Review

Enhanced Surface Immunomodification of Engineered Hydrogel Materials through Chondrocyte Modulation for the Treatment of Osteoarthritis

Jiapei Yao1,2,†, Zhennan Huo1,2,†, Jie Xu1,2, Jingjing Shang2,3, Yiping Weng1,2, Dongmei Xu1,2, Ting Liu1,2, Yong Huang1,2,* and Xindie Zhou1,2,4,⋆

1 Department of Orthopedics, The Affiliated Changzhou Second People’s Hospital of Nanjing Medical University, Changzhou 213000, China; yaojiapei@126.com (J.Y.); 974488202@163.com (Z.H.); 1889653982@163.com (J.X.); czwengyiping@163.com (Y.W.); xdmcgey@163.com (D.X.); ltgcye@163.com (T.L.)
2 Changzhou Medical Center, Nanjing Medical University, Changzhou 213000, China; shang0308@126.com
3 Department of Pharmacy, The Affiliated Changzhou Second People’s Hospital of Nanjing Medical University, Changzhou 213000, China
4 Department of Orthopedics, Gonghe County Hospital of Traditional Chinese Medicine, Hainan Tibetan Autonomous Prefecture 811800, China
* Correspondence: huangyong@njmu.edu.cn (Y.H.); zhouxindie@njmu.edu.cn (X.Z.)
† These authors contributed equally to this work.

Abstract: Osteoarthritis (OA) is characterized by cartilage degeneration and synovial inflammation, with chondrocytes playing a pivotal role in this disease. However, inflammatory mediators, mechanical stress, and oxidative stress can compromise functionality. The occurrence and progression of OA are intrinsically linked to the immune response. Current research on the treatment of OA mainly concentrates on the synergistic application of drugs and tissue engineering. The surface of engineered hydrogel materials can be immunomodified to affect the function of chondrocytes in drug therapy, gene therapy, and cell therapy. Prior studies have concentrated on the drug-loading function of hydrogels but overlooked the immunomodulatory role of chondrocytes. These modifications can inhibit the proliferation and differentiation of chondrocytes, reduce the inflammatory response, and promote cartilage regeneration. The surface immunomodification of engineered hydrogel materials can significantly enhance their efficacy in the treatment of OA. Thus, immunomodulatory tissue engineering has significant potential for treating osteoarthritis.

Keywords: osteoarthritis; hydrogel; chondrocytes; cartilage; immunomodification

1. Introduction

Osteoarthritis (OA) is a chronic musculoskeletal disease predominantly observed in middle-aged and elderly individuals. It is characterized by the disruption of articular cartilage integrity or chondral sclerosis, as well as biochemical and biomechanical alterations of the extracellular matrix [1,2]. This series of changes can result in joint damage, particularly affecting the hands, small joints of the spine, hip joints, and knee joints. Consequently, OA is a leading cause of physical disability among middle-aged and elderly populations [3]. As of 2020, 595 million people worldwide were diagnosed with OA, constituting 7.6% of the global population. The prevalence of OA is higher in women than in men and increases with age. The number of OA cases per site is projected to increase globally by 48.6% to 95.1% between 2020 and 2050 [4]. The pathogenesis of OA is complex, involving a variety of factors, including age, gender, genetics, obesity, excessive physical activity, trauma history, and previous joint surgeries resulting from other joint injuries [5]. Despite extensive research efforts to elucidate its pathogenesis, the underlying mechanisms remain unclear. However, several inflammatory mediators are closely associated with its development [6].
Treatment options for OA include both surgical and non-surgical interventions, including peri-knee osteotomy, partial knee replacement (unicomdylar joint replacement), and total knee replacement, the choice of which depends on the patient’s condition and the extent of joint damage or deformity [7]. However, surgery is not only costly but carries risks of serious postoperative complications [8,9]. Therefore, managing OA symptoms in their early stages is crucial to alleviating its burden on patients (Figure 1). Non-surgical symptom management strategies include psychosocial–behavioral modifications, such as health education and functional exercises, that promote lifestyle changes, as well as local or oral medication. However, medications have limited efficacy and cannot reverse cartilage degeneration [10]. Consequently, an urgent need exists to explore novel technologies or enhancements to existing treatment modalities that can restore normal histoarchitectural and the physico-mechanical integrity of the osteoarticular joint by repairing chondrocytes and cartilage in early-stage OA.

![Figure 1](image.png)

**Figure 1.** Stages of osteoarthritis and potential therapeutic target points. Preventative therapy can be applied before disease initiation in normal joints. Targeting progression can be achieved through interventions that prevent joints from worsening over time. During progression, it is critical to differentiate between early and late stages, as interventions aimed at slowing progression and enhancing repair are more effective in the early stages of disease, while total joint replacement (TJR) may become the sole option at late stages. Reprinted with permission from John Wiley & Sons Ltd. (2017) [11].

The integration of tissue engineering and clinical medicine offers a novel approach to treating OA [12,13]. Identifying effective chondrogenic factors, ensuring an adequate supply of chondrogenic precursor cells, and utilizing cell-friendly and biocompatible biomaterials are crucial to facilitate the widespread application of tissue engineering in OA treatment. Biomaterials are specifically designed and manufactured to create a physical environment that not only supports cellular activity but also facilitates tissue regeneration. Within the context of OA treatment, biomaterials can be either implanted and immobilized within the articular cartilage through arthroscopy or microarthrotomy or directly interact with chondrocytes. This approach provides better control over disease symptoms during the early stages of OA development and contributes to slowing down disease progression [14]. Among various biomaterials, hydrogels exhibit desirable characteristics, including high water absorption, degradability, porosity, and biocompatibility, similar to the natural extracellular matrix. Consequently, hydrogels have been recognized as one of the most suitable biomaterials for cartilage regeneration [15]. Hydrogels also demonstrate properties that modulate immune cells, potentially serving as a foundation for effective immunotherapy against OA [16]. This review paper discusses recent advancements in the immune modification of engineered hydrogel surfaces, focusing on chondrocyte modulation for OA treatment.
2. Cartilage and Chondrocytes in OA

2.1. Pathological Changes in OA

The pathological changes in OA primarily manifest as cartilage degradation and synovial inflammation [17]. These changes can be classified as primary and secondary OA based on etiology. Primary OA is associated with factors like heredity and individual constitution. Secondary OA is linked to various factors, including trauma, bone and joint infections, congenital and hereditary diseases, endocrine disorders, and metabolic conditions [18]. Despite numerous studies, the etiology and pathogenesis of OA remain elusive. The onset of OA is attributed to multifactorial interplay involving age, obesity, genetic predisposition, endocrine and metabolic disorders, inflammation, and trauma [19]. Age-related systemic inflammation is associated with the development of OA in humans [20]. Articular chondrocytes in older adults release higher levels of pro-inflammatory cytokines compared to those in younger adults [21,22]. Chronic and persistent inflammation leads to elevated levels of interleukin 6 (IL-6), mitochondrial dysfunction, oxidative stress, chondrocyte apoptosis, and calcification of the cartilage matrix. Collectively, these processes contribute to cartilage degeneration and the development of OA. Heightened inflammatory responses associated with obesity, such as tumor necrosis factor-α, IL-6, and C-reactive protein, exacerbate OA progression. Additionally, the mechanical stimulation of joint surfaces upregulates the expression of inflammatory factors, thereby promoting cartilage degeneration [23]. Notably, articular cartilage damage from joint trauma plays a pivotal role in OA progression. Mechanical trauma triggers augmented cellular metabolism, the accumulation of reactive oxygen species (ROS), the activation of matrix-degrading enzymes, joint inflammatory mediators, and the induction of chondrocyte death, ultimately leading to irreversible damage to articular cartilage (Figure 2).

Figure 2. Factors related to the pathogenesis of OA.

2.2. Cartilage Degeneration in OA

Cartilage is a dense, avascular connective tissue comprising a high concentration of negatively charged polysulfated polysaccharides (35% dry weight), type II collagen (50%–60% dry weight), and a low density of chondrocytes (<5% dry weight). Cartilage plays pivotal roles in joint function, facilitating lubrication, supporting weight-bearing, and enabling smooth movement [24]. It is classified into three types: hyaline cartilage, fibrocartilage, and elastic cartilage. OA induces pathological alterations across the joint structure, initially characterized by the degeneration of cartilaginous tissue and remodeling of the subchondral bone [25,26]. Cartilage degeneration may be attributed to a decline in chondrocyte numbers within aging articular cartilage, hindering proper regeneration and remodeling processes. Articular cartilage affected by OA undergoes a range of changes, including structural, biochemical, and biomechanical alterations. These changes can lead
to a loss of articular cartilage integrity, ultimately resulting in its remodeling. Adjacent structures undergo self-modeling, generating new formations with distinct morphological and functional characteristics [27]. Normal articular cartilage is considered simple due to the absence of vascular nerve distribution and the exclusive presence of chondrocytes (Figure 3). In healthy articular cartilage, chondrocytes exert inhibitory effects on proliferation and differentiation, whereas they exhibit increased proliferation and hypertrophy in diseased cartilage. Chondrocyte functionality is modulated by inflammatory mediators and mechanical and oxidative stress, leading to hypertrophic differentiation and premature senescence. Consequently, they become more susceptible to the impact of pro-inflammatory and pro-catabolic mediators [28]. The reparative process involves chondrocyte migration from the periphery to the injury site, where they proliferate and differentiate, synthesizing and secreting new matrix components to rebuild damaged cartilage. However, the limited proliferative capacity, slow matrix turnover, and insufficient cell supply in adult chondrocytes result in the low self-repairing ability of articular cartilage. Once damaged, it becomes highly susceptible to replacement by fibrous tissue, rendering the restoration of normal function and structure extremely challenging.

Figure 3. Mechanisms for osteoarthritis of the knee. Healthy articular cartilage (left): Chondrocytes thrive in the hypoxic environment within the cartilage due to the absence of blood vessels. Hypoxia plays a crucial role in chondrocyte function and survival. The main function of cartilage involves the absorption and removal of mechanical load, which is essential for maintaining cartilage homeostasis. Osteoarthritis articular cartilage (right): The development of blood vessels (vascular channels) facilitates biochemical communication between bone and cartilage, involving cytokines, chemokines, and alarmins. This process initiates a vicious cycle of cartilage degradation. Reprinted with permission from Licensee MDPI, Basel, Switzerland (2021) [29].

2.3. OA and Chondrocytes

Chondrocytes, specialized cells located in articular cartilage tissue, play a crucial role in the maintenance and repair of this tissue’s structure and function [30]. These cells, which are round or oval in shape, possess abundant cytoplasm and organelles responsible for the synthesis and secretion of collagen, proteoglycans, and other matrix molecules vital for the maintenance of cartilage integrity [31]. Chondrocytes exhibit low metabolic activity and a limited cell division capacity [32]. The major sources of chondrocytes include mature chondrocytes, mesenchymal stem cells (MSCs) from bone marrow, adipose stem cells from adipose tissue, and chondrocyte precursor cells like chondroblasts [33]. In early OA stages, chondrocytes enlarge and aggregate into clusters or masses, sometimes with 50 or more cells per cluster, termed “chondrocyte clones”. This phenomenon serves as evidence of cartilage metabolic activity and chondrocyte replication capacity in OA. In advanced stages
of OA, cartilage shows key signs of chondrocyte death, including decreases in cell count and lumen emptying. Senescence, induced by various deleterious biomechanical factors, is a significant risk factor in OA, causing stress and irreversible damage that leads to chondrocyte death. Studies have shown a significant reduction in the cellular structure of articular cartilage with age and a moderate-to-strong correlation between cartilage damage and chondrocyte apoptosis [34]. A decrease in chondrocytes through apoptosis, necrosis, or impaired chondrogenesis can lead to the loss of articular cartilage structure. Thus, controlling chondrocytopenia represents an effective target for mitigating cartilage degeneration, with the loss of chondrocyte viability being a key hallmark of OA [35]. Modulating inflammatory responses, cell proliferation, and differentiation can promote chondrocyte repair and regeneration [36] (Figure 4).

![Figure 4. The different phases of endochondral bone formation. Reprinted with permission from 2023 Current Osteoporosis Reports [37].](image)

3. Biomaterials in OA Therapy

The biomaterial-assisted treatment of OA has shown significant potential in enhancing the self-repairing capability of articular cartilage. The key concept of tissue engineering, a comprehensive strategy for tissue regeneration and repair, encompasses four interconnected elements: scaffolds, cells, signals, and mechanical forces [38]. The inherent properties of biomaterials can be used to effectively enhance chondrocyte proliferation and differentiation, mitigate cartilage degradation, and regulate inflammatory responses. Consequently, this approach holds immense promise for OA therapy. The biomaterials commonly employed in OA treatment include metals, ceramics, nano-microstructured materials, bioprinting-enabled biomaterials, hydrogels, liposomal materials, and decellularized matrix materials [39].

The biomaterials used in OA therapy are categorized into two main types: non-biologically active and biologically active materials. Non-biologically active materials, while successful in clinical practice, must be surgically removed due to their inert nature. Otherwise, they remain in the body indefinitely [40]. Bioactive materials must (a) fulfill a paramount biological function, which is restoring the function of damaged tissue once the replacement fills the bone defect; (b) ensure biocompatibility to prevent cytotoxicity,
immunogenicity, genotoxicity, mutagenicity, thrombogenicity, and swelling at the implant site; (c) be bioabsorbable or biodegradable, allowing for cellular proliferation in the surrounding tissues and eventual metabolism or excretion; (d) possess sufficient mechanical strength to maintain its structure; and (e) provide space for the exchange of nutrients, oxygen, and metabolic waste. Biomaterials with large pores can facilitate the creation of microenvironments conducive to cell proliferation and differentiation.

Research on biomaterials for OA therapy has gradually increased over the last decade [41]. Biomaterials are preferred for bone regeneration and defect repair due to their osteoinductivity (promoting progenitor cell differentiation into osteoblasts), osteoconductivity (supporting bone growth and inward growth of surrounding bone), and osteointegration (incorporating into the surrounding bone) properties [42]. Numerous studies on bone replacement materials have demonstrated that by following the tissue engineering paradigm, the ideal material can be resorbed and replaced over time by the body’s newly regenerated biological tissues. Given the biological inertness of some implanted materials, biodegradable materials have become the primary therapeutic choice for clinical OA treatment, offering mechanical support, aiding in bone tissue regeneration and repair, and degrading in vivo. Clinical studies [43] have highlighted hydrogel materials’ superior potential in promoting cartilage formation. Their ability to form in situ scaffolds without open surgery and to be injected intra-articularly without impairing chondrocyte colonization or differentiation has broadened their application in OA treatment protocols.

4. Hydrogel Materials with Immunomodulatory Functions against Cartilage and Chondrocytes

Hydrogels are three-dimensional networks of cross-linked biopolymeric molecules, like proteins and polysaccharides, capable of absorbing substantial amounts of water [44]. Their distinctive attributes, which include encapsulation, protection, and controlled-release mechanisms, make them suitable for constructing conveyor systems [45]. Hydrogels have been extensively researched in drug delivery, pain management, immunomodulation, wound healing, and cardiology due to their biocompatibility, biodegradability, and ability to regulate drug release kinetics.

Hydrogels can be primarily categorized into natural and synthetic sources [46]. Natural hydrogels include collagen, gelatin, chitosan, fibrin, and alginate. Natural hydrogels are known for their biocompatibility and biodegradability, making them suitable for modified intra-articular drug delivery [47]. Synthetic hydrogels include polyvinyl alcohol, polyethylene glycol, and polycaprolactone. Polymeric synthetic hydrogels include polylactic acid, polyglycolic acid, polylactic acid–glycolic acid, and polyester amide. Polyvinyl alcohol, polyethylene glycol, and polycaprolactone are commonly used in the treatment of OA. Synthetic hydrogels, with their high mechanical properties, are suitable for intra-articular drug delivery. They act as scaffolds for cell growth, lubricate the joint cavity, and reduce joint load. Synthetic hydrogels can be modified to reduce toxicity and carry no thrombogenic or tumorigenic risks after intravascular delivery, offering major therapeutic effects, like cartilage protection and regeneration, and anti-inflammatory effects, aligning with clinical treatment goals [48–50] (Table 1).
Table 1. Hydrogel for osteoarthritis treatment.

<table>
<thead>
<tr>
<th>Type</th>
<th>Trait</th>
<th>Model</th>
<th>Function</th>
<th>Limitation</th>
<th>Type</th>
<th>Cell</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural hydrogel</td>
<td>Chitosan: An amino acid polysaccharide with a chemical structure similar to glycosaminoglycans naturally found in cartilage.</td>
<td>Injectable; adhesive</td>
<td>Biocompatible, it promotes cellular activity and tissue regeneration.</td>
<td>Low solubility and poor mechanical properties.</td>
<td>In vitro</td>
<td>Human chondrocytes</td>
<td>[51]</td>
</tr>
<tr>
<td>Silk fibroin</td>
<td>Composed of natural silk proteins.</td>
<td>Injectable</td>
<td>Mechanical properties, biocompatible, enzymatically degradable, hemocompatible.</td>
<td>May cause an immune response.</td>
<td>In vitro</td>
<td>Human chondrocytes</td>
<td>[52]</td>
</tr>
<tr>
<td>Collagen</td>
<td>Type II collagen is a major component of natural cartilage tissue, and type I collagen is the most widely available and used collagen type in tissue-engineered scaffolds.</td>
<td>Injectable; adhesive</td>
<td>Regulates chondrocyte proliferation and induces cartilage repair.</td>
<td>Low solubility, poor mechanical properties, and fast degradation rate.</td>
<td>In vitro</td>
<td>Bovine chondrocytes</td>
<td>[53]</td>
</tr>
<tr>
<td>Cellulose</td>
<td>Natural cellulose.</td>
<td>Injectable</td>
<td>Non-toxic, high strength and stiffness, excellent water affinity, renewability, and versatility.</td>
<td>May cause an immune response.</td>
<td>In vitro</td>
<td>Rat chondrocytes</td>
<td>[54]</td>
</tr>
<tr>
<td>Alginate</td>
<td>A heteropolysaccharide extracted from brown algae composed of βD-mannuronic acid and α-L-glucuronic acid monomers.</td>
<td>Injectable; adhesive</td>
<td>Biocompatible, non-toxic, non-immunogenic, low cost.</td>
<td>Lack of cell adhesion motifs and weak mechanical properties.</td>
<td>In vitro</td>
<td>Human chondrocytes</td>
<td>[55]</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Extracellular matrix of epithelial and neural tissues.</td>
<td>Injectable; adhesive</td>
<td>Promotes chondrocyte growth, metabolism, and maintenance of the chondrocyte phenotype. Commonly used as a lubricant in synovial fluid.</td>
<td>Lubrication only.</td>
<td>In vitro/in vivo</td>
<td>Rat chondrocytes</td>
<td>[56,57]</td>
</tr>
<tr>
<td>Gelatin</td>
<td>Collagen hydrolysis product of the extracellular matrix, consisting of heterogeneous single- and multi-chain polypeptides.</td>
<td>Injectable; adhesive</td>
<td>Excellent loading efficiency to promote cell attachment.</td>
<td>Failure to ensure cell attachment and the formation of new tissue around the site of injury.</td>
<td>In vivo</td>
<td>Mouse chondrocytes</td>
<td>[58]</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>The extracellular matrix of many connective tissues, including cartilage.</td>
<td>Injectable</td>
<td>Biocompatible and bioactive, it promotes chondrocyte proliferation and differentiation, cartilage matrix synthesis, and remodeling.</td>
<td>Poor cell adhesion and lower mechanical properties.</td>
<td>In vitro</td>
<td>Human chondrocytes</td>
<td>[59]</td>
</tr>
<tr>
<td>Type</td>
<td>Trait</td>
<td>Model</td>
<td>Function</td>
<td>Limitation</td>
<td>Type</td>
<td>Cell</td>
<td>Ref.</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>---------------</td>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>--------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Synthetic hydrogel</td>
<td>Polyvinyl alcohol (PVA)</td>
<td>Injectable</td>
<td>High expansion, porous, good viscoelastic properties, mechanical support.</td>
<td>Poor biocompatibility.</td>
<td>In vitro/in vivo</td>
<td>Goat chondrocytes</td>
<td>[60,61]</td>
</tr>
<tr>
<td></td>
<td>Poly(ethylene glycol) PEG</td>
<td>Injectable; adhesive</td>
<td>Soluble and biocompatible. Commonly used in drug delivery, biomaterials, and cosmetics.</td>
<td>Rapid proliferation and clearance, interferes with metabolism and immune response.</td>
<td>In vitro</td>
<td>Rat chondrocytes</td>
<td>[62]</td>
</tr>
<tr>
<td></td>
<td>Poly-ε-caprolactone(PCL)</td>
<td>Injectable</td>
<td>Biocompatibility and mechanical properties, drug retardation, bioactivity.</td>
<td>Poor biological activity and low cellular interaction capacity.</td>
<td>In vitro</td>
<td>Rabbit articular chondrocytes</td>
<td>[63]</td>
</tr>
</tbody>
</table>
Hydrogels are utilized in diverse methods for OA treatment, outlined as follows: (1) To reduce joint inflammation or repair tissue defects through hydrogels’ pressure-resisting and lubricating properties. (2) As carriers for substance delivery with implantation via injection or surgery, which enhances the effectiveness of the transported substance. (3) As scaffolds for cell transport to encourage cell adhesion, proliferation, and differentiation.

The primary roles of hydrogel materials in OA treatment include viscosupplementation cartilage regeneration and immunomodulation. Viscosupplementation mimics self-secreted synovial fluid properties like adequate space-filling, lubrication, free radical scavenging, and cellular activity modulation. Intra-articular hydrogel injections provide effective lubrication and shock absorption [64]. Reconstructing joint homeostasis often involves increasing joint fluid viscosity by hyaluronic acid (HA) injections to reduce pain and improve function [65]. The properties of hydrogel also aid in reducing bone destruction and promoting cartilage regeneration. Hydrogel improves cartilage defects by fostering a microenvironment that nourishes and promotes surrounding tissue proliferation, filling in damaged areas, even without additional materials [27]. Hydrogel can target and modulate the immune responses of chondrocytes through its structure [66]. Previous studies indicated that high-molecular-weight HA fosters a more potent anti-inflammatory environment compared to low-molecular-weight HA. HA with molecular weights above 1000 kDa offers anti-inflammatory, cushioning, and moisturizing benefits, whereas HA around 250 kDa is more angiogenic, immunostimulatory, and pro-inflammatory [67].

5. Application of Hydrogel Materials in OA Immunotherapy
5.1. Drug Delivery Function
5.1.1. Responsive Modulation

Responsive modulation in the joint cavity enables precise delivery by leveraging hydrogel’s delivery function and biomaterial properties [68]. The significant secretion of matrix-degrading and degradation-activating enzymes occurs in OA. Targeting specific enzymes can alter their physical or chemical properties [69]. Paul et al. showed that enzyme pretreatment significantly enhanced chondrocyte adhesion and increased cell density without affecting proteoglycan deposition [70]. Enzyme-responsive biomaterials can utilize tissue-specific enzyme activity variations to regulate substance delivery precisely, enabling targeted drug administration in specific physiological environments [71]. Matrix metalloproteinase (MMP), crucial in OA degradation, is synthesized by chondrocytes under inflammatory conditions, causing cartilage erosion by breaking down type II collagen and aggregated proteoglycans [58].

In OA lesions, synovial fluid pH decreases from 7.4 to 6.0 due to local tissue hypoxia metabolism and acidosis [72]. Certain hydrogels exhibit antioxidant and anti-inflammatory effects through pH-dependent alterations in hydrophobicity or internal gas generation, alleviating OA symptoms [73]. Leveraging pH responsiveness has been proposed to facilitate the release of growth factors, effectively inhibiting cartilage matrix degradation and synergizing with bioactive material in viscosupplementation [74]. Zhang et al. developed an injectable hydrogel for hydrogen release, which demonstrated reduced inflammatory cell apoptosis and significant pathological improvements in rat OA models [75]. Enhancing biomaterial sensitivity to environmental pH changes should be considered in future studies to accommodate diverse environments in OA therapy.

ROS generation primarily occurs via the electron transport chain in mitochondria under physiological conditions, playing crucial roles in immune defense, apoptosis regulation, and intracellular signaling. Recent studies showed a significant increase in ROS levels in the joints of OA patients, with effective ROS clearance shown to alleviate OA symptoms [76]. Zhang et al. developed a system capable of scavenging multiple ROS types and triggering polymer degradation [77]. Elevated ROS levels in the OA tissue microenvironment create advantageous conditions for responsive drug release.

Simple and manipulable exogenous stimuli have gained attention for drug release initiation compared to endogenous factors like enzymes, ROS, and pH. The release be-
Behavior of responsive biomaterials can be modulated by applying light, heat, magnetism, or ultrasound to the injured site. These advantages offer significant potential for using stimuli-responsive biomaterials in OA treatment. For example, a study used two ionically cross-linked hydrogels polymerized with visible light as cell carriers to enhance chondrocyte viability [78]. This approach leverages the hydrogel’s biocompatibility and mechanical properties to facilitate strong binding between new cartilage and surrounding tissue. Zhu et al. utilized an injectable thermo-responsive hydrogel for cell proliferation and chondrogenic differentiation via the Wnt/β-collagen pathway and pain alleviation by modulating cytokine expression in OA [79]. Stimulus-responsive biomaterials allow for the flexible addition or removal of external stimuli, enabling personalized, continuous, or intermittent OA treatment modalities.

5.1.2. Target Transmission

Hydrogels enable precise targeted delivery based on the physiological nature of articular cartilage, elevating the delivery precision level. The pore size and porosity of the cartilage matrix influence drug penetration, and alterations in pore size occur as OA progresses. Smaller particle-sized substances exhibit enhanced cartilage penetration and cellular uptake, which are key for targeted therapy in OA [80]. Hydrogels can specifically target cartilage and directly deliver bioactive factors to lesion sites, including antioxidants, anti-inflammatory agents, and growth factors targeting chondrocytes [81–83]. Li et al. validated that intra-articular injections of biofactors directly to inflamed sites in an OA animal model promoted cartilage repair when combined with hydrogels [29]. Wei et al. administered an injectable substance via intra-articular injection, resulting in complete defect repair with a smooth surface resembling normal cartilage and remarkable therapeutic effects [84].

Multiple studies have highlighted the clinical significance and potential of multi-targeted RNA interference technology for simultaneously targeting three or more pathways [85,86]. Zhu et al. conducted a comprehensive study using cellular experiments, animal experiments, and bioinformatics to inhibit cartilage aging and promote regeneration with hydrogel as a carrier, targeting specific genes and pathways [87].

Multi-target therapy offers diverse treatment outcomes [88]. In one study, researchers developed an injectable curcumin-loaded microgel that showed dual effects: reducing inflammation and promoting chondrocyte proliferation and differentiation [89]. Multi-targeted therapy broadens the range of OA treatment options.

5.2. Medication

The effects of drugs on cartilage and chondrocytes in OA are limited. Medications commonly used for OA include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, analgesics, and immunosuppressants [82–90]. For instance, the sustained release of dexamethasone, with anti-inflammatory and immunosuppressive properties, by a hydrogel carrier enhances cartilage quality, alleviates arthritis symptoms, and promotes cartilage repair. A previous study showed that dexamethasone delivered via a hydrogel carrier exhibited prolonged anti-inflammatory effects [91]. HA’s stability and supportive role in cartilage regeneration make it a common choice for constructing drug delivery systems [60]. Besides intra-articular delivery, transdermal drug delivery is also an efficient method [92,93]. However, transdermal medications are limited to those that alleviate symptoms but do not alter disease progression or repair cartilage [94]. Some medications may have side effects, like gastrointestinal issues with NSAIDs or joint destruction risks with glucocorticoids. Consequently, there is a lack of drugs capable of modifying OA progression.

5.3. Platelet-Rich Plasma Therapy

Combining platelet-rich plasma therapy (PRP) with hydrogel enhances chondrocyte and cartilage regeneration. PRP, an autologous blood product derived from the patient’s own blood, offers high safety and minimal side effects [95,96]. PRP contains bioactive
5.4. Cell Therapy

The use of combined chondrocyte and hydrogel therapy in OA focuses on cell-based interventions, specifically targeting cartilage repair and the proliferation and differentiation of chondrocytes. The commonly employed cell types include stem cells and progenitor cells [102]. Cellular therapy exerts therapeutic effects on OA by implanting cells in the damaged region and releasing regenerative factors (Figure 5).

![Figure 5. Schematic diagram illustrating the current clinical approaches to cell-based therapy for cartilage tissue engineering. Reprinted with permission from John Burke et al. (2016) [103].](image)

Selecting suitable cells for transplantation is crucial because of the lack of blood vessels, nerves, and diverse cell populations in articular cartilage [104]. Extensive studies have shown that chondrocytes and MSCs are optimal for cell transplantation because they are easier to isolate, proliferate, and synthesize cartilage-specific molecules [105–107]. However, clinical outcomes and cartilage repair may vary due to differing chondrogenic potential and immunomodulatory abilities of the cell types. Chondrocyte implantation is believed to modulate the immune response by inhibiting inflammation, modulating immune cell function, increasing immune tolerance, and reducing autoimmune responses [108,109]. Chondrocytes can also regulate the innate immune system through interactions with myeloid dendritic cells, natural killer cells, macrophages, and other cells [110,111]. Studies showed better therapeutic effects in OA applications.

Despite cell therapy’s potential for treating OA, insufficient research evidence limits its widespread use [112,113]. This limitation is attributed to the complexity and cost of equipment and techniques required for cell therapy. Additionally, varying cell sources and cell quality impact therapeutic effects and treatment efficacy. Obtaining sufficient high-quality cells is also challenging [114]. While cell therapy has fewer side effects, concerns factors like platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), insulin-like growth factor (IGF), and fibroblast growth factor (FGF), crucial for regulating chondrocyte survival and metabolism [94]. Studies indicated that PRP promoted chondrocyte proliferation and matrix production while reducing inflammation [97–99]. Intra-articular injections of PRP-enhanced hydrogel significantly improved OA symptom management, function, and pain relief compared to traditional HA injections or placebo [60]. The effect of PRP can be short-lived, requiring regular injections to maintain treatment efficacy. However, using hydrogel with PRP enables long-term sustained release, ensuring stable and lasting results [100,101].
like immune reactions and infections persist [93]. Therefore, high-quality randomized controlled trials with large sample sizes are essential to evaluate cell therapy’s efficacy and safety for treating OA.

5.5. Gene Therapy

Gene therapy with hydrogels enables targeted interventions at genetic or signaling pathway levels, addressing OA’s root cause [115]. RNA interference technology shows promise for arthritis treatment by selectively inhibiting gene product expression [116]. Gene therapy’s sustained effects surpass those of conventional drug therapy, potentially yielding long-term or permanent outcomes from a single session [117,118]. Garcia et al. achieved gene silencing by modulating the immune response by interfering with the translation process. Employing various gene-editing strategies offers patients safer and more efficacious therapeutic alternatives [119]. Wang et al. effectively regulated chondrocyte senescence and enzyme production using gene knockout and insertion techniques [120]. Bonato et al. combined gene editing with tissue engineering to target the TAK1 gene, suppressing inflammation and producing engineered cartilage with enhanced anti-inflammatory and mechanical properties [121]. Precise gene-editing technology promises to minimize adverse reactions and side effects [122].

Gene therapy has been extensively used for treating OA. However, challenges remain for its successful implementation. First, gene therapy may raise safety concerns, including immune reactions, infections, and the risk of gene mutations from editing. Second, the lack of techniques for precise gene transfer in OA therapy presents a challenge for accurate gene delivery to target cells [123]. Unstable factors also contribute to uncertainty in treatment outcomes. Although gene therapy offers long-lasting effects, its efficacy depends on factors like patient characteristics, disease status, and progression. Lastly, standardization and regulation issues in gene therapy practices persist, especially in clinical trials and applications where uniform norms are lacking.

5.6. Regulation of Cell Signaling Pathways

Hydrogels act as cell guidance materials, promoting cartilage formation and repair by modulating pathways, such as RhoA signaling [124]. Formica et al. explored an alginate hydrogel that released RhoA inhibitors to enhance chondrocyte differentiation and cartilage formation [14]. This material, which contained chondrocytes, showed favorable biocompatibility, sustained enzymatic activity, and improved properties in vitro and in vivo. The nuclear factor-κB (NF-κB) signaling pathway is crucial in inflammation, leading to the production of factors like IL-1β, IL-6, IL-17, and IL-8, stimulating inflammation and worsening OA. Inhibiting the NF-κB pathway may alleviate OA [125]. Zhang et al. attenuated OA progression by inhibiting the NF-κB pathway and suppressing chondrocyte senescence [126]. The aberrant activation of pathways, like JAK-STAT, MAPK, and Wnt, plays key roles in cell functions. Their dysregulation may lead to excessive chondrocyte proliferation and cartilage degradation, worsening OA [127,128]. Ruscitto et al. [129] showed improved knee function and reduced OA pathology by downregulating Wnt activity. The authors noted better knee function and lower arthropathology scores post-ACL injury compared to other groups.

5.7. Biosensors

Hydrogels have been widely investigated as biosensors for detecting specific biomolecules like proteins or DNA [130,131]. Numerous studies have developed hydrogel-based biosensors capable of detecting biomolecules by modulating properties such as color, fluorescence, and conductivity. Additionally, research is exploring hydrogels as biosensors for disease markers like cancer or inflammation indicators. These studies underscore the wide-ranging applications of hydrogel-based biosensors in biomedicine [132]. Scalzone et al. [133] developed a biomimetic in vitro model for arthritic environments, showing how immune cells differentiated into chondrocytes exhibit physiological behavior under healthy and
pathological conditions, mimicking cytokine-induced arthritis. The findings included reduced glycosaminoglycan production, increased calcification and collagen content, and decreased osteogenic marker expression. This approach offers a valuable tool for studying OA progression (Figure 6).

Figure 6. Application of hydrogel materials in OA immunotherapy.

6. Challenges

While hydrogel applications in OA treatment and cartilage repair show potential, they also present challenges and limitations. Despite general biocompatibility, some hydrogels may trigger immune or inflammatory reactions [134–136]. Perrier-Groult et al. [16] observed no blood–lymphatic system stimulation with allogeneic chondrocyte implants using hydrogels or collagen sponges, except for a mild inflammatory reaction to the collagen sponge. Hydrogels are often mechanically weak and may not withstand physiological loads, particularly in high-stress areas such as joints [137]. The rate of hydrogel degradation must match that of new tissue formation, with studies suggesting that degradation that is too fast or slow can impact repair outcomes [138]. The preparation and application techniques for hydrogels, including ensuring in vivo positioning and stability and improving drug delivery efficiency, require optimization. Further clinical trials are needed to validate their effectiveness and safety.

7. Conclusions and Future Perspectives

The onset and progression of OA are linked to the immune response, with current research focusing on combining medicine and tissue engineering to deliver anti-inflammatory drugs, proteins, cells, or gene editing within joints for local inflammation control. Hydrogels offer anti-inflammatory benefits and modify the immunomodulatory functions of immune cells, enhancing chondrocyte proliferation and differentiation in OA therapy. This immunomodulatory approach in tissue engineering holds great potential for OA therapy. The tissue engineering-based reconstruction of articular cartilage can be used to treat OA cartilage damage. However, significant challenges in effectively intervening in severe cases with moderate-to-advanced large defects persist [86]. Despite the limitations of immunotherapy for OA, the in-depth exploration of chondrocytes and extensive research into biomaterials like hydrogels show significant potential.

Author Contributions: Conceptualization: X.Z.; funding acquisition: Y.H. and X.Z.; supervision: Y.W., D.X. and T.L.; writing—original draft: J.Y. and Z.H.; writing—review and editing: J.X., J.S. and Y.H. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by Qinghai Province basic research project (2024-ZJ-760), Basic Research Project of Changzhou Medical Center of Nanjing Medical University (CMCB202314), Science and Technology Project of Changzhou Health Commission (ZD202319 and QN202356), and Changzhou High-Level Medical Talents Training Project (2022CZBJ059 and 2022CZBJ061), and a
nursing research project from The Affiliated Changzhou Second People's Hospital of Nanjing Medical University (2020HZD002).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data are contained within the article.

**Conflicts of Interest:** The authors declare no conflicts of interest.

**Abbreviations**

- ASCs: Adipose stem cells
- FGF: Fibroblast growth factor
- HA: Hyaluronic acid
- IGF: Insulin-like growth factor
- IL-6: Interleukin 6
- MMP: Matrix metalloproteinase
- MSCs: Mesenchymal stem cells
- NF-κB: Nuclear factor-κB
- NSAIDs: Nonsteroidal anti-inflammatory drugs
- OA: Osteoarthritis
- PDGF: Platelet-derived growth factor
- ROS: Reactive oxygen species
- TGF-β: Transforming growth factor β

**References**


11. Poulet, B. Models to define the stages of articular cartilage degradation in osteoarthritis development. *Int. J. Exp. Pathol.* 2017, 98, 120–126. [CrossRef]


63. Xu, J.; Fang, Q.; Liu, Y.; Zhou, Y.; Ye, Z.; Tan, W.-S. In situ ornamenting poly(ε-caprolactone) electrospun fibers with different fiber diameters using chondrocyte-derived extracellular matrix for chondrogenesis of mesenchymal stem cells. *Colloids Surfaces B Biointerfaces* 2021, 197, 111374. [CrossRef]


68. Yang, Z.; Jiang, W.; Xiong, C.; Shang, J.; Huang, Y.; Zhou, X.; Zhang, S. Calciptiol suppresses GPX4-mediated ferroptosis in OA chondrocytes by blocking the TGF-β1 pathway. *Cytokine* 2023, 171, 156382. [CrossRef] [PubMed]


130. Sokolov, P.; Samokhvalov, P.; Sukhanova, A.; Nabiev, I. Biosensors Based on Inorganic Composite Fluorescent Hydrogels. *Nanomaterials* 2023, 13, 1748. [CrossRef] [PubMed]


136. Zhou, X.; Jiang, L.; Fan, G.; Yang, H.; Wu, L.; Huang, Y.; Xu, N.; Li, J. Role of the ciRS-7/miR-7 axis in the regulation of proliferation, apoptosis and inflammation of chondrocytes induced by IL-1β. *Int. Immunopharmacol.* 2019, 71, 233–240. [CrossRef]


**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.