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Review Paper

Moving Beyond 'Wear and Tear': The New Frontier of Cartilage Regeneration in Osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is the most common chronic degenerative joint disease and a leading cause of pain, disability, and reduced quality of life worldwide. The disease is characterized by progressive degradation of articular cartilage, subchondral bone remodeling , synovial inflammation, and joint dysfunction. Due to the avascular and aneural nature of cartilage, its intrinsic healing capacity is extremely limited, making cartilage regeneration a major challenge in orthopedic and regenerative medicine. Conventional therapies such as analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), physiotherapy, and joint replacement primarily focus on symptom relief rather than restoring damaged cartilage. Recent advances in regenerative medicine have introduced innovative approaches including stem cell therapy, tissue engineering, biomaterials, extracellular vesicles, growth factor delivery, gene therapy, and three-dimensional (3D) bioprinting. These strategies aim to regenerate functional cartilage, restore joint homeostasis, and potentially modify disease progression. Although promising results have been reported in preclinical studies and early clinical trials, several challenges remain regarding long-term efficacy, safety, standardization, and regulatory approval. This review discusses cartilage biology, OA pathogenesis, current regenerative strategies, clinical translation, existing challenges, and future perspectives for cartilage regeneration in osteoarthritis. Osteoarthritis (OA) is a major cause of chronic pain and disability worldwide. Traditionally regarded as a wear-and-tear disease, OA is now recognized as a complex biological disorder involving cartilage degradation, inflammation, and joint remodeling. Recent advances in regenerative medicine have shifted the focus from symptom management to cartilage restoration. Emerging approaches such as stem cell therapy, biomaterials, hydrogels, exosomes, gene therapy, and 3D bioprinting offer promising opportunities to regenerate damaged cartilage and restore joint function. [5,6,10]

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INTRODUCTION

Osteoarthritis is a progressive musculoskeletal disorder affecting millions of individuals worldwide. It is characterized by degeneration of articular cartilage, structural changes in subchondral bone, synovial inflammation, and gradual loss of joint function. The burden of OA is increasing due to population aging, obesity, sedentary lifestyles, and increased life expectancy. The knee, hip, hand, and spine are among the most commonly affected joints. Articular cartilage plays a crucial role in providing a smooth, lubricated surface for joint movement while distributing mechanical loads across the joint. However, cartilage has a very limited capacity for self-repair because it lacks blood vessels, lymphatics, and nerves. Once damaged, cartilage degeneration often progresses, eventually leading to pain, stiffness, and disability. Current treatment options for OA primarily focus on symptom management through medications, physical therapy, and surgical interventions. While total joint replacement remains highly effective for end-stage disease, it is associated with complications, high costs, and limited implant lifespan. Therefore, there is a growing need for therapies capable of restoring cartilage structure and function rather than simply alleviating symptoms. Regenerative medicine has emerged as a promising field that combines cellular therapies, biomaterials, tissue engineering, and molecular biology to regenerate damaged tissues. Advances in these technologies have opened new possibilities for cartilage repair and disease modification in OA. Understanding cartilage biology and disease mechanisms is essential for developing successful regenerative therapies. [5,6,9,10]

Cartilage Biology

Articular cartilage is a specialized connective tissue covering the ends of bones within synovial joints. Its primary function is to facilitate smooth joint movement while minimizing friction and absorbing mechanical stress. Articular cartilage is a smooth connective tissue covering the ends of bones in synovial joints. It consists primarily of chondrocytes and extracellular matrix (ECM). The ECM contains water, type II collagen, and proteoglycans such as aggrecan. Cartilage is organized into superficial, middle, deep, and calcified zones. Due to the absence of blood vessels, nerves, and lymphatics, cartilage has very limited self-healing capacity. [1,6,16,28,30]

The tissue consists of two major components:

Chondrocytes: Chondrocytes are the only cellular component of cartilage and are responsible for synthesizing and maintaining the extracellular matrix (ECM). These cells regulate tissue homeostasis by balancing matrix synthesis and degradation. [1,6,16,28,30]

Extracellular Matrix: The ECM accounts for approximately 95% of cartilage volume and is composed primarily of:

- Type II collagen
- Proteoglycans (especially aggrecan)
- Glycosaminoglycans
- Water

Collagen fibers provide tensile strength, whereas proteoglycans attract water molecules, enabling resistance to compressive forces. [16,28,30]

Zonal organisation: Superficial zone, Middle (transitional) zone, Deep zone, Calcified cartilage zone

Each zone exhibits distinct cellular density, collagen orientation, and biomechanical properties that contribute to overall tissue function. [16,28,30]

Limited Regenerative Capacity Unlike most tissues, cartilage lacks direct vascular supply.

Nutrient exchange occurs through diffusion from synovial fluid. Consequently, injured cartilage poor healing potential, making regenerative interventions necessary for effective repairs. [1,6,16]

Pathology of Osteoarthritis

OA was traditionally considered as simple "wear-and-tear" disease; however, it is now recognized as a complex disorder involving mechanical, inflammatory, biochemical, and genetic factors. [6,10,29,30]

Cartilage Degradation:The earliest pathological event in OA involves disruption of ECM homeostasis. Chondrocytes become activated and produce degradative enzymes, including: [6,10,29,30]

• Matrix metalloproteinases (MMPs)
• Aggrecanases (ADAMTS)

These enzymes break down collagen and proteoglycans, resulting in loss of cartilage integrity.

Inflammatory Processes: Inflammatory cytokines play an important role in OA progression. Key mediators include:

• Interleukin-1β (IL-1β)
• Tumor necrosis factor-alpha (TNF-α)
• Interleukin-6 (IL-6)

These molecules stimulate matrix degradation while suppressing cartilage repair mechanisms.

With disease progression, chondrocytes exhibit:

Chondrocyte dysfunction

• Reduced anabolic activity
• Increased apoptosis
• Cellular senescence
• Altered metabolic responses

These changes further accelerate cartilage destruction.

Subchondral Bone Remodeling

Structural changes occur beneath the cartilage, including:

• Bone sclerosis
• Osteophyte formation
• Bone marrow lesions

These abnormalities alter load distribution and contribute to disease progression.

Synovial Inflammation

Synovitis is frequently observed in OA and contributes to pain and inflammatory signalling within the joint environment.

Collectively, these pathological processes create a hostile microenvironment that impairs natural cartilage repair and necessitates advanced regenerative approaches. [6,10,29,30]

Regenerative Strategies

Recent advances in regenerative medicine have led to the development of several promising approaches for cartilage repair and regeneration. Mesenchymal stem cells (MSCs) derived from bone marrow, adipose tissue, and umbilical cord can differentiate into cartilage-forming cells and release anti-inflammatory factors. Induced pluripotent stem cells (iPSCs) provide patient-specific regenerative potential. Biomaterials and hydrogels serve as scaffolds that support cell survival and controlled growth-factor release. Exosome-based therapies provide cell-free regenerative signals, while gene therapy and CRISPR-based approaches target inflammatory pathways. Three-dimensional bioprinting enables creation of patient-specific cartilage constructs. [2,3,4,7,26]

Mesenchymal Stem Cell Therapy

Mesenchymal stem cells (MSCs) are multipotent cells capable of differentiating into chondrocytes and producing cartilage matrix. [3,4,11,12,17]

Common MSC sources include:

MSCs exert therapeutic effects through:

• Bone marrow
• Adipose tissue
• Umbilical cord tissue
• Synovial membrane
• Chondrogenic differentiation
• Immunomodulation
• Anti-inflammatory activity
• Secretion of trophic factors

Clinical studies have demonstrated improvements in pain, function, and cartilage quality following MSC administration.

Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPSCs) are generated by reprogramming adult somatic cells into a pluripotent state.

Advantages it includes:

• Unlimited proliferative capacity
• Patient-specific therapy
• Ability to generate chondrocytes

However, concerns regarding tumour formation and genomic instability currently limit widespread clinical application.

Tissue Engineering

Cartilage tissue engineering combines cells, scaffolds, and signalling molecules to create functional cartilage substitutes. [2,13,25]

The classical tissue engineering triad consists of:

1. Cells
2. Biomaterial scaffolds
3. Bioactive molecules

This approach aims to replicate the native cartilage microenvironment and promote tissue regeneration.

Biomaterial-Based Therapies

Biomaterials provide structural support and facilitate cell survival and differentiation.

Common biomaterials include:

Natural Biomaterials

• Collagen
• Hyaluronic acid
• Alginate
• Chitosan

Synthetic Biomaterials

• Polycaprolactone
• Polyethylene glycol
• Polylactic acid

These materials can be engineered to mimic native cartilage architecture and mechanical properties.

Hydrogel Systems

Hydrogels have gained significant attention due to their high-water content and cartilage-like characteristics.

Advantages include:

• Injectable delivery
• Biocompatibility
• Controlled release of bioactive molecules
• Enhanced cell viability

Hydrogels are increasingly used as carriers for stem cells and growth factors.

Growth Factor Therapy

Growth factors regulate cartilage development and repair.

Important growth factors include:

• Transforming growth factor-beta (TGF-β)
• Bone morphogenetic proteins (BMPs)
• Insulin-like growth factor-1 (IGF-1)
• Fibroblast growth factors (FGFs)

These molecules promote chondrocyte proliferation and matrix synthesis.

Extracellular Vesicles and Exosomes

Exosomes are nanosized extracellular vesicles secreted by stem cells and other cell types.

They contain:

• Proteins
• Lipids
• Messenger RNA
• MicroRNA

Exosome-based therapy offers several advantages:

• Reduced immunogenicity
• Lower tumorigenic risk
• Easier storage and handling
• Cell-free therapeutic approach

Preclinical studies have demonstrated their ability to reduce inflammation and promote cartilage repair.

Gene Therapy

Gene therapy involves introducing therapeutic genes into target cells to enhance cartilage regeneration.

Potential targets include:

• Anti-inflammatory genes
• Growth factor genes
• Matrix synthesis regulators

Gene-editing technologies such as CRISPR-Cas9 offer exciting possibilities for correcting disease associated pathways and enhancing regenerative potential. [10,22]

Three-Dimensional Bioprinting

3D bioprinting enables precise fabrication of cartilage constructs using cells and biomaterials.

Benefits include:Customized tissue architecture, Patient-specific implants, Controlled cell distribution, Improved structural organization [2,13,26]

Bioprinting may eventually facilitate production of functional cartilage replacements for clinical use.

Therapeutic interpretation

Autologous Chondrocyte Implantation (ACI) represents one of the earliest regenerative approaches and has shown success in focal cartilage defects. However, advanced OA remains difficult to treat because transplanted cells often experience poor survival in the inflammatory joint environment. Current therapies may also generate fibrocartilage instead of durable hyaline cartilage. [12,17,25]

Stem Cell Clinical Trials

Numerous clinical trials have investigated MSC-based therapies for OA.

Reported outcomes include:

• Pain reduction
• Improved joint function
• Enhanced quality of life
• Increased cartilage thickness in some patients

However, variability in cell sources, dosing protocols, and outcome measures complicates interpretation of results.

Autologous Chondrocyte Implantation

Autologous chondrocyte implantation (ACI) represents one of the earliest successful regenerative cartilage therapies.

The procedure involves:

1. Harvesting healthy cartilage cells
2. Expanding chondrocytes in vitro
3. Reimplanting cells into cartilage defects

Although effective for focal cartilage lesions, its application in advanced OA remains limited.

Biomaterial and Scaffold-Based Trials

Clinical studies evaluating scaffold-assisted cartilage repair have shown encouraging results regarding tissue integration and symptom improvement. However, long-term durability remains uncertain. [2,13,25]

Regulatory Considerations

Clinical translation requires compliance with stringent regulatory standards related to: • Manufacturing quality

• Safety assessment
• Product consistency
• Long-term monitoring

Challenges

Despite substantial progress, several challenges continue to limit successful cartilage regeneration. Major challenges include maintaining long-term cell viability, reproducing native cartilage architecture, preventing fibrocartilage formation, addressing patient variability, ensuring manufacturing consistency, and meeting regulatory requirements. High development costs and complex production processes also limit widespread clinical adoption. [12,17,26]

Limited Cell Survival: Following transplantation, many therapeutic cells fail to survive due to:
• Inflammatory microenvironment
• Mechanical stress
• Nutrient limitations

Disease Environment: The inflammatory and catabolic environment characteristic of OA can impair regenerative processes and reduce treatment effectiveness [12,17,26]

Incomplete Integration: Regenerated tissue often fails to integrate seamlessly with surrounding native cartilage, compromising mechanical performance. [12,17,26]

Manufacturing Complexity: Advanced regenerative products require sophisticated manufacturing facilities and quality control systems, increasing production costs. [12,17,26]

Formation of Fibrinocartilage

Many repair techniques generate fibrocartilage rather than hyaline cartilage. Fibrocartilage possesses inferior mechanical properties and may deteriorate over time. [12,17,26]

Patient Variability:Treatment outcomes may vary based on:
• Age
• Disease severity
• Genetic factors
• Metabolic status
• Comorbidities

Ethical and Regulatory Issues: Stem cell-based and gene-based therapies face ethical considerations and complex regulatory pathways that may delay clinical implementation. [12,17,26]

FUTURE PERSPECTIVES

The future of cartilage regeneration is likely to involve integrated and personalized therapeutic approaches. Future OA treatment is expected to integrate stem cells, smart biomaterials, exosomes, gene editing, and artificial intelligence-driven patient selection. Personalized regenerative therapies combined with advanced biomaterials may significantly improve clinical outcomes and potentially reverse disease progression. [26,27,29]
Personalized Regenerative Medicine: Advances in genomics and biomarker research may enable individualized treatment strategies tailored to each patient's biological profile. [26,27,29]
Combination Therapies: Combining multiple regenerative approaches may enhance therapeutic outcomes. Examples include:
• MSCs with hydrogels
• Exosomes with biomaterials
• Gene therapy withtissue engineering

Smart Biomaterials:

Next-generationbiomaterials are being developed with capabilities such as:
• Controlled drug release
• Mechanical responsiveness
• Bioactive signaling

These materials may provide superior support for cartilage regeneration.

Artificial Intelligence and Digital Health:

Artificial intelligence may assist in:
• Patient selection
• Disease prediction
• Treatment optimization
• Clinical outcome monitoring

Advanced Bioprinting:

Future bioprinting technologies may generate fully functional cartilage constructs capable of replacing damaged tissue with high anatomical precision. [26,27,29]

Cell-Free Therapies:

Exosome-based and biomolecule-based treatments may overcome many limitations associated with living cell transplantation while maintaining regenerative efficacy. [26,27,29]

Large-Scale Clinical Trials:

Robust multicentred randomized controlled trials will be essential to establish long-term safety, efficacy, and cost-effectiveness of emerging therapies. [26,27,29]

CONCLUSION

One of the most promising strategies for OA treatment is the regeneration of cartilage tissues. Recent advances in stem cell therapies, tissue engineering, bio materials, exosomes, gene therapy, and 3D bioprinting open new horizons for cartilage repair and disease-modifying treatments. The ability to regenerate cartilage tissues using innovative medical technologies and extensive clinical testing will fundamentally change the way OA is treated and enable millions of people around the world to return to active lives free from the limitations of joint diseases. [5,6,26,27]

REFERENCES

1. Role of chondrocytes in cartilage formation, progression of osteoarthritis and cartilage regenerationH Akkiraju, A Nohe - Journal of developmental biology, 2015 - mdpi.com
2. Biomaterial-based scaffolds in promotion of cartilage regeneration: recent advances and emerging applicationsJ Liang, P Liu, X Yang, L Liu, Y Zhang, Q Wang… - Journal of Orthopaedic …, 2023 - Elsevier
3. Native joint-resident mesenchymal stem cells for cartilage repair in osteoarthritisD McGonagle, TG Baboolal, E Jones - Nature Reviews Rheumatology, 2017 - nature.com
4. A comprehensive review of stem cells for cartilage regeneration in osteoarthritisG Kalamegam, A Memic, E Budd, M Abbas… - Cell Biology and …, 2018 - Springer
5. Cartilage regeneration for osteoarthritisA Eccleston - Nat Rev Drug Discov, 2023 - nature.com
6. Articular cartilage regeneration in osteoarthritisL Roseti, G Desando, C Cavallo, M Petretta, B Grigolo - Cells, 2019 - mdpi.com
7. Regenerative approaches for cartilage repair in the treatment of osteoarthritisMH Li, R Xiao, JB Li, Q Zhu - Osteoarthritis and cartilage, 2017 - Elsevier
8. Articular cartilage regeneration by activated skeletal stem cellsMP Murphy, LS Koepke, MT Lopez, X Tong… - Nature medicine, 2020 - nature.com
9. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation.JA Buckwalter, HJ Mankin - Instructional course lectures, 1998 - europepmc.org

10. Osteoarthritis and cartilage regeneration: focus on pathophysiology and molecular mechanisms
S Grässel, A Aszodi - International Journal of Molecular Sciences, 2019 - mdpi.com
11. Mesenchymal stem cells in connective tissue engineering and regenerative medicine: applications in cartilage repair and osteoarthritis therapy [5,6,26,27] Mobasheri, C Csaki, AL Clutterbuck… - Histology and …, 2009 - hh.um.es
12. Clinical trials with mesenchymal stem cell therapies for osteoarthritis: challenges in the regeneration of articular cartilage [5,6,26,27]DC Carneiro, LT Araújo, GC Santos… - International journal of …, 2023 - mdpi.com
13. Cartilage tissue engineering: From biomaterials and stem cells to osteoarthritis treatmentsC Vinatier, J Guicheux - Annals of physical and rehabilitation medicine, 2016 - Elsevier
14. The role of growth factors in cartilage repairLA Fortier, JU Barker, EJ Strauss… - Clinical Orthopaedics …, 2011 - journals.lww.com
15. Exercise as an adjuvant to cartilage regeneration therapyJK Smith - International Journal of Molecular Sciences, 2020 - mdpi.com
16. rticular cartilage: structure and regenerationJ Becerra, JA Andrades, E Guerado… - … Engineering Part B …, 2010 - journals.sagepub.com
17. Mesenchymal stromal cell-based therapy for cartilage regeneration in knee osteoarthritisXN Xiang, SY Zhu, HC He, X Yu, Y Xu… - Stem cell research & …, 2022 - Springer
18. Alternative and complementary therapies in osteoarthritis and cartilage repairNR Fuggle, C Cooper, ROC Oreffo, AJ Price… - Aging clinical and …, 2020 - Springer
19. The role of chondrocyte senescence in the pathogenesis of osteoarthritis and in limiting cartilage repairJA Martin, JA Buckwalter - JBJS, 2003 - journals.lww.com
20. Growth factors in the treatment of early osteoarthritisR Civinini, L Nistri, C Martini, B Redl… - Clinical Cases in …, 2013 - pmc.ncbi.nlm.nih.gov
21. Mechanosignalling in cartilage: an emerging target for the treatment of osteoarthritisT Hodgkinson, DC Kelly, CM Curtin… - Nature Reviews …, 2022 - nature.com
22. Current research on pharmacologic and regenerative therapies for osteoarthritisW Zhang, H Ouyang, CR Dass, J Xu - Bone research, 2016 - nature.com
23. Bone morphogenetic proteins for articular cartilage regenerationZH Deng, YS Li, X Gao, GH Lei, J Huard - Osteoarthritis and cartilage, 2018 - Elsevier
24. uman cartilage-derived progenitor cells from committed chondrocytes for efficient cartilage repair and regenerationY Jiang, Y Cai, W Zhang, Z Yin, C Hu… - Stem Cells …, 2016 - academic.oup.com
25. The clinical status of cartilage tissue regeneration in humansB Mollon, R Kandel, J Chahal… - Osteoarthritis and …, 2013 - Elsevier
26. A review of recent innovations in cartilage regeneration strategies for the treatment of primary osteoarthritis of the knee: intra-articular injections [5,6,26,27]NA Householder, A Raghuram… - … Journal of Sports …, 2023 - journals.sagepub.com
27. Molecular signaling pathways in osteoarthritis and biomaterials for cartilage regeneration: a reviewSP Hiruthyaswamy, A Bose, A Upadhyay, T Raha… - …, 2025 - Taylor & Francis

28. Cartilage biology in osteoarthritis—lessons from developmental biologyAA Pitsillides, F Beier - Nature Reviews Rheumatology, 2011 - nature.com
29. Osteoarthritis year in review 2021: biologyY Jiang - Osteoarthritis and cartilage, 2022 - Elsevier… of research articles published between the 2020 and 2021 Osteoarthritis Research
30. The role of the cartilage matrix in osteoarthritisD Heinegård, T Saxne - Nature Reviews Rheumatology, 2011 - nature.com

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