

Review

Mesenchymal Stem Cells as a Regenerative Treatment for Musculoskeletal Pain

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Abstract

Mesenchymal stem cells (MSCs) have become a focus of regenerative medicine research due to their potential utility in treating a variety of musculoskeletal disorders. Multiple qualities make them an ideal candidate to address musculoskeletal structural degeneration and inflammation, including their multi-lineage differentiation capacity, relative ease of extraction, and paracrine signaling capabilities. This narrative review examines the literature surrounding MSC-related therapies in musculoskeletal disorders, with a particular emphasis on mechanical and cellular factors affecting therapeutic efficacy. Multiple clinical and preclinical studies find that MSCs bolster tissue repair through a combination of extracellular matrix remodeling, inflammatory modulation, and regenerative signaling pathways. In addition, mechanotransduction signaling pathways have been discovered that convert mechanical tensile shear stress, compression, and strain forces into regulatory signals for matrix remodeling and tissue proliferation. Additional studies suggest that MSC efficacy and optimization are greatly influenced by a cell's mechanical environment within the body. Further understanding of these mechanical factors can greatly bolster emerging regenerative therapies increasingly being utilized for musculoskeletal conditions.

Keywords: mesenchymal stem cells; mechanotransduction; mechanobiology; musculoskeletal conditions; regenerative medicine; stem cell differentiation; pain



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1. Introduction

Chronic musculoskeletal (MSK) pain affects approximately 30% of the global population and is one of the leading causes of long-term disability worldwide [1]. Standard therapies include physical therapy, steroid injections, anti-inflammatory medications, opioids, and surgical management, aiming to reduce symptomatic burden [2]. However, these modalities often show limited efficacy, and patients pose the risk of developing dependency and drug-related toxicity. Consequently, regenerative medicine exhibits therapeutic promise aimed at supporting structural integrity and functional recovery, providing potential advances in early detection and treatment of many MSK conditions.

Within the field of regenerative medicine, the growing literature has identified mesenchymal stem cells (MSCs) as a promising candidate for clinical applications due to their

relative ease of extraction and potential for rapid expansion to clinical scale within in vitro conditions [3]. MSCs are also referred to as multipotent mesenchymal stromal cells and can be isolated from a wide variety of sources, including bone marrow, adipose tissue, amniotic fluid, and synovial fluid [3–5]. Numerous factors make MSCs an ideal cell source for tissue regeneration, including their multilineage differentiation capacity, ability to secrete chemokines and growth factors affecting extracellular matrix remodeling and cellular recruitment, and anti-inflammatory and immunoregulatory properties [3–5].

The application of MSCs in chronic musculoskeletal pain medicine has evolved over the past decade. Chronic conditions such as osteoarthritis and degenerative disc disease have seen some promising benefits from the application of these cells. Clinical investigations observing intra-articular MSC injections have shown significant improvements in pain and functional recovery [6]. Furthermore, numerous reviews examine the robust evidence for the regenerative capacity of MSCs in arthritic and chondral disease processes [7–10].

Considering these advances, further understanding of the biomechanical processes influencing regenerative efficacy is necessary for effective implementation. Recent studies point to the conversion of shear and stretch forces, substrate stiffness, and compression forces into biochemical signals by MSCs that can subsequently affect lineage choice [11–13]. These mechanotransduction signals run through a complex system of integrins, focal adhesions, Linker of Nucleoskeleton and Cytoskeleton (LINC) complex proteins, and transcriptional effectors such as YAP/TAZ [14,15]. This dynamic is increasingly being characterized as a constant interplay between cellular mechanosensors and the extracellular matrix. The regulatory systems underlying MSC differentiation and behavior may provide an avenue to optimize its use in regenerative medicine, providing the potential to lead to better patient outcomes in musculoskeletal pain. In this review, we discuss the mechanobiological processes governing MSC therapy in regenerative pain medicine and its clinical application to MSK disorders.

2. Methods

This narrative review aimed to investigate current evidence regarding MSC biology, mechanobiology, and regenerative applications to musculoskeletal pain medicine. To construct our review methodology, a comprehensive literature search was conducted using the PubMed and Google Scholar databases, including articles spanning 2006 to 2026. The literature analyzed comprised current investigations, pertinent historical data, and meta-analyses. Our search extended to literature reviews, complete manuscripts, and comparative studies about MSC mechanobiology. Representative search terms included combinations of the following: (“mesenchymal stem cells”) AND (mechanobiology OR mechanotransduction OR mechanotherapy OR mechanosensing OR mechanical loading) AND (“interventional pain” OR “musculoskeletal pain” OR regeneration). Additional searches were performed using combinations of terms regarding stem cell differentiation, integrin pathways, tissue proliferation, extracellular matrix, osteoarthritis, tendon, regenerative rehabilitation, YAP/TAZ signaling, focal adhesion kinase (FAK), and RhoA/ROCK signaling.

Studies were included if they investigated MSC biology, mechanobiology, mechanotransduction, regenerative mechanisms, or evaluated MSC-based therapies in MSK tissues or pain models. Included studies also consisted of original studies, translational investigations, clinical trials, systematic reviews, and meta-analyses published in English. Studies were subsequently excluded if they focused on non-MSC cell populations, unrelated regenerative therapies, non-musculoskeletal pain conditions, or were conference abstracts or editorials.

Each author independently performed a literature search and screened abstracts for relevance. After determination of inclusion, full manuscripts were subsequently reviewed. Additional references were then obtained through manual review of reference lists from relevant publications from pertinent manuscripts. Final inclusion of studies in the review was based on unanimous agreement. The search identified approximately 117 articles, of which 102 full-text articles were reviewed, and 88 publications were ultimately included in the narrative synthesis. Data extracted from the included studies encompassed publication year, study objective, study design, variables assessed, mechanistic pathways investigated, and principal findings relevant to MSC mechanobiology and differentiation. This manuscript is a narrative review, and thus the selected literature was analyzed qualitatively with emphasis on mechanistic understanding, translational applications, emerging clinical data, and areas of further investigation.

3. Fundamentals of Stem Cell Therapy

3.1. Types/Sources

Stem cells are characterized by undifferentiated cells with the ability to self-renew and the capacity to specialize into different cell types [16,17]. Related to developmental potential, stem cells can be divided into embryonic, induced pluripotent, or adult stem cells. Limited by ethical concerns and the risk of tumor formation, embryonic stem cells are pluripotent and can generate cells from all three germ layers [16,18]. Induced pluripotent stem cells, while having genomic instability and oncogenic potential, are produced by reprogramming of somatic cells and offer patient-specific alternatives. Finally, adult stem cells contribute to tissue maintenance and repair throughout the whole body. Among these, MSCs have surfaced as the most thoroughly researched cell type in regenerative medicine and are relevant to musculoskeletal applications [17,19].

The International Society for Cellular Therapy, now the International Society for Cell & Gene Therapy (ISCT), originally established minimal criteria for MSC identification that included expression of CD73, CD90, and CD105, absence of hematopoietic markers (CD34, CD45, CD14, CD11b, CD19, and HLA-DR), the ability for osteogenic, adipogenic, and chondrogenic differentiation, and plastic adherence in culture [20,21]. Although this framework provides a standardized foundation to identify MSCs, it does not establish stemness, functional potency, or therapeutic efficacy. The 2025 ISCT recommendations for reporting MSC clinical trials in autoimmune diseases favor the term “mesenchymal stromal cell” when MSCs are used primarily as immunomodulatory products and prefer identifying the tissue source as a prefix in the product name [22]. These recommendations also call for reporting whether a product represents a heterogeneous or selected cell population, relevant donor characteristics, positive and negative identity markers with predefined release criteria, cell recovery and viability, and potency assays aligned with the proposed mechanism of action. Critical manufacturing and administration variables, including isolation and culture methods, in vitro cellular age, fresh or cryopreserved status, formulation, batch identity and comparability, dose, concentration, route, and rate of administration, should be transparently reported. Therefore, MSC products that share similar surface-marker profiles should not automatically be considered as biologically equivalent or expected to produce comparable clinical effects [22].

Specifically, MSCs can be derived from bone marrow, adipose tissue, umbilical cords, synovium, and amniotic fluid. Bone marrow-derived MSCs, despite providing low cell yield that declines with age, remain one of the most researched cell types and retain robust differentiation potential [23,24]. With a higher cell yield, adipose tissue provides a minimally invasive source of MSCs [23,25]. Restricted by allogeneic use, perinatally derived MSCs from umbilical cords, particularly those isolated from Wharton’s jelly, offer

potent immunomodulatory properties and a high proliferative capacity [23,24,26]. No single source has emerged as clearly superior across all therapeutic applications.

Although MSCs from varying tissue types can be compared as if they represent products that are interchangeable, the evidence illustrates that the origin of the tissue greatly influences differentiation potential, proliferative capacity, secretory profile, and immunomodulatory function. Moreover, rather than differences in diseases reflecting varying clinical outcomes, it may be the differences between MSC products.

The source-specific differences suggest that it is not as important which tissue is the universally “best” MSC, but rather which product is most specific for a particular condition and route of delivery. Autologous products avoid donor–recipient incompatibility; however, they require an invasive harvest that may be affected by patient age, inflammatory state, or metabolic disease. An allogeneic product, while possibly standardized and administered without a separate harvest, has the potential for functional changes during expansion and cryopreservation. Donor, source, dose, culture condition, viability at administration, and secretory potency should be treated as components of the intervention and not minor methodological details.

3.2. Preclinical Mechanisms and Evidence for Analgesia

Paracrine signaling, as opposed to direct engraftment and tissue replacement, is believed to drive the therapeutic effects of MSCs [27]. Bioactive paracrine factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), transforming growth factor-beta ($\text{TGF-}\beta$), and stromal cell-derived factor-1 (SDF-1) are secreted from MSCs to promote angiogenesis, cellular proliferation, extracellular matrix remodeling, and tissue repair [28]. Additionally, suppression of proinflammatory cytokines, enhancing anti-inflammatory signaling, inhibiting T-cell proliferation, and promotion of macrophage polarization toward anti-inflammatory phenotypes illustrate MSCs’ potent immunomodulation [27,29].

Previous research suggests that these effects are accomplished through MSC-derived extracellular vesicles (EVs), nanoscale membrane-bound particles containing proteins, lipids, mRNA, and microRNA [21,30,31]. These vesicles offer many advantages such as reduced tumorigenic risk, easier storage, and improved manufacturing scalability, as well as many of the regenerative and immunomodulatory properties of MSCs. These EV-based therapies can provide a cell-free alternative to previously established stem cell transplantations [28].

Related to mediated influences in multiple biological pathways involved in pain generation and persistence, MSCs remain a relevant contender for chronic MSK pain therapy. They attenuate pain signaling through reduction in key nociceptive mediators including nerve growth factor (NGF), calcitonin gene-related peptide (CGRP), and substance P, which is an 11-amino acid neuropeptide released from peripheral sensory nerve terminals that promotes neurogenic inflammation and nociceptive transmission via the neurokinin-1 receptor (NK1R) [32]. MSC administration has also been shown to decrease neuroinflammation through suppression of spinal synaptic plasticity by $\text{TGF-}\beta$ 1, inhibit microglial activation, reduce neuronal hyperexcitability, and promote tissue repair in experimental studies [33]. MSC-derived EVs suggest analgesic effects independent of structural regeneration by preventing sensory neuron hyperexcitability in osteoarthritis models [34]. Regarding neuropathic pain, MSC therapy studies have reduced neuronal injury markers and enhanced remyelination [33]. Collectively, these findings support the hypothesis that MSCs have the ability to influence neurobiological and inflammatory processes of chronic pain. Uncertainty remains as to whether the modulation of these pathways translates

into substantial clinical analgesia, as improvements in experimental biomarkers have not corresponded to significant pain reduction in human studies.

Even with compelling evidence that attempts to demonstrate mechanisms of EVs, the contribution of each suggested pathway remains unknown. With most mechanistic data originating from animal models or in vitro studies, it is difficult to determine which EV mechanisms prevail in humans or if there is a mixture of simultaneous synergetic pathways. Therefore, proposed mechanisms should be interpreted as biologically plausible rather than definitively established in human models.

3.3. Preclinical Evidence for MSK Pain and Repair

A direct antinociceptive mechanism is supported in animal models, with a murine osteoarthritis model reducing pain-related behavior and preventing hyperexcitability in knee-innervating sensory neurons, even though joint damage was not reduced with both human MSCs and MSC-derived EVs [34]. In murine peripheral nerve injury models, bone marrow stromal cells reduced neuroinflammation, dorsal root ganglion injury, hyperalgesia, and allodynia through secretions of TGF- β 1 [35]. These experiments support the mechanistic approach for the proposition that MSCs may influence both neuropathic and inflammatory components of musculoskeletal pain. They also strengthen the rationale for neural sensitization and measuring pain from structural repair.

The preclinical evidence demonstrates that effectiveness can depend on product characteristics. In rat osteoarthritis models, early- and late-passage MSCs result in different responses to pain, where late-passage cells attenuated established pain behavior but early-passage cells transiently worsened it. Neither of these characteristics altered the joint pathology [36]. Although this result should not be generalized into a preferred passage for humans, it exemplifies that phenotypically similar MSCs may have different biological outcomes. This highlights the need for functional potency assays over surface-marker characterization alone for prediction of therapeutic activity. Without these measures, future studies with similar MSC preparations cannot evaluate similar biological therapies. Therefore, potency assays linked to proposed mechanisms such as modulation of neuron excitability or inflammatory signaling may be more informative than surface marker identifiers alone.

Still, the preclinical findings remain hypothetical rather than proof of clinical MSC analgesia. Rodent osteoarthritis and nerve injury compress disease development into a shorter period and cannot fully reproduce the psychological, metabolic, mechanical, and centrally mediated contributors to chronic human pain. Additionally, many studies administer MSCs during early disease states or immediately following injury, while patients enrolled in clinical trials suffer from established musculoskeletal pathology. Preclinical models may overestimate the therapeutic benefit of MSCs by targeting an early stage of disease that may be reversible. The most defensible interpretation from preclinical studies identifies plausible mechanisms and outcomes of measures without establishing population, delivery route, durability, or human dose.

3.4. Human Clinical Evidence and Applications to Musculoskeletal Pain

Knee osteoarthritis is the most clinically mature musculoskeletal indication for MSC-based treatment because of the accessibility of the joint to local injection, and the pain is influenced by peripheral sensitization, subchondral pathology, and inflammation. In a randomized study of 30 participants, a single injection of 40 million allogeneic bone marrow-derived MSCs improved function and pain compared with hyaluronic acid at one year [37]. Subsequent phase I/II trials found that repeated umbilical cord-derived MSC administration produced greater therapeutic improvements than a single dose of

hyaluronic acid [38]. These studies support further investigation of MSC-derived benefits. While the smaller studies show promising results, the larger studies are inconsistent.

In a 480-participant randomized trial, bone marrow aspirate concentrate (BMAC), stromal vascular fraction (SVF), and allogeneic umbilical cord tissue-derived MSCs were compared to corticosteroid injection. While all groups improved, there was no specific therapy that was superior to corticosteroid injection at 12 months, and no treatment produced improvement in MRI osteoarthritis scores [39]. The ADIPOA2 phase 2b trial similarly found that a single injection of 2 or 10 million autologous adipose-derived culture-expanded MSCs was not superior to saline for pain or function in mild-to-moderate knee osteoarthritis. Strict responder rates at six months were 47.3% with MSCs and 54.8% with placebo [40].

Clinical investigation in tendon and rotator-cuff pain remains in early stages. In a dose-escalation study, 18 patients with partial-thickness rotator-cuff tears received autologous adipose-derived MSCs and demonstrated advances in pain, function, and defect size without adverse treatment effects [41]. These findings support larger controlled trials but do not yet justify extrapolating knee osteoarthritis protocols to tendon disease. Cautious interpretation must be taken with early-phase studies as the emphasis focuses on ability and safety rather than efficacy. Limited follow-up, lack of adequate control groups, and small sample sizes reduce confidence that can be attributed to MSC therapy versus the history of tendon healing or placebo effects.

However, several barriers continue to limit the clinical translation of MSCs. Variability of donors' characteristics, tissue sources, and cell processing and manufacturing results in inconsistent cellular products and therapeutic outcomes [42,43]. Moreover, optimal cell source, dosing strategy, delivery route, or the use of autologous versus allogeneic products are still up for debate [44]. With more than 1000 clinical trials involving MSCs being registered, no MSC-based therapy has been approved by the U.S. Food and Drug Administration. The absence of approval despite the large number of clinical trials stresses the gap between biologic promise and reproducible clinical efficacy. To establish the safety and efficacy of MSC-based therapies for chronic MSK pain, future progress will depend on standardized manufacturing processes, validated potency assays, and well-designed randomized controlled trials.

Inconsistency across randomized trials suggests that treatment efficacy is likely dependent on cell source, manufacturing methods, expansion protocols, dosing strategies, disease severity, outcome measures, and comparator interventions rather than solely the presence or absence of MSC therapy. Consequently, this emphasizes the need for the expansion of biologic and methodological standardization instead of negative trials being interpreted as disapproving of MSCs' therapeutic potential. Future studies must emphasize standardized manufacturing, validated potency assays, and adequately powered randomized trials designed to identify susceptible patient populations that could benefit from MSCs instead of labeling it as a uniform therapeutic class.

4. Mechanobiology and Stem Cell Fate Regulation

4.1. Cellular Mechanosensing

Cellular mechanosensing describes a cell's ability to detect mechanical cues within its microenvironment, including extracellular matrix (ECM) stiffness, tissue stretch or strain, cellular compression, and surface topology. Beyond detecting these cues, cells must also convert them into appropriate biological responses. Through mechanotransduction, cells can activate or inhibit signaling pathways that regulate proliferation, apoptosis, and differentiation [45]. Cells detect these cues through at least two structurally distinct classes of mechanosensors. Adhesion-based sensors, principally integrins and their associated focal adhesion complexes, transduce sustained tension over seconds to minutes and couple

directly to cytoskeletal and transcriptional machinery. Mechanically gated ion channels, including the Piezo family, operate on a millisecond timescale, converting membrane tension into cation influx and an immediate rise in intracellular calcium [46]. These systems are complementary rather than redundant: the former governs durable adaptation to matrix mechanics and the latter rapid electrical and calcium-dependent responses.

After a cell receives a mechanical input, mechanotransduction pathways convert extracellular mechanical cues into intracellular biochemical signals. Integrins are transmembrane receptors that bridge the extracellular matrix (ECM) and the intracellular cytoskeleton, making them key initiators of these pathways. Upon ligand binding and mechanical stimulation, integrins undergo conformational activation, cluster at the cell surface, and recruit adaptor and signaling proteins to form focal adhesions. These focal adhesions transmit mechanical information into downstream biochemical pathways, enabling the cell to adapt its behavior in response to changes in the surrounding ECM [47]. Talin also functions as a direct molecular force sensor within this complex. Once integrins are engaged and actomyosin tension is transmitted across the adhesion, the talin rod domain unfolds under physiologically relevant piconewton forces, exposing cryptic binding sites for vinculin [48]. Vinculin recruitment reinforces the integrin–actin linkage and drives focal adhesion maturation, providing a concrete molecular mechanism by which mechanical load is converted into a biochemical binding event.

Collectively, mechanosensing is best viewed not merely as a fundamental biological process, but as a key determinant of regenerative therapy outcomes. Once injected, MSCs continuously interpret the local mechanical environment so that practically identical cell preparations may undergo distinct intracellular programs depending on tissue stiffness, strain, and matrix organization. In this sense, mechanosensing offers one plausible explanation for the variability observed across clinical trials in regenerative medicine.

4.2. Mechanotransduction Signaling Pathways

Mechanotransduction describes the process the cell uses to convert its physical input into intracellular signals. Some important mechanotransduction pathways include the focal adhesion kinase (FAK) and cellular Src (c-Src) pathway involved in cellular adhesion, the Ras homolog gene family, member A (RhoA) and the downstream effector Rho-associated protein kinase or Rho-associated coiled-coil kinase (ROCK) involved in cytoskeletal tension, the Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) involved in differentiation and proliferation of MSCs, and the transforming growth factor- β 1 (TGF- β 1) and small mother against decapentaplegic (SMAD) pathway involved in tissue fibrosis [49–52]. Lastly, the Piezo1 mechanosensitive cation channel couples membrane tension to calcium influx and calcium-dependent transcriptional programs [53].

The FAK/c-Src pathway involves the recruitment of c-Src by FAK to activate numerous other downstream pathways. Integrin activation leads to the activation of FAK through autophosphorylation. The activated FAK allows for the binding and phosphorylation of c-Src, which creates the FAK/c-Src complex. The FAK/c-Src complex leads to the activation of other pathways that affect outcomes such as cell survival, proliferation, and migration [47]. The RhoA/ROCK pathway is one of the pathways activated by the FAK/c-Src complex, and one of its functions is to increase the tension of the cellular cytoskeleton. RhoA becomes activated when bound to guanine triphosphate (GTP) and begins to interact with ROCK. The activation of the RhoA/ROCK pathway leads to the stabilization of actin filaments and increased actomyosin assembly and contractility [50]. In turn, this increased contractility leads to a stiffer ECM, which promotes the maturation of focal adhesions. This signaling pattern leads to the activation of the downstream YAP/TAZ pathway, which will ultimately lead to the determination and regulation of the fate of the MSC [54].

Piezo1 provides a parallel entry point into these pathways. Increased membrane tension gates the channel directly, permitting calcium influx that activates calcium-dependent effectors including CaMKII, with downstream convergence on ERK1/2, Wnt/ β -catenin, and YAP/TAZ signaling [53]. One route to YAP is notably direct: activated CaMKII phosphorylates FAK and Src, which suppresses the activity of the Hippo pathway kinases MST1/2, reducing YAP phosphorylation at Ser127 and permitting nuclear translocation [53]. In skeletal tissue, loss of Piezo1 in mesenchymal or osteoblast progenitors impairs osteoblast differentiation and load-induced bone formation, establishing the channel as a non-redundant mechanosensor in this lineage [55,56]. Channel-based mechanosensing therefore converges on the same FAK/Src and YAP/TAZ nodes described above and below, meaning that adhesion-based and channel-based sensing are integrated at the signaling and transcriptional level rather than operating in isolation.

These pathways should not be regarded as independent molecular cascades, but rather as an integrated signaling network in which changes in extracellular loading propagate through focal adhesions, cytoskeletal tension, calcium signaling, and nuclear transcription. This systems-level organization implies that pharmacologically targeting any single pathway, without also addressing the surrounding mechanical environment, is likely to yield only limited regenerative benefit.

4.3. Stem Cell Differentiation

YAP/TAZ activation has been linked to increased contractility of actin and the tension of the actin cytoskeleton [51]. The Hippo pathway is the regulator of the YAP/TAZ transcriptional coactivators and is what ultimately allows them to migrate into the nucleus [57]. Once activated, the YAP/TAZ complex migrates from the cytoplasm to the nucleus to act as transcriptional coactivators, binding to transcriptional enhanced associate domain (TEAD) transcriptional factors to determine the differentiation of MSCs [58]. On stiffer matrices, which contain numerous mature focal adhesions with high RhoA/ROCK activity, YAP/TAZ complexes are more active [54]. On softer, less rigid matrices, YAP/TAZ are inactive and subsequently degraded. This activation and inactivation of the YAP/TAZ complex lead to the differentiation of MSCs into cells such as osteoblasts, adipocytes, and fibroblasts or myofibroblasts in the setting of tissue damage and repair.

Because mechanical stimulation follows a biological dose–response, greater stimulation is not inherently better: physiological stiffness favors regenerative differentiation, whereas the sustained stiffening of chronic inflammation can drive fibroblast activation and pathological fibrosis. The aim is to restore normal signaling, not to maximize it.

4.4. Regeneration vs. Fibrosis

The entirety of this cellular response can be understood as a spectrum, ranging from regeneration to fibrosis. Regeneration describes the ability of a tissue to heal with appropriately balanced ECM deposition and degradation, restoring the tissue back to its original function [59]. Fibrosis occurs when this balance is lost: ECM is deposited in excess and matrix-degrading activity is concurrently suppressed so that functional tissue is progressively replaced by disorganized scar [60]. In the setting of chronic inflammation, ECM is deposited, and the increased contractility leads to a positive feedback loop of signaling pathways, leading to the formation of scar tissue or fibrosis [61]. Fibrosis is mediated mainly by TGF- β 1, which activates downstream SMAD signaling, leading to the overexpression of pro-fibrotic genes [52]. Due to the complex and overlapping cellular and molecular pathways that lead to ECM deposition and scar formation, a multifaceted approach seems to be the most likely to succeed.

This balance may help explain why regenerative interventions show variable clinical efficacy. When implanted MSCs encounter a persistently fibrotic microenvironment, marked by excessive stiffness, chronic inflammation, and abnormal mechanical loading, profibrotic pathways may override regenerative signaling despite successful cell delivery. Modifying the host tissue environment may therefore be as important as optimizing the cellular product itself.

4.5. Translational Implications for Pain Medicine

Mechanotransduction is relevant to musculoskeletal pain medicine because it is a mechanism of nociception itself, not merely of tissue remodeling. The mechanically gated ion channel PIEZO2, expressed in primary sensory neurons, is required for tactile allodynia: individuals with loss-of-function PIEZO2 mutations fail to develop painful responses to light touch after cutaneous sensitization, while their responses to noxious mechanical stimuli remain intact [62]. This dissociation carries a specific therapeutic implication. Most analgesics act by dampening nociceptive signaling broadly, which is why analgesia and loss of protective sensation tend to co-occur. A mechanosensor required for allodynia but dispensable for nociception offers a possible target that separates the two, relieving the evoked pain that dominates inflammatory and neuropathic presentations without abolishing the acute pain that protects tissue. The same channel family is expressed in joint tissue, where Piezo1 in chondrocytes contributes to endochondral ossification and osteoarthritis development, indicating that mechanically gated signaling operates in the peripheral tissues that generate chronic musculoskeletal pain as well as in the neurons that transmit it [63].

Mechanotransduction is also relevant because it determines whether regenerative interventions for MSK pain succeed and may explain why their results have been so inconsistent. Cell-based therapies for osteoarthritis and disc degeneration are evaluated against pain endpoints, yet the evidence remains divided: a dose-focused meta-analysis reported substantial WOMAC improvement at twelve months in knee osteoarthritis, whereas an earlier meta-analysis of thirteen randomized trials found no difference from placebo in pain. This null result was subsequently contested on the grounds that MSC preparations differed substantially across the included trials [64]. That objection is itself a mechanobiological argument. Because YAP/TAZ activity, and consequently MSC lineage commitment, is set by substrate stiffness, two trials using nominally the same therapy may in fact be testing functionally different products [54]. The practical implication is therefore concrete: substrate stiffness and mechanical preconditioning should be specified and reported as trial variables rather than treated as incidental manufacturing detail, and potency assays for these products should capture mechanosensitive attributes. Until they are, negative analgesic trials cannot be distinguished from trials of an inadequately specified intervention.

There are a few limiting factors for this body of evidence. First, much of the mechanistic chain rests on *in vitro* and animal work. The pathway data in the preceding sections derive largely from cultured cells and murine models, and the human evidence that mechanotransduction shapes clinical pain remains largely inferential, with some exceptions. Second, the clinical literature on mechanically informed cell therapies is small and dominated by early-phase studies with short follow-up. In addition, a few of the studies report the substrate and expansion conditions that the preceding sections argue are determinative, so that even where trial results converge, the absence of standardized manufacturing and potency reporting makes it difficult to attribute outcomes to an intervention with confidence. In conclusion, adequately powered, mechanistically stratified trials that treat mechanical parameters as pre-specified variables are the clearest unmet need in translating this biology to patients.

This mechanobiological framework offers a plausible explanation for the variability observed across clinical MSC trials. Expansion on rigid tissue-culture plastic, differences in scaffold stiffness, post-injection loading, and local matrix mechanics all shape YAP/TAZ activity, cytoskeletal tension, and MSC secretory behavior both before and after implantation. As a result, identical cell doses delivered into mechanically distinct environments may display fundamentally different regenerative phenotypes. Clinical variability may reflect differences in the mechanical environment as much as differences in the cellular product itself.

Taken together, these observations suggest that mechanobiology should move beyond a theoretical framework to become a practical component of regenerative trial design. Rather than treating mechanical variables as uncontrolled background conditions, future studies should prospectively incorporate substrate stiffness, rehabilitation protocols, loading history, and potency testing into their design. This would allow investigators to distinguish whether variability in clinical efficacy reflects genuine biological failure or differences in the mechanical environment encountered by transplanted MSCs.

5. Mesenchymal Stem Cells in Interventional Pain

Stem cell therapies are widely being investigated in interventional pain for many chronic pain conditions involving structural tissue degeneration that include degenerative disc disease, facet arthropathy, osteoarthritis (OA), and tendinopathy [65–68]. Target tissues are commonly characterized by chronic inflammation, limited vascularization, and mechanical stress, creating an environment that promotes continued degeneration that can further compromise tissue function and contribute to pain [69,70]. This creates a complex environment that influences therapeutic outcomes not only based on the regenerative potential of injected cells but also based on cell delivery, post-injection retention, survival, and functional activity [69–71].

5.1. Injection Therapies

Injection-based delivery of MSC therapy is the most practical approach in interventional pain, allowing cells to be directly placed into targeted tissues without open implantation. With intervertebral discs and osteoarthritic joints being highly targeted areas of study in chronic pain, intradiscal and intra-articular injections are the most clinically developed routes. MSC injections' intended purpose is to allow MSCs to exert local anti-inflammatory effects while also supporting regeneration of damaged local tissues [72]. Clinical responses have been variable across injections, with improvements in pain and function not always corresponding with evidence of structural repair, suggesting symptomatic improvement may occur without regeneration of damaged tissues.

Among the intradiscal studies, the DREAM trial, a phase IIB, double-blind, single-center, randomized trial of autologous bone marrow-derived MSCs, enrolled 52 patients with chronic lower back pain and moderate-to-advanced multilevel disc degeneration. In this study, the injections demonstrated structural improvement in disc height index and favorable safety profiles. However, they did not have a significant advantage over the sham group at six months follow-up [65]. The improvement in disc height with no consistent improvement in pain relief at six months suggests that structural changes in imaging may not directly translate into clinical benefit. Longer follow-up will help determine whether structural changes translate into pain relief. Also, it remains unclear whether the change in disc height represented true tissue regeneration or a temporary effect of the injection volume.

Other intradiscal studies reported more favorable clinical results. A randomized controlled trial of 24 patients with degenerative disc disease treated with allogeneic bone

marrow-derived MSCs reported an improvement in pain and disability with MRI evidence suggestive of partial disc improvement in a responder subgroup of approximately 40% [73]. A randomized placebo-controlled study of 100 patients with chronic low back pain and moderate degenerative disc disease followed patients for 36 months and found that allogeneic mesenchymal precursor cell treatment improved pain and disability scores at several time points compared with controls [74]. Intra-articular MSC studies for knee osteoarthritis have also produced encouraging but heterogeneous results, with some studies reporting improvement in pain and function while others show no clear benefit of MSCs over corticosteroids or placebo [37,75]. A systematic review and dual network meta-analysis that evaluated intra-articular injection therapies for OA reported that MSC injections showed more favorable results than cell-free treatments and that adipose-derived and umbilical cord-derived MSCs were more favorable than bone marrow-derived MSCs [66,76]. However, in a systematic review and meta-analysis of randomized controlled trials, Dai et al. found no clear advantage over placebo when minimum clinically important difference thresholds were applied [64]. In addition, Mautner et al., as previously mentioned, found no advantage of cell-based injections over corticosteroid injection at one year [39].

Whilst the goal of corticosteroid injections is to provide symptomatic relief, the goal of MSC therapy is to restore or preserve cartilage, possibly addressing the degenerative defect that is contributing to pain and dysfunction [9,77]. Even though corticosteroid injections provide temporary short-term pain relief by suppressing inflammation, they do not regenerate damaged cartilage. Repeated corticosteroid injections have been associated with greater cartilage loss, highlighting a limitation of symptom-based treatments [78].

Collectively, the injection studies suggest that MSC therapies demonstrate a potential to improve pain and function in some patients, but these improvements do not consistently concur with structural tissue repair [39,64,65,73,74]. Overall, these findings suggest that variability in follow-up time, patient selection, disease severity, trial design, cell source, and dose may influence outcomes. The variability makes it challenging to decide which factors led to the treatment response. Symptomatic improvement may reflect anti-inflammatory effects rather than true regeneration. Regeneration may also depend on whether the local tissue environment promotes differentiation and extracellular matrix production for injected cell survival and retention [69,70]. Future studies should investigate pain and function in conjunction with structural imaging, baseline disease severity, cell persistence, post-injection activity, and longer-term follow-up.

5.2. Mechanical Loading on Therapy Outcomes: Preclinical and Translational Evidence

Although injection therapies provide a minimally invasive route for MSC delivery, discs and joints are exposed to many different factors including compression, tension, shear stress, hydrostatic pressure, and cyclic loading. These forces can influence MSC viability, differentiation, gene expression, and extracellular matrix remodeling [79]. Mechanical loading represents a fundamental consideration in interventional pain due to the dynamic nature of targets [80–82]. Therapeutic outcomes may not depend only on cell products but on mechanical conditions that the cell experiences post-injection, which can determine whether MSCs survive, differentiate, and generate an ECM that can restore the structure and function of the damaged tissues [83].

Preclinical studies show that controlled loading can be beneficial in reparative MSC behavior. Dynamic loading has been shown to stimulate extracellular matrix gene transcription and increase glycosaminoglycan deposition in MSC constructs [81]. Cyclic compression at 10% strain and frequencies greater than 0.5 Hz maintained MSC viability and promoted chondrogenesis in fibrin gel scaffolds [82]. The effects of mechanical loading on MSCs may depend on the magnitude, type, frequency, and duration of the applied force [79,81,82].

These effects suggest that post-injection rehabilitation protocols may involve finding a balance between protection from excessive loading and providing enough mechanical stimulation to support extracellular matrix organization. These findings, however, are based on preclinical controlled models, making the timing, extent, and duration of mechanical loading needed to support regeneration in patients unclear.

Biomaterial carrier studies provide evidence that mechanical support may improve outcomes. Thorpe et al. demonstrated that an injectable hydrogel integrated with nucleus pulposus tissue supported MSC delivery, promoted production of aggrecan, collagen type II, and chondroitin sulfate, filled disc fissures, remained in place during loading, and restored intervertebral disc stiffness [69]. These findings suggest that MSC therapy success may depend on the delivery system that can withstand the mechanical load while supporting MSC survival, signaling, and matrix remodeling, supporting the value in combining mechanical support with biological regeneration [84,85]. Even though improvements in disc stiffness support a possible mechanical benefit in ex vivo models, these findings do not establish tissue repair in real patients. Future studies should be aimed at determining whether biomaterial-loaded-MSCs provide greater benefits structurally and functionally over biomaterial alone or cell-free injections.

Overall, these studies on loading and biomaterials suggest that outcomes may not only depend on just injected cells, but also on the mechanical environment of the cells after injection [69,79,83]. Extracellular matrix remodeling and MSC differentiation may be influenced by mechanical loading through focal adhesion and YAP/TAZ signaling [51,54]. However, a causal relationship between mechanical loading, structural regeneration, and pain relief in patients has not yet been fully established because much of the current evidence is derived from preclinical and ex vivo models [69,81,82]. Activity after injection may influence the conditions of the injected cells, highlighting the need to define rehabilitation protocols for MSC therapy. Future studies should be aimed at testing loading protocols and their effects on cell retention, tissue regeneration, pain, and function.

5.3. Mesenchymal Stem Cell Optimization

Additionally, even with accurate delivery and mechanical support, MSC therapy may have a limited therapeutic effect if the cells cannot survive post-injection environmental conditions of inflammation, low oxygen tension, acidic pH, low glucose, and mechanical stress. Stem cell survival is a key challenge in MSC therapy in interventional pain, with common targets that include intervertebral discs and articular cartilages characterized by limited vascularity and nutrients. These stressors can create an unfavorable environment that may decrease MSCs' potential to exert their anti-inflammatory, immunomodulatory, and regenerative effects [70]. These conditions make cell survival an essential part of regeneration, allowing cells to remain viable long enough to exert their effects [86].

Hypoxic preconditioning is a method studied to improve MSC survival. One study found that hypoxic preconditioning improves survival of bone marrow-derived MSC in low-oxygen, nutrient-limited 3D disc and cartilage models. The same study found that decreased MSC survival with TGF- β 3 priming and glycosaminoglycan production remained donor-dependent. This suggests preparation requires optimization for both cell survival and extracellular matrix production [70]. Other studies also support hypoxic preconditioning. A study by Beegle et al. also supports hypoxic preconditioning altering cell metabolism and improving cell retention post-transplantation [71]. Hu et al. demonstrated that hypoxic preconditioning increased survival and angiogenesis signaling that included hypoxia-inducible factor-1 alpha (HIF-1 α), vascular endothelial growth factor/fetal liver kinase-1 (VEGF/Flk-1), angiopoietin-1, erythropoietin (EPO), B-cell lymphoma 2 (Bcl-2), and B-cell lymphoma-extra-large (Bcl-xL), while reducing caspase-3 activation. Even

though this study was performed with a myocardial infarction model, it suggests that preconditioning MSCs to stress prior to transplantation may improve survival [86]. These findings suggest that preparation strategies may need to be tailored to the target tissue due to the possible tradeoff between optimizing MSC survival and ECM production [70].

Collectively, these studies suggest that MSC preparation can influence cellular survival and function after delivery. MSC preparation should be seen more as part of the intervention rather than just part of the manufacturing [70,71,86]. Optimization of MSCs should be extended beyond hypoxic preconditioning and considered alongside other strategies such as biomaterial support, mechanical conditioning, functional potency, and cell retention in relation to the target tissue [69–71,83]. A major limitation is that these factors have mainly been evaluated in preclinical models and individually. Clinical studies are needed to determine which combination of preparation methods improves cell retention, matrix production, tissue regeneration, pain, and function.

The advancement of MSC-based therapies in interventional pain medicine will warrant special attention to both the cellular product and the tissue environment that they encounter after implantation [69–71,83]. An approach that integrates cell selection, delivery, loading, and post-injection conditions may allow for cell injection to progress toward a more targeted approach of tissue repair and sustained clinical benefit.

6. Critical Analysis and Synthesis of the Literature

A critical analysis of the current literature reflects that the therapeutic potential of MSCs for chronic musculoskeletal pain is biologically plausible but remains highly dependent on numerous post-injection mechanobiological factors. MSCs may influence chronic musculoskeletal pain through immunomodulation, reduction in neuroinflammation, modulation of nociceptive mediators, and the promotion of tissue repair [27–36]. However, these mechanisms have not been independently established. In particular, the notion that MSCs can reduce pain and neuronal sensory hyperexcitability without reversing structural pathology implies that analgesia may occur independently of structural tissue regeneration [34,35]. Therefore, this challenges the assumption that musculoskeletal pain relief necessarily represents successful structural repair and suggests that early clinical improvements may be primarily mediated through anti-inflammatory or neuromodulatory effects.

Additionally, MSCs with similar phenotypic characteristics may produce substantially different biologic effects due to different preparation and extraction protocols, leading to the variable biologic effects seen in preclinical studies [36]. The available clinical literature echoes this concern: while several early phase studies report improvements in pain and function, larger randomized controlled trials have failed to consistently demonstrate superior effect over placebo or sham interventions [39,40,64,65,73–75]. Collectively, these findings suggest that “MSC therapy” should not be interpreted as a single standardized intervention. Rather, cell source, donor characteristics, manufacturing and expansion conditions, dose, delivery route, viability, and functional potency may all contribute to treatment responses. Consequently, negative clinical trials should not necessarily be interpreted as evidence that MSCs lack therapeutic potential, but neither should positive early-phase studies be interpreted as evidence of established regenerative efficacy.

Further critical analysis of the mechanobiological literature provides a complementary framework that may help to explain this observed heterogeneity. After implantation, MSC behavior is largely influenced by its mechanobiological environment. Mechanical cues including substrate stiffness, tensile strain, compression, and membrane tension, are translated through integrins, focal adhesion complexes, mechanically gated ion channels, and downstream FAK/c-Src, RhoA/ROCK, calcium-dependent, and YAP/TAZ signaling pathways [45–58]. Through these pathways, cytoskeletal tension, lineage commitment,

extracellular matrix production, fibrosis, and cellular survival are directly regulated. This may provide a plausible mechanism through which mechanically distinct environments can produce varying MSC phenotypes despite similar cell dose administrations. This concept is particularly relevant to interventional pain physicians since target tissues such as intervertebral discs, articular cartilage, and tendons are continuously exposed to mechanical loading conditions that may influence MSC behavior. Preclinical and ex vivo studies demonstrate that the magnitude, frequency, and duration of mechanical stimulation can alter MSC viability, differentiation, matrix production, and retention, while biomaterial strategies may provide mechanical support that improves cell localization and tissue-specific matrix production [69,79,81–85]. It should be noted, however, that the majority of the evidence linking mechanical conditions to MSC behavior originates from in vitro, animal, or ex vivo models. Clinical trials have rarely characterized the mechanical environment of target tissues, expansion substrates, post-injection loading conditions, or the functional state of implanted cells. Therefore, at this time, current evidence cannot definitively establish that mechanical differences are directly responsible for the variability in patient pain levels or functional outcomes.

Ultimately, the major limitation of the current body of evidence is the absence of integrated clinical studies linking the aforementioned mechanisms to meaningful patient outcomes. Current trials often evaluate MSC source, dose, or delivery strategy independently while omitting specific characterizations of mechanobiological variables. Consequently, it is difficult to determine whether inconsistent clinical outcomes reflect contaminated cellular product, inadequate dosing or delivery, unfavorable host environments, or inappropriate mechanical conditions. Future studies should thus incorporate standardized characterization of MSC products with clinically meaningful pain and functional outcome measurements. Doing so would aid in identifying which MSC products, tissue characteristics, and mechanical loading conditions are most likely to produce durable clinical benefit in patients.

7. Conclusions

The present review has explored the regenerative potential of MSCs through both their inherent immunomodulatory effects and their ability to differentiate into numerous mesodermal tissue lineages. Beyond these properties, MSCs contribute to tissue repair by regulating extracellular matrix remodeling, tissue homeostasis, and inflammatory microenvironments. In addition, several cellular mechanotransduction pathways such as FAK/c-Src, RhoA/ROCK, and YAP/TAZ have emerged as central regulators of MSC behavior and tissue regeneration.

These pathways, in addition to integrin networks, are directly dependent on mechanical variables such as tensile strain, compression, and substrate stiffness. Through activation of these signaling networks, the local biomechanical environment governs MSC survival, engraftment, and long-term tissue remodeling. This may explain the variability in MSC phenotypes seen across regenerative medicine trials despite identical manufacturing protocols. Successful implantation of MSC therapies is therefore contingent on optimizing tissue microenvironments and mechanical loading conditions in vivo, emphasizing that mechanobiology should be considered a core component of regenerative medicine.

Further research into these pathways can offer a deeper understanding to significantly influence regenerative outcomes. Unlike conventional therapies that primarily target inflammation, MSC-based therapies seek to restore tissue structure, biomechanics, and function by targeting the underlying pathology leading to MSK pain. Therefore, pain relief in this context is a consequence of successful regeneration rather than the primary therapeutic endpoint. However, the current body of mechanistic evidence largely derives

from in vitro and preclinical models, with clinical studies remaining heterogeneous regarding cell source, manufacturing, dosing strategies, and rehabilitation protocols. These limitations make it difficult to ascertain the true etiology of inconsistent clinical outcomes regarding biomechanical factors, and addressing this gap should become a priority for future translational research.

Ultimately, the shift in focus to the biomechanical environment of MSCs has far-reaching implications for the development of further regenerative medical therapies for MSK-related conditions. Continued investigation into the mechanobiologic properties governing MSC differentiation and function can play a pivotal role in translating these therapies into more predictable and durable clinical outcomes. MSC therapies, as part of a multifaceted treatment approach, thus have the potential to redefine the management of MSK disorders from symptomatic control towards true restoration of tissue integrity and functional recovery in many MSK pain patients. A summary of mechanobiologic factors influencing MSC function and their clinical implications is included in Table 1. Lastly, a figure outlining the clinical effects of MSC injection therapies is included in Figure 1.

Table 1. Mechanobiological Factors Influencing Mesenchymal Stem Cell Function and Regenerative Outcomes in Musculoskeletal Pain Medicine.

Mechanobiological Component	Effect on MSC Function	Regenerative Significance	Clinical Implications
Extracellular Matrix (ECM) Stiffness	Matrix stiffness regulates cytoskeletal tension and mechanotransduction, directing MSC lineage commitment toward osteogenic, chondrogenic, or fibrogenic phenotypes through integrin- and YAP/TAZ-mediated signaling [45,49,51,54].	Appropriate biomechanical cues promote tissue-specific extracellular matrix synthesis, structural remodeling, and restoration of native tissue architecture while minimizing maladaptive fibrosis [51,52,59,61].	Engineering scaffold stiffness and recreating native tissue biomechanics may improve cartilage and disc regeneration, providing more durable restoration of joint function and reducing the structural abnormalities responsible for chronic musculoskeletal pain rather than simply suppressing inflammation [10,44,66].
Integrin–Focal Adhesion Signaling	Binding of ECM ligands activates integrins, FAK, and downstream signaling pathways that regulate MSC adhesion, migration, proliferation, survival, and mechanosensing [45,47,49].	Efficient focal adhesion formation enhances MSC engraftment and integration into injured musculoskeletal tissues, improving regenerative potential [47,49].	Optimizing the extracellular matrix microenvironment and delivery platform may improve MSC retention following image-guided injection, increasing tissue repair and long-term functional recovery after regenerative procedures [5,44,49].
YAP/TAZ Mechanotransduction	Mechanical loading regulates nuclear localization of YAP/TAZ, altering transcription of genes governing proliferation, differentiation, extracellular matrix synthesis, and stem cell fate [51,54,57,58].	Balanced YAP/TAZ activation promotes regenerative remodeling while limiting excessive fibrosis and aberrant tissue repair [51,52,54,57,58].	Understanding YAP/TAZ signaling provides a mechanistic basis for integrating regenerative biologics with rehabilitation protocols, where controlled mechanical loading may enhance cartilage regeneration, preserve joint biomechanics, and prolong clinical benefit [8,51,57].
RhoA/ROCK Cytoskeletal Signaling	Cytoskeletal contractility regulates intracellular tension, cell morphology, migration, and lineage specification through RhoA/ROCK-mediated actomyosin remodeling [50].	Appropriate regulation supports organized extracellular matrix deposition and tissue regeneration, whereas excessive activation may contribute to fibrosis and degeneration [50,52,61].	Modulating post-procedural mechanical loading may optimize MSC differentiation while limiting fibrotic healing, providing an opportunity to personalize rehabilitation following regenerative interventions [50,61].
Mechanical Loading (Compression, Tension, Shear Stress)	Physiologic mechanical stimuli activate mechanotransduction pathways that enhance MSC proliferation, differentiation, and secretion of trophic and reparative factors [45,51,54].	Controlled mechanical stimulation promotes matrix synthesis, angiogenesis, and functional integration of regenerated tissue while preserving biomechanical properties [51,57,59].	Regenerative rehabilitation combining MSC therapy with progressive mechanical loading may maximize structural repair, improve functional recovery, and provide more sustained pain relief than biologic therapy or rehabilitation alone [44,59].

Table 1.
Cont.

Mechanobiological Component	Effect on MSC Function	Regenerative Significance	Clinical Implications
MSC Immunomodulation and Paracrine Signaling	MSCs secrete cytokines, chemokines, growth factors, and extracellular vesicles that suppress pro-inflammatory mediators while promoting endogenous tissue repair and angiogenesis [44,59].	Rather than solely reducing inflammation, MSCs establish a regenerative microenvironment that facilitates structural healing and restoration of tissue homeostasis [44,59,61].	Unlike corticosteroid injections that primarily suppress inflammation, MSC therapy aims to restore damaged cartilage and other musculoskeletal tissues, addressing the underlying structural pathology responsible for chronic pain while simultaneously reducing inflammation [65,66,87,88].
Stem Cell Survival and Engraftment	Long-term therapeutic activity depends on MSC viability, persistence, immune compatibility, and responsiveness to the surrounding mechanical microenvironment [44,45].	Improved engraftment prolongs regenerative signaling, extracellular matrix remodeling, and functional tissue restoration [44,59].	Biomaterial carriers, hydrogels, and mechanically optimized delivery systems may enhance long-term regenerative efficacy and produce more durable improvements in pain and physical function following MSC therapy [3,59,65].

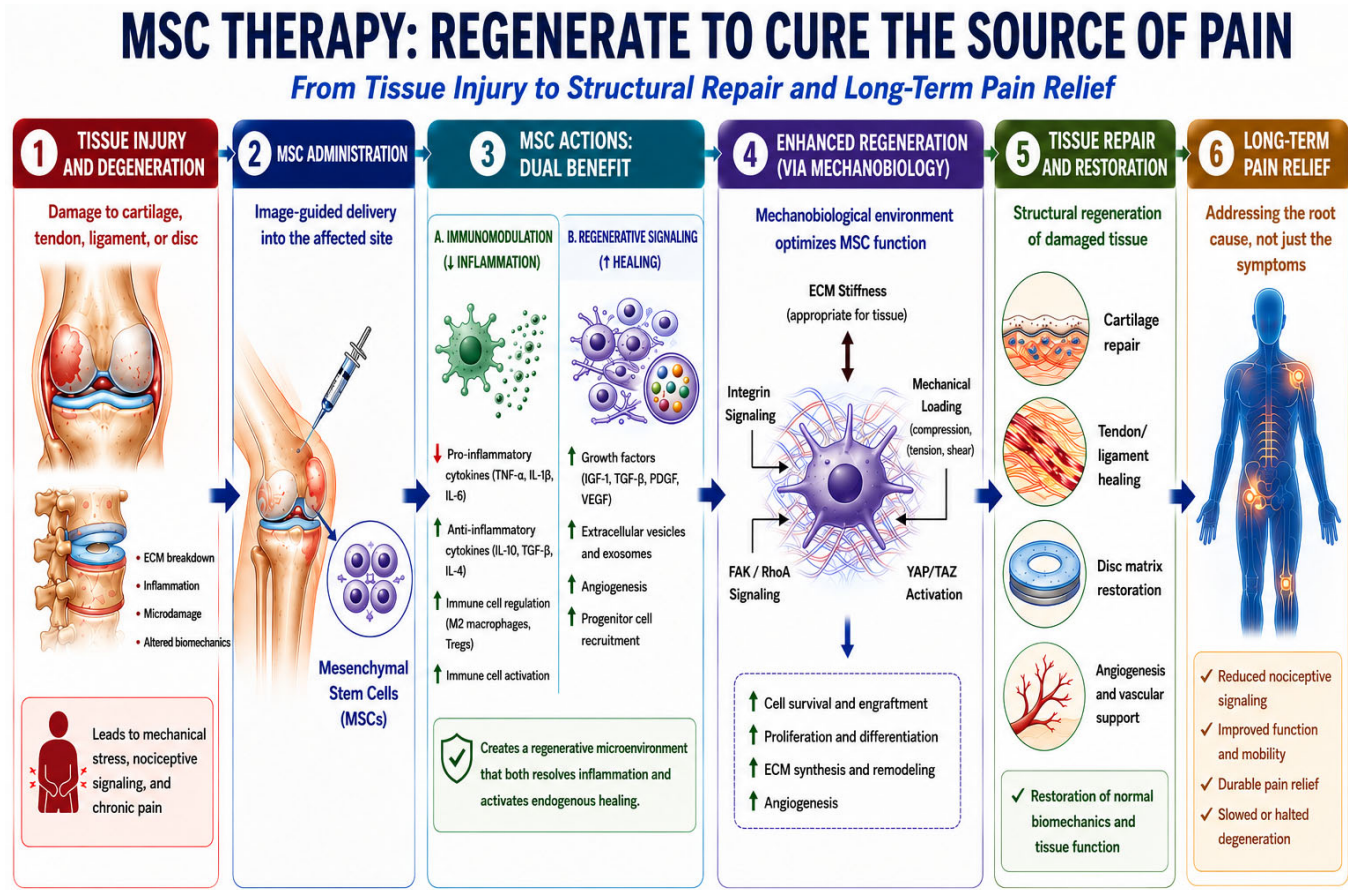


Figure 1. Clinical applications of MSC injection therapies and their localized effects. Note: Image generated using ChatGPT V5.5 from the prompt ‘generate an image outlining the benefit of MSC injection therapy for MSK conditions. Include the regulation of inflammatory markers and integrin and regenerative signaling of surrounding tissue. Also include the effect of mechanical loading, FAK/RhoA, and YAP/TAZ on overall cartilage repair and therapeutic benefit’.

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