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Review Article

Exosomes as novel biological therapeutics in rheumatoid arthritis– mechanisms, applications, and changes: a systematic review

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory condition that leads to persistent joint inflammation (synovitis), progressive cartilage damage, bone loss, and systemic complications.

Despite the development of many new disease-modifying antirheumatic drugs (DMARDs) and biologic agents, a large number of RA patients still suffer from active disease, side effects, or lack of response to treatment. Exosomes, which are a type of extracellular vesicle (EV), have become an attractive alternative as a cell-free therapeutic agent due to their ability to mediate intercellular communication and regulate immune responses.

Aim and Objective: To systematically review the available evidence on the therapeutic role of exosomes in rheumatoid arthritis, including their mechanism of action, therapeutic effectiveness, sources, engineered applications, and challenges in translating them into clinical use.

Methodology: A systematic literature review was conducted using studies published between 2015 and 2026 from PubMed, Scopus, Web of Science, and Google Scholar. Search terms used were “rheumatoid arthritis”, “exosomes”, “extracellular vesicles”, “mesenchymal stem cell-derived exosomes”, and “exosome therapy”. Studies included were original research articles, animal studies, preclinical investigations, systematic reviews, and clinical reports.

Results: Thirty-five relevant studies met the inclusion criteria. Studies show that exosomes produced by mesenchymal stem cells, dendritic cells, macrophages, and synovial fibroblasts regulate immune responses, suppress inflammatory cytokines, affect T-cell differentiation, inhibit osteoclastogenesis, and stimulate cartilage repair. In addition, engineered exosomes allow for targeted delivery of anti-inflammatory molecules and microRNAs.

Conclusion: Exosome therapy is a promising next-generation treatment option for rheumatoid arthritis. However, while preclinical results are encouraging, standardization of exosome isolation, characterization, dosing, and large-scale clinical trials will be required before exosome therapy can be routinely used in clinical settings.

Keywords: Rheumatoid arthritis, Exosomes, Extracellular vesicles, Mesenchymal stem cells, Immunomodulation, Regenerative medicine

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1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder that primarily affects synovial joints and causes significant morbidity and disability. RA affects approximately 0.5-1% of the global population and is characterized by persistent synovial inflammation, progressive cartilage degradation, bone erosion, joint deformity, and a significant reduction in quality of life.

In addition to affecting synovial joints, RA can also affect other organs such as lungs, cardiovascular system, and eyes; therefore, increasing overall disease burden and mortality. Although the exact cause of RA is not fully understood; however, genetic susceptibility, environmental factors, and dysregulated immune responses are known to play key roles in disease initiation and progression.[1]

Pathogenesis of RA involves complex interactions between innate and adaptive immune cells. Activated macrophages, dendritic cells, T lymphocytes, B lymphocytes, and fibroblast-like synoviocytes (FLS) produce pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), and interleukin-6 (IL-6); thereby contributing to chronic inflammation.

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These mediators lead to synovial hyperplasia, pannus formation, osteoclast activation, and progressive destruction of cartilage and bone.[2] Treatment options for RA include conventional disease-modifying antirheumatic drugs (DMARDs), biologic therapies targeting specific inflammatory pathways, and Janus kinase (JAK) inhibitors.

Although these therapies have significantly improved disease management; however, a large number of patients fail to achieve sustained remission, experience disease relapse, or develop adverse drug reactions that limit long-term use.[3] Advances in regenerative medicine and cell-based therapies have increased interest in the therapeutic potential of exosomes. Exosomes are small extracellular vesicles (typically 30–150 nm in diameter) secreted by various cell types that participate in intercellular communication.[4] Exosomes contain a variety of proteins, lipids, messenger RNAs, microRNAs, and other bioactive molecules that can regulate cellular function and immune responses.[5] Recent studies suggest that exosomes have a dual role in RA.

While exosomes produced by inflammatory cells may contribute to disease progression; however, exosomes produced by mesenchymal stem cells (MSCs) possess potent anti-inflammatory, immunomodulatory, and tissue-regenerative properties; making them attractive candidates for novel therapeutic interventions.[6] Therefore; this systematic review aims to evaluate the current evidence on the role of exosome therapy in rheumatoid arthritis; specifically focusing on their mechanisms of action, therapeutic efficacy, challenges, and future clinical applications.

2. Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Search Strategy Electronic databases including PubMed, Scopus, Web of Science, Embase, and Google Scholar were searched for studies published from January 2015 to March 2026. Search terms used were:

1. Rheumatoid arthritis AND exosomes.
2. Extracellular vesicles AND rheumatoid arthritis.
3. Mesenchymal stem cell-derived exosomes.
4. Exosome therapy in autoimmune diseases.
5. Engineered exosomes and rheumatoid arthritis.

2.1. Inclusion criteria

1. Studies investigating exosomes or extracellular vesicles in rheumatoid arthritis.
2. Experimental animal studies.
3. In vitro investigations.
4. Clinical studies and observational reports.
5. Systematic reviews and meta-analyses.
6. Publications written in English.

2.2. Exclusion criteria

1. Publications written in languages other than English.
2. Conference abstracts without full text.
3. Duplicate studies.
4. Studies unrelated to rheumatoid arthritis.
5. Editorials and opinion articles without primary data.

2.3. Data extraction

Data regarding study design, exosome source, mechanisms, therapeutic outcomes, inflammatory markers, and clinical implications were extracted and synthesized.

Exosomes originate from endosomal pathways via formation of multivesicular bodies and subsequent release into the extracellular environment.[7] Exosomes contain bioactive cargo including Proteins, Cytokines, Growth factors, DNA fragments, Messenger RNA and MicroRNAs, Exosomes act as mediators of intercellular communication and regulate immune responses, tissue regeneration, angiogenesis, and inflammatory signaling.[8] Exosomes play a major role in RA pathophysiology. Activated fibroblast-like synoviocytes secrete exosomes containing pro-inflammatory mediators that activate macrophages and T cells.[9] These exosomes increase production of TNF-alpha, IL-1beta, IL-6 and Matrix metalloproteinases (MMPs) which lead to synovial hyperplasia and joint damage.[10] Exosomes may contain citrullinated proteins that serve as autoantigens.[11] These autoantigens stimulate autoantibody production and perpetuate autoimmune responses characteristic of RA.

Exosome-mediated signaling stimulates osteoclast differentiation via activation of receptor activator of nuclear factor kappa-B ligand (RANKL) pathways.[12] As a result, increased bone erosion and joint damage occur.

Mesenchymal Stem Cell-Derived Exosomes (MSC-derived exosomes) are the most commonly studied therapeutic exosomes in RA.[13] Sources include Bone marrow MSCs, Umbilical cord MSCs, Adipose-derived MSCs, Synovial MSCs These exosomes possess Anti-inflammatory properties, Immunomodulatory effects, Tissue-regenerative properties, without the risks associated with live-cell transplantation.[14]

Dendritic Cell-Derived Exosomes can induce immune tolerance and suppress autoreactive T-cell responses.[15]

Macrophage-Derived Exosomes M2 have anti-inflammatory properties and promote tissue repair.[16]

Exosome Therapy in Rheumatoid Arthritis works by Regulation of T Cell Responses, MSC-derived exosomes suppress Th1 and Th17 differentiation while promoting regulatory T cells (Tregs).[17] This shift restores immune tolerance and reduces autoimmune inflammation. Exosomes stimulate polarization of macrophages from pro-inflammatory M1 phenotype to anti-inflammatory M2 phenotype.[18] This reduces cytokine release and synovial inflammation. There is Suppression of Pro-Inflammatory Cytokines following exosome administration.[19] Several studies have shown significant reductions in TNF-alpha, IL-1beta, IL-6, IFN-gamma. Exosomal miRNAs inhibit osteoclast differentiation and bone resorption pathways.[20] MSC-derived exosomes stimulate chondrocyte proliferation and extracellular matrix synthesis while decreasing apoptosis.[21]

Exosomes exert many of their biological effects through miRNA cargo. miR-150-5p Suppresses angiogenesis and inflammatory responses.[22] miR-124a Inhibits synovial fibroblast proliferation.[23] miR-146a Reduces NF-kappa-B activation and inflammatory cytokine production.[24] miR-34a Regulates osteoclast differentiation and bone remodeling.[25] miR-21 Promotes tissue repair and immune regulation.[26]

Natural exosomes have served as a template for developing engineered exosome systems. Drug-Loaded Exosomes Exosomes can deliver Methotrexate, Dexamethasone and Small interfering RNA directly to inflamed joints.[27] Ligand-modified exosomes improve targeting efficiency toward inflamed synovial tissues.[28] Gene-Loaded Exosomes, Exosomes containing anti-inflammatory genes and microRNAs demonstrate superior therapeutic efficacy in animal models.[29]

Exosomes offer several advantages over stem-cell transplantation because they Have lower immunogenicity, Avoid tumorigenic risks, Are easier to store, Have greater stability hence provide base for Potential Clinical Applications in Cell-Free Regenerative Therapy.

Exosomal miRNAs may serve as diagnostic and prognostic biomarkers in RA. Engineered exosomes could allow for individualized treatment strategies targeting specific inflammatory pathways.[30] Despite promising findings, several obstacles exist, There is a Standardization Issues Currently no universally accepted protocols exist for Isolation, Purification, Characterization and Quantification of exosomes.[31] Large-scale production remains difficult and expensive. There are Regulatory Concerns also as International regulatory frameworks for exosome therapeutics are still developing. There are Limited Human Studies as Most available evidence comes from in vitro and animal experiments. Large randomized clinical trials are lacking.

3. Future Perspectives

Future research should focus on

1. Large multicenter clinical trials.
2. Standardized manufacturing protocols.
3. Good Manufacturing Practice (GMP) production.
4. Optimization of dosing regimens.
5. Development of engineered exosomes.
6. Combination therapies with biologics and DMARDs.
7. Long-term safety evaluations.

Advances in nanomedicine and bioengineering may accelerate translation of exosome therapies into clinical rheumatology practice.

4. Conclusion and Recommendations

Exosome therapy has emerged as a highly promising and innovative strategy for managing rheumatoid arthritis (RA). Exosomes produced by mesenchymal stem cells and other cell sources exhibit potent anti-inflammatory, immunomodulatory, anti-osteoclastogenic, and tissue-regenerative properties in preclinical studies. By regulating immune responses and promoting joint repair; they provide a novel cell-free therapeutic alternative with several advantages over conventional stem-cell therapy including lower immunogenicity, improved safety, easier storage, and better delivery to target tissues.

However, despite these encouraging findings; translating exosome therapy into routine clinical practice remains challenging due to issues related to large-scale production, standardization of isolation methods, quality control, long-term safety assessment, and regulatory approval. Further research is needed to optimize exosome sources, dosing protocols, and delivery systems.

5. Recommendations

Future studies should focus on conducting large multicenter randomized controlled trials; establishing standardized manufacturing guidelines; evaluating long-term safety and efficacy; and developing regulatory frameworks to facilitate clinical application of exosome-based therapies in rheumatoid arthritis.

6. Source of Funding

None.

7. Conflict of Interest

None.

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