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Review Article

Advancements in cartilage regeneration: A comprehensive review of biological therapies and clinical applications

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Abstract

The main purpose of this review paper is to explore the recent advancements in cartilage regeneration techniques, focusing on stem cell therapy, platelet-rich plasma (PRP), gene therapy, and growth factor delivery. The research question addresses how these biological therapies can overcome the current limitations in cartilage repair and enhance clinical outcomes.

The review conducted an extensive literature search using databases such as PubMed, Scopus, and Web of Science. The methodologies of the included studies were critically analyzed to assess their effectiveness and limitations.

The findings indicate that stem cell therapy, particularly using mesenchymal stem cells, shows promise in enhancing cartilage repair through their differentiation potential and paracrine effects. PRP has been found to improve joint function and reduce pain, especially when combined with hyaluronic acid or stem cells. Gene therapy utilizing CRISPR/Cas9 technology presents a novel approach for precise gene modification, potentially improving cartilage repair mechanisms. Growth factor delivery systems, including hydrogels, have demonstrated the ability to enhance chondrogenesis and tissue regeneration.

Keywords: Cartilage Regeneration, Stem Cell Therapy, Mesenchymal Stem Cells (MSCs), Biomaterials, Platelet-Rich Plasma (PRP), Orthopedic Innovations

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1. Introduction

Recent advancements in biological therapies have shown promising results in enhancing cartilage repair and regeneration. Stem cell therapy, particularly with mesenchymal stem cells (MSCs), has garnered significant attention due to their ability to differentiate into chondrocytes and modulate the inflammatory environment. MSCs can be isolated from various tissues, including bone marrow, adipose tissue, and synovium, and have shown potential in both preclinical and clinical studies for cartilage repair.[1] Platelet-rich plasma (PRP) therapy, which involves the use of autologous blood with concentrated platelets, has also been investigated for its ability to release growth factors that promote tissue healing and regeneration.[2] Gene therapy represents another innovative approach, with recent advancements in gene editing technologies such as CRISPR/Cas9 offering new possibilities for targeted treatment. It aims to enhance cartilage repair by modulating gene expression to promote chondrocyte function and reduce inflammation.[3] The use of growth factors and cytokines, such as transforming growth factor-beta (TGF-β) and bone morphogenetic proteins (BMPs), has also been explored for their potential to stimulate chondrocyte proliferation and matrix synthesis.[4] Factors influencing the efficacy of these treatments include the source and quality of cells, the delivery method, and the patient's specific condition.[5-6] 3D bioprinting allows for the precise fabrication of scaffolds that mimic the native cartilage structure, providing an optimal environment for cell growth and tissue regeneration.[6]

The objective of this review is to provide a comprehensive overview of recent advancements in cartilage regeneration, focusing on the various biological therapies that have been developed. The scope of the review encompasses both preclinical studies and clinical trials, highlighting the mechanisms, clinical applications, and outcomes of these therapies. Additionally, emerging trends and future directions in the field, such as the integration of gene therapy, 3D

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bioprinting, and personalized medicine strategies, are discussed. The development of effective therapies for cartilage regeneration is crucial for improving the quality of life for patients suffering from cartilage injuries and degenerative diseases like osteoarthritis.

2. Overview of Biological Therapies

Biological and non-biological therapies for cartilage regeneration encompass a range of treatments that use biological agents to repair and regenerate damaged cartilage. These therapies have evolved significantly over the past few decades, with early research focusing on the use of autologous chondrocyte implantation (ACI) and progressing to more advanced techniques involving stem cells, PRP, gene therapy, and growth factors. (**Figure 1**Fig. 1 & Table 1)

2.1. Stem cell therapy

Stem cell therapy has emerged as a promising approach for cartilage regeneration, primarily focusing on the use of mesenchymal stem cells (MSCs) due to their ability to differentiate into chondrocytes, the cells responsible for cartilage formation. MSCs can be derived from various sources, including bone marrow, adipose tissue, and synovial fluid, each offering unique advantages (**Figure 2**Fig. 2). Bone marrow-derived MSCs are well-studied and have shown significant potential in cartilage repair due to their high chondrogenic capacity and ability to secrete bioactive molecules that modulate the immune response and reduce inflammation.[1,7-9] Recent advancements have explored the use of biomaterials such as hydrogels and nanofibers that release growth factors like transforming growth factor-beta (TGF-β) and bone morphogenetic protein (BMP) in a controlled manner, further enhancing MSC chondrogenesis.[10] Moreover, preconditioning MSCs with specific growth factors or mechanical stimuli before implantation can improve their differentiation potential and promote better integration with host tissues.[11]

Clinical studies have demonstrated the potential of stem cell therapy in cartilage repair.[12] Scaffold-based approaches, where stem cells are seeded onto biomaterial scaffolds, have shown enhanced cartilage regeneration in animal models and early clinical trials.[13] Numerous studies have explored the efficacy of stem cell therapy for cartilage regeneration. A notable study by Wakitani et al.[14] reported successful cartilage repair in patients with knee osteoarthritis following autologous MSC transplantation. Another study by Emadedin et al.[15] demonstrated improved clinical outcomes in patients with knee osteoarthritis treated with intra-articular injection of autologous MSCs. These include the need for standardized protocols for cell isolation and expansion, optimizing delivery methods, and ensuring long-term safety and efficacy. Future research aims to address these issues and explore the use of combination therapies, such as stem cells with growth factors or gene therapy, to enhance therapeutic outcomes.[16]

2.2. Platelet-rich plasma (PRP)

Platelet-rich plasma (PRP) therapy is a regenerative medicine approach that leverages the body's natural healing processes. PRP is derived from the patient's own blood, which is centrifuged to concentrate platelets and growth factors (**Figure 3**Fig. 3). These concentrated platelets are then injected into the damaged cartilage area, where they release a variety of growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF), which are crucial for cell proliferation, angiogenesis, and tissue regeneration.[5]

PRP therapy is particularly beneficial in treating degenerative conditions like osteoarthritis (OA), where it has been shown to reduce pain and improve joint function.[2] PRP is often considered for patients who have not responded to conventional treatments and offers a minimally invasive option with a relatively low risk of adverse effects. The biological activity of PRP enhances the repair process by improving the function of chondrocytes and increasing the synthesis of cartilage matrix components.[17] The clinical effectiveness of PRP can vary depending on the preparation method, platelet concentration, and the specific condition being treated. Studies have demonstrated that leukocyte-poor PRP might offer better outcomes for joint disorders as it reduces the inflammatory response typically associated with leukocyte-rich PRP.[18] Research continues to refine PRP formulations and explore its combination with other regenerative therapies, such as stem cells and scaffold-based techniques, to maximize cartilage repair potential.[19-21]

2.3. Gene therapy

Gene therapy for cartilage regeneration involves the delivery of genes encoding therapeutic proteins to enhance tissue repair and regeneration.[22] Gene therapy offers a cutting-edge approach to cartilage regeneration by targeting and modifying specific genes involved in cartilage degeneration and repair. Recent advances in gene editing technologies, such as CRISPR/Cas9, have enabled precise modification of specific genes involved in cartilage degradation, such as matrix metalloproteinases (MMPs). By knocking out or downregulating these genes, researchers aim to reduce the breakdown of cartilage matrix and promote tissue repair.[4] Furthermore, gene therapy can be used to deliver anti-inflammatory cytokines, thereby reducing inflammation and slowing the progression of degenerative diseases like osteoarthritis.[23] Although gene therapy holds great promise, there are challenges to be addressed, including ensuring efficient and targeted delivery of therapeutic genes, minimizing immune responses, and maintaining long-term gene expression. Ongoing research is focused on developing safer and more efficient vectors, as well as exploring combination therapies that integrate gene therapy with other regenerative techniques to enhance cartilage repair.[24]

nde et al.[33] demonstrated the potential of growth factor therapy in treating cartilage lesions. The researchers reported that the use of TGF-β led to significant improvements in cartilage repair in a rabbit model. Another study by Orth et al.[34] found that the use of BMP-2 enhanced cartilage regeneration in a rat model. Future research aims to develop advanced delivery systems, such as biomaterial scaffolds and nanoparticles, and explore the use of combination therapies to enhance efficacy.[35]

2.5. Autologous chondrocyte implantation (ACI)

Autologous chondrocyte implantation (ACI) is a well-established technique used to treat cartilage defects, particularly in the knee. The procedure involves harvesting healthy chondrocytes from a non-weight-bearing area of the joint, expanding them in vitro, and implanting them into the damaged area (**Figure 4**Fig. 4). This approach aims to regenerate cartilage by utilizing the patient's own cells, thereby minimizing the risk of immune rejection and adverse immune responses.[36] The ACI procedure consists of two main stages. First, a small biopsy of healthy cartilage is taken from the patient. The chondrocytes are then isolated, cultured, and expanded over a period of weeks in a laboratory setting. In the second stage, the cultured chondrocytes are implanted into the defect, where they are expected to produce new cartilage matrix and integrate with the surrounding tissue.[37]

Over the years, ACI has evolved with advancements such as matrix-assisted ACI (MACI), where the cells are embedded in a scaffold made of biodegradable materials before implantation. This scaffold supports the chondrocytes and enhances the distribution and retention of the cells within the defect.[38-39]

2.6. Microfracture surgery

However, the long-term success of microfracture is limited, as fibrocartilage lacks the mechanical properties and durability of native hyaline cartilage. Over time, the fibrocartilage can degenerate, leading to recurrent symptoms. Additionally, microfracture is generally less effective for larger defects or in older patients, where the regenerative capacity is diminished.[40] Despite these limitations, microfracture remains a widely used procedure due to its cost-effectiveness and ability to provide temporary relief from symptoms (**Figure 5**Fig. 5). Recent research is focused on enhancing the outcomes of microfracture by combining it with other regenerative techniques, such as the application of scaffolds or biologics like platelet-rich plasma (PRP) to improve the quality of the repair tissue.[41-42]

2.6. Osteochondral autograft transplantation (OAT)

Osteochondral autograft transplantation (OAT) involves transferring healthy cartilage and subchondral bone from a non-weight-bearing area of the joint to the damaged area (**Figure 6**Fig. 6). This technique is particularly useful for treating focal cartilage defects, as it allows for the transplantation of mature hyaline cartilage, which closely resembles the native cartilage in its structure and function.[43] The OAT procedure involves harvesting one or more cylindrical plugs of healthy cartilage and bone from the donor site and implanting them into the defect. The plugs are typically harvested from the patient's own joint, ensuring compatibility and reducing the risk of immune rejection. The transplanted cartilage provides an immediate restoration of the joint surface, while the underlying bone integrates with the surrounding tissue to provide structural support (Matsusue et al., 1993).[44]

While OAT can be effective for small to medium-sized defects, its application is limited by the availability of donor tissue and potential morbidity at the harvest site. Additionally, there is a risk of graft failure or incomplete integration, particularly in larger defects or in patients with underlying joint pathology.[45-46]

2.7. Osteochondral allograft transplantation

Osteochondral allograft transplantation involves the use of donor tissue from a cadaver to repair large cartilage defects that cannot be adequately treated with autografts. This technique allows for the transplantation of mature hyaline cartilage along with the underlying bone, providing both structural support and immediate restoration of the joint surface.[47] Allograft transplantation is particularly useful for treating large or complex defects, as it provides a larger amount of donor tissue without the morbidity associated with harvesting autografts. Additionally, allografts can be shaped to fit the defect precisely, allowing for a more anatomically accurate repair.[48] The use of fresh or cryopreserved allografts can also facilitate the transplantation of viable chondrocytes, enhancing the regenerative potential of the graft.[49]

Long-term outcomes of allograft transplantation can be variable, and research is ongoing to improve graft preservation techniques and to develop immunomodulatory strategies to enhance graft integration.[50]

2.8. Tissue engineering and scaffold-based approaches

Tissue engineering represents a promising frontier in cartilage regeneration, utilizing a combination of cells, biomaterials, and bioactive molecules to repair or replace damaged cartilage. This multidisciplinary approach aims to create functional tissue constructs that can integrate with the host tissue and restore normal joint function. Scaffold-based approaches are central to tissue engineering, providing a three-dimensional framework that supports cell attachment, proliferation, and differentiation.[51] Scaffolds are typically made from biocompatible materials such as collagen, hyaluronic acid, or synthetic polymers like polylactic acid (PLA) and polyglycolic acid (PGA). These materials can be engineered to mimic the natural extracellular matrix of cartilage, promoting the development of new tissue with appropriate mechanical and biological properties. Scaffold

design can also incorporate growth factors and other bioactive molecules to enhance chondrogenesis and guide tissue development.[52]

Advancements in scaffold fabrication techniques, such as 3D printing and electrospinning, allow for the creation of complex structures with tailored porosity and mechanical properties. This enables the design of scaffolds that can be customized to the specific needs of individual patients and defect geometries.[53] Furthermore, scaffolds can be seeded with various cell types, including chondrocytes, mesenchymal stem cells, and induced pluripotent stem cells (iPSCs), to facilitate tissue formation.[54-55]

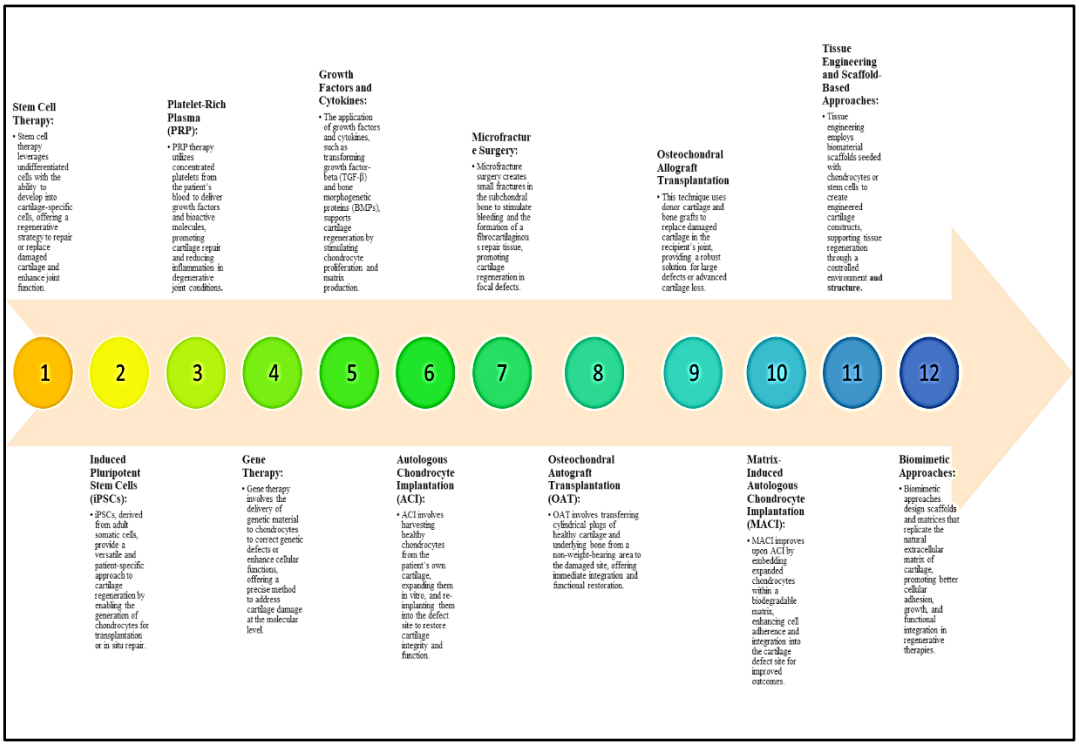

Figure 1: List of techniques used in cartilage regeneration

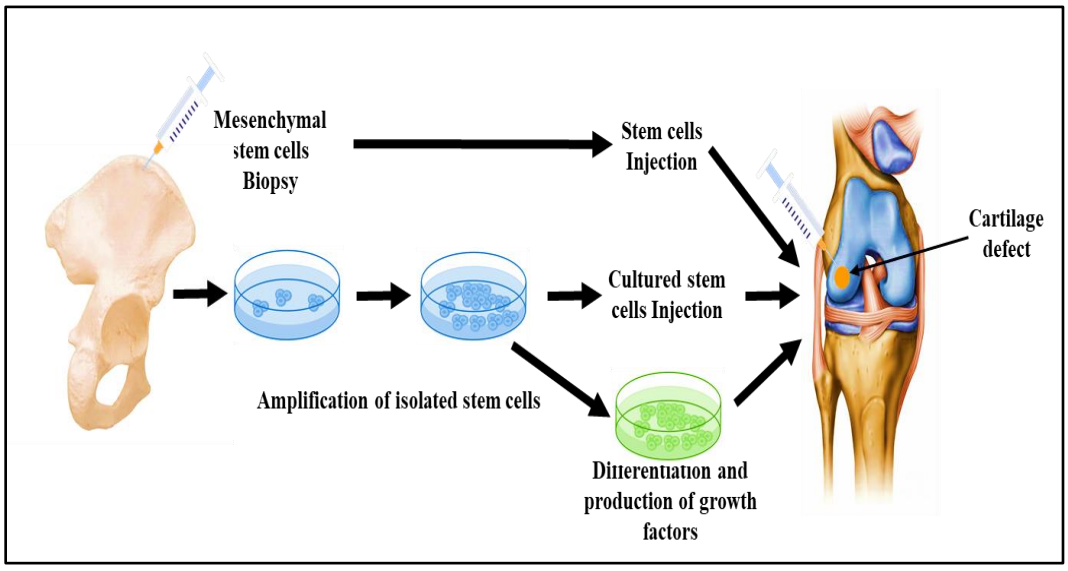

Figure 2: Schematic representation of cell therapy for cartilage based on stem cell implantation and growth factors.

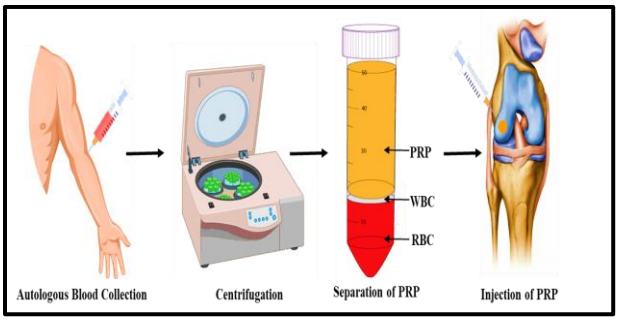

Figure 3: Schematic representation of PRP therapy for cartilage injury

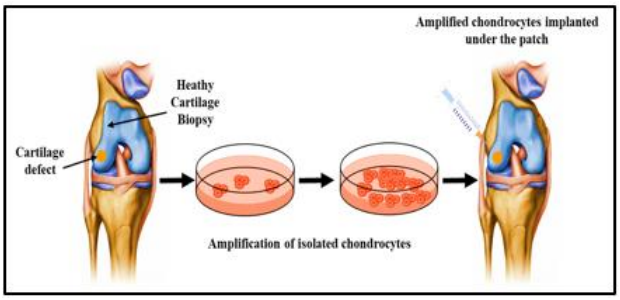

Figure 4: Steps of autologous chondrocyte implantation (ACI)

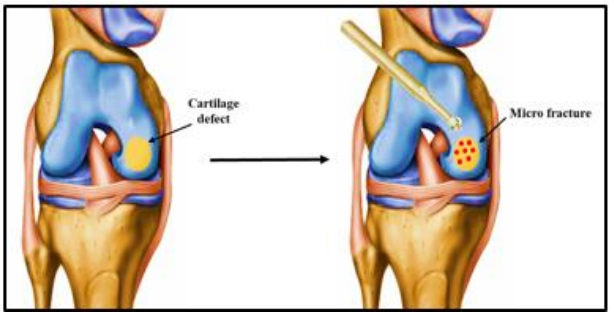

Figure 5: Micro fracture technique/Bone marrow stimulation technique

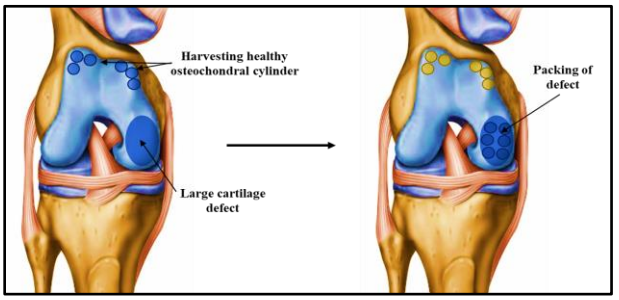

Figure 6: Osteochondral autograft transplantation (OAT)/ mosaicplasty

Table 1: Recent study in cartilage regeneration techniques.

Sr. no.	Researchers	Technique	Details	Outcomes
Mesenchymal Stem Cells (MSCs)				
1	Jo et al.[12]	Intra-articular injection of MSCs	Reduced pain and improved function in osteoarthritis patients	Improved clinical outcomes
2	Wu et al.[13]	Scaffold-based MSC therapy	Enhanced cartilage regeneration in animal models and early clinical trials	Significant cartilage repair
3	Jiang et al.[8]	Adipose-derived MSCs	Noted for their abundance and ease of harvest, showing promise in clinical applications	Positive clinical outcomes
Platelet-Rich Plasma (PRP)				
1	Bennell et al.[5]	PRP injections	Demonstrated significant improvements in knee osteoarthritis patients	Reduced pain and improved function
2	Cerza et al.[1]	PRP vs. hyaluronic acid	PRP more effective in reducing pain and improving function	Superior efficacy of PRP
3	Khoshbin et al. [18]	Leukocyte-poor PRP	Found better outcomes for joint disorders compared to leukocyte-rich PRP	Better clinical outcomes
Gene Therapy				
1	Barry et al.[4]	CRISPR/Cas9 gene editing	Targeted modification of genes involved in cartilage degradation	Effective gene modification
2	Liu et al.[23]	Anti-inflammatory cytokines	Reducing inflammation and slowing osteoarthritis progression	Reduced inflammation and disease progression
3	Madry et al.[24]	Gene therapy with other regenerative techniques	Explored combination therapies to enhance cartilage repair	Enhanced cartilage regeneration
4	Pagnotto et al.[2]	Gene editing with AAV vectors	Improved cartilage repair by targeting specific genes	Enhanced tissue regeneration and function
Hydrogels				

3	Eslahi et al.[6]	Smart hydrogels	Responded to environmental stimuli to enhance cartilage repair	Dynamic response for better outcomes
Tissue Engineering				
1	Daly et al.[9]	Bioprinting	Precise control over scaffold architecture for cartilage regeneration	Improved cartilage formation
Growth Factors				
1	Fortier et al.[30]	BMP-7 delivery	Positive outcomes in a goat model of cartilage injury	Improved cartilage repair outcomes
2	Madry et al.[27]	TGF-β gene delivery	Successful cartilage regeneration in rabbit model	Enhanced cartilage repair
3	Chen et al.[35]	Growth factor-loaded hydrogels	Enhanced cartilage repair and regeneration in vitro and in vivo	Significant improvement in cartilage quality
Allograft Transplantation				
1	Assenmacher et al.[48]	Osteochondral allograft transplantation	Use of donor tissue to repair cartilage defects	Effective for large and complex defects

11. Biomimetic approaches

Biomimetic approaches to cartilage regeneration aim to replicate the natural structure and function of cartilage by designing materials and systems that mimic the biological and mechanical properties of native tissue. These approaches draw inspiration from the natural cartilage matrix, which is composed of collagen fibers, proteoglycans, and a network of chondrocytes embedded within a hydrated gel-like matrix.[56] Biomimetic scaffolds are engineered to provide a supportive environment that encourages the growth and differentiation of chondrocytes or stem cells into cartilage tissue. These scaffolds often incorporate nanostructured materials and bioactive molecules that promote cell adhesion, proliferation, and matrix production.[57] For example, scaffolds can be functionalized with peptides that mimic the natural binding sites of growth factors or extracellular matrix components, enhancing their ability to support tissue development.[58]

The use of hydrogels in biomimetic cartilage regeneration has gained attention due to their high water content and ability to simulate the viscoelastic properties of cartilage. Hydrogels can be designed to release bioactive molecules in a controlled manner, providing sustained stimulation for tissue growth and repair.[59] Moreover, advances in material science have led to the development of smart hydrogels that respond to environmental stimuli, such as temperature or pH changes, to enhance tissue regeneration.[60] Researchers are exploring the use of multi-functional materials and hybrid systems that combine the advantages of different biomaterials to create more effective and durable cartilage repair solutions.

3. Future Perspectives

Emerging trends in research include the development of combination therapies, the use of advanced biomaterials for controlled delivery of biological agents, and the exploration of gene editing technologies for precise and targeted treatment. These approaches hold promise for improving the efficacy and safety of biological therapies for cartilage regeneration. Personalized medicine approaches aim to tailor treatments to individual patients based on their genetic, molecular, and clinical profiles. This approach has the potential to enhance the effectiveness of biological therapies for cartilage repair and improve patient outcomes. Integration of multidisciplinary approaches, including tissue engineering, regenerative medicine, and biomedical engineering, is essential for advancing the field of cartilage regeneration. Collaborative efforts between researchers, clinicians, and industry partners can drive innovation and accelerate the translation of new therapies to clinical practice.

4. Conclusion

Biological therapies hold great promise for the regeneration of damaged cartilage and the treatment of various cartilage injuries. Advances in stem cell therapy, PRP, gene therapy, and growth factor delivery have shown promising results in preclinical and clinical studies. However, several challenges remain, including the need for standardized protocols, improved delivery methods, and addressing biological barriers. Future research should focus on overcoming these challenges, exploring combination therapies, and advancing personalized medicine approaches to improve patient outcomes. Continued collaboration between researchers, clinicians, and industry partners will be essential for the successful translation of biological therapies for cartilage regeneration to clinical practice.

5. Source of Funding

None.

6. Conflict of Interest

None.

References

1. Cerza F, Carni S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, Ciuffreda M. Comparison between hyaluronic acid and platelet-rich

plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med.* 2012;40(12):2822-7.
2. Pagnotto MR, Wang Z, Karpie JC, Ferretti M, Xiao X, Chu CR. Adeno-associated viral gene transfer of transforming growth factor-β1 to human mesenchymal stem cells improves cartilage repair. *Gene ther.* 2007;14(10):804-13.
3. Zhao L, Huang J, Fan Y, Li J, You T, He S. Exploration of CRISPR/Cas9-based gene editing as therapy for osteoarthritis. *Ann Rheum Dis.* 2019;78(5):676-82.
4. Barry F, Murphy M. Mesenchymal stem cells in cartilage regeneration: A comprehensive review. *Nat Rev Rheumatol.* 2013;9(9):568-79.
5. Bennell KL, Paterson KL, Metcalf BR, Duong V, Eyles J, Kasza J. Effect of intra-articular platelet-rich plasma vs placebo injection on pain and medial tibial cartilage volume in patients with knee osteoarthritis: the RESTORE randomized clinical trial. *Jama.* 2001;326(20):1-15.
6. Eslahi N, Abdorahim M, Simchi A. Smart polymeric hydrogels for cartilage tissue engineering: a review on the chemistry and biological functions. *Biomacromolecules.*2016;17(11):3441-63.
7. Harrell CR, Fellabaum C, Arsenijevic A, Volarevic V. Mesenchymal stem cell-based therapy of osteoarthritis: Current knowledge and future perspectives. *Biomed Pharmacother*. 2019;109:2318-26.
8. Jiang S, Tian G, Li X, Yang Z, Wang F, Tian Z, Huang B. Research progress on stem cell therapies for articular cartilage regeneration. *Stem Cells Int.* 2021;(1):8882505.
9. Daly AC, Freeman FE, Gonzalez-Fernandez T, Critchley SE, Nulty J, Kelly DJ. 3D bioprinting for cartilage and osteochondral tissue engineering. *Adv Healthc Mater.* 2017;6(22):1700298.
10. Guo X, Xi L, Yu M, Fan Z, Wang W, Ju A, Liang Z, Zhou G, Ren W. Regeneration of articular cartilage defects: Therapeutic strategies and perspectives. *J Tissue Eng*. 2023;14:20417314231164765.
11. Perdoni C, McGrath JA, Tolar J. Preconditioning of mesenchymal stem cells for improved transplantation efficacy in recessive dystrophic epidermolysis bullosa. *Stem Cell Res Ther.* 2014;5(6):1-2.
12. Jo CH, Lee YG, Shin WH, Kim H, Chai JW, Jeong EC Shim H. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. *Stem Cells.* 2014'32(5):1254-66.
13. Wu CC, Sheu SY, Hsu LH, Yang KC, Tseng CC, Kuo TF. Intra-articular Injection of platelet-rich fibrin releasates in combination with bone marrow-derived mesenchymal stem cells in the treatment of articular cartilage defects: An in vivo study in rabbits. *J Biomed Mater Res B* 2017;(6):1536-43.
14. Wakitani S, Kawaguchi A, Tokuhara Y, Takaoka K. Present status of and future direction for articular cartilage repair. *J Bone Miner*. 2008;26(2):115-122.
15. Emadedin M, Aghdami N, Taghiyar L, Rezazadeh K, Farjad R, Verdi J, Baharvand H. Intraarticular injection of autologous mesenchymal stem cells in six patients with knee osteoarthritis: A pilot study. *J Bone J Surg,* 2012;31(1):508-514.
16. Murphy MB, Moncivais K, Caplan AI. Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. *Exp Mol Med*. 2013;45(11):e54.
17. Dai WL, Zhou AG, Zhang H, Zhang J. Efficacy of platelet-rich plasma in the treatment of knee 7osteoarthritis: a meta-analysis of randomized controlled trials. *Arthroscopy*. 2013;33(3): 659-70.
18. Khoshbin A, Leroux T, Wasserstein D, Marks P, Theodoropoulos J, Ogilvie-Harris D. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. *Arthroscopy.* 2013;29(12): 2037-48.
19. Xiong Y, Gong C, Peng X, Liu X, Su X, Tao X. Efficacy and safety of platelet-rich plasma injections for the treatment of osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Front Med.* 2023;10:1204144.
20. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, Plateletrich plasma intraarticular injection versus hyaluronic acid visco supplementation as treatments for cartilage pathology: From early degeneration to osteoarthritis. *Arthroscopy.* 2011;27(11):1490-501.
21. Cavallo C, Roffi A, Grigolo B, Mariani E, Pratelli L, Merli G. Filardo G. Platelet-rich plasma: the choice of activation method affects the release of bioactive molecules. *Biomed Res Int.* 2016;(1): 6591717.
22. Evans CH, Huard J. Gene therapy approaches to regenerating the musculoskeletal system. *Nat Rev Rheumatol.* 2015;11(4):234-42.
23. Liu S, Deng Z, Chen K, Jian S, Zhou F, Yang Y. Cartilage tissue engineering: From proinflammatory and anti-inflammatory cytokines to osteoarthritis treatments. *Mol Med Rep*. 2022;25(3):1-5.
24. Madry H, Orth P, Cucchiarini M. Gene therapy for cartilage repair. Cartilage 2011;2(3):201-225.
25. Evans CH, Robbins PD Ghivizzani SC. Gene therapy for arthritis: What next? Arthritis Rheumatol. 2006;54(6):1714-29.
26. Robbins PD Ghivizzani SC (2006) Viral vectors for gene therapy. Pharmacol. Ther 80(1): 3547-3552.
27. Rodriguez-Merchan EC, Valentino LA. The role of gene therapy in cartilage repair. *Arch Bone J Surg.* 2019;7(2):79.
28. Li X, Shen L, Deng Z, Huang Z. New treatment for osteoarthritis: Gene therapy. *Precis Clin Med*. 2023;6(2):14.
29. Madry H, Cucchiarini M. Clinical potential and challenges of using genetically modified cells for articular cartilage repair. *Croat Med J.* 2014;52(3):245-61.
30. Fortier LA, Barker JU, Strauss EJ, McCarrel TM, Cole BJ. The role of growth factors in cartilage repair. *Clin Orthop Relat Res.* 2011;469(10):2706-15.
31. Liu S, Deng Z, Chen K, Jian S, Zhou F, Yang Y. Cartilage tissue engineering: From proinflammatory and anti-inflammatory cytokines to osteoarthritis treatments. *Mol Med Rep.* 2022;25(3):1-15.
32. Saris DB, Vanlauwe J, Victor J, Almqvist KF, Verdonk R, Bellemans J. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. *Am J Sports Med.* 2014;37(1):1013-9.
33. Grande DA, Pitman MI, Peterson L, Menche D, Klein M. The repair of experimentally produced defects in rabbit articular cartilage by autologous chondrocyte transplantation. *J Orthop Res.* 1989;7(2):208-18.
34. Orth P, ReyRico A, Venkatesan JK, Madry H, Cucchiarini M. Current perspectives in stem cell research for knee cartilage repair. *Stem Cells Int.* 2014;14:111-5.
35. Chen FM, Zhang M, Wu ZF, Sun HH. Toward delivery of multiple growth factors in tissue engineering. *Biomat.*2006;31(24):6279-308.
36. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med*. 1994;331(14):889-95.
37. Biant LC, Bentley G, Vijayan S, Skinner JA, Carrington RW. Long-term results of autologous chondrocyte implantation in the knee for chronic chondral and osteochondral defects. *Am J Sports Med.* 2014;42(9):2178-83.
38. Schuette HB, Kraeutler MJ, McCarty EC. Matrix-assisted autologous chondrocyte transplantation in the knee: a systematic review of mid-to long-term clinical outcomes. *Orthop J Sports Med*. 2017;5(6): 2325967117709250.
39. Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, Waugh N. Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation. *Health Technol*, 2005;9(7):1-9.
40. Erggelet C, Vavken P. Microfracture for the treatment of cartilage defects in the knee joint - A golden standard? J Orthop Trauma 2016;7(3):145-52.
41. Orth P, Rey-Rico A, Venkatesa JK, Madry H, Cucchiarini M. Current perspectives in stem cell research for knee cartilage repair. *Stem Cells Cloning.* 2014;6:1-17.
42. Kreuz PC, Steinwachs MR, Erggelet C, Krause SJ, Konrad G, Uhl M. Results after microfracture of full-thickness chondral defects in

different compartments in the knee. *Osteoarthritis Cartilage*. 2006;14(11):1119-25.
43. Hangody L, Füles P. Autologous osteochondral mosaicplasty for the treatment of full-thickness defects of weight-bearing joints: Ten years of experimental and clinical experience. *J Bone J Surg.* 2003;85(2):25-32.
44. Patil S, Tapasvi SR. Osteochondral autografts. *Curr Rev Musculoskelet Med*. 2015;8(4):423-8.
45. Marcacci M, Kon E, Delcogliano M, Filardo G, Busacca M, Zaffagnini S. Arthroscopic autologous osteochondral grafting for cartilage defects of the knee: prospective study results at a minimum 7-year follow-up. *Am J Sports Med.* 2007;35(12):2014-21.
46. Dean CS, Chahla J, Cruz RS, LaPrade RF. Fresh osteochondral allograft transplantation for treatment of articular cartilage defects of the knee. *Arthrosc Tech.* 2016;5(1):e157-e61.
47. Chui K, Jeys L, Snow M. Knee salvage procedures: The indications, techniques and outcomes of large osteochondral allografts. *World J. Orthop*, 2015;46(3):340.
48. Assenmacher AT, Pareek A, Reardon PJ, Macalena JA, Stuart MJ. Long-term outcomes after osteochondral allograft: a systematic review at long-term follow-up of 12.3 years. *Arthrosc J Arthrosc Relat Surg*. 2016;32(10):2160-8.
49. Sherman SL, Garrity J, Baue K, Cook J, Stannard J, Bugbee W. Fresh osteochondral allograft transplantation for the knee: current concepts. *J Am Acad Orthop Surg.* 2014;22(2):121-33.
50. Wagner KR, DeFroda SF, Sivasundaram L, Kaiser JT, Meeker ZD, Condron NB, Cole BJ. Osteochondral allograft transplantation for focal cartilage defects of the femoral condyles. *JBJS Essent Surg Tech*.2022;12(3):e21.
51. Langer R, Vacanti JP. Tissue engineering. *Science,*1993:260(5110): 920-6.
52. Place ES, Evans ND, Stevens MM. Complexity in biomaterials for tissue engineering. *Nat Mater*. 2009:8(6):457-70.
53. He HY, Zhang JY, Mi X, Hu Y, Gu XY. Rapid prototyping for tissue-engineered bone scaffold by 3D printing and biocompatibility study. *Int J Clin Exp Med.* 2015;8(7):11777.
54. Johnstone B, Alini M, Cucchiarini M, Dodge GR, Eglin D, Guilak F, Madry H, Mata A, Mauck RL, Semino CE, Stoddart MJ Tissue engineering for articular cartilage repair - the state of the art. *Eur Cell Mater.* 2013;25(248):e67.
55. Vinatier C, Guicheux J. Cartilage tissue engineering: From biomaterials and stem cells to osteoarthritis treatments. *Ann Phys Rehabil Med*. 2016;59(3):139-44.
56. Buckwalter JA, Mankin HJ. Articular cartilage: Tissue design and chondrocyte-matrix interactions. *Instr Course Lect*. 1998;47:477-86.
57. Kim HD, Amirthalingam S, Kim SL, Lee SS, Rangasamy J, Hwang NS. Biomimetic materials and fabrication approaches for bone tissue engineering. *Adv Healthc Mater.* 2017;6(23):1700612.
58. Smith KA, Dang M, Baker AE, Fuehrmann T, Fokina A. Shoichet MS. Synthesis of an enzyme-mediated reversible cross-linked hydrogel for cell culture. *Biomacromolecules.* 2021;22(12):5118-27.
59. Ibrahim DM, Sani ES, Solima AM, Zandi N, Mostafavi E, Youssef AM. Bioactive and elastic nanocomposites with antimicrobial properties for bone tissue regeneration. *ACS Appl Bio Mater.* 2020;3(5):3313-25.
60. Nguyen MK, Lee DS. Injectable biodegradable hydrogels. *Macromol Biosci*. 2010;10(6):563-79.

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