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Lubricant of Motion: Synovial Fluid-Derived Mesenchymal Stromal/Stem Cells for Cartilage and Joint Regeneration

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ABSTRACT

Synovial fluid has historically been regarded as a specialized biological lubricant responsible for reducing friction, distributing mechanical loads, and supporting cartilage nutrition within diarthrodial joints. Recent advances in regenerative medicine have revealed that synovial fluid also contains mesenchymal stromal/stem cell (MSC)-like populations with significant regenerative and immunomodulatory properties. These synovial fluid-derived mesenchymal stromal/stem cells (SF-MSCs) are believed to originate predominantly from the synovial membrane and other joint-associated progenitor niches, exhibiting robust clonogenicity, multilineage differentiation, and superior chondrogenic potential. Emerging evidence suggests that SF-MSCs contribute to joint homeostasis through cartilage matrix production, immunomodulation, and paracrine signaling mediated by extracellular vesicles and exosomes. Consequently, SF-MSCs have attracted considerable interest as a candidate cell source for cartilage repair, meniscal regeneration, osteochondral reconstruction, disease modeling, and cell-free regenerative therapies. Although encouraging preclinical and early clinical studies support their therapeutic promise, significant challenges remain regarding cellular heterogeneity, standardization, manufacturing, and long-term efficacy. This commentary reviews the biological characteristics, mechanisms of action, translational applications, current limitations, and future perspectives of SF-MSCs in orthopedic regenerative medicine.

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Introduction

Joint disease has affected human populations for millennia. Evidence of degenerative and inflammatory arthritis has been observed in ancient Egyptian mummies, while early medical writings by Hippocrates described joint pain, stiffness, and structural disability [1]. For centuries, arthritis was viewed largely as an inevitable consequence of aging, trauma, or systemic metabolic imbalance. The development of modern anatomy and pathology eventually led to the recognition of the synovial joint as a biologically active organ composed of cartilage, the synovial membrane, intra-articular ligaments, and synovial fluid. By the twentieth century, synovial fluid was understood to provide lubrication, nutrient transport, shock absorption, and mechanical protection.

The concept of synovial fluid as a regenerative niche emerged only recently following the identification of multipotent mesenchymal stromal/stem cell populations within the joint fluid [2, 3]. This discovery fundamentally transformed the perception of synovial fluid from a passive mechanical lubricant to an active biological reservoir participating in tissue homeostasis, inflammation control, and cellular repair.

Articular cartilage injuries and degenerative joint diseases remain among the leading causes of chronic disability worldwide. Because mature articular cartilage is avascular and alymphatic, it exhibits limited intrinsic healing capacity [4]; thus, the functional restoration of damaged cartilage remains a paramount challenge in orthopedic medicine. Existing clinical interventions, including microfracture, osteochondral grafting, and total joint arthroplasty, often provide symptomatic relief but fail to fully restore the structural and biomechanical properties of native hyaline cartilage.

Within this context, mesenchymal stromal/stem cells (MSCs) have emerged as promising therapeu-

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tic candidates due to their regenerative, trophic, and immunomodulatory properties. Among the various body fluid-derived stem cell sources currently being explored globally, as summarized [2, 3], synovial fluid-derived MSCs (SF-MSCs) have gained rapid attention owing to their intimate association with the joint microenvironment and their superior chondrogenic potential [5].

Because SF-MSCs can be repeatedly obtained through minimally invasive arthrocentesis, they may serve not only as therapeutic products but also as dynamic biological reporters of intra-articular health. Longitudinal analysis of SF-MSC phenotypes, transcriptomes, secretomes, and extracellular vesicle cargo may enable patient stratification, disease monitoring, and prediction of therapeutic response.

Unlike bone marrow- or adipose-derived MSCs, SF-MSCs reside directly within the synovial cavity, representing a tissue-specific population naturally adapted to cartilage maintenance and localized repair [6]. Accumulating evidence indicates that SF-MSCs possess robust chondrogenic potential, potent immunomodulatory activities, and the ability to promote tissue repair through both direct differentiation and paracrine signaling [4]. These properties position SF-MSCs as promising candidates for the regenerative treatment of focal cartilage defects, meniscal injuries, and degenerative joint disorders [5].

2. Cellular Identity and Characterization of SF-MSCs

Consistent with the International Society for Cell & Gene Therapy (ISCT) criteria for defining MSCs, which are outlined comprehensively [7, 8], SF-MSCs characteristically express the canonical surface markers CD73, CD90, and CD105. Concurrently, they lack the expression of hematopoietic and endothelial markers, including CD34, CD45, CD14, CD11b, CD79a, CD19, and HLA-DR, as established by the clinical consensus criteria [8, 9]. However, marker expression profile intensity may vary depending on donor demographics, underlying joint pathology, and ex vivo culture conditions.

Functionally, SF-MSCs exhibit clonogenicity, sustained self-renewal capacity, and multilineage differentiation potential toward chondrogenic, osteogenic, and adipogenic lineages [10]. Among adult MSC populations, SF-MSCs are particularly noteworthy for their robust chondrogenic differentiation, frequently demonstrating elevated expression of master transcription factors and matrix proteins, including SOX9, COL2A1, and ACAN, accompanied by abundant synthesis of type II collagen and sulfated glycosaminoglycans [11, 12]. Importantly, although the term "stem cell" is widely utilized in literature, definitive evidence demonstrating long-term self-renewal and in vivo multipotency at the single-cell level remains limited. Therefore, the designation "mesenchymal stromal/stem cell" more accurately reflects the current state of scientific knowledge, as argued by Caplan [13].

3. Tissue Origin of Synovial Fluid Stem Cells

The precise anatomical origin of SF-MSCs remains incompletely understood, though it is widely accepted to be a multi-niche phenomenon involving distinct intra-articular zones [14]:

- **Synovial Membrane:** Current evidence suggests that the synovial membrane serves as the principal reservoir for SF-MSCs. The synovium contains resident MSC populations capable of detached migration into the joint cavity during physiological tissue turnover, mechanical trauma, or localized inflammation [15].
- **Synovial Intima:** The synovial intimal layer contains fibroblast-like synoviocytes and macrophage-like synoviocytes that play essential roles in maintaining joint homeostasis. Progenitor populations located within this specialized layer directly contribute to the detached SF-MSC pool [16].
- **Cartilage-Associated Progenitors:** Cartilage surface progenitor cells and osteochondral junction stem cells may be dynamically mobilized following structural injury and subsequently released into the synovial fluid [17].
- **Perivascular Niches:** Perivascular MSC-like cells present within vascularized synovial tissues may also contribute to the regenerative cell populations identified within synovial fluid during injury responses [18].

Synovial Membrane MSCs Versus Synovial Fluid MSCs

The terms synovial membrane-derived mesenchymal stromal/stem cells (SM-MSCs) and synovial fluid-derived mesenchymal stromal/stem cells (SF-MSCs) are often used interchangeably in regenerative medicine literature. However, these populations originate from distinct anatomical compartments and exhibit unique biological signatures [15]. Understanding their similarities and differences is critical

Table 1. Comparative Analysis of Synovial Membrane-Derived and Synovial Fluid-Derived MSCs

Characteristic	Synovial Membrane MSCs (SM-MSCs)	Synovial Fluid MSCs (SF-MSCs)
Anatomical Location	Synovial membrane (intima and subintima)	Synovial fluid cavity
Origin	Resident synovial progenitor cells	Mobilized from synovial membrane and joint tissues
Collection Method	Arthroscopic biopsy or surgical harvest	Joint aspiration (arthrocentesis)
Cell Yield	Relatively consistent	Variable and disease-dependent
Phenotype	Classical MSC markers ($CD73^+$, $CD90^+$, $CD105^+$)	Similar MSC markers but highly heterogeneous
Chondrogenic Potential	Extremely high	High to very high
Response to Injury	Tissue-resident regenerative cells	Injury-responsive, mobilized repair cells
Immuno-modulation	Strong	Strong
Clinical Advantages	Robust cartilage-forming capacity	Minimally invasive harvest; repeated sampling
Major Limitation	Requires invasive tissue biopsy	Lower baseline cell numbers; heterogeneity
Emerging Application	Cartilage and osteochondral engineering	Cell therapy, exosome therapy, disease monitoring

for interpreting experimental findings and optimizing cell-based therapies for joint regeneration.

To clarify these anatomical distinctions, a side-by-side assessment of their baseline phenotypes is provided in the text. As detailed in the comparative analysis shown in **Table 1**, SM-MSCs reside within the intimal and subintimal layers of the synovial membrane, constituting a native progenitor cell population responsible for maintaining synovial tissue architecture. In contrast, SF-MSCs are isolated directly from the fluid phase of the joint cavity, where they originate primarily from the synovial membrane and, to a lesser extent, from cartilage, meniscal, ligamentous, and other joint-associated progenitor niches. Notably, the absolute yield of SF-MSCs increases significantly following joint injury or during the progression of osteoarthritis, suggesting a directed mobilization of reparative cells into the joint cavity [10].

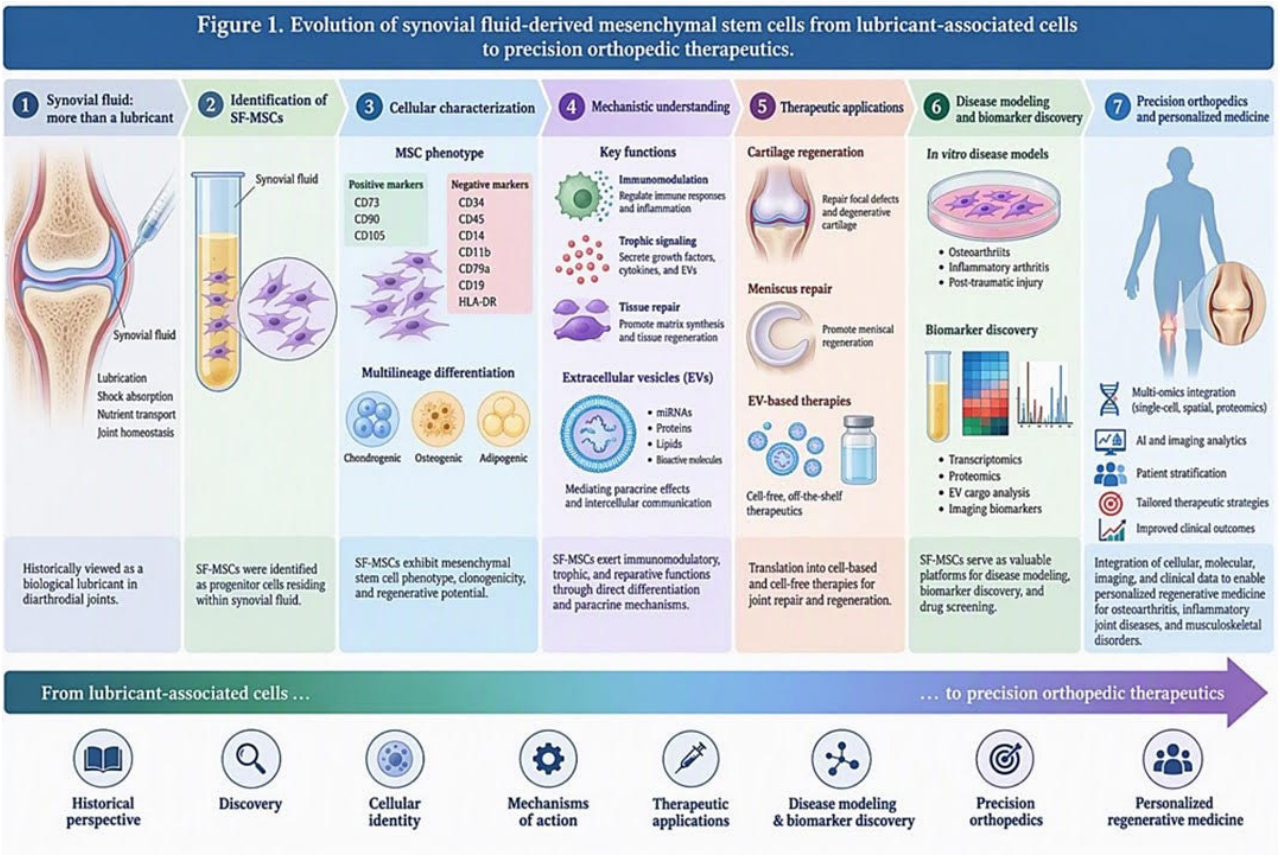
Both populations express canonical MSC markers ($CD73^+$, $CD90^+$, $CD105^+$) while lacking hematopoietic lineages. Nevertheless, SF-MSCs frequently exhibit a more heterogeneous phenotype because the synovial fluid compartment acts as a sink for cells released from multiple intra-articular tissues. While SM-MSCs are anchored within the synovial tissue microenvironment, SF-MSCs represent a dynamically responsive cell population that actively reflects the pathological state of the joint, shifting their profiles in response to inflammation or mechanical loading. From a clinical translation perspective, harvesting SM-MSCs requires arthroscopy or invasive surgical biopsy. Conversely, SF-MSCs can be obtained via minimally invasive joint aspiration (arthrocentesis), offering profound practical advantages for repeated sampling, disease monitoring, and autologous cell therapy design [4]. To review the comprehensive stemness properties, growth dynamics, and differentiation profiles of these cells, please refer to the data matrix presented in **Table 2**.

Table 2. Biological Differentiation and Profile Matrix of SF-MSCs [19, 20]

Feature	Synovial Fluid Mesenchymal Stromal/Stem Cells
Primary Source	Synovial membrane and joint-associated tissues
Collection Method	Arthrocentesis
Harvest Invasiveness	Minimally invasive
MSC Surface Markers	$CD73^+$, $CD90^+$, $CD105^+$
Hematopoietic Markers	$CD34^-$, $CD45^-$
Growth Capacity	High ex vivo expansion capacity
Chondrogenic Potential	Very high; robust matrix synthesis
Osteogenic Potential	Moderate to high
Adipogenic Potential	Moderate
Immunomodulatory Activity	High; potent secretome profile
Major Clinical Interest	Cartilage, meniscus, and joint regeneration

The evolution of SF-MSC research from their initial discovery within synovial fluid to emerging

Figure 1. Evolution of synovial fluid-derived mesenchymal stem cells from lubricant-associated cells to precision orthopedic therapeutics. SF-MSCs were initially identified as progenitor cells residing within synovial fluid and subsequently characterized by their mesenchymal stem cell phenotype and regenerative capacity. Advances in mechanistic understanding revealed their immunomodulatory, trophic, and reparative functions, leading to applications in cartilage regeneration and EV-based therapies. More recently, SF-MSCs have emerged as valuable platforms for disease modeling, biomarker discovery, and precision orthopedics. Integration of cellular, molecular, imaging, and clinical data may ultimately enable personalized regenerative medicine strategies for osteoarthritis, inflammatory joint diseases, and musculoskeletal disorders.



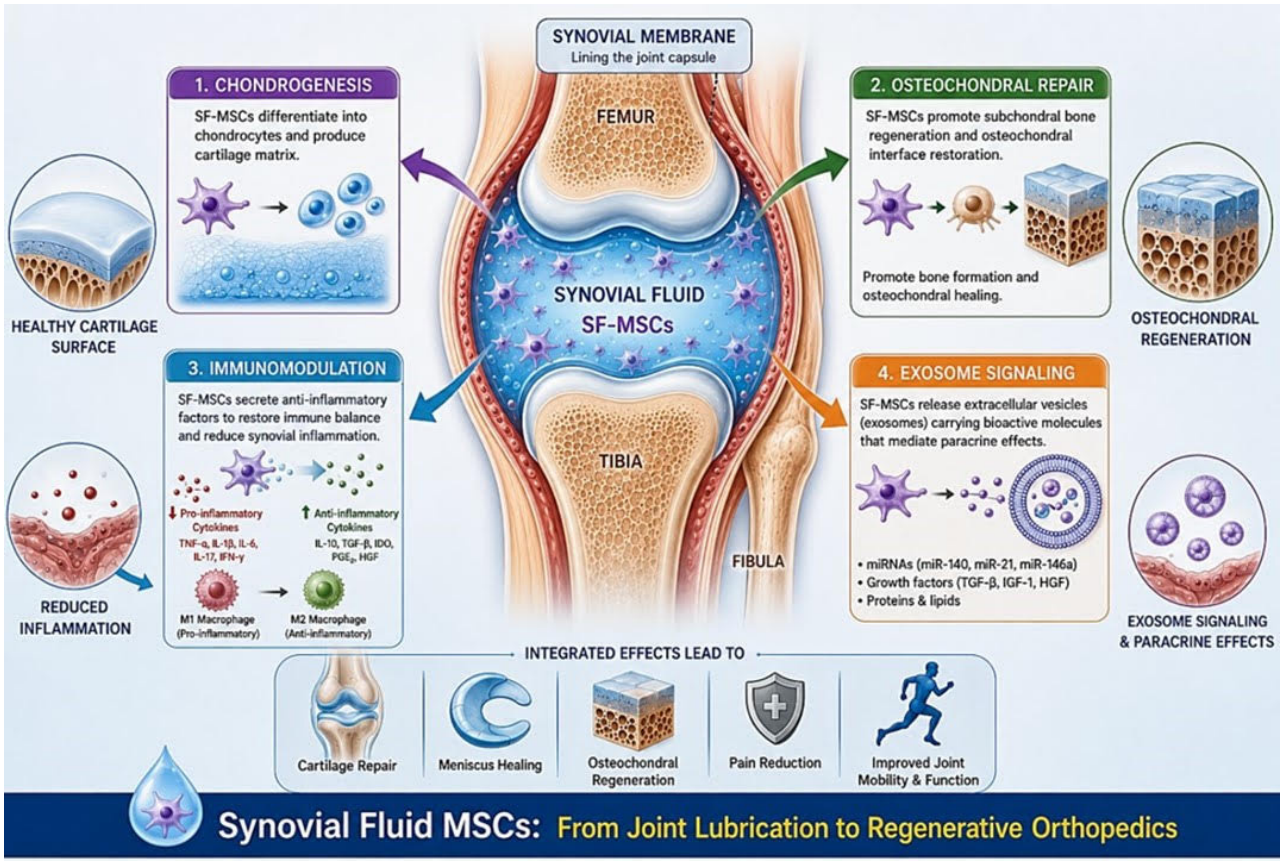
applications in precision orthopedics and personalized regenerative medicine is summarized in **Figure 1.**

Importantly, SF-MSCs isolated from healthy joints differ markedly from those obtained from osteoarthritic or inflammatory joints. Osteoarthritis-associated SF-MSCs frequently display reduced proliferative capacity, increased cellular senescence, inflammatory priming, transcriptomic reprogramming, and altered lineage differentiation potential. These disease-associated changes likely reflect a dynamic response to chronic joint inflammation and tissue degeneration, although whether they represent compensatory regenerative mechanisms or progressive cellular dysfunction remains incompletely understood. Notably, the molecular, phenotypic, and functional alterations observed in SF-MSCs may themselves constitute a novel class of biological markers capable of reflecting disease activity, progression, and therapeutic response. As a result, SF-MSCs represent not only a promising regenerative cell source but also a potentially informative living biomarker platform for monitoring joint health and guiding precision medicine approaches in osteoarthritis and inflammatory arthropathies.

4. Mechanisms of Action Underlying Joint Repair

Current evidence suggests that the therapeutic effects of SF-MSCs are mediated primarily through paracrine and immunomodulatory mechanisms rather than direct physical tissue replacement alone [21, 22]. SF-MSCs secrete a broad repertoire of bioactive molecules, including transforming growth factor-β (TGF-β), hepatocyte growth factor (HGF), prostaglandin E2 (PGE_2), and interleukin-10 (IL-10), which modulate inflammation and promote tissue repair. These factors influence both innate and adaptive immune responses, contributing to macrophage

Figure 2. Mechanistic pathways of Synovial Fluid-Derived Mesenchymal Stromal/Stem Cells (SF-MSCs) in joint regeneration. As shown in this schematic diagram, SF-MSCs target joint repair via four integrated axes: (1) Chondrogenesis, promoting direct differentiation into cartilage-matrix-producing chondrocytes; (2) Osteochondral Repair, reconstructing bone-cartilage tissue layers; (3) Immunomodulation, suppressing M1 pro-inflammatory macrophages (TNF-α, IL-1β, IL-6, IFN-γ) and upregulating reparative M2 macrophages alongside protective cytokines (IL-10, TGF-β, IDO, PGE_2, HGF); and (4) Exosome Signaling, where extracellular vesicles deliver structural microRNAs (miR-140, miR-21, miR-146a) and therapeutic proteins. Collectively, these integrated activities promote cartilage repair, meniscal healing, osteochondral regeneration, pain reduction, and overall functional mobility.



polarization toward anti-inflammatory (M2) phenotypes and the suppression of excessive T-cell activation [23].

The spatial organization of these multi-lineage repair mechanisms can be seen in the structural diagram labeled as **Figure 2**, which charts the four main therapeutic pathways within the knee joint cavity. As illustrated visually in **Figure 2**, these pathways encompass localized chondrogenesis, osteochondral matrix rebuilding, macrophage polarization, and paracrine exosome trafficking.

In addition, SF-MSCs release extracellular vesicles (EVs) and exosomes containing regulatory microRNAs (miRNAs), proteins, functional lipids, and growth factors. Increasing evidence indicates that these vesicles contribute substantially to chondroprotection by enhancing extracellular matrix synthesis, reducing chondrocyte apoptosis, suppressing catabolic signaling cascades, and promoting tissue remodeling [24, 25]. While direct differentiation into functional chondrocytes occurs under specific intra-articular conditions, the relative contribution of physical engraftment versus paracrine signaling remains an area of active investigation [26, 27]. The precise molecular factors involved in these pathways are detailed sequentially in **Table 3**, which defines the biological function and therapeutic significance of each secreted component.

Increasing interest has shifted toward engineered SF-MSC-derived extracellular vesicles, which may provide enhanced therapeutic efficacy while avoiding concerns associated with cell engraftment, viability, and regulatory complexity.

Table 3. Molecular Mechanisms Underlying SF-MSC-Mediated Joint Regeneration

Molecular Factor	Biological Function	Role in SF-MSC -Mediated Regeneration	Therapeutic Significance
TGF-β [28]	Master regulator of chondrogenesis and ECM synthesis	Activates SMAD signaling pathways; drives MSC chondrogenic differentiation	Critical for cartilage repair and tissue-engineering strategies
SOX9 [20]	Master transcription factor for cartilage development	Regulates chondrocyte differentiation and cartilage-specific gene expression	Essential for the maintenance of the chondrogenic phenotype
COL2A1 [20]	Principal structural component of hyaline cartilage	Synthesized by differentiating SF-MSCs during structural matrix repair	Gold-standard marker of successful cartilage formation
ACAN [20]	Major cartilage proteoglycan for compressive resilience	Enhances ECM organization and water retention within cartilage tissue	Restores biomechanical cartilage function and loading capacity
IL-10 [29]	Potent anti-inflammatory cytokine	Suppresses pro-inflammatory cascades; drives M2 macrophage polarization	Reduces joint inflammation and cartilage degradation
PGE2 [30]	Immunomodulatory lipid mediator	Mediates SF-MSC-induced regulation of immune cell activity	Supports the resolution of chronic synovial inflammation
Exosomal miRNAs [31]	Regulatory non-coding RNAs in EVs	Modulate chondrocyte survival and ECM synthesis via paracrine signaling	Basis for emerging cell-free regenerative therapies
miR-140 [32]	Cartilage-specific microRNA	Promotes chondrogenesis and inhibits cartilage catabolism	Supports cartilage preservation in osteoarthritis models
miR-21 [33]	Pro-survival and anti-apoptotic miRNA	Enhances tissue repair and suppresses inflammatory pathways	Facilitates cartilage regeneration and host cell survival
miR-146a [34]	Anti-inflammatory microRNA	Downregulates NF-κB-mediated inflammatory signaling	Reduces osteoarthritis-associated synovitis
EVs [32, 33]	Intercellular Communication particles	Deliver proteins, growth factors, and regulatory RNAs to target cells	Promotes repair while avoiding risks of cell transplantation

5. Translational and Disease Modeling Applications

Disease Modeling Platforms

- **Osteoarthritis (OA):** SF-MSCs provide a high-fidelity human platform for studying the pathological mechanisms of cartilage degeneration, chondrocyte senescence, inflammatory signaling networks, and matrix metalloproteinase breakdown [35].
- **Rheumatoid Arthritis (RA):** Patient-derived SF-MSCs permit the localized investigation of chronic synovitis, immune dysregulation, autoantibody-driven disease progression, and cellular crosstalk [36].
- **Precision Orthopedics:** Three-dimensional cell culture systems, high-throughput cartilage constructs, and organoid-like models generated from SF-MSCs have emerged as powerful platforms for personalized drug screening, biomarker discovery, and targeted therapeutics [37].

Regenerative Orthopedic Applications

The clinical utility of these cells is heavily evaluated against alternative stem cell compartments [12, 38, 39]. As contrasted systematically in **Table 4**, SF-MSCs demonstrate superior joint specificity and matrix production over bone marrow-derived MSCs (BM-MSCs) and adipose-derived stem cells (ADSCs).

- **Articular Cartilage Repair:** SF-MSCs have demonstrated significant promise in repairing focal cartilage defects through direct chondrogenic differentiation and paracrine support of endogenous repair mechanisms.
- **Meniscus Regeneration:** Experimental studies have shown that SF-MSCs can promote

Table 4. Comparative Analysis of Major MSC Sources for Orthopedic Regeneration [41, 42]

Characteristic	SF-MSCs	BM-MSCs	ADSCs
Primary Source	Synovial fluid	Bone marrow	Adipose tissue
Harvest Method	Arthrocentesis	Bone marrow aspiration	Liposuction
Harvest Invasiveness	Low	Moderate to High	Moderate
Cell Yield	Low to moderate	Low	High
Expansion Capacity	High	Moderate	High
Chondrogenic Potential	Very high	High	Moderate
Osteogenic Potential	Moderate-high	Highest	Moderate
Adipogenic Potential	Moderate	Moderate	Highest
Joint Specificity	Excellent	Limited	Limited
Cartilage Matrix Prod.	Highest	Moderate-high	Moderate
Immunomodulation	High	High	High
Clinical Experience	Emerging	Extensive	Extensive
Major Advantage	Native joint adaptation	Strong osteogenesis	High baseline cell yield
Major Limitation	Limited clinical data	Highly invasive harvest	Lower chondrogenesis

functional fibrocartilage formation and significantly improve structural meniscal healing and integration [40].

- **Osteochondral Defect Repair:** Combination therapies involving SF-MSCs, localized growth factors, biomaterial scaffolds, and bioprinted constructs have shown encouraging structural outcomes in preclinical large-animal models [35].
- **Cell-Free Therapies:** SF-MSC-derived extracellular vesicles represent a promising alternative to cell transplantation, offering improved safety profiles, easier manufacturing scalability, and streamlined regulatory feasibility as detailed in the secretome analyses [24, 25, 27].

The historical milestones validating these applications are tracked chronologically in the text. For a comprehensive overview of the foundational studies in this domain, see **Table 5**, which details landmark preclinical investigations ranging from small-animal models to scaffold-assisted tissue engineering.

6. Clinical Translation, Limitations, and Future Perspectives

Clinical Status

The translational appeal of SF-MSCs stems from three major advantages: (1) minimally invasive acquisition through arthrocentesis, (2) strong chondrogenic potential, and (3) biological pre-adaptation to the native intra-articular microenvironment. Preclinical studies across various models of cartilage injury, osteoarthritis, meniscal damage, and osteochondral defects have consistently demonstrated beneficial effects on cartilage preservation, extracellular matrix deposition, inflammation reduction, and functional recovery [20, 26, 51]. However, clinical evidence remains substantially less mature than the preclinical literature. Early clinical studies have suggested improvements in pain, function, and imaging-based outcomes; however, the overall quality of evidence remains limited due to small sample sizes and methodological heterogeneity [21, 52, 53]. To review the specific clinical profiles gathered from human patients so far, please examine the human trials summarized in **Table 6**.

Nevertheless, most completed human trials have been limited by small sample sizes, non-randomized designs, heterogeneous manufacturing protocols, and relatively short follow-up periods. Crucially, definitive clinical evidence demonstrating durable, long-term regeneration of hyaline cartilage and structural disease modification remains lacking. Consequently, SF-MSC therapies should currently be categorized as promising investigational approaches rather than established clinical standards of care. Large-scale, multicenter randomized controlled trials (RCTs) employing standardized cell characterization, standardized manufacturing procedures, validated dosing regimens, and uniform outcome measures are manda-

Table 5. Landmark Preclinical Studies of SF-MSCs in Joint Regeneration

Study Model	Cell source	Experimental Condition	Major Findings	Translational Significance	Refs
Human knee aspirates	SF-MSCs	Chondrogenic differentiation assays	Demonstrated clonogenic growth and robust chondrogenic potential	Established SF-MSCs as a cartilage progenitor population	ALTAIE A, et al., 2022 [43]
Rabbit model	SF-MSCs	Osteochondral cartilage defect repair	Enhanced cartilage matrix deposition and improved defect filling	Provided proof-of-concept for cartilage regeneration	JIA Z, et al., 2018 [44]
Rat OA model	SF-MSCs	Intra-articular cell injection	Reduced inflammatory cytokines and slowed cartilage degeneration	Demonstrated clear disease-modifying effects	FURUOKA H, et al., 2023 [45]
Meniscal injury model	Synovial MSCs	Meniscus repair	Improved meniscal healing and integration with native tissue	Supported application in meniscal regeneration	XIAO W F, et al., 2021 [46]
Large animal model	Synovial MSCs	Scaffolds for osteochondral repair	Increased hyaline-like cartilage formation and structural repair	Enhanced translational relevance for clinical repair	KOGA Y, et al., 2025 [47]
Exosome-based studies	SF-MSC EVs	Experimental osteoarthritis	Suppressed inflammation and promoted chondrocyte survival	Supported development of cell-free therapies	ZHANG S, et al., 2019 [48]
Synovectomy models	SM Progenitors	Joint injury response	Demonstrated mobilization of regenerative progenitor cells post-injury	Suggested activation of endogenous repair mechanisms	JONES E A, et al., 2008 [49]
Scaffold-assisted engineering	SF-MSCs	Biomaterial constructs	Improved cell retention, matrix production, and maturation	Advanced strategies for clinical translation	ZHANG X, et al., 2020 [50]

tory before widespread clinical implementation can be justified. In addition, single-cell RNA sequencing, spatial transcriptomics, and multiomic profiling are expected to uncover previously unrecognized SF-MSC subpopulations with distinct regenerative and immunomodulatory functions.

Current Limitations and Knowledge Gaps

Several critical biological and technical hurdles continue to hinder the seamless clinical translation of SF-MSCs:

- Incomplete understanding of the exact in vivo fate and long-term integration profile of transplanted SF-MSCs.
- Significant donor-to-donor variability driven by age, sex, and systemic health status.
- A lack of universally standardized isolation, expansion, and functional potency assays as highlighted in the cell manufacturing guidelines [59, 60].
- Disease-induced alterations in cell composition and fitness between healthy and advanced osteoarthritic joints.
- Limited long-term safety data regarding potential ectopic tissue formation or senescent transformations as discussed in the safety overviews[26, 37].
- Regulatory, scalable, and economic manufacturing challenges associated with advanced therapy medicinal products (ATMPs).
- The absence of large-scale, long-term randomized controlled trials.

Furthermore, advanced osteoarthritis itself may fundamentally compromise the inherent biological properties of autologous SF-MSCs, raising critical logistical questions regarding whether autologous cells derived from highly diseased joints retain sufficient therapeutic efficacy.

Table 6. Representative Clinical Evidence of Synovial-Derived MSC Therapies

Study Type	Sample number	Cell Source	Target Disease	Follow-up	Clinical Outcome Summary	Refs
Pilot clinical study	**5**	Synovial MSCs	Cartilage defects	24 months	Improved defect filling and localized cartilage repair	Shimomura, K., et al., 2018 [54]
Case series	**1**	Synovial MSCs	Meniscus injury	2 years	Enhanced structural healing and symptom improvement	Sekiya, I., et al., 2019 [55]
Phase I/II trial	**14**	Synovial MSCs	Knee osteoarthritis	30 weeks	Significantly reduced pain scores and improved function	Sekiya, I., et al., 2021 [56]
Observational study	**3**	Joint MSCs	Osteoarthritis	5 years	Improved WOMAC and objective clinical indices	Davatchi, F., et al., 2016 [57]
Scaffold-assisted	**5**	Synovial MSCs	Focal cartilage defects	24 months	Improved post-op MRI and histological outcomes	Shimomura, K., et al., 2018 [54]
Translational studies	**3**	SFSC Exosomes	Osteoarthritis	not applicable	Reduced synovial inflammation; enhanced preservation	Petta, D., et al, 2024 [58]
Registry studies	**17**	Synovial MSCs	Degenerative disorders	12 months	Favorable short-term safety and tolerability profile	Tucker, J. D., et al., 2021 [53]

Future Perspectives

Several key research priorities will shape the next generation of SF-MSC-based orthopedics:

- *Standardization:* Establishing rigorous international consensus definitions and phenotypic characterization criteria based on the baseline frameworks [8].
- *Lineage Tracing*: Utilizing single-cell transcriptomics and spatial molecular profiling to map the exact cellular hierarchy and mobilization pathways of SF-MSCs, building upon the basic tracking methods [52, 60].
- *GMP Manufacturing:* Developing automated, closed-system, Good Manufacturing Practice (GMP)-compliant expansion protocols.
- *Bio-Engineering*: Integrating SF-MSCs with advanced biomimetic hydrogels, functionalized scaffolds, and 3D bioprinting technologies.
- *Cell-Free Evolution:* Advancing engineered extracellular vesicle- and exosome-based therapeutics to bypass cellular regulatory hurdles, following the microRNA mapping [24, 61].
- *Clinical Trials*: Designing and launching robust, multi-center, double-blind randomized clinical trials with long-term follow-up periods to build upon the ten-year tracking data [62].

Conclusion

Synovial fluid-derived mesenchymal stromal/stem cells represent a highly unique cell population

residing within the joint microenvironment that combines strong chondrogenic capacity with potent immunomodulatory and trophic activities. Emerging evidence confirms that these cells contribute actively to cartilage homeostasis and serve as valuable tools for cartilage repair, meniscal regeneration, osteochondral reconstruction, disease modeling, and extracellular vesicle-based therapies. Gross biological and translational challenges remain, specifically regarding cellular identity clarification, standardization of manufacturing protocols, and the generation of high-level clinical evidence. However, with continued cross-disciplinary advances in stem cell biology, biomaterial interfaces, and precision regenerative medicine, SF-MSCs are poised to become a cornerstone component of future strategies aimed at preserving joint function and delaying the progression of degenerative musculoskeletal diseases.

Declarations

Competing Interests: The authors declare that they have no competing financial or non-financial interests.

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