issue of teratoma development from undifferentiated iPSCs [31].

3.2 Bioactive Molecules and Gene Delivery (Growth Factors, Controlled Release Systems, Gene Editing)

The body produces physiologically active polypeptides called growth factors (GF), such as TGF- β , BMPs, IGF-1, FGF, and PDGF, that promote cellular differentiation, growth, and division [33, 34]. growth factors (GFs) upregulate chondrogenic genes such as SOX9, ACAN, and COL2A1 [34, 35], which stimulate chondrocyte production of proteoglycans, aggrecan, type II collagen, and the proliferation of MSCs. It also promotes chondrogenic differentiation of MSCs into chondrocytes and reduces the catabolic effects of cytokines like IL-1 and MMP [33-36]. However, growth factors (GFs) are susceptible to rupturing within the body and have a short half-life. Appropriate controlled-release methods are needed to prevent enzymatic degradation and ensure that growth factors are gradually released at the injury site [37]. They target chondrocytes and MSCs involved in cartilage regeneration [38]. These systems must be biocompatible, have a high loading capacity of drugs, and have sustained growth factors (GF) release; they shouldn't reduce their biological activity [37]. Release systems can be produced from organic materials such as collagen, gelatin, hyaluronic acid, chitosan, and PLGA; inorganic materials like hydroxyapatite and calcium phosphate; or a combination of both. A variety of advanced techniques have been used for controlled release, such as hydrogels, which can decrease the release of protein by extending delivery time [38], and also nanoparticles (NP) that can deliver the growth factors inside and outside the cells [39]. As an alternative for release systems, gene delivery can transform the cells into protein manufacturers [40], and that's by using (viral or non-viral) gene delivery vectors and gene-activated matrices [40, 41], associated with biomaterial platforms that protect the genes from degradation and deliver them to the targeted cell [41]. As osteoarthritis (OA) occurs, the upregulation of harmful biomolecules takes place, such as nerve growth factor (NGF), interleukin-1 β (IL-1 β), and matrix metalloproteinase 13 (MMP13) [42], and to reduce those harmful molecules, several gene editing methods have been used, including CRISPR/Cas9, which is accurate in targeting the cells and easy to operate [43]; modulating joint microRNAs [44]; and RNA interference (RNAi), which alters defective genes by delivering their short interfering RNA (siRNA) [45]. Other cell-free therapy

particles include exosomes, which are intraluminal vesicles surrounded by a lipid bilayer, and characterized by their small (nano) size, ranging from 50-200 nm, and the lack of self-replication. They are released from various types of cells via multivesicular bodies [46]. They play a major role in cartilage regeneration since they transfer cell content, support the bidirectional signals between the Mesenchymal stem cells and chondrocytes to facilitate chondrogenesis, ECM deposition, and cell proliferation [47]. An overview of the therapeutic strategies for cartilage repair in terms of cell source and gene-related approaches is illustrated in Figure 2. The diagram illustrates different therapeutic approaches for AC repair, cell-based strategies, and bioactive molecule/gene delivery. Cell-based strategies include extracting chondrocytes for ACI/MACI; another approach involves using stem cells (MSCs, iPSCs) guided by growth factors, delivered either with scaffolds or scaffold-free methods. Moreover, the bioactive molecules such as growth factors (GF) that upregulate chondrogenic genes (SOX9, ACAN, COL2A1) require controlled-release biomaterials (hydrogels, nanoparticles) to protect, target, and sustain their effects. It also shows gene-related approaches (vectors, CRISPR, microRNAs, RNAi) that program cells and temper catabolic mediators, integrating delivery materials to improve regeneration.

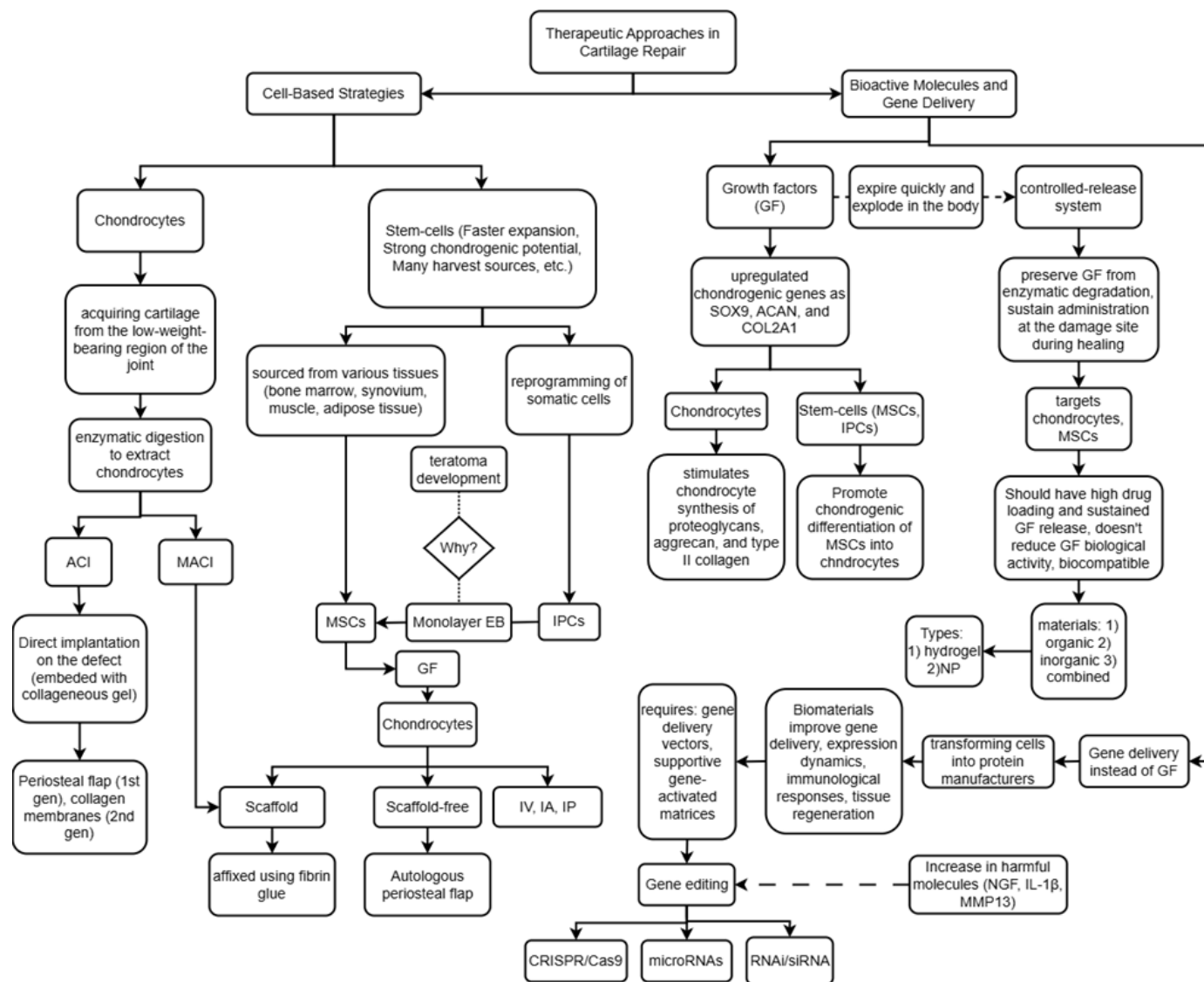


Figure 2 Integrated Therapeutic Pathways for Articular Cartilage (AC) Repair: Cell-Based, Growth-Factor, and Gene-Delivery Strategies.

3.3 Biomaterial Scaffolds

Temporary supporting structures called scaffolds provide a three-dimensional (3D) framework that supports tissue generation and formation while creating the appropriate microenvironment for cell development, differentiation, and tissue production [48, 49]. Scaffolds must have mechanical competency, external geometry, surface characteristics, porosity and pore size, biodegradability, healing efficiency, and biocompatibility (noncytotoxic) [48-52], in order to enable the loading of an appropriate cell source to allow effective bioactive chemical adhesion and infiltration [51]. Typically, sponges, hydrogels, or nanofibers are made using biodegradable polymers as scaffolds [48].

3.3.1 Natural vs. Synthetic

Scaffolds are typically made of natural biomaterials, synthetic polymeric materials, or composite materials. Collagen, alginate, gelatin, chitosan, collagen/glycosaminoglycan, collagen/hyaluronan, and silk are examples of natural scaffolding materials. These hold the unique advantages of strong cell adhesion, biodegradability, and biocompatibility [48]. Collagen can be made into foam, gel, sponge, or membrane [51]; it serves as crucial for cellular adhesion and differentiation [48]. because of its high tissue compatibility, low toxicity, and easy biodegradation [49, 52]. Fibrin may act as a synthetic extracellular matrix scaffold, a gel-based artificial ECM, as well as a delivery mesh for cell encapsulation [48]. However, its application is limited by its common drawbacks, including weak mechanical properties and an unstable degradation rate [49, 52]. Wet silk has a high mechanical strength and low inflammatory properties [48]. In cartilage homeostasis, hyaluronan plays a multi-functional role [51]. and can be used to differentiate mesenchymal stem cells into chondrogenic stem cells [48]. Since collagen and hyaluronan provide a substrate that is comparable to that of genuine articular cartilage (AC), they are now among the most widely utilized natural scaffolds in clinical applications [51]. Chemically synthesized polymer scaffolding materials include polylactic acid (PLA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), and their copolymers [48, 51]. Compared to collagen-based scaffolds, PGA- and PLA-based scaffolds have been shown to enhance chondrocyte proliferation, differentiation, maturation, and proteoglycan promotion [51]. Their benefits include a programmable breakdown rate that may be adapted to the tissue growth in the artificial extracellular matrix, relatively high mechanical strength, and ease of fabrication into a variety of shapes. However, their application in CTE is limited by their drawbacks, which include acute chondrocyte death, giant cell responses, inflammation, and the production of acidic compounds after breakdown; additionally, they are costly and have poor cell adhesion [49].

3.3.2 Injection Delivery Method of Scaffolds

The scaffolds are commonly fabricated as hydrogels before injection. Hydrogels are three-dimensional (3D) networks of cross-linked hydrophilic copolymers or homopolymers [53, 54]. Hydrogels are classified by material source (natural or synthetic) and biodegradability. PEG and PLGA-based systems are widely used, among others [48, 53]. Requirements have to be followed for achieving a perfect injectable scaffold, like simplicity of use in physiological circumstances, high potential for biodegradability and good biocompatibility, the capacity to imitate the cartilage ECM characteristics, and filling the site of defect while interacting with natural surrounding cartilage tissue. Assured injectability (gelation upon injection), and, lastly, a sustained release if linked to local

drug delivery [53]. Advantages include simplicity of use, robust plasticity, excellent biocompatibility and biodegradability, non-invasive or minimally invasive delivery through arthroscopy or direct injection, enhanced cellular metabolite and nutrient supply through elastic properties, cell encapsulation, and efficient and effective delivery of bioactive molecules [53, 54].

3.3.3 Three-Dimensional (3D) Bioprinting

Using three-dimensional (3D) bioprinting, scaffolds with scalable shapes and physicochemical characteristics may be designed and built [55]. Three-dimensional (3D) bioprinting depends on the methods of three-dimensional (3D) printing, which incorporate biomaterials, bioactive agents, and even living cells to fabricate constructs that are similar to native tissues. Three-dimensional (3D) bioprinting can be divided into the following categories: *ex situ*-based printing, such as fused deposition modeling (FDM), direct ink writing (DIW), stereolithography (SLA), selective laser sintering (SLS), etc. [56]. *In situ*-based, including direct-write bioprinting, inkjet bioprinting, and laser-assisted bioprinting (LAB). However, when externally printed scaffolds are transferred to their site of implantation, problems, including shape mismatch, unstable adherence, and contamination, occur, which restricts clinical uses. With improved tissue integration and surface creation capabilities, *in situ* three-dimensional (3D) bioprinting has better clinical promise than traditional three-dimensional (3D) bioprinting [55]. Common biocompatible polymeric materials utilized for implantable structures include polylactic acid (PLA), polyglycolic acid (PGA) or its copolymer PLGA, polycaprolactone (PCL), and polyethylene glycol (PEG)-based blends [57]. Hydrogels are among the most widely chosen native-like polymers for three-dimensional (3D)-printed cartilage scaffolds because of their huge water-holding capacity within their polymer networks. They mimic the natural cartilage's structure and composition. The affordability, ease of use, high material compatibility, and ability to blend different materials are all benefits of direct ink printing. Although SLA (or DLP) has many benefits, there are drawbacks: Liquid photosensitive resins require specific reactive groups for cross-linking and curing with photo initiators; additionally, the materials must be transparent and have low scattering in order for the scanning light to pass through them uniformly. However, the increased heat generated by the laser readily causes the deterioration of biological materials. The main benefits of this printing process are its high printing speed, ease of use, and lack of support. Simple construction, ease of use, low material loss rate, and cheap maintenance costs are the benefits of the printer built on this technology [56]. Certain four-dimensional (4D) printing uses shape-memory polymer materials that allow scaffold surface microscale architecture to be temporally deformed, which serves as a cell-fate switch that activates rapid proliferation of MSC and stimulates controlled differentiation [58]. An overview of the scaffold as a therapeutic strategy for cartilage repair is illustrated in Figure 3. The diagram illustrates the various materials used to fabricate the appropriate scaffold before transplantation or delivery. It also highlights advanced fabrication techniques, such as three-dimensional (3D) bioprinting, with its *ex situ* and *in situ*-based applications and their benefits. Additionally, the diagram shows injection as a method for delivering a scaffold to the injury site.

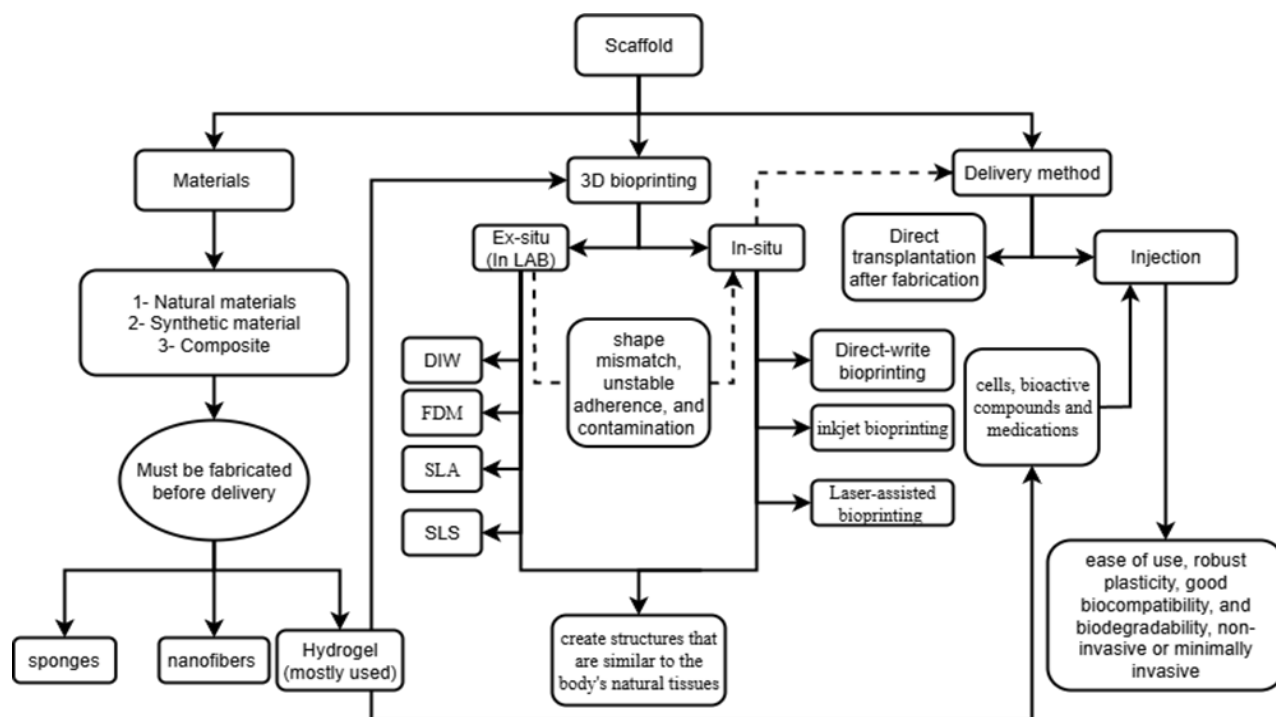


Figure 3 Scaffold Materials, Bioprinting Strategies, and Delivery Pathways.

4. *In Vivo* Models and Evaluation Strategies

As a result of tissue engineering, viable and nonviable tissues are altered in structure and architecture in order to make these constructs more effective in biological environments. Currently, *in vitro* tissue engineering has several drawbacks, such as insufficient vascularization, and additional research is necessary. *In vivo* bone tissue engineering differs from traditional tissue engineering in that the body is used as a bioreactor for the reconstruction of tissue defects and is an emerging regenerative medicine field [59]. Testing of biomaterial tissue compatibility *in vivo* primarily focuses on determining whether a biomaterial is compatible with tissue or whether it is biocompatible with an implant in a biological area. The assessment of tissue compatibility *in vivo* requires understanding a biomaterial's toxicological properties as well as its morphological properties. In addition, the surrounding tissues are examined within a specified period of time. In order to determine how the materials respond *in vivo*, their histopathological examination is conducted [60].

To determine whether these mechanical characteristics were affected by IGF-I supplementation of transplanted chondrocytes, Kenneth R., et al. [61] analyzed the integration utilizing qualitative histological techniques after *in vivo* repair. An eight-month study in an equine model investigated the impact of IGF-I on chondrocyte transplantation by creating osteochondral blocks. IGF-I treatment did not impact these mechanical properties. Furthermore, the researchers implanted cultured epiphyseal cartilage-derived chondrocytes into NOD/Shi-scid IL-2Rgnull (NOG) mice. The investigations done by Michiyo N., et al. [62] focused on the role of bFGF (basic fibroblast growth factor) in cell growth and morphology; cells treated with bFGF grow at a faster rate compared to those that are untreated. After two weeks of implantation, cartilage formation occurred within the same period.

The feasibility of chondrocyte-seeded cell-derived ECM scaffolds is evaluated by Cheng Z., et al. [63] by implanting them in nude mice. Porous cell-derived ECM scaffolds were prepared by freezing

and drying porcine chondrocytes using freeze-drying methods. Histology showed that newly synthesized sulfated proteoglycans continued to accumulate. Researchers observed the clear presence of type II collagen throughout the study using three methods: Western blot, immunohistochemistry, and reverse transcriptase polymerase chain reaction (RT-PCR). According to Guangzhao T., et al. [64], mouse bone marrow-derived macrophages (BMDMs) were stimulated by pepsin-solubilized decellularized cartilage matrix (PDCM) after preparation of porcine articular cartilage (AC)-derived DCM. PDCM-activated macrophages could promote invasion, migration, bone marrow mesenchymal stem cell differentiation, and proliferation. Following the demonstration of a model of osteochondral defects in the rat knee, early IL-4-based immunomodulatory effect optimization of the cell-free DCM scaffold achieved good cartilage regeneration. In order to achieve scaffold-free three-dimensional (3D) cartilage regeneration, Yingying H., et al. [65] developed a new cartilaginous organoids bioassembly (COBA) technique, which showed batch-to-batch efficiency, structural integration, and functional reconstruction. A COBA approach was demonstrated to integrate cartilaginous organoids into cartilage tissue via mold-supported *in vitro* and *in vivo* culture modes and to preserve the shape and mechanical strength of the cartilage tissue as a whole. Also, a variety of decellularization methods were screened and compared in a study [66]. The observed regeneration of subchondral bone and formation of fibrocartilage resulted from the implantation of three-dimensional (3D) porous scaffolds derived from decellularized cartilage into osteochondral flaws in a rabbit model. This study proposes an optimal cartilage tissue decellularization protocol for generating decellularized cartilage powders capable of being processed into biocompatible and bioactive two-dimensional (2D) and three-dimensional (3D) structures. Moreover, [67] reported that three-dimensional alginate-coated scaffolds were used, the multi-differentiation ability of peripheral blood-derived mesenchymal stem cells (PBMSCs) has been proven, and the mechanism of interaction between three elements PBMSCs, Icaritin (ICA), and stromal cell-derived factor (SDF-1 α) has been investigated. After a 12-week therapeutic course, a three-dimensional alginate-coated scaffold (GAIS) was found to stimulate cartilage regeneration in mice with osteochondral bone defects. Furthermore, the microcarrier environment was studied by Wei L., et al. [68], who constructed two homologous cell types and compared their behavior in the microcarriers. The migration and proliferation of ADSCs, and their advantages, have been highlighted by microcarrier environments. By utilizing a dynamic culture system in three-dimensional (3D) conditions, ADSC microtissue (ADSCs-MT) and BMSC microtissue (BMSCs-MT) were then created. ADSCs-MT showed significantly greater cartilage regeneration abilities than BMSCs-MT in both *in vitro* and *in vivo* experiments. In the study [69], the authors investigated the potential of using such structures for cartilage repair *in vivo*. Autologous adipose-derived stem cells (ADSCs) were selected as a cell source to fill innovative cartilage ECM-derived scaffolds before they were implanted into rabbit cartilage defects. High-quality cartilage repairs that were mechanically and biochemically equivalent to natural cartilage were seen in rabbits after ADSC-loaded cartilage ECM scaffolds were implanted.

Santos M., et al. [70] experimented with a rabbit model to regenerate a defective articular cartilage (AC) by using scaffolds made of PCL alone and cell-seeded PCL scaffolds. After a duration of three months, the defects were filled with white cartilage-based tissue. The experiment showed a noticeably better integration into the natural peripheral cartilage than the control (cell pellet). Thus, the PCL scaffold demonstrated potential for aiding the regrowth of articular cartilage (AC) through tissue engineering. Also, Zahra A., et al. [71] investigated the outcomes of adipose-derived mesenchymal stem cell (ASC) seeding on composite scaffolds comprising polycaprolactone/silk

fibroin/gelatin/ascorbic acid for meniscus repair. Allogeneic ASCs were implanted into rabbits undergoing unilateral punch defects in the medial meniscus of the right knee after they were engrafted with PCL/SF/Gel/AA. Macroscopic and histological studies were conducted at 2 months post-implantation to determine whether new cartilage was present. Moreover, an investigation by Hun J., et al. [72] in mini-pigs used three-dimensional (3D) printing to fabricate scaffolds containing GMP-grade polycaprolactone (PCL), and then implantation after discectomy effectively led to TMJ disc regeneration *in situ* within three months, exhibiting multi-scale mechanical capabilities and native-like heterogeneity without any indication of cartilage injury. Furthermore, Rebecca L., et al. [73] conducted a study to evaluate the possibility of treating osteochondral defects through the use of a combined cooperative culture of MSCs and articular chondrocytes. Cow-derived cartilage cells (bovine chondrocytes) and rat MSCs have been used. These cells were cultured either individually or in co-culture on PCL scaffolds and then implanted in the trochlear flaws of a rat. Microscopic examination revealed a thicker hyaline cartilage combined with increased staining of safranin O produced by both co-cultures and chondrocytes. The main tissue produced by MSCs alone, blank scaffolds, and empty controls was fibrocartilage.

An artificial meniscus was developed by Masanori K., et al. [74] using PVA-H for salvaging, and the results were reported one year after the animal operation. The present study examined the results after 2 years of surgical intervention in order to further evaluate the effectiveness of the artificial meniscus. After two years, it was discovered that the knee joint's PVA-H-implanted cartilage was in excellent condition, whereas osteoarthritis (OA) progressed in the knee joint implanted with meniscectomy. Also, by using the SOL-GEL synthesis method, Yudong Z., et al. [75] prepared a bioactive PVA/HA hydrogel for the treatment of articular cartilage (AC) defects in rabbit knees using a gradual-stirral PVA/HA cartilage implant. As a result of macro- and histological observations of animal experiments, implanted hydrogels formed a close association with ambient tissues, and bone-like tissue developed from the underlying bone. This development helped produce a deeper and more stable bond between the replaced tissue and the cartilage at the base of the implant. According to Johanna M., et al. [76], the use of a recombinant viral vector, adeno-associated virus (rAAV), designed to carry the gene encoding insulin-like growth factor I (IGF-I) can improve the treatment of full-thickness chondral flaws in minipigs. After micro-puncture surgery, the treatment is administered through an alginate hydrogel over the course of one year in comparison to the reference (lacZ/AlgPH155) treatment. Moreover, a study has been conducted on a hydrogel composed of gelatin and oxidized chondroitin sulfate; the combination also includes bone marrow stem cell-derived exosomes [77]. Under fluid-irrigated arthroscopic conditions, the hydrogel was successfully injected into cartilage defects in pigs and gelled *in situ*. A study conducted *in vitro* and *in vivo* demonstrated that sustained release of exosomes modulated macrophage M2 polarization through the Nuclear Factor kappa B (NF- κ B) pathway. To replicate an ECM that is adaptable and based on the hyaline cartilage's inherent structure, Zhijian Z., et al. [78] designed a self-assembly glycopeptide hydrogel incorporating RGD-functional peptides and polysaccharide fucoidan. Increasing the deposition of cartilage ECM by chondrocytes by cultivating glycopeptide hydrogels not only enhanced intracellular antioxidant properties to resist ROS damage but also enhanced cartilage ECM deposition.

Furthermore, according to Xi Y., et al. [79], a study on an advanced hybrid hydrogel containing hydroxypropyl chitin and oxidized chondroitin sulfate (HPCH-OCS) has been produced by a Schiff base reaction that is injectable and thermosensitive. When combined with microfracture, HPCH-

OCS hydrogels effectively repaired cartilage flaws and promoted cartilage regrowth *in vivo*. Also, a dual-network hydrogel, GelMA-FT/Sr²⁺, presented by Congcong D., et al. [80] in the study, exhibits excellent lubrication properties and accelerates cartilage repair. In addition to methacrylated gelatin (GelMA), strontium ions (Sr²⁺) and N-fluorenylmethoxycarbonyl-L-tryptophan (FT) networks are incorporated into the hydrogel. A rat model of cartilage damage also confirmed that the hydrogel effectively promotes cartilage repair. In order to enhance stem cell-based cartilage regeneration, Xinyue R., et al. [81] constructed a cartilage-specific matrix hydrogel (CMH) with a dual microparticle delivery system (dM-PDs). CMH scaffolds provided a three-dimensional (3D) environment that supported tissue growth, and the dM-PDs promoted chondrogenic differentiation and anti-angiogenic effects afterward. An *in vivo* study has confirmed that transforming growth factor-beta (TGF- β 3) and levatinib microparticles delivered sequentially regulate cartilage regeneration stages, preventing ossification and stabilizing the cartilage phenotype.

Paniz H., et al. [82] combined different proportions of chitosan, silk fibroin, and gelatin scaffolds to understand the effects of these scaffolds on biological tissues. Rabbits were randomly subjected to scaffolds with and without seeded chondrocytes. In a defect filled with a cell-seeded scaffold, 65.9% of new hyaline cartilage was formed, while the opposite occurred in the control group, where no new cartilage tissue formed at all. These results were demonstrated by multitype diagnosis staining. Also, using salt-leaching, freeze-drying, and crosslinking methodologies, Feifei Z., et al. [83] constructed scaffolds of silk fibroin and silk fibroin/CS for cartilage restoration *in vivo*. After 6 and 12 weeks of implantation, silk-CS scaffolds produced more tissue development and structural repair than silk scaffolds, according to ICRS histological assessments of a rabbit osteochondral defect model. Moreover, using three-dimensional (3D) printing procedures, Weili S., et al. [84] developed a scaffold that has a refined structure and function; this scaffold is made from a gelatin and silk fibroin composite material, combined with affinity peptides of bone-derived mesenchymal stem cells. Because of its distinct structural design, capacity to attract BMSC, and other exceptional qualities, it seems to be a promising material for knee cartilage regeneration. Furthermore, a study in [85] evaluated the viability of a composite scaffold comprising fibrin glue and hyaluronic acid (HA). The chondrocytes were captured from rabbit model knees and enzymatically digested. Two scaffolds were produced; one is a composite of fibrin and HA, and the other is from fibrin alone. Both were implanted in a nude mouse model for one, two, and four weeks, respectively. Fibrin/HA specimens formed cartilage-like tissue at a much earlier stage than fibrin specimens. These specimens exhibited substantially higher levels of extracellular matrix molecules, glycosaminoglycans, and collagen at each time point than fibrin specimens.

Jianhua Y., et al. [86] performed cartilage regeneration and repair as a part of their experiments by transplanting adipose tissue-derived mesenchymal stem cells (ADSCs). This transplantation was done using glycol chitosan/dibenzaldehyde-terminated polyethylene glycol (GCS/DF-PEG) hydrogels. It should be noted that although the *in vivo* outcomes were good, there are still certain issues. It is noteworthy that the repair time in the body is relatively short, and there is uncertainty about the effects of the repair, which is considered chronic. Also, Karthikeyan R., et al. [87] hypothesized that a multi-layered chitosan-gelatin (CG) scaffold that mimicked the ECM and collagen architecture of articular cartilage (AC) would have similar outcomes, as well as comparing its results *in vitro* and *in vivo* to random alignment of CG scaffolds. Mesenchymal stem cells (MSCs) from rabbit bone marrow were differentiated into chondrogenic cells. Training of cartilage occurred in both multi-layered and randomly treated subjects with and without cells. On immunostaining, the cartilage appeared to be

hyaline. Compared to the randomly aligned scaffolds, cartilage formed in the defects treated with multi-layered cells was significantly thicker. Also, B. Gurer et al. [88] proposed that chondrocytes can be isolated from the body, forced to undergo a proliferative phase, and kept in the defective area for one session of treatment. Incubators provide the appropriate conditions by mimicking an *in vivo* environment. A second group underwent matrix-induced autologous chondrocyte implantation (MACI) in two sessions, while the third group received no treatment. The glycosaminoglycan and type II collagen concentrations within repair tissues were determined macroscopically, histomorphometrically, and biochemically after 15 weeks of follow-up. Moreover, Maryam T., et al. [89] developed a multilayer osteochondral scaffold that matches the heterogeneity of osteochondral tissue by combining laser sintering and material extrusion technologies with additive manufacturing. The scaffold is created using a collagen composite system reinforced with a titanium metal alloy combined with a polylactic acid-based matrix. When compared to the collagen–HAp scaffold, the multi-layered scaffold showed widespread and much greater bone in-growth over the course of the 12-week *in vivo* assessment period. In addition to providing robust support for cartilage repair, mechanical fixation encouraged the development of hyaline-like cartilage. Guillermo B., et al. [90] conducted an experiment to understand the useful effects of a biomaterial with immunomodulatory properties on a full chondral defect; the scaffold is made from collagen and chondroitin sulfate and has been tested in an orthotopic Lapine *in vivo* model. In addition to enhancing cartilaginous tissue production and suppressing cartilage degeneration, the scaffolds also enhanced tissue interaction with the repair substance and the regrowth of cartilage tissue over a duration of 12 weeks of recovery.

Kazunobu A.I., et al. [91] used knee joints from a rabbit model to assess the effects of a double network hydrogel made from poly-(2-acrylamido-2-methylpropane sulfonic acid) and poly-(N,N'-dimethylacrylamide) on the cartilage counterface during contact, as well as on the characteristics of friction outside the body (*ex vivo*) in healthy cartilage. Based on the study's findings, PAMPS/PDMAAm DN gel has been determined to be a promising material for the creation of artificial cartilage because it has a very low friction coefficient when compared to normal cartilage and does not significantly harm counterface cartilage *in vivo*. Through the use of tissue engineering approaches, María S., et al. [92] investigated long-term cartilage repair *in vivo* (1 week–12 months); adult chondrocyte pre-planted scaffolds were compared to assess the role of the cell source after 3 months. A stable poly(EA-co-HEA) copolymer scaffold maintained mechanical properties without degradation. As a result of indigenous chondrocyte proliferation and scaffold embedding, hyaline-like cartilage was observed on the condylar surface within one week, followed by cartilage and bone integration after three months.

The previous description of tissue engineering (TE) has developed as a potential technique for cartilage repair by integrating biomaterials, stem cells, and bioactive molecules. However, conventional *in vitro* approaches remain limited by inadequate vascularization, leading to increased interest in *in vivo* models that utilize the body as a bioreactor. Several recent studies emphasize the importance of evaluating scaffold biocompatibility, histopathology, and long-term integration. The effects of growth factors, such as IGF-I and β FGF, were demonstrated to increase chondrocyte proliferation but have limited mechanical improvements. Decellularized and cell-seeded scaffolds derived from the extracellular matrix (ECM) exhibited sustained proteoglycan and type II collagen deposition *in vivo*. Hyaline-like cartilage was formed with improved structural restoration using polycaprolactone, silk fibroin, and composite scaffolds. At the same time, exosome-functionalized

hydrogels with icariin, Sr^{2+} , and exosome-functionalized hydrogels accelerated repair and modulated immunity. In addition to three-dimensional cartilage reconstruction, bio-assembly techniques for organoids and microcarrier-based ADSC constructs have also been demonstrated to be effective. In addition, artificial meniscus models and PVA hydrogels significantly reduced osteoarthritic progression during long-term assessments and preserved joint integrity. Advances in three-dimensional (3D) printing and multilayered scaffolds have enabled osteochondral regeneration with superior bone ingrowth and cartilage integration. As a result, these investigations showed the translational chance of combining advanced scaffolds with cell-based therapies as well as bioactive delivery systems for durable cartilage regeneration. Despite the extensive use of preclinical *in vivo* models to evaluate cartilage repair strategies, there are important differences in translational relevance. Rodents and rabbits can be valuable models for understanding biological mechanisms and early-stage therapeutic screening; however, their joints, cartilage thickness, and biomechanical loading conditions differ significantly from those of humans. As a result, large animal models, such as goats, sheep, and pigs, offer a close anatomical and biomechanical similarity to human joints and are therefore more appropriate for evaluating the clinical feasibility of emerging therapies. It remains challenging, however, to translate promising preclinical outcomes into successful clinical therapies. By evaluating biomaterial scaffolds, stem cell-based therapies, and advanced tissue engineering approaches in human patients, translational and clinical studies have begun to bridge this gap. To maximize the translational potential of cartilage regeneration strategies, it is imperative that findings from preclinical models and clinical investigations be integrated. Table 1 provides a concise summary of all the *in vivo* studies discussed above.

Table 1 Summary studies for *in vivo* experiments.

Scaffold structure	Animal model	Site of implantation	Conclusion	Ref./year	General comments
Insulin-like Growth Factor 1 (IGF-I)	Horses	The lateral trochlear ridge of each patellofemoral joint.	Repair tissue showed lower mechanical properties than intact cartilage (tensile modulus 0.65 vs. 5.2 MPa; integration strength 1.2 MPa). IGF-I treatment (2.7 MPa) did not significantly affect these properties.	[61]/2006	This study suggests that alternative treatments for cartilage repair can be assessed and compared using the methods presented.
polyvinyl alcohol-hydrogel (PVA-H)	Rabbit	Bilateral Knees	According to the present study, a PVA-H artificial meniscus can supplement the meniscus function two years after surgery. Despite many cases showing regenerative meniscectomy-like tissue in the meniscectomy group, these tissues were unable to prevent further OA.	[74]/2005	Results indicate that an artificial meniscus fabricated with PVA-H can be clinically applied as a new treatment for meniscal replacement.
Fibrin/HA	Nude Mice	Subcutaneously	Long-term (four weeks) nude mouse implantation was found to maintain structural integrity. The histological and biochemical evaluation of the composite matrix also indicated significant benefits from the inclusion of HA.	[85]/2005	According to the study, fibrin/HA composites may serve as a reliable vehicle for delivering cells as well as a structural basis for tissue-engineered cartilage.
cell-derived ECM scaffold	Nude Mice	subcutaneously	It has been demonstrated and evaluated that the cell-derived ECM scaffold has the potential to produce hyaline-like cartilage <i>in vivo</i> , and that the scaffold is a promising biomaterial structure.	[63]/2007	An evaluation of the molecular structure of the ECM scaffold is suggested in this study in order to optimize the culture conditions, for example by adding growth factors or changing culture periods <i>in vitro</i> ; and, in turn, by verifying the

					cultivation <i>in vitro</i> to ensure proper implantation in the joints treated with the ECM scaffold.
PVA/HA hydrogel	Rabbit	knee joint	The hydrogel implants and ambient tissues were tightly coupled, with abundant chondrocytes proliferating around PVA/HA hydrogels without degradation of cartilage. On the bottom of the PVA/HA hydrogels, osteoid tissue developed, creating deeper cartilage-implant interactions.	[75]/2009	Gradual-structure PVA/HA hybrid hydrogels showed potential as artificial cartilage, promoting natural bonding with subchondral bone and enabling long-term fixation.
PAMPS/PDMAAm DN gel	Rabbit	knee joint	<i>In vivo</i> , the PAMPS/PDMAAm DN gel exhibits a very low friction coefficient. It has no significant adverse effects on the counterface cartilage, making it a potentially useful material for the development of artificial cartilages.	[91]/2010	According to the study, PAMPS/PDMAAm DN gel is a promising material for the future development of artificial cartilage.
polycaprolactone (PCL)	Rabbit	knee joint	PCL scaffolds maintained mechanical strength <i>in vivo</i> and promoted cartilage formation. An appropriate biomechanical environment facilitates the repair of damaged tissue through mechanical transduction carried out by the scaffold.	[70]/2010	Based on the findings, it is strongly suggested that efficient mechanical transduction of stimuli during tissue regeneration is critical.
polycaprolactone (PCL)	Rats	Knee joint	Co-cultures of articular chondrocytes and MSCs effectively repaired cartilage defects, even with reduced chondrocyte numbers.	[73]/2014	In this study, articular chondrocytes and MSCs were co-cultured to repair cartilage defects in the rat trochlear groove.
Autologous adipose-derived stem cells (ADSCs)	Rabbit	Knee joint	The mechanical properties and biochemical components of cartilage repair tissue induced by ADSC-loaded cartilage ECM scaffolds were comparable to those of native cartilage.	[69]/2014	The study added that further studies should be carried out on larger animal models in order to explore

				the feasibility of using these techniques in humans.	
Cartilage-specific matrix hydrogel (CMH) + dual microparticle-based programmed delivery system (dM-PDs)	Nude mice	Subcutaneous	The regeneration of cartilage using stem cells was accomplished by sequentially dynamically regulating <i>in vivo</i> by using a dual microparticle-based programmed delivery system.	[81]/2024	The present study provides a novel approach to cartilage regeneration based on stem cells for the future repair of multiple cartilage defects.
poly(ethyl acrylate-co-hydroxyethyl acrylate) copolymer	Rabbit	knee joint	In three months, superficial articular cartilage (AC) regenerated, with hyaline-like cartilage covering scaffolds advancing toward subchondral bone, while surrounding tissues were well integrated. Controls (without scaffold implantation) revealed fibrous cartilage, whereas pre-seed scaffolds improved tissue growth within scaffold pores.	[92]/2015	This study strongly suggests that scaffolds play an important role in the transmission of stress to cells in order to guide cartilage repair in humans for therapeutic purposes.
silk fibroin/chondroitin sulfate	Rabbit	knee joint	The scaffold consists of silk fibroin/chondroitin sulfate and provides immuno-inhibitory properties as well as the ability to enhance cartilage self-healing abilities.	[83]/2017	It is possible that a well-designed bioactive scaffold can improve cartilage regeneration based on the results of this investigation.
silk fibroin + gelatin	Rabbit	knee joint	As a result of its unique structural design, ability to recruit BMSCs, and other superior properties, the dually optimized scaffold has demonstrated superior cartilage repair capabilities for knee joints due to its efficient recruiting ability and ability to serve as a physical barrier to blood clots.	[84]/2017	This study suggests that further studies should be conducted in large animal studies and preclinical applications beyond knee cartilage.
Matrix-induced autologous chondrocyte	Sheep	knee joint	A comparison of MACI and MIV groups revealed better healing rates than others, and they were	[88]/2018	In addition to the suggestion of further studies, human studies are

implantation (MACI)/Collagen membrane (MIV group)			similar. There was no improvement in the results with collagenase or growth factors added. Collagenase had no harmful effects on the surrounding cartilage.		also required to determine if the treatment is similarly effective.
Chitosan-Gelatin	Rabbit	knee joint	There has been evidence that zonal arrangements influence MSC chondrogenesis and lead to superior hyaline cartilage formation. As a stand-alone graft or an impregnated biomolecule to boost endogenous cartilage regeneration, the multilayered scaffold, when combined with endogenous stem cells, stimulated hyaline cartilage regeneration <i>in vivo</i> .	[87]/2020	According to the study, MSCs loaded on multilayered zonal scaffolds promoted superior regeneration of hyaline articular cartilage (AC) with multi-layered zonal architecture.
Decellularized Cartilage Extracellular Matrix (DCM)	Rat	Knee joint	Based on the study, pepsin-solubilized DCM (PDCM) stimulated bone marrow macrophages to become constructive macrophages. Polarized macrophages promoted the invasion, proliferation, and differentiation of bone marrow mesenchymal stem cells.	[64]/2021	The combination of a decellularized cartilage ECM scaffold with an active and accurate immune regulation strategy offers promising potential for the safe and efficient regeneration of cartilage in human clinical practice.
polycaprolactone/silk fibroin/gelatin/ascorbic acid (PCL/SF/Gel/AA)	Rabbit	Knee joint	Results showed that the composite scaffolds of PCL/SF/Gel/AA seeded with allogeneic ASCs were effective in improving meniscus healing in rabbits with damaged menisci.	[71]/2021	Study findings suggest that <i>in vivo</i> analyses with longer tracking time and larger animal models are required to validate the clinical effectiveness of the three-dimensional (3D) PCL/SF/Gel/AA composite constructs seeded with mesenchymal stem cells for the development of meniscus tissues.

Hydrogel (alginate)-guided therapeutic rAAV gene	Pigs	Knee joint	IGF-I/AlgPH155 significantly improved cartilage repair and reduced osteoarthritis and inflammation after one year compared to lacZ/AlgPH155, with no adverse or immune reactions.	[76]/2021	Accordingly, such hydrogel-guided, rAAV-mediated activation of therapeutic gene sequences may be suitable for arthroscopic stimulation of marrow based on the symmetric pattern of enhanced long-term cartilage repair.
Chitosan (C)+gelatin (G) + silk (S) fibroin	Rabbit	Knee joint	In all experimental groups, <i>in vivo</i> examinations of the CGS 2:2:3 scaffold exhibited adequate biocompatibility.	[82]/2021	As a result of the study, it was suggested that CGS 2:2:3 would be an effective scaffold for cartilage tissue engineering.
glycol chitosan/dibenzaldehyde- terminated polyethylene glycol (GCS/DF-PEG)	Rats	Knee joint	Based on the results of the study, Adipose-derived mesenchymal stem cells and GCS/DFPEG hydrogel complexes transplanted into the cartilage defect area demonstrated notable cartilage regeneration.	[86]/2021	The mechanism of cartilage repair using this type of stem cell transplantation does not seem to be clear at this time.
A titanium + polylactic acid matrix-reinforced collagen	Sheep	Knee joint	The multilayer scaffold achieved stable mechanical fixation as a result of improved bone ingrowth into the porous Ti matrix during the assessment period. Additionally, the multi-layer scaffold group had a higher bone mineral density than the collagen-HAP scaffold group, which resulted in increased cartilage filling.	[89]/2022	Using this multi-layer scaffold technology, osteoarthritis patients can repair large chondral and osteochondral defects and provide clinicians with an alternative treatment option if their arthritis has progressed beyond a small defect, but a full joint replacement is still possible.
Osteogenic Collagen- Chondroitin Sulfate	Rabbit	Knee joint	Compared to untreated controls at 6 and 12 weeks post-surgery, porous biomimetic collagen scaffolds demonstrated improved histological,	[90]/2022	According to the results presented, biomimetic materials could serve as a clinical solution for cartilage tissue

			molecular, and cellular composition and organized tissue structure.		repair as they modulate the immune environment to facilitate regenerative processes and suppress cartilage degradation.
Hydrogel-Exos	Pig	Knee joint	As a result of both <i>in vitro</i> and <i>in vivo</i> validations, Hydrogel-Exos has been shown to enhance chondrogenesis by providing ECM components and allowing the sustained release of chondrogenic and anti-inflammatory exosomes, enabling cartilage repair and joint function restoration after mophilic cartilage defects.	[77]/2024	Hemophilic articular cartilage (AC) damage poses complex challenges, and this new approach provides an innovative approach that can be applied during arthroscopic procedures.
Cartilaginous organoids bioassembly	Nude mice + Goats	Subcutaneous in nude mice/injectable rhinoplasty in goats.	As a result of the cartilaginous organoids bioassembly technique, separated cartilaginous organoids can be integrated into a continuous cartilage tissue, and the nasal dorsa can then be raised after minimally invasive injection in goats.	[65]/2024	In light of the study's conclusions, there is much to be done to realize clinically relevant organoid-based translational applications from bench to bedside, including long-term observation and more thorough assessment in goat models.
Decellularized cartilage (DCC)	Rabbit	Knee joint	The three-dimensional (3D) porous scaffolds were demonstrated <i>in vivo</i> to promote subchondral bone regeneration and fibrocartilage tissue formation after implantation in rabbits with osteochondral defects.	[66]/2024	The study anticipates that the structure's ability to regenerate tissues may be enhanced. Additionally, improvements can be made to the three-dimensional (3D) fabrication technique, including assessing the ability of decellularized cartilage to form hydrogels.

A three-dimensional alginate-coated scaffold (GAIS)	Mice	Knee joint	In this study, GAIS was shown to stimulate the differentiation of stem cells into chondrocytes both <i>in vitro</i> and <i>in vivo</i> , however, the mechanisms underlying this process were not comprehensively elucidated.	[67]/2024	Further research is recommended to thoroughly investigate the capacity of GAIS to stimulate the differentiation of stem cells in the future.
Glycopeptide hydrogel incorporating RGD-	Rabbit	Knee joint	Through the enhancement of anabolic metabolism in chondrocytes, glycopeptide hydrogels rewire chondrocyte function and rebuild the ECM microenvironment through the preservation of redox equilibrium, making them an effective tool for engineering cartilage tissue.	[78]/2024	A glycopeptide-based ECM biomimetic strategy holds immense promise for cartilage regeneration, whereas activation of the fucoidan-NRF2-antioxidant axis has the potential to significantly advance tissue engineering bionics.
Hydroxypropyl chitin and oxidized chondroitin sulfate (HPCH-OCS) hydrogel	Rat	Knee joint	Combined with microfracture, the HPCH-OCS hydrogel offers an effective strategy for the regeneration of clinical cartilage.	[79]/2024	A new approach to the treatment of cartilage defects may be possible with HPCH-OCS hydrogels.
GelMA-FT/Sr ²⁺ hydrogel	Rat	Knee joint	The GelMA-FT/Sr ²⁺ hydrogel has exceptional lubrication capabilities, is capable of attracting stem cells, and facilitates the repair of cartilage defects.	[80]/2025	Using this dual-network hydrogel architecture, the limitations encountered with the exclusive use of GelMA hydrogels can be effectively overcome, facilitating the rehabilitation of cartilage defects in the joints.
Polycaprolactone (PCL)	Pig	Temporomandibular Joint	The regeneration of temporomandibular joint discs <i>in situ</i> has been achieved after scaffold implantation following discectomy in mini-pigs within three months, displaying native-like heterogeneity and multi-scale mechanical	[72]/2025	Based on the findings of our study, our cell-free, bioactive scaffolds equipped with non-invasive tracking technology show a significant potential for <i>in situ</i> tissue

			properties without damaging cartilage, and allowing reliable tracking of scaffold degradation <i>in vivo</i> through non-invasive imaging.		engineering of temporomandibular joint discs.
ADSCs + BMSCs with cECM microcarriers	Mice	Knee joint	ADSCs-MT demonstrated excellent chondrogenic abilities and strong paracrine properties, enabling them to protect inflammatory chondrocytes effectively <i>in vivo</i> and stimulate cartilage regeneration.	[68]/2025	It is demonstrated in this study that microtissues can be made and that cartilage regeneration can be effectively enhanced through the use of these microtissues.
Fibroblast growth factor 2 (FGF-2)	Mice	Subcutaneous	Cells treated with bFGF showed higher levels of proliferation and differentiation compared to cells not treated with bFGF.	[62]/2025	By using epiphyseal chondrocytes, this study may lead to the development of new alternative therapies for bone and cartilage.

5. Challenges, Clinical Translation, and Future Directions

Using the literature reviewed in this study as a basis, we have identified several critical barriers and opportunities influencing the advancement of cartilage repair *in vivo*. The insights highlight the multifaceted nature of current limitations, including biological, technological, and translational challenges, as well as opportunities for advancement. By combining these perspectives, it is possible to identify research priorities and guide future strategies to achieve more predictable and durable clinical outcomes in cartilage regeneration. Despite promising outcomes reported in animal models, a substantial gap continues between preclinical studies and successful translation into human clinical trials in cartilage repair. This discrepancy arises from several factors, including differences between human joints and animal models in anatomical and biomechanical properties, variations in cartilage thickness and loading conditions, and regulatory and safety considerations when using advanced biomaterials and cells. Additionally, engineered cartilage constructs must be thoroughly validated before clinical application for their long-term durability and integration. Future clinical translation studies should emphasize the use of clinically relevant large-animal models, standardized experimental protocols, long-term functional evaluation, and early collaboration among researchers, clinicians, and regulatory agencies in order to accelerate clinical translation. These strategies may facilitate the development of cartilage regeneration therapies that are more reliable and clinically applicable.

5.1 Challenges

- Long-term survival of engineered cartilage is limited by limited vascularization and nutrient supply.
- Integration of scaffolds is complicated by immune rejection and variability in host response.
- Failure under load is caused by mechanical mismatches between the engineered constructs and the native cartilage.
- In the absence of standardized animal models, reproducibility and cross-study comparisons are hampered.
- Bioactivity *in vivo* is limited by the short half-life and uncontrolled release of growth factors.

5.2 Clinical Translation

- The results of early-stage clinical trials using cell-seeded scaffolds (e.g., MACI, MSCs) have been encouraging, but scalability and cost remain significant obstacles.
- Therapy based on gene editing and exosomes is complicated by regulatory hurdles.
- It is possible that the clinical adoption of the three-dimensional (3D) bioprinting and multilayered scaffolds is delayed due to manufacturing challenges.
- There are limited data regarding the long-term safety of iPSCs and genome editing, in particular regarding tumorigenicity.
- Clinical acceptance is dependent on the integration of arthroscopic, minimally invasive techniques.

5.3 Future Perspectives

- Developing biomimetic scaffolds that can respond dynamically to load.
- Enhancing the healing process through the integration of immunomodulatory biomaterials.
- Chondrogenesis can be precisely modulated with CRISPR and RNA-based gene therapies.
- Developing scaffold-free and organoid-based systems for cartilage repair on a large scale.
- Utilizing smart diagnostics and artificial intelligence to predict the outcome of regenerative strategies.

6. Conclusion

Cartilage repair is characterized by avascularity, low cellularity, and limited self-healing ability. *In vivo* studies indicate that combining biomaterials, bioactive molecules, and stem cells facilitates cartilage repair. The use of polycaprolactone, silk fibroin, and hydrogel scaffolds provides strong biomechanical support and biocompatibility. Functionalization of these scaffolds with exosomes, icariin, and growth factors improves immunomodulation and regeneration. With scaffold-free bio-assemblies and three-dimensional (3D) bioprinting, customized constructs can be generated that mimic native cartilage organization. However, clinical translation is limited due to poor vascularization, mechanical instability, and variable host responses. For future applications, standardization of models, long-term validation, and cost-effective production are imperative. Next-generation strategies will integrate biomaterials, gene editing, and smart delivery systems to produce personalized, long-lasting results.

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Author Contributions

All authors contributed to the conceptualization and design of the review. [Ali A. Al-Allaq, Abdullah A. Abdulhakeem] conducted the literature search and drafted the initial manuscript. [Jwan Kh. Hammood, Hassan Fouad] critically revised the content and contributed to the organization and structure of the manuscript. All authors discussed the content, provided critical feedback, and approved the final version of the manuscript.

Competing Interests

The author reports there are no competing interest.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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