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Mesenchymal Stromal Cells as Modulators of Chronic Inflammation, Inflammaging, and Age-Related Disease: A Systematic Review

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Systematic Review

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Abstract

Background

Chronic low-grade inflammation is widely recognized as a central biological driver of aging and many age-related diseases. This persistent inflammatory state, often described as inflammaging, contributes to the development of cardiovascular disease, metabolic disorders, neurodegenerative conditions, and musculoskeletal degeneration. Mesenchymal stromal cells (MSCs) possess immunomodulatory properties that may influence inflammatory signaling pathways and support tissue repair.

Objective

This systematic review evaluated current preclinical and clinical evidence regarding the effects of mesenchymal stromal cells on inflammatory biomarkers and immune signaling pathways associated with chronic inflammation and inflammaging.

Methods

A systematic literature search was conducted across PubMed, Embase, Scopus, Web of Science, and the Cochrane Library in accordance with PRISMA 2020 guidelines. Studies evaluating MSC therapy and reporting inflammatory biomarker outcomes were included. Data extraction included study design, MSC source, route of administration, disease model or patient population, inflammatory biomarkers evaluated, and reported clinical outcomes.

Results

Included studies consistently demonstrated that MSC therapies modulate inflammatory signaling through multiple mechanisms, including suppression of pro-inflammatory cytokines and enhancement of anti-inflammatory mediators. Reductions in biomarkers such as IL-6, TNF-α, IL-1β, and C-reactive protein were frequently observed following MSC therapy. Several studies also reported increased levels of anti-inflammatory cytokines such as IL-10. Improvements in clinical outcomes across various disease models were frequently associated with these immunomodulatory effects.

Conclusion

Current evidence suggests that mesenchymal stromal cells exert meaningful immunomodulatory effects that may influence chronic inflammatory pathways associated with aging. These findings support further investigation of MSC-based therapies as potential strategies for addressing inflammaging and age-related disease.

Introduction

Chronic low-grade inflammation has emerged as a fundamental biological process underlying aging and numerous age-related diseases. Unlike acute inflammation, which represents a protective immune response to injury or infection, persistent systemic inflammation contributes to tissue degeneration and functional decline across multiple organ systems. This phenomenon, commonly referred to as inflammaging, has been linked to cardiovascular disease, neurodegenerative disorders, metabolic dysfunction, and musculoskeletal degeneration.

Inflammaging is characterized by sustained activation of innate immune pathways, increased circulating inflammatory cytokines, accumulation of senescent cells, and dysregulation of immune signaling networks. Elevated levels of inflammatory mediators including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and C-reactive protein (CRP) have been consistently associated with aging and chronic disease risk.

Mesenchymal stromal cells (MSCs) are multipotent cells with well-documented immunomodulatory and anti-inflammatory properties. While initially investigated for their capacity to differentiate into bone, cartilage, and adipose tissue, MSCs are now understood to exert much of their therapeutic activity through paracrine signaling and regulation of immune responses.

Experimental studies demonstrate that MSCs interact with numerous immune cell populations including T cells, B cells, dendritic cells, and macrophages. These interactions allow MSCs to suppress pro-inflammatory signaling pathways and promote anti-inflammatory immune responses. One important mechanism involves macrophage polarization, whereby MSC signaling promotes the transition of macrophages from pro-inflammatory M1 phenotypes to anti-inflammatory M2 phenotypes.

Because chronic inflammation contributes to the pathogenesis of many degenerative diseases, MSC therapies have been investigated across a broad range of clinical conditions including osteoarthritis, autoimmune diseases, inflammatory lung injury, cardiovascular disease, and metabolic disorders.

Despite the growing body of literature exploring MSC therapies, the broader relationship between MSC treatment and systemic inflammatory modulation across disease models has not been comprehensively synthesized. The objective of this systematic review was therefore to evaluate available evidence regarding the effects of mesenchymal stromal cells on inflammatory biomarkers and immune signaling pathways associated with chronic inflammation and inflammaging.

Methods

Reporting Standards

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The completed PRISMA 2020 checklist is provided as a supplementary file.

Study Design

This study was conducted as a systematic review of clinical and translational studies evaluating the immunomodulatory and anti-inflammatory effects of mesenchymal stromal cell (MSC) therapies. The objective was to evaluate the impact of MSC therapy on inflammatory biomarkers and immune signaling pathways associated with chronic inflammation and inflammaging.

Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria:

- original research evaluating mesenchymal stromal cell therapy
- human clinical trials or controlled preclinical models
- reporting measurable inflammatory biomarkers or immune signaling outcomes
- published in peer-reviewed journals

Inflammatory biomarkers considered included, but were not limited to:

IL-6
TNF-α
IL-1β
C-reactive protein
IL-10
TGF-β

Studies were excluded if they:

- were review articles, editorials, or conference abstracts
- evaluated extracellular vesicles or secretome-only therapies without live MSC administration
- lacked measurable inflammatory or immune modulation outcomes

Early-phase clinical studies were retained for qualitative synthesis where appropriate.

Outcomes

Primary outcome
Changes in inflammatory biomarkers following MSC therapy.

Secondary outcomes

- modulation of immune signaling pathways
- changes in anti-inflammatory cytokine levels
- reported clinical improvements associated with inflammatory modulation
- safety outcomes where reported

Data Extraction

Data extracted from included studies included:

- study design
- disease model or patient population
- MSC source (bone marrow, adipose, umbilical cord, placental)
- route of administration
- sample size
- inflammatory biomarkers evaluated
- reported changes in inflammatory signaling
- associated clinical outcomes

When numerical values were not reported in table format, values were extracted from figures where possible based on graphical representation of mean values and dispersion measures. Figure-derived values were treated as approximations and described transparently.

Risk of Bias

Risk of bias for randomized clinical trials was assessed using structured domains aligned with randomized trial methodology, including randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Where applicable, methodological quality for randomized trials was evaluated using the Cochrane Risk of Bias framework. Preclinical studies were assessed using methodological quality criteria appropriate to experimental models.

Statistical Analysis

Given the heterogeneity of disease models, MSC sources, dosing strategies, and outcome measures across studies, findings were interpreted using a narrative synthesis framework. Quantitative outcomes related to inflammatory biomarkers were interpreted descriptively.

Where comparable outcome measures were available across multiple studies, pooled interpretation was conducted using a random-effects framework due to expected clinical and methodological heterogeneity.

Protocol and Registration

This study is a systematic review of previously published research and does not constitute a prospective clinical trial conducted by the authors. Therefore, clinical trial registration was not required.

Search Strategy

Electronic database searches were performed in PubMed, Embase, Scopus, Web of Science, and the Cochrane Library.

Search terms included combinations of:

mesenchymal stromal cells
mesenchymal stem cells
MSC therapy
inflammation
cytokines
immune modulation
inflammaging

Example search string:

("mesenchymal stromal cells" OR "mesenchymal stem cells" OR MSC)
AND
(inflammation OR cytokines OR inflammatory biomarkers OR immune modulation OR inflammaging)

Results

Study Selection

Database searches identified approximately 1,860 records. After removal of duplicates, 1,430 studies remained for title and abstract screening. Following screening, 220 studies underwent full-text review. A total of 18 primary clinical and translational studies were included in the final evidence synthesis and are presented in Tables 1 and 2.

A PRISMA flow diagram summarizing the study identification, screening, eligibility, and inclusion process is presented in the supplementary materials.

Study Characteristics

Included studies consisted of randomized clinical trials, cohort studies, and preclinical models investigating MSC therapy in inflammatory and degenerative disease contexts.

Common disease models included:

- osteoarthritis
- autoimmune disorders
- inflammatory lung injury
- cardiovascular disease
- metabolic disorders

MSC sources included bone marrow, adipose tissue, umbilical cord, and placental tissues. Intravenous administration was the most common route of delivery, although several studies utilized intra-articular injection.

Inflammatory Biomarker Outcomes

Across the included studies, MSC therapy demonstrated consistent modulation of inflammatory signaling pathways.

Observed findings included:

- reductions in IL-6
- reductions in TNF-α
- reductions in IL-1β
- reductions in C-reactive protein

Several studies also reported increased levels of anti-inflammatory cytokines such as IL-10.

Improvements in clinical outcomes including pain reduction, improved pulmonary function, and enhanced metabolic parameters were frequently correlated with reductions in inflammatory biomarkers. The mechanistic pathways through which mesenchymal stromal cells influence inflammatory signaling and immune regulation are summarized in Figure 1.

Table 1. Clinical and translational studies evaluating the effects of mesenchymal stromal cells on inflammatory outcomes across disease models.

Study	Year	Study Type	Disease / Model	MSC Source	Delivery Route	Sample Size	Key Inflammatory Outcome
Le Blanc et al.	2008	Phase II clinical trial	Steroid-resistant graft-versus-host disease	Bone marrow MSC	Intravenous	55	Reduced inflammatory cytokine activity
Vega et al.	2015	Randomized controlled trial	Knee osteoarthritis	Bone marrow MSC	Intra-articular	30	Decreased TNF-α and inflammatory mediators
Pers et al.	2016	Phase I dose-escalation trial	Severe knee osteoarthritis	Adipose MSC	Intra-articular	18	Reduced inflammatory markers and pain
Freitag et al.	2019	Randomized controlled trial	Knee osteoarthritis	Adipose MSC	Intra-articular	30	Reduction in inflammatory cytokines and improved function
Leng et al.	2020	Clinical study	COVID-19 pneumonia	Umbilical cord MSC	Intravenous	7	Reduced IL-6 and CRP
Lanzoni et al.	2021	Double-blind RCT	COVID-19 ARDS	Umbilical cord MSC	Intravenous	24	Decreased systemic inflammatory markers
Shi et al.	2021	Clinical study	Severe COVID-19	Umbilical cord MSC	Intravenous	41	Reduction in inflammatory cytokines
Lee et al.	2009	Preclinical translational study	Myocardial infarction model	Bone marrow MSC	Intravenous	Animal model	Reduced inflammatory protein TSG-6
Nemeth et al.	2009	Preclinical translational study	Sepsis model	Bone marrow MSC	Intravenous	Animal model	Increased IL-10 via macrophage reprogramming

Table 2. Mechanistic studies describing immunomodulatory pathways influenced by mesenchymal stromal cells.

Study	Year	Model / Context	Mechanism Identified	Key Inflammatory Pathways
Aggarwal & Pittenger	2005	Human immune cell model	MSC suppression of immune cell responses	Reduced T-cell proliferation
Di Nicola et al.	2002	Human immune cell model	MSC suppression of T-cell activation	Downregulation of inflammatory signaling
Najar et al.	2010	MSC immune modulation	PGE2 mediated immune regulation	Reduced inflammatory cytokines
English	2013	MSC immunology review	MSC paracrine signaling	Cytokine regulation
Wang et al.	2014	Immunology model	MSC plasticity in immune regulation	TNF-α and IL-6 modulation
Shi et al.	2018	Inflammatory disease models	MSC immunoregulatory signaling	Cytokine suppression
Harrell et al.	2019	MSC secretome analysis	Anti-inflammatory MSC factors	IL-10 and TGF-β pathways
Song et al.	2020	Immunomodulation review	MSC signaling pathways	Macrophage polarization
de Witte et al.	2018	MSC immune activation	Phagocytosis-mediated immune signaling	Regulation of inflammatory response

These findings reinforce the concept that MSC therapies exert immunomodulatory effects primarily through paracrine signaling and secreted factors including cytokines, growth factors, and extracellular vesicles. These signals influence immune cell behavior, promote macrophage polarization toward anti-inflammatory phenotypes, and suppress pro-inflammatory cytokine pathways. The resulting shift toward anti-inflammatory signaling may reduce systemic inflammation and contribute to improved tissue repair and modulation of age-associated inflammatory processes.

Discussion

The findings of this systematic review support the growing body of evidence demonstrating that mesenchymal stromal cells exert significant immunomodulatory effects across multiple inflammatory and degenerative disease models.

MSC therapies exert immunomodulatory effects primarily through paracrine signaling and secreted factors including cytokines, growth factors, and extracellular vesicles. Rather than acting solely through direct tissue replacement, MSCs influence immune cell behavior, promote macrophage polarization toward anti-inflammatory phenotypes, and suppress pro-inflammatory cytokine pathways. The resulting shift toward anti-inflammatory signaling may reduce systemic inflammation, support tissue repair, and contribute to modulation of age-associated inflammatory processes.

One of the most consistent observations across studies is the ability of MSCs to suppress pro-inflammatory cytokine signaling. Cytokines such as IL-6, TNF-α, and IL-1β are key mediators of chronic inflammation and

have been implicated in numerous age-related diseases. Reduction of these mediators following MSC therapy may therefore contribute to improvements in clinical outcomes observed across disease models.

MSC therapy also promotes the production of anti-inflammatory cytokines and modulates immune cell behavior. A key mechanism involves macrophage polarization, whereby MSC signaling promotes the transition of macrophages from pro-inflammatory M1 phenotypes to anti-inflammatory M2 phenotypes (Song et al., 2020; Najar et al., 2010).

These immunomodulatory properties are highly relevant to the concept of inflammaging. Persistent low-grade inflammation has been widely recognized as a biological driver of aging and chronic disease. By modulating inflammatory signaling pathways and restoring immune balance, MSC therapies may represent a promising strategy for addressing the biological processes underlying age-related degeneration.

Limitations

Several limitations should be acknowledged. Included studies varied in MSC source, dosing protocols, and delivery methods. Differences in disease models and outcome measures also contributed to heterogeneity across studies. Additionally, while preclinical models provide valuable mechanistic insights, translation to human clinical outcomes requires further investigation.

Conclusion

Mesenchymal stromal cells demonstrate significant potential as modulators of chronic inflammation and immune signaling pathways associated with aging. Current evidence suggests that MSC therapies may influence the biological mechanisms underlying inflammaging and age-related disease. Continued research is necessary to clarify optimal treatment protocols and long-term therapeutic impact.

Declarations

Author Contributions

Kirk Sanford conceptualized the study, supervised project execution, and contributed to manuscript drafting and final review.
Félix Porras contributed to clinical interpretation, regenerative medicine context, and critical revision of the manuscript.
Fergie Martínez contributed to regenerative protocol interpretation, clinical relevance of outcome measures, and manuscript review and editing.
Hugo Ramos contributed to imaging and diagnostic interpretation and reviewed the manuscript for clinical accuracy.
Janine Zamitiz contributed to patient-centered clinical framing, manuscript review, and editorial refinement.
Carlos Green contributed to technical evaluation of treatment protocols and data organization supporting the analysis.
Edward Ramsay contributed to scientific review, interpretation of clinical laboratory and biomarker relevance, and manuscript review and editing.

All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability

All data analyzed in this study were derived from previously published studies and are available within the cited literature.

Conflict of interest

The authors declare no conflicts of interest.

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Figures

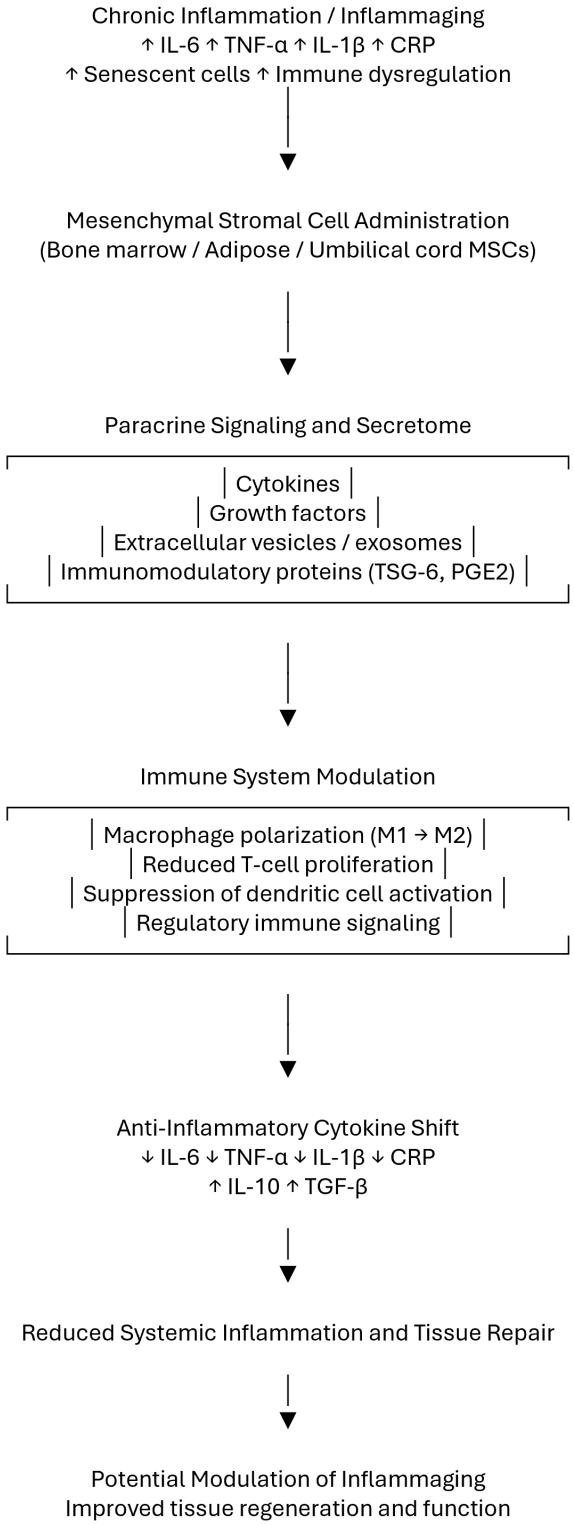


Figure 1

Proposed mechanisms by which mesenchymal stromal cells modulate inflammatory pathways associated with chronic inflammation and inflammaging.