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Bio-engineered strategies for osteochondral defect repair

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ABSTRACT

Due to the absence of blood vessels and nerves, the regenerative potential of articular cartilage is significantly constrained. This implies that the impact of a ruptured cartilage extends to the entire joint. Osteoarthritis, a health condition, may arise due to injury and the progressive breakdown of joint tissues. The progression of osteoarthritis can be accelerated by the extensive degradation of articular cartilage, which is ranked as the third most prevalent musculoskeletal disorder necessitating rehabilitation, following low back pain and fractures. The existing therapeutic interventions for cartilage repair exhibit limited efficacy and seldom achieve complete restoration of both functional capacity and tissue homeostasis. Emerging technological advancements in the field of tissue engineering hold significant promise for the development of viable substitutes for cartilage tissue, capable of exhibiting functional properties. The overarching strategy involves ensuring that the cell source is enriched with bioactive molecules that facilitate cellular differentiation and/or maturation. This review provides a comprehensive summary of recent advancements in the field of cartilage tissue engineering. Additionally, it offers an overview of recent clinical trials that have been conducted to examine the latest research developments and clinical applications pertaining to weakened articular cartilage and osteoarthritis.

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1. INTRODUCTION

The progressive nature of cartilage degeneration poses increasing challenges for physicians due to the limited self-regeneration capabilities of chondrocytes, the exclusive cellular constituents of cartilage, as well as the absence of blood vessels, nerves, and lymphatics. The degeneration of articular cartilage, which serves as a protective covering for synovial joints, is widely recognised as the most commonly observed form of cartilage deterioration Figure 1. The prevalence of articular cartilage damage poses a significant clinical concern, as it contributes to the progression of osteoarthritis. This condition is ranked third among musculoskeletal disorders requiring rehabilitation, following low back pain and fractures [1]–[3].

Additionally, the prevalence of articular cartilage degradation and the propensity for osteoarthritis are further exacerbated by the ageing global population. According to a study conducted in 2019, the prevalence of osteoarthritis in the adult population aged 30 years and above was estimated to be 320.7 million cases worldwide. Projections indicate that this figure is anticipated to increase to 367.7 million cases by the year 2028 [4].

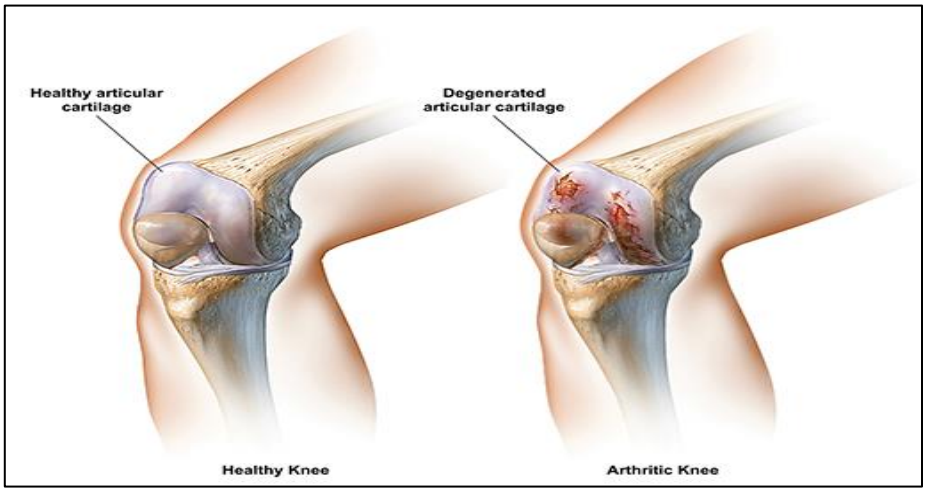

Figure 1. Degenerated articular cartilage

There are three distinct categories of restorative procedures utilised for the treatment of articular cartilage degradation. These categories include symptomatic medication, restorative interventions, and regenerative approaches. Anti-inflammatory medications, such as ibuprofen, acetaminophen, and ibuprofen, can be considered as illustrative examples of indicative pharmaceuticals. Restorative therapy encompasses various techniques, including microfracture, abrasion arthroplasty, drilling, osteochondral allograft transplantation, and mosaicplasty. On the other hand, regeneration treatment involves autologous chondrocyte implantation and matrix-induced autologous chondrocyte implantation. Restorative and regeneration techniques have been documented as effective means of treating chondral and subchondral defects, aiming to restore the original state of articular cartilage. However, these methods do not provide a comprehensive solution to halt the degeneration of articular cartilage. Consequently, tissue engineering approaches have been developed to tackle this concern. The field of articular cartilage tissue engineering has made substantial progress since its inception and is now being recognised as a promising avenue for restoring natural articular cartilage [5]–[7].

2. TISSUE ENGINEERING STRATEGIES FOR ARTICULAR CARTILAGE REGENERATION

The field of articular cartilage engineering has produced a diverse range of biomaterials, bio-fabrication techniques, and assessment methodologies [7], [8]. The objective of these advancements is to develop tissue that closely resembles natural articular cartilage in terms of its structural, biochemical, and mechanical properties. The following section provides a discussion on the ongoing clinical trials, in-vitro and in-vivo studies, as well as preclinical investigations that are being conducted to evaluate the efficacy and safety of synthetic cartilage tissue. Figure 2 illustrates various techniques utilised in the field of tissue engineering for the purpose of regenerating articular cartilage.

2.1. Scaffold-based strategies

Numerous scaffolds have been constructed for various applications in the fabrication of articular cartilage tissue [9], [10]. The primary purpose of these scaffolds is to induce cellular differentiation and proliferation, while simultaneously facilitating the controlled release of chondrogenic bioactive molecules. The primary objective of the study conducted by Nürnberger *et al.* (2021) [11] was to develop a scaffold possessing a distinct architecture capable of regulating the process of extracellular matrix formation and organisation in the context of cartilage defect repair. The accomplishment involved the incorporation of native articular cartilage extracellular matrix within trilayered zones through the utilisation of a CO_2 laser. The in vivo model of decellularized GAG-depleted fibre [11] demonstrates an enhanced capacity to direct the alignment of nascent fibres in a parallel orientation, thereby facilitating the regeneration of cartilage-like tissues.

The present study aimed to investigate the impact of recombinant transglutaminase 4 and synovial membrane-derived mesenchymal stem cells, which were encapsulated in a collagen-hyaluronan-fibrinogen hybrid, on an osteochondral defect in a rabbit model. The regenerative capacity of articular cartilage is augmented by the presence of recombinant human transglutaminase 4, as it possesses the capability to elevate the expression of integrin 1 and facilitate the reorganisation of actin [12]. The utilisation of human skin collagen as a structural framework holds potential for the cultivation of articular cartilage tissue. In their

study, Dang *et al*. (2021) [13] devised an experimental configuration wherein a dermal collagen sheet and adipose-derived mesenchymal stem cells were combined and cultivated on collagen substrates. The researchers discovered that the presence of cutaneous collagen had a significant impact on the shape and growth of chondrocytes in an in vitro setting.

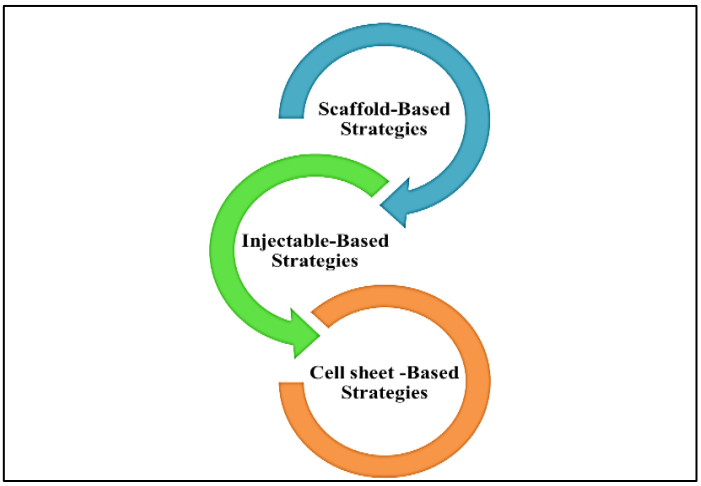

Figure 2. Articular cartilage tissue engineering strategies

Dufour *et al.* (2021) [14] incorporated chondrogenic mixes to treat fibrin and chondrocytes in their research study. The efficacy of self-assembling peptide scaffolds in conjunction with chondrocytes for the repair of osteochondral injury was demonstrated to a similar extent in both in vitro and in vivo experiments. Co-culturing, a novel advancement in cartilage tissue engineering methodologies, offers a means to address the limited regenerative capabilities of articular cartilage by preserving the chondrocyte phenotype and enhancing the regeneration of the extracellular matrix of cartilage. In their study, Owida *et al*. (2017) [15] conducted an in vitro investigation on a co-culture system involving mesenchymal stem cells and chondrocytes. This was achieved by integrating three distinct cultures of chondrocytes and mesenchymal stromal cells. According to the study conducted by [15], it was found that the co-culture method resulted in superior extracellular matrix formation in cartilage compared to single-cell cultures. In their study, Scalzone *et al*. (2019) [16] employed a thermo-sensitive hydrogel composed of chitosan-glycerophosphate to fabricate a three-dimensional scaffold in vitro. This scaffold was utilised for the encapsulation of mesenchymal stromal cells derived from bone marrow. Subsequently, the researchers combined these cells with spheroids of chondrocytes from human articular cartilage. The co-culture method demonstrated promising outcomes in the regeneration of cartilage, indicating a potential role for mesenchymal stromal cells in enhancing the metabolic activity of chondrocytes, which is frequently diminished in damaged tissues. The second category of co-culture model encompasses the interaction between chondrocytes and various other cell types [16]. The study conducted by Duan *et al*. (2021) [17] utilised rabbit chondrocytes and alginate spheres encapsulated with membranes. In order to assess the efficacy of the co-culture approach in the treatment of osteochondral lesions in white rabbit models, three tissue engineered constructs were subjected to in vivo testing, comparing their performance against chondrocytes and chondrons in isolation. The co-culture method demonstrated comparable efficacy to the use of chondrocytes in isolation in terms of collagen type II, aggrecan, and GAG production.

In the context of cell-free articular cartilage healing, it is common practise to utilise natural scaffolds, predominantly composed of collagen type I. In a study conducted by Szychlinska *et al.* (2020), [18] outbred rat models were utilised to investigate the effectiveness of collagen type I natural scaffolds in facilitating articular cartilage regeneration in vivo. The researchers observed that these scaffolds demonstrated biocompatibility and successfully attracted host cells for the regeneration process within the femoropatellar groove cartilage lesions. Previous studies have examined scaffolds composed of collagen type I, although these investigations were conducted in different experimental settings. In 2020, Wang *et al*. [19] employed a sheet technique utilising biological chondrocytes to facilitate osteochondral regeneration through the utilisation of allogeneic bone marrow mesenchymal stromal cells. The achievement was attained through the production of cell sheets, which were subsequently subjected to decellularization using sodium

dodecyl sulphate, resulting in the production of decellularized extracellular matrix scaffolds. In the experiment, it was observed that the application of sodium dodecyl sulphate (SDS) at a concentration of 0.5% yielded the most favourable outcomes in treating an osteochondral defect model in rabbits. The present study demonstrated that this particular concentration effectively promoted the restoration of both periosteal bone tissue and avascular articular cartilage, thereby contributing to overall tissue health. In a study conducted in 2018, Dai *et al.* [20] introduced an innovative scaffold composed of poly (lactide-co-glycolide) with microtubular pores arranged in a radial orientation [19]. Milner *et al.* (2018) [21] introduced a novel scaffold that emulates the mechanical properties exhibited by articular cartilage. The efficacy of this scaffold in facilitating the migration and distribution of bone marrow mesenchymal stromal cells was demonstrated in in vitro and in vivo studies utilising rabbit models with osteochondral defects. Comparatively, the observed migration and distribution were found to be more effective when compared to random poly (lactide-co-glycolide) scaffolds [20]. The fabrication and evaluation of an in vitro tri network hydrogel, comprising of two biphasic double network hydrogels and a polymer, were successfully conducted. The results demonstrated that the hydrogel displayed exceptional resistance properties and had the ability to prevent concurrent chondral injury during partial joint restoration [21]. Previous studies have demonstrated the augmentation of cell-free scaffolds through the concurrent administration of bioactive compounds. In a publication from 2019, Lolli *et al.* [22] conducted a study wherein they incorporated a miRNA inhibitor that targets miR-221 into a scaffold composed of fibrin/HA. This incorporation was done with or without the use of a lipofectamine carrier. The suppression of miR-221 in infiltrating cells provides benefits for calves with osteochondral abnormalities both in vitro and in vivo. This assertion holds particular validity when employing the lipofectamine carrier.

Jiang *et al*. (2021) [23] conducted a study examining the regenerative potential of articular cartilage injuries. Specifically, the researchers investigated the therapeutic efficacy of utilising exosomes derived from human Wharton's jelly mesenchymal stem cells in conjunction with an extracellular matrix and pig acellular cartilage scaffold. In this study, exosomes obtained from human Wharton's jelly mesenchymal stem cells were administered to sprague-dawley rat models to investigate their impact on the regulation of articular cartilage. Additionally, exosomes were incorporated into an acellular cartilage extracellular matrix scaffold implant and applied to rabbit models to examine their potential for articular cartilage repair. The studies conducted have demonstrated that exosomes derived from human Wharton's jelly mesenchymal stem cells possess properties that contribute to both anti-inflammatory effects and the regeneration of osteochondral tissues. Davachi *et al*. (2022) [24] employed enzymatic crosslinking utilising horseradish peroxidase to fabricate a scaffold composed of hyaluronic acid and chitosan, which exhibited properties reminiscent of cartilage. The in vitro assessment revealed that the expression of cartilage-like markers from mesenchymal stem cells exhibited greater promise when compared to the control samples [24]. Huang *et al*. (2022) [25] utilised a composite 3D-microenvironment by employing GelMA hydrogel incorporated with chondrocyte extracellular matrix microspheres that were modified with the peptide sequence PFSSTKT. The findings of in vitro studies have demonstrated that the composite of the 3D-microenvironment has the ability to modulate the migratory behaviour of mesenchymal stem cells derived from rabbit bone marrow. The utilisation of a 3D-microenvironment composite, in conjunction with mesenchymal stem cells derived from rabbit bone marrow, was found to be effective in repairing damaged tissue following a two-week period of in vivo grafting. In a study conducted on rabbits, the regeneration of hyaline cartilage was achieved through the use of a 3D-microenvironment composite. In contrast, the control group only exhibited restoration of fibrous tissue.

2.2. Injectable-based strategies

It is advisable to prioritise treatments for the recovery of articular cartilage that are minimally invasive, as they hold the potential to eventually supplant invasive surgical procedures. In the context of administering injectable treatments, it is customary to adhere to the practise of restricting the delivery of cells to the specific region that is affected [26]. In 2021, Wasai *et al.* [27] employed minimally invasive techniques to implant an allogeneic polydactyly-derived chondrocyte plug. The findings indicate that the administration of a chondrocyte plug derived from an individual with polydactyly does not exhibit a statistically significant impact on cell availability. The intra-articular injection of a chondrocyte plug derived from polydactyly presents itself as a potentially feasible and minimally invasive point-of-care treatment for osteoarthritis. In order to investigate the potential of weekly intra-articular injections of autologous adipose-derived mesenchymal stem cell sheets in preventing the onset of osteoarthritis in vivo, Takagi *et al*. (2020) [28] utilised a rabbit model. In contrast to the control group, the individuals who were administered adipose-derived mesenchymal stem cells exhibited significantly reduced cartilage degradation and a decelerated advancement of osteoarthritis. Köhnke *et al*. (2021) [29] conducted an in vivo study using a rabbit model to assess the efficacy of adipose-derived mesenchymal stem cell injections for the management of osteoarthritis in the temporomandibular joint. Following a one-month period of observation, it was observed that the most

effective method for regenerating articular cartilage was through the use of stem cells, particularly when they were implanted in hyaluronan. However, no statistically significant variations were found among the four groups in relation to tissue porosity and mineralization heterogeneity. Qu *et al*. (2021) [30] reported the utilisation of an alkaline treatment approach employing open-porous poly (lactide-co-glycolide) micro-particles for the purpose of delivering mesenchymal stromal cells derived from bone marrow. The outcomes of their study demonstrated enhanced healing of cartilage defects in a rat model of cartilage injury.

In their study, Co *et al*. (2021) [31] utilised injectable biomolecules within a protective treatment strategy grounded in click chemistry, with the aim of mitigating post-traumatic osteoarthritis. A two-pronged strategy was devised, involving the utilisation of polyethylene glycol to specifically target and eliminate chondrocytes that were metabolically inactive, followed by the transplantation of metabolically active chondrocytes to the affected region. Autogenic cartilage implantation has demonstrated favourable outcomes in the context of post-traumatic osteoarthritis defects, particularly in relation to the mitigation of cartilage damage. Furthermore, advanced methodologies incorporated bioactive compounds to enhance the process of articular cartilage repair. In a recent publication by Xu *et al*. (2021) [32], a novel tissue engineering strategy was examined for the treatment of osteoarthritis. The study focused on the manipulation of exosomes to incorporate peptide synthesis derived from mesenchymal stromal cells associated with osteoarthritis. The presence of an inferiority complex was substantiated through the utilisation of in vitro and in vivo investigations employing S rat models of knee osteoarthritis. The method of keratogenic transfer has been proposed as a technique for the restoration of cartilage, as described in reference.

Yuan *et al*. (2021) [33] conducted a study on the utilisation of cell-free injectables in animal models to investigate cartilage abnormalities in mice and rabbits. The researchers successfully employed an innovative, low-risk, and highly effective one-step ultrasonication crosslinking technique for the repair of damaged cartilage tissue. In their study, Schaeffer *et al*. (2020) [34] administered micro-porosity annealed particle gel via injection into the knee joint of sprague-dawley rat models. Subsequently, they subjected the gel to light annealing in order to assess its potential as a non-cellular injectable therapy for articular cartilage injury. In comparison to saline injections, the utilisation of microporous annealed particle hydrogels demonstrated enhanced and sustained integration within defects. Several researchers directed their efforts towards the development and characterization of injectable nanocomposite hydrogels.

In 2021, Tang *et al.* [35] developed a thermosensitive hydrogel composed of poly (l,d-lactide)-poly(ethylene glycol)-poly(d,l-lactide) to enhance the administration of platelet lysate. The experiments conducted on rats regarding osteoarthritis and osteochondral osteoarthritis demonstrated satisfactory preservation of cartilage tissue in the initial stages of cartilage degeneration, as well as expedited regeneration of cartilage during the later stages of osteoarthritis. In order to address full-thickness cartilage damage, Wu *et al.* (2020) [36] devised a strategy involving the integration of a hyaluronan hydrogel, resembling an injectable capsule, in conjunction with poly (lactide-co-glycolide) particles. The system underwent evaluation using rabbit models, yielding favourable outcomes.

Zhou *et al.* (2022) [37] developed a hydrogel composed of a three-dimensional microenvironment of catechol-modified chitosan for the purpose of cartilage regeneration. The utilisation of bone mesenchymal stem cells encapsulated in a hydrogel matrix demonstrated promising potential in stimulating cellular proliferation and promoting the development of cartilage-like tissue in a rat experimental model. The results of the gross evaluation and histological analysis demonstrated that the hydrogel containing bone mesenchymal stem cells exhibited superior efficacy compared to the untreated group and hydrogel alone in the in vivo repair of cartilage lesions. In a similar manner, Bhattacharjee *et al.* (2022) [38] endeavoured to establish a non-surgical injectable approach for repairing articular cartilage injuries. This was achieved through the utilisation of adipose-derived stem cells and amnion membrane derived from human placentas. This study demonstrates the capacity of injectable hydrogels to facilitate the regeneration of cartilage tissue in a rat model of osteoarthritis [38]. It has been observed that the regenerative properties of hydrogel are comparable, and that the utilisation of injectable hydrogels exhibits a synergistic impact by concurrently promoting anti-inflammatory responses and chondrogenesis, thereby facilitating the regeneration of cartilage tissue.

2.3. Cell sheet-based strategies

Cell sheet technology is widely utilised in the field due to its ability to generate implantable cell sheets that are densely populated with high-density cells connected by a compact extracellular matrix, all achieved without the need for biomolecule catalysts [39], [40]. A recent study conducted by Wongin *et al.* (2021) [41] examined cell sheet technology in the context of generating chondrocyte sheet-cancellous bone tissues. The researchers cultivated a tri-chondrocyte sheet on cancellous bone to investigate the feasibility of this approach. To accomplish this objective, the researchers employed a rabbit model of cartilage injury. The findings of this study demonstrated that the utilisation of chondrocyte sheets facilitated the production of

cartilage resembling hyaline, while the implementation of chondrocyte sheet-cancellous bone tissues aided in the restoration of osteochondral damage. Takizawa *et al.* (2020) [42] conducted a study wherein they transplanted and analysed cell sheets composed of human chondrocytes. Additionally, the researchers investigated human synoviocytes as part of their investigation. According to the findings of these in vivo studies, it was observed that the number of cells in all groups decreased after a period of 12 weeks. Notably, only the chondrocyte-based sheet demonstrated the ability to effectively cover the lesions by combining articular cartilage and fibrous tissue. The cell sheet technique has been commonly utilised for both mesenchymal stromal cells and differentiated cells. In the year 2020, Thorp *et al.* [43] successfully isolated mesenchymal stromal cells from bone marrow and employed them in the fabrication of cartilaginous cell sheet constructs. Human articular cartilage is utilised to verify the occurrence of chondrogenesis, the preservation of cartilaginous potential, and the natural adhesion of the articular membrane. In the year 2020, an endeavour was undertaken by you and your team to further explore the application of human amniotic mesenchymal stem cells in the field of cell sheet technology. Subsequently, cell sheets originating from human amniotic mesenchymal stem cells were impregnated with cartilage particles and subjected to assessment within a rabbit model of hyaline cartilage injury. The results indicated that the combination of human amniotic mesenchymal stem cell sheets and cartilage particles exhibited the capacity to regenerate structurally and histologically sound cartilage and subchondral bone. Cell sheet technology is widely employed in this context due to its ability to generate implantable sheets of cells that exhibit a high cell density, facilitated by a dense extracellular matrix, without the need for biomolecule catalysts [39], [40].

Wongin *et al.* (2021) [41] conducted a recent study investigating cell sheet technology, specifically focusing on the cultivation of a tri-chondrocyte sheet on cancellous bone. The objective of this investigation was to evaluate the potential of this approach in generating chondrocyte sheet-cancellous bone tissues. To accomplish this objective, investigators employed a rabbit model of cartilage injury, wherein the outcomes demonstrated that the implementation of chondrocyte sheets facilitated the production of cartilage resembling hyaline tissue. Additionally, the application of chondrocyte sheet-cancellous bone constructs exhibited efficacy in the restoration of osteochondral impairments. In a study conducted by Takizawa *et al*. (2020) [42], cell sheets consisting of human chondrocytes were transplanted and subsequently analysed. Additionally, the researchers investigated human synoviocytes as part of their investigation. According to the findings of this in vivo study, the cell count in all groups exhibited a decrease after a period of 12 weeks. Notably, only the chondrocyte-based sheet demonstrated the ability to effectively cover the lesions by combining articular cartilage and fibrous tissue. The cell sheet technique has been commonly utilised for both mesenchymal stromal cells and differentiated cells. In 2020, Thorp *et al*. [43] successfully isolated mesenchymal stromal cells from bone marrow and employed them in the fabrication of cartilaginous cell sheet constructs. The utilisation of human articular cartilage serves as a means to validate chondrogenesis, assess the preservation of cartilaginous potential, and examine the natural adhesion of the articular membrane. In the year 2020, an endeavour was undertaken by you and your team to further explore the application of human amniotic mesenchymal stem cells in the field of cell sheet technology. Subsequently, cell sheets originating from human amniotic mesenchymal stem cells were infused with cartilage particles and assessed within a rabbit model of hyaline cartilage injury. The study conducted by researchers utilised a sheet-cartilage particle complex to investigate the regenerative capabilities of human amniotic mesenchymal stem cells in relation to cartilage and subchondral bone regeneration [44]. Table 1 presents advantages and disadvantages of articular cartilage tissue engineering approaches.

Table 1. Representative of advantages and disadvantages of articular cartilage tissue engineering approaches

Articular cartilage tissue engineering approaches	Advantages	Disadvantages
Scaffold-dependent approaches	- Provide 3D microenvironment which is mimicking native articular cartilage tissue structure - Promote cell growth and differentiation and to deliver bioactive molecules that promote chondrogenesis - Mimicking the articular cartilage's mechanical properties	- The long-term safety of the scaffold - Undefined degradation rate - Potential toxic degradation of by-products - Potential of immune resistance
Injectable-dependent approaches	- Cells can be delivered to the defect site only - Minimally invasive or non-invasive surgical procedures for articular cartilage regeneration	- Undefined degradation rate - Potential toxic degradation of by-products - Potential of immune resistance - No immediate structural and biomechanical alteration
Cell sheet approaches	- Extensive cellular resources and a rapid proliferative rate and capacity for chondrogenic differentiation - No immune resistance - Promotes proliferation and accelerates chondrogenesis	- No immediate structural and lack of the articular cartilage's mechanical properties - Potential disease transmission - Limitations in clinical trials experiments

3. CONCLUSION

Despite significant advancements in the field of articular cartilage tissue design over the past twenty years, there remain several obstacles that must be surmounted prior to its practical application in clinical contexts. The tissue of articular cartilage is not inherently intended for direct translation or replication in the process of translating research findings to clinical applications. The intricate nature of articular cartilage tissue presents challenges that cannot be easily overcome in the transition from research findings to clinical applications. Unlike other tissues, articular cartilage is not inherently designed for straightforward translation or replication, adding complexity to the process of developing clinically viable solutions.

The challenges encountered in translational research underscore the limited transferability observed when attempting to analyze and address barriers in the field. For instance, the turnover of chondrocytes poses potential risks such as damage to mitochondria or the endoplasmic reticulum, cellular demise, or an increase in reactive oxygen species levels. Another complication arises from discerning alterations in articular cartilage due to natural maturation versus changes in the extracellular matrix.

To effectively address aberrations in cartilage resulting from dysfunctions in the extracellular matrix, the adoption of multiplex tissue design techniques may be necessary. Moreover, when it comes to assessing and managing joint injuries, arthroscopic visualization remains the primary modality beyond the knee joint. However, despite advancements, investigating articular cartilage injuries before the onset of osteoarthritis has proven unproductive across laboratory experiments, animal studies, and clinical environments. This challenge persists due to the utilization of models that may not authentically replicate abnormalities, irrespective of the specific research setting. Furthermore, it is paramount to replicate experiments across a spectrum of settings, including in vitro, ex vivo, and clinical in vivo environments, while also conducting extensive preliminary investigations and long-term follow-up studies in clinical settings. Emphasizing long-term recovery outcomes takes precedence over short-term symptomatic improvements and radiological assessments in clinical decision-making.

Moreover, incorporating accessibility considerations introduces further complexities to the challenges previously discussed. Given the vast body of research and the diverse components and advancements in tissue design, the field of cell-based tissue design poses significant hurdles. Non-cellular tissue engineering, while promising, faces limitations such as a scarcity of research studies, a predominant focus on collagen type I platforms, and a limited understanding of its underlying mechanisms and comparative advantages compared to cell-based tissue engineering and other existing interventions. Various additional factors, including modifications in organisms and their microenvironment, can influence the adaptability of organisms and subsequently impact the clinical interpretation of these findings. Therefore, comprehensive investigations and analyses are necessary to fully understand the implications and potential applications of tissue engineering approaches in clinical practice. The recreation of the articular cartilage microenvironment stands as a pivotal step toward achieving robust cartilage regeneration. The intricacies of articular cartilage tissue design offer numerous potential advantages in addressing the challenges associated with treating and preventing cartilage degeneration. However, it is essential to acknowledge that this innovative approach comes with a few associated limitations that warrant careful consideration and further exploration. Despite these challenges, the prospect of recreating the articular cartilage microenvironment holds great promise for advancing the field of regenerative medicine and improving the quality of life for individuals affected by cartilage-related disorders.

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