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Mesenchymal Stem Cells (MSCs) - from Arnold Caplan to Present, Clinical Applications, and Markers to Predict Orthopaedic Outcomes

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Abstract

Mesenchymal Stem Cells (MSCs) have gained prominence in regenerative orthopaedics since their initial characterization by Arnold Caplan in 1991. This review outlines the historical development and evolving understanding of MSCs including their redefinition as "medicinal signaling cells" based on their paracrine and immunomodulatory properties. The literature is reviewed regarding MSC sources-such as bone marrow adipose tissue and umbilical cord-and their respective roles in orthopaedic applications. Evidence is synthesized on the use of MSCs in treating tendon ligament meniscal and osteochondral injuries. Additionally recent advances in acellular MSC-based therapies particularly secretomes and exosomes are explored. The review further evaluates current strategies for MSC quantification and characterization including colony-forming units nucleated cell counts and surface markers such as CD271 and assesses their potential correlation with clinical outcomes. Ongoing challenges related to standardization and outcome prediction are identified underscoring the need for further research to optimize the clinical application of MSCs in musculoskeletal medicine.

Introduction

Since the introduction of Mesenchymal Stem Cells (MSCs) and "the mesengenic process" by Arnold Caplan in 1991 [1], regenerative orthopaedics using biologic augmentation has become an ever-growing field. Through MSC's immunomodulatory and trophic effects, many orthopaedic pathologies such as degenerative osteoarthritis [2-15], chondral defects [16-34], tendinopathies, meniscal lesions, and muscle pathologies can be treated. As understanding of the origin and function of MSCs grow, new sources are uncovered and optimization for the processing and use further opens the door in making MSCs an increasingly reliable and effective point-of-care treatment. Similar to Platelet Rich Plasma (PRP) [35-39], variable results of MSCs may be a result of the lack of standardization in preparation or identification and quantification of specific biomarkers to ensure consistent and reproducible results. This article will review the history of MSCs, their current uses, and possible ways to predict clinical outcomes.

Arnold Caplan and the Origin of Mesenchymal Stem Cells

Arnold Caplan proposed the concept of the "mesengenic process", during which he recognized a specific category of cells that he originally referred to as "mesenchymal stem cells" [1]. Caplan observed that MSCs play a crucial role in the formation of cartilage and bone during the early stages of embryonic development. He proposed that MSCs are not limited to embryos but can also be extracted from adult tissues. Once isolated from adult sources, MSCs participate in mechanisms of tissue repair and cellular turnover. The term "mesengenic process" refers to the division and proliferation of MSCs, leading to the differenti-

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ation of subsequent cells into specific tissue lineages influenced by both intrinsic and extrinsic factors. This differentiation process commits MSCs to phenotypic pathways, allowing them to mature into various tissue types including osteocytes, hypertrophic chondrocytes, myotubules, stromal cells, tendon/ligament fibroblasts, adipocytes, and other connective tissue cells.

At the same time, the findings of Ashton and Fridenshteĭn et al. indicated that osteogenic precursor cells extracted from bone marrow have the ability to demonstrate multipotency and undergo differentiation [40,41]. These cells were later described as a sub-population of non-hematopoietic stromal cells. Through implantation of the non-hematopoeitic stromal cells harvested from bone marrow, multiple tissue types could be observed [42]. Within isolated bone marrow cell suspensions, distinct colonies originating from single cells were identified. These distinct colonies were termed as "Colony Forming Units" (CFUs) [43].

With the increasing acceptance of the mesengenic theory and the subsequent exploration of MSCs recent research has confirmed the hypothesis that MSCs possess the ability to differentiate into a variety of specific cell lineages [44-47]. It was not until 17 years after the first publication of the "mesengenic process" that a major breakthrough in the understanding of MSCs was achieved. Caplan et al. demonstrated the association between MSCs and perivascular cells, which were subsequently named "pericytes", by identifying cells that possessed biomarkers for both MSCs and pericytes [48]. This discovery was further investigated by Caplan by validating the link between MSCs and pericytes through the isolation of pericytes and in vitro expansion. These cells did show multipotency and phenotypic plasticity, producing distinct adipogenic, chondrogenic, myogenic, and osteogenic lineages [49,50]. He theorized that if MSCs are indeed derived from activated pericytes, then it should be possible to isolate them from all forms of vascularized tissue [48,50,51].

By establishing a connection between MSCs and pericytes, Caplan raised doubts about the "stemness" of what he previously referred to as "mesenchymal stem cells." He elaborated on the process of pericyte activation following injury. When vascularized tissues suffer damage due to injury, disease, or inflammation, pericytes located on blood vessels are released and subsequently differentiate into MSCs. Once these MSCs are liberated from pericytes and stimulated by surrounding immune factors, they operate similarly to natural "drugstores", exerting trophic and immunomodulatory effects through the release of bioactive factors and cytokines (Table 1) [52-54]. The trophic characteristics of MSCs stem from the release of bioactive factors that create an optimal regenerative microenvironment exhibiting anti-apoptotic, anti-scarring, angiogenic, and mitotic effects. The repair and reconstruction of tissues are enhanced as activated MSCs revert to a more stable pericyte phenotype.

Table 1: MicroRNA immunomodulatory molecules cytokine receptors and growth factor expression of MSCs.

MicroRNAs	Immunomodulatory Molecules	Surface Markers and Cytokine Receptors	Secreted Growth Factors and Cytokines
miRNA-1224	LL37 antibac pep	SSEA-4	LIF
miRNA-486-5p	HO-1	SSEA-3	SCF
miRNA-451	Gal-9	HLA-G	GM-CSF inducible
miRNA-222-3p	Gal-1	(HLA Class II -inducible)	G-CSF
let-7a-5p	TSG-6	HLA Class I	M-CSF
miRNA-199	Inos	CD332 FGFR2	FLT-3 Ligand
miRNA-191-5p	IDO	CD331 FGFR1	FGF2
miRNA-146b	HLA-G	CD222 IGF2R	VEGF
miRNA-145	LIF	CD221 IGF1R	
miRNA-143-3p	IL10	CD166 IGF1R	
miRNA-133b	IL-6	CD146 MCAM	
miRNA-125b	IL-1RA	CD140b PDGFRB	
miRNA-29	PGE2 antibac too	CD120b TNFIIR	
miRNA-24	HGF	CD120a TNFIR	
miRNA-23b	TGF	CDw119 IFNγR	
miRNA-21		CD117 KIT	
miRNA-10b		CD106 VCAM-1	
miRNA-10a		CD105 Endoglin	**Integrins-positive**
miRNA-9-5p		CD90 Thy -1	CD104 β4
		CD73 Ectonucleotidase	CD61 β3
Hemato-negative	**Integrins-negative**	CD71 Transferrin Rec	CD29 β1
CD45	CD49d α4	CD62L L-Selectin	CD51 aα
CD34	CD18 Cβ2	CD58 LFA-3	CD49e αv
CD14	CD11a αL	CD54 ICAM-1	CD49c α3
CD11b		CD44 HA Rec	CD49b α2
CD4		CD9	CD49a α1

Bioactive factors and cytokines secreted by MSCs also have immunomodulatory attributes as they inhibit T cell exposure to antigens and T cell progenitor expansion, protecting the body against self-harm and autoimmunity. These bioactive factors also inhibit complement-mediated consequences from mononuclear cell proliferation, reduce neutrophils bound to endothelial cells and their ability to migrate to injured areas, and inhibit apoptosis of activated neutrophils [55-58]. The activation and recruitment of neutrophils are stimulated by the secretion of multiple cytokines, notably IL-6, IL-8, and MIF. These cells also utilize chemoattractant mediators, such as anaphylotoxins and chemokines. Furthermore, activated MSCs inhibit the degranulation of mast cells, the proliferation of cytoplasmic granule contents, and the secretion of pro-inflammatory cytokines [59]. MSCs are able to inhibit the proliferation of de novo-induced NK cells, partially suppress the proliferation of activated NK cells, and contribute to the reduction of the cytotoxic activity associated with NK cells [61,62]. Alongside lymphocytes, this combination successfully inhibits the activation of CD4+ and CD8+ T cells, as well as B lymphocytes. This inhibition correlates with a decrease in pro-inflammatory cytokines, such as IFN-γ and TNF-α, while promoting an increase in the production of anti-inflammatory cytokines [63,64]. MSCs facilitate the conversion of pro-inflammatory M1 macrophages into anti-inflammatory M2 macrophages by secreting prostaglandin E2. Prostaglandin E2 engages with the EP4 receptor found on activated M1 macrophages, leading to a reduction in the secretion of pro-inflammatory cytokines, such as TNF-α and IL-1β, while simultaneously promoting the release of anti-inflammatory mediators like IL-10 from M2 macrophages [65]. By diminishing chronic inflammatory responses activated, MSCs effectively reduce apoptosis particularly in ischemic environments. They hinder the progression of myofibroblast formation which helps to prevent scar tissue and they encourage the mitotic activity of intrinsic tissue progenitors that are essential for tissue repair. Additionally, through their pericyte-like functions, they enhance and stabilize angiogenesis and vessel formation [48,50,53].

The nomenclature to describe MSCs as “mesenchymal stem cells” soon became criticized as comprehension of these specific cells improved. Given that MSCs are recognized for their multipotent nature secretory functions and phenotypic plasticity, the traditional descriptors of “stemness” and self-renewal are inadequate for characterizing MSCs, thereby excluding them from the conventional definition of “stem cells.” Caplan agreed with criticisms and the need for more suitable nomenclature for MSCs. With their secretory and trophic properties, Caplan saw MSCs as a multidrug “drugstore” that supported and promoted natural regeneration. In this context, he advocated for the term “medicinal signaling cells”, seeking to uphold the “MSC” acronym which was already well-known to the majority of the global research and clinical population [52,66-68].

Bone Marrow-derived MSCs

MSCs have been recognized and extracted from a wide array of tissues across the human body, such as bone marrow, adipose tissue, amniotic fluid, umbilical cord, synovial tissue, and connective tissues including tendons and ligaments, as well as from the heart, liver, and dental tissues [69-79]. However, despite many various sources of MSCs around the body, bone marrow and adipose tissue have become the most common sources used for orthopaedic clinical application [3-12,80].

Bone marrow was the progenitor source of MSCs in early research, owing to its ease of harvest, background of understanding at the time, and known capacity for multipotency [42,43,81]. In addition to MSCs and several bioactive factors, bone marrow also encompasses a diverse array of cell types, including red blood cells, leukocytes, platelets, adipocytes, both hematopoietic and non-hematopoietic precursor cells, and supportive stromal cells [82,83]. It is theorized that centrifugation can be employed to concentrate Bone Marrow Aspirate (BMA), along with its various components, which include bone marrow-derived mesenchymal stem cells (BM-MSCs) and other bioactive entities, such as growth factors (e.g. PDGF, TGF-β), proteins (e.g. BMPs), platelets, and immune cells (e.g. neutrophils, lymphocytes, monocytes). This results in the production of Bone Marrow Aspirate Concentrate (BMAC), which may enhance regenerative potential [82,84]. However, even with centrifugation, MSCs only compose approximately 0.001% to 0.01% of the cells in BMAC [47,85-87]. Moreover, conflicting evidence suggests that centrifugation and BMAC indeed have higher concentrations of MSCs [86-91].

Adipose-derived MSCs

The discovery of MSCs in adipose tissue dates back to 2001 and its subsequent rise in popularity has positioned it as one of the leading sources of MSCs in current regenerative medicine practices [92]. Adipose-derived MSCs (A-MSC) are typically isolated from the abdomen, thigh, gluteal area, arm, and Hoffa’s fat pad. Similar to MSCs derived from bone marrow, A-MSCs possess the potential for multipotency and the ability to produce distinct phenotypes in response to the surrounding environment through immunomodulatory and trophic cascades [69,93]. Adipose tissue can yield up to a 500-fold increase in the amount of MSCs with 1 gram of aspirated adipose tissue, yielding approximately 3.5×10^5 to 6.0×10^6 A-MSCs compared to 500 to 5.0×10^4 MSCs derived from 1 gram of bone marrow aspirate [94]. This accounts for the substantially higher concentration of MSCs in adipose tissue compared to that in bone marrow. Due to the multiple available harvest sites, a large number of MSCs can be obtained from a single individual, with high capability to proliferate rapidly in vitro and have low cell senescence after months of culture and expansion [95,96]. The identification of the stroma and the capacity to immediately utilize the Stromal Vascular Fraction (SVF), which has a high prevalence of A-MSCs and stromal cells for therapeutic purposes, has made adipose tissue a suitable candidate for clinical applications.

Numerous strategies are available for isolating A-MSCs from subcutaneous tissues, utilizing either an enzymatic [69,97-99] or mechanical digestion process [4,5,10,14,100-110]. These A-MSCs are not isolated alone, but as a component of a processed SVF, which is composed of endothelial progenitor cells, adipocytes, preadipocytes, fibroblasts, macrophages, pericytes, and red blood cells [111]. Enzymatic digestion techniques commonly employ collagenase, which targets particular amino acid sequences and are subsequently followed by a series of differential centrifugation processes [94-98], yielding 2.0 to 6.0×10^6 cells, with cell vitality of more than 90%. Collagenase digestion has been shown to be more efficient compared to mechanical SVF isolation; however, these methods are typically more time-consuming, requires several challenging and technical steps, dedicated equipment, and is generally more expensive [99,112-114]. Enzymatic digestion techniques also may violate local laws and policies as processing goes beyond “minimal manipulation” regulations [115,116]. The extraction of A-MSCs and SVF via enzyme-free methods usually employs mechanical or physical forces to weaken the structural integrity

of the extracellular matrix found in adipose tissue and its peri-adventitial components. One main advantage of using mechanical digestion is that the native extracellular matrix and perivascular structures are maintained and act as a scaffold providing biophysical support [117,118].

Umbilical Cord-derived MSCs

Functioning as a crucial prenatal organ, the umbilical cord connects the placenta to the fetus or newborn, allowing for the exchange of essential nutrients and oxygen. This structure is composed of a two-layered epithelial and mesenchymal amniotic membrane, a perivascular region with surrounding blood vessels, and Wharton's jelly which provides the necessary elasticity to the organ [119]. The umbilical cord is an exceptional source for obtaining a considerable number of MSCs, with the harvesting process being non-invasive, painless, and posing no risk to the donor. The collection and application of Umbilical Cord-Derived MSCs (UC-MSCs) are less constrained by legal regulations and ethical considerations [120,121]. Additionally, UC-MSCs avoid the common limitations associated with MSCs derived from bone marrow or adipose tissue, such as cell senescence due to donor age, limited ability to proliferate, and an increased risk of transmitting infectious diseases [122-125].

UC-MSCs have no morphologic difference compared to A-MSCs and thry express the classic MSC markers CD44, CD73, CD- 90, and CD105, while being negative for CD3, CD14, CD19, CD34, and CD45 [126-128]. In comparison to BM-MSCs, A-MSCs and UC-MSCs have higher proliferative potential [122,126,128-132]. UC-MSCs reach saturation density more quickly than A-MSCs, demonstrating their higher proliferative potential. However, UC-MSCs demonstrate lower plating efficiency and yield fewer CFUs compared to A-MSCs, possibly due to the primitive nature of UC-MSCs and their need for cell-cell contact to grow. A-MSCs show higher matrix mineralization and osteocalcin expression, however, they are equivalent to UC-MSCs in osteonectin expression, making A-MSCs superior to UC-MSCs in terms of bone formation. UC-MSCs and A-MSCs are similar in terms of chondrogenic differentiation and they both acquire rounded morphologies indicative of chondrocytes, express type 2 collagen, and have mRNA expression of aggrecan and collagen type 2 in equivalent numbers. This indicates that both have equivalent and efficient chondrogenic differentiation potential [126].

MSCs in Tendon Injuries

The innate healing capacity of tendons is typically low, which often leads to the formation of fibrosis and adhesions. Tendons that are injured, "pathological," or regenerated usually show diminished mechanical properties relative to their healthy uninjured counterparts. The use of MSCs has been shown to aid in tendon healing through their trophic and immunomodulatory functions, allowing improved tendon development signals and tendon repair capabilities. Following tendon injury, there is decreased tissue perfusion leading to a hypoxic environment in the tendon [133]. Decreased vascularity and hypoxia induces inflammatory responses in tendon tissue and tenocytes resulting in decreased synthesis of the collagen matrix [134]. By applying MSCs to injured tendon tissue, VEGF is secreted to enhance angiogenesis and capillary permeability through the proliferation and differentiation of vascular endothelial cells [135-138]. By promoting neovascularization, nutrients and growth factors can be more efficiently recruited to injured areas, improving intrinsic tendon repair.

Tendon fibroblasts or tenocytes produce various ECM components, such as proteoglycans, collagen, and fibronectin, which help maintain ECM stability [139]. Tenocytes migrate to the site of injury and proliferate, producing collagen and glycoproteins, which enhance tissue regeneration during the proliferation phase of tendon healing [140]. However, during the proliferation and remodeling phases, there is decreased vascularity secondary to tendon injury leading to poor blood supply and decreased levels of tenocytes, causing slow and inefficient tendon healing. Fibrosis and fibrous tissue develop, causing incomplete recovery due to the lack of ECM components during these healing phases, producing mechanically inferior tissue [141]. MSCs on the other hand enhances the endogenous expansion and proliferation of tendon progenitor cells and tenocytes through secretion of growth factors, allowing the induction of tendon progenitor cells and tenocyte differentiation [142-144]. MSCs can also promote tendon healing indirectly by inhibiting the differentiation of progenitor cells down non-tendinous lineages, such as adipogenesis, osteogenesis, and chondrogenesis, directing more of these cells to differentiate into tenocytes [145]. By promoting tenocyte proliferation and differentiation, increased numbers of tenocytes are available to promote ECM deposition, improving the quality of tendon healing.

Normal tendons have high levels of type I collagen in their ECM, which plays an important role in providing tensile strength for tendons, while type III collagen is seen in lower quantities and is weaker in bearing mechanical loads [71,146]. Matrix Metalloproteases (MMPs) are vital in the remodeling phase of tendon repair as they break down damaged collagen [148,149]. During the early phases of tendon healing VEGF increases the expression of MMPs, which helps improve neovascularization; however, at the later remodeling phase of healing, these MMPs degrade both type I and type III collagen and proteoglycans in ECM, which may limit the strength of newly-remodeled tissue [150]. Through precise signaling from the actions of MSCs, MMPs genes can be down regulated, allowing greater collagen synthesis and improved tendon healing by increasing the ratio of type I/type III collagen [151]. Other proteins, such as decorin, TNMD, and type I/III collagen α1, are highly expressed in the early stages of tendon healing in response to MSCs applied to injured tendons [152]. Decorin promotes collagen production by regulating cell proliferation [153]. TNMD promotes the proliferation, migration, and differentiation of tenocytes and tendon progenitor cells, preventing fibrosis and scar formation while also promoting collagen remodeling through regulation of type I collagen levels [154]. MSCs also secrete other growth factors that increase the strength of repaired tendons, such as TGF-β, bFGF, and EGF, which accelerate ECM deposition and remodeling and promote collagen synthesis and maturation [155-158].

By understanding the physiology in which MSCs can enhance tendon healing through direct and indirect mechanisms, we can harness these characteristics to improve clinical outcomes. Morton-Gonzaba et al. [159] demonstrated in their meta-analysis that one of the biggest benefits of using MSCs for rotator cuff injuries is the significantly increased ultimate load-to-failure seen. They noted that despite an increased ultimate load-to-failure, there was no increase in overall stiffness, ultimate tensile strength, cross-sectional area, mechanical deformation, or energy absorbed. However, bone morphology at the insertion of the rotator cuff tendons saw an improved bone mineral density trabecular thickness and bone volume fraction with no improvement in trabecular separation or total bone trabecular

number.

Earlier studies showed MSC augmentation during rotator cuff repair improved the healing rate and quality of the repair surface. Hernigou et al. [160] showed 100% of their MSC augmented cases had healing of the rotator cuff tear at 6 months compared to only 67% who underwent rotator cuff repair only. Longevity of rotator cuff repairs was also improved in the MSC augmented group where 87% had intact repairs at 10 years while there were only 44% with intact repairs amongst the repair only group. They correlated that the number of MSCs implanted had the most significance as those with decreased tendon integrity at 10-year follow-up received fewer MSCs. Kim et al. [161] had similar results, showing improved retear rates in the augmented group (14%) compared to the repair only group (28.5%) at the mean final follow-up of approximately 28 months.

In a randomized controlled trial by Cole et al. [162], they demonstrated that the application of MSCs derived from bone marrow showed improved clinical outcomes at 6 months and was sustained until the last follow-up at 2 years. Specifically, in terms of range of motion, there was significant improvement in internal rotation, external rotation, abduction, and forward flexion in the group who underwent rotator cuff repair augmented with MSCs. In comparison with the control group only undergoing rotator cuff repair, there was no significant improvement in range of motion or strength in any postoperative follow-up. Postoperative analysis was done using MRI and 57% of the rotator cuff repair only group had Suguya 4 or 5 grades compared to only 18% in the repair group augmented with MSCs. Additional analysis showed a strong correlation between MSC augmentation and Sugaya score ≤3. In terms of failure, there was no significant difference between the two groups.

MSCs not only are effective as augmentation to rotator cuff repairs but also may act as a standalone therapy. Jo et al. [164] demonstrated improved clinical scores for patients with partial rotator cuff tears treated with low-doses (1.0×10^7 cells), mid-doses (5.0×10^7 cells) and high-doses (1.0×10^8 cells) of MSCs. VAS scores were significantly decreased in all 3 doses; however, the mid-dose showed the most decrease at both 1-year and 2-year follow-ups. External rotation had significant improvement with the mid- and high-doses, while internal rotation significantly improved with only the high-dose. Low-doses of MSCs only had an increase in infraspinatus strength by 20% at 2 years while the high-dose group showed improvement in strength in the supraspinatus, infraspinatus, and teres minor by 72.3%, 60.3%, and 55.1% at 2 years. SPADI, Constant, ASES, UCLA SST, DASH, overall function, and satisfaction all had significant improvements at 2 years with the mid- and high-doses. Structurally, the high-dose group showed a 100% decrease in defect volume on the bursal-side at 2 years.

Centeno et al. [165] compared treating partial rotator cuff tears using a combination of bone marrow derived MSCs and a PRP derivative platelet lysate to exercise treatment. The MSC + PRP group showed significant improvement in DASH scores in 3 months with continued improvement through 2 years of follow-up. Minimal Clinically Important Difference (MCID) for DASH scores was achieved in 61% by 3 months, 91% by 1 year, and 94% by 2 years. Compared to the exercise group, only 40% met the MCID by 3 months and dropped to only 20% in 6 months. Numeric Pain Scale (NPS) scores had significant improvement as early as 1 month in the group treated with MSCs + PRP while the exercise group never demonstrated any significant improvement at any time point. MCID for NPS was reached by 43% at 1 month, 91% at 1 year, and 88% by 2 years in the MSCs + PRP group, while MCID in the exercise group was met by 22% at 1 month, 30% at 3 months, and 20% at 6 months before crossing over patients. Modified SANE scores were also significantly better in the MSCs + PRP group.

MSCs have also been investigated in other tendon pathologies. Early phase clinical trials have been shown to have promising results in Achilles tendinopathy, showing significantly improved VAS, MOXFQ, EQ-5D-5L, and VISA-A scores at 3 months and 6 months follow-up [166]. MSCs have also been shown to improve patellar tendon structure on ultrasound and ultrasound tissue characterization compared to leukocyte poor PRP as early as 6 months, with normalization of tendon structure seen on MRI, with both groups showing improved and equivalent clinical outcomes [167].

MSCs in Ligament Injuries

Ligament healing usually occurs in a manner similar to tendon healing, resulting in scar tissue with diminished mechanical characteristics related to its structure, composition, and functional capabilities when compared to the native tissue. Normal ligament healing goes through phases of inflammation, proliferation, and remodeling. The inflammatory phase is characterized by the recruitment of immune cells, such as macrophages (M1 and M2), T lymphocytes, and neutrophils to the injury site. This is followed by the arrival of more macrophages, along with endothelial cells and fibroblasts, all of which play a role in producing granulation tissue. Throughout the proliferation phase, the levels of type I procollagen diminish, whereas type III collagen levels rise. As remodeling occurs, the ratio of type I collagen to type III collagen increases, thereby enhancing the tensile strength of the tissue. In an ideal scenario, the healing process leads to diminished inflammation, well-structured collagen fibers, natural levels of type I collagen, the absence of scar tissue, and mechanical properties that closely resemble those of native tissue [168].

Early suppression of inflammatory cells and cytokines could be essential for promoting better regenerative healing of ligaments, facilitating their restoration to their initial composition. The role of MSCs in ligament healing could be the key through their immunomodulatory properties. When MSCs are introduced to a ligament injury, they generate elevated amounts of CD206, which serves as an anti-inflammatory marker for M2 macrophages along with interleukins IL-10, IL-12, and TNF-α. By converting M1 pro-inflammatory macrophages into M2 anti-inflammatory macrophages, MSCs hold the potential to diminish inflammation and lower the incidence of fibrosis and scar tissue. A diminished population of M1 macrophages in the vicinity of the injury can result in a lower concentration of inflammatory cytokines, like IFN-γ, IL-1α, and IL-12, ultimately promoting better ligament healing [169-171].

Early studies demonstrated MSCs with or without the use of biologic scaffolds had the ability to improve ligament healing in incomplete or partially torn ACL injuries when combined with primary repair. These studies showed significantly improved functional and clinical outcomes, high return to sport rates, decreased side-to-side anterior translation difference, and high long term survival rates [172-177]. Other studies showed the benefit of MSCs in the healing of ACL reconstructions, demonstrating early ligamentization of Bone-patellar Tendon-Bone (BTB) augmented allografts augmented with MSCs, with su-

perior early signal intensity ratio on radioimaging, as well as improved PROMs during the early post-operative period compared to BTB allograft reconstruction alone [178]. Centeno et al. demonstrated the efficacy of non-operative treatment using a combined injection of MSCs and PRP for grade 1 2 and 3 ACL tears. They showed improved modified SANE scores beyond 1 month follow-up, as well as improved NPS, LEFS, and IKDC scores at an average of 23 months. Mean gray values also improved showing lower signals and denser anterior cruciate ligaments [179,180].

MSCs in Meniscal Injuries

The meniscus is a particularly difficult structure in terms of healing. The outer or peripheral one-third of the meniscus, typically referred to as the "red-red zone", receives perfusion from radial branches from the peripheral capsular plexus and is the most perfused area, making this the only area capable of healing. The middle one-third of the meniscus, called the "red-white zone", is the transition zone between the perfused red-red zone and the inner or most central "white-white zone", and is partially vascularized as this is the area where many of the radial branches terminate. The inner one-third is avascular and has no perfusion as vascularity of the meniscus typically extends between 10% to 25% from the periphery [181-184]. Meniscal healing relies on both extrinsic and intrinsic factors. Extrinsic factors rely on the vascular areas of the meniscus where undifferentiated mesenchymal cells supply nutrients and induce healing. Intrinsic factors rely on the self-regenerative capacity of the meniscal fibrocartilage and surrounding synovial fluid [185,186].

One of the first studies to investigate MSC treatment in meniscal lesions was done by Vangsness et al. In the study, they described administering an intraarticular injection of allogenic MSCs 7 to 10 days post partial medial meniscectomy, in which more than 50% of the meniscus was excised. They demonstrated by MRI that the group given 50×10^6 MSCs had significantly increased meniscal volume (defined a priori as a 15% threshold) for 24% of patients, while only 6% of patients given $150x10^6$ MSCs had significant increased meniscal volume. VAS and Lysholm knee scale total scores were also significantly improved for those given MSCs [187].

Whitehouse et al. [188] marked one of the earliest accounts of employing autologous MSC augmentation in the repair of meniscal injuries associated with avascular lesions. The meniscal tears were repaired arthroscopically with MSC-implanted collagen scaffolds, either sutured around or positioned between the reattached meniscal fragments. Of 5 patients, the implant survived without further intervention. The other 2 were considered as treatment failure due to recurrence of pain, swelling, or locking of the knee at approximately 15 months postimplantation, and repair secondary to retear at the repair site or partial healing. In all 3 successfully-treated patients, there were significant improvements in outcome scores (IKDC and Tegner-Lysholm) and range of motion at the final follow-up of 24 months. Despite eventually being considered as treatment failure at 15 months, the 2 treatment failures had significantly improved Tegner-Lysholm scores and range of motion. At 12 months postimplantation, MRI showed an intact and undisplaced meniscus with diminishing high signals in the 3 successfully treated patients.

Sekiya et al. [189] described administering MSCs 14 days after meniscal repairs done on degenerative meniscus flaps or horizontal tear lesions. They noted that Total Lysholm knee scores were significantly improved in all patients at 1-year follow-up and was maintained until the last follow-up of 2 years. Swelling and pain subscores were significantly higher at 1-year and 2-year follow-ups, while limping and stairs subscores were significantly improved at 2-year follow-up. KOOS, pain, daily living, and sports/recreational activity scores were significantly improved at 2 years along with NRS, general, and subcategories as well. Tegner activity scale scores also did not decrease after MSC administration during follow-ups. At 2-year follow-up, 3D MRI was done showing indistinguishable meniscus tears. Sekiya et al. later showed the possibility of treating medial meniscus flap tears located at the central area of the posterior junctional zone with meniscal repair augmented with MSCs in which 50% of his patients showed complete and stable restoration and the other 50% showed partial restoration upon second look arthroscopy done at 52 weeks posttreatment. They also noted that Lysholm scores were also significantly higher at 4- and 52-weeks posttreatment [190].

Dancy et al. investigated the effects of biologic augmentation either with PRP or BMAC in those who underwent isolated meniscus repair or meniscus repair with concomitant ACL reconstruction. The study found no significant difference in the revision rates between patients who had isolated meniscus repairs and those who received isolated meniscus repairs enhanced with PRP or BMAC. However, when these augmented repairs were compared to matched controls who did not receive augmentation, a notable reduction in the rate of revision surgery was observed among patients who underwent PRP or BMAC augmented meniscus repair with concomitant ACL reconstruction. It is important to note that in this study, there was no separate analysis of PRP augmentation versus BMAC augmentation, and the use of either biologic was counted as a single group [191].

MSCs in Osteochondral Injuries

Cartilage is especially prone to damage due to its avascular nature, low cellular density, and the limited capacity for chondrocyte migration and proliferation. Such damage can lead to pain, restricted range of motion, and diminished functionality. Osteochondral lesions obstruct the smooth movement of joints by creating irregularities which adversely affect the role of cartilage as shock absorber and force distributor. MSCs play a significant role in cartilage regeneration by facilitating chondrogenesis and enhancing the proliferation and ECM deposition of chondrocytes. This is achieved through their paracrine and immunomodulatory effects, which involve the secretion of various cytokines and growth factors, including TGF-β, IGF-1, TSP-2, VEGF, HGF, ADAMTSs, MMPs and, TIMPs. These mediators are instrumental in fostering endogenous growth, promoting the proliferation of progenitor cells, preventing chondrocyte apoptosis and degeneration, enhancing angiogenesis, and mitigating oxidative stress, all while maintaining a stable and mature phenotype that minimizes fibrosis and hypertrophy [192-194].

Since 2008, the intra-articular application of MSCs has been explored notably in the study conducted by Centeno et al., which revealed increases in meniscal volume and the restoration of cartilage defects [195]. Initial investigations showed significant improvements in pain metrics, functional outcomes, and the coverage of cartilage defects, which advanced from 27% to 100% as verified through MRI or subsequent second-look arthroscopy [196-204]. Several recent systematic reviews and meta-analysis of case controls, cohorts, and randomized

controlled trials demonstrated the efficacy and safety of MSCs on chondral lesions and osteoarthritis [205-211].

MSCs are not only applicable as stand-alone intra-articular injections, but can also serve to enhance current techniques for cartilage reconstruction. In a meta-analysis conducted by Chiang et al., five studies were reviewed to evaluate the effectiveness of marrow stimulation alone versus those augmented with MSCs in treating osteoarthritis and chondral lesions. The findings revealed a significant improvement in IKDC, Lysholm, and MOCART scores, suggesting enhanced clinical and functional results along with observable cartilage fill on MRI. [198,212-216].

The use of Autologous Chondrocyte Implantation (ACI) techniques has been the standard treatment for osteochondral lesions. However, as far as we are aware, there is a lack of research that directly contrasts isolated ACI methods with matched ACI techniques enhanced by MSCs. Nejadnik et al. and Teo et al. [212,218] have shown that MSCs maintain their effectiveness in both short- and long-term evaluations. Their research compared the outcomes of ACI and BM-MSCs both of which were placed beneath periosteal membrane patches. The results at the 2-year and 10-year follow-ups indicated no significant differences in the IKDC, Tegner, and Lysholm scores between the two treatment groups, confirming the comparable efficacy of MSCs in cartilage reconstruction. It was noted that a significant benefit of MSCs compared to chondrocytes lies in the paracrine properties of MSCs. Their capacity to influence the local environment and attract progenitor cells could play a crucial role in the regeneration of cartilage.

Shetty et al. performed a randomized controlled trial comparing BM-MSCs mixed with a suspension of hyaluronic acid and gel ACI. Following a six-year follow-up, the study concluded that there was no notable difference between the two treatments concerning IKDC, KOOS, Lysholm, and MOCART scores [219]. In a randomized controlled trial by Akgun et al., it was found that participants in the matrix-induced Autologous Mesenchymal stem cell Implantation (m-AMI) group achieved significantly higher functional scores in the KOOS, pain symptoms, ADL, and sports/recreational activity subscales compared to those in the matrix-induced Autologous Chondrocyte Implantation (m-ACI) group. Nevertheless, after two years of follow-up, no significant differences were noted in the Tegner and VAS scores. The study also highlighted that the m-ACI group demonstrated better defect in-fill and surface contour [220].

The application of bioengineered scaffolds has enhanced the efficacy of MSCs by offering a substrate for their seeding and creating a conducive environment for their proliferation. These scaffolds facilitate the transfer and delivery of MSCs to the targeted defect site [221]. Common scaffolds used today are hyaluronic acid membranes or collagen type I/III matrices. The study by Buda et al. demonstrated a notable increase in IKDC and KOOS scores at the 24-month follow-up after treating chondral defects with hyaluronic acid membrane scaffolds infused with BM-MSCs. Additionally, MRI findings indicated that 80% of the patients showed nearly complete defect filling and satisfactory graft integration. Histochemical assessments revealed that the regenerated cartilage tissue contained proteoglycans and type-II collagen, both of which are established markers of hyaline cartilage [222].

A hyaluronan-based scaffold (Hyalofast® Anika Therapeutics Inc. MA USA) was investigated by Gobbi et al. in full-thickness chondral defects of the knee in patients older than 45 years and found all their evaluated scores to have significantly improved at final follow-up of 4 years. A prior study also by Gobbi et al. similarly showed effectiveness of the hyaluronan-based scaffold, particularly in the patellofemoral joint, where MRI at 24 months showed 71% of the population to have an almost normal cartilage and second-look arthroscopy revealed the repaired surface to be nearly normal with hyaline-like appearance on histologic review.

Gobbi et al. evaluated the short- and long-term outcomes of patients undergoing Hyaluronic Acid Membrane scaffold augmented with Bone Marrow Aspirate Concentrate (HA-BMAC) and showed significant improvement in functional, clinical, and pain assessments, particularly in patients older than 45 years [7,11,19,24,27,31,33]. Their studies in 2011 and 2014, with fairly large average chondral lesion sizes of 9.2 cm^2 and 8.3 cm^2, respectively used a collagen-based matrix with a one-stage surgery, the results of which showed significant improvements in VAS, IKDC, KOOS, Lysholm, Marx, SF-36, and Tegner scores [631].

Scaffold-based cartilage therapy can be derived from sources other than bone marrow. Sciarretta et al. demonstrated significant mid-term success over five years with their LIPO-AMIC approach, which merges A-MSCs with a collagen scaffold. Significant improvement in clinical and functional scores, such as the IKDC and Lysholm, were recorded as early as six months post-treatment, with further increases identified during the five-year follow-up. MRI findings demonstrated the early restoration of the subchondral lamina, the advancement of chondral tissue maturation, and the filling of the osteochondral defect. MOCART scores were also significantly improved starting at 2 years follow-up and maintained at up to 5 years follow-up [223].

Future Trends of MSCs: Secretomes and Exosomes

The secretomes of MSCs comprise both soluble and insoluble components. The soluble components encompass a range of growth factors, chemokines, and cytokines, whereas the insoluble components are primarily Extracellular Vesicles (EVs). These EVs are categorized into four distinct types based on their size: exosomes (30-150 nm), microvesicles (100-1000 nm), apoptotic bodies (50-5000 nm), and oncosomes (1-10 μm) [224-226]. MSC-derived exosomes are a type of EV that carry out biological functions through their active biomolecular components which include peptides, lipids, proteins, nucleic acids, organelles, receptors, enzymes, and transcription factors [227228]. The factors found in MSC secretomes and exosomes are influenced by their tissue origin, the culture techniques used, and the characteristics of the cellular environment [229-231].

A clinical study by Rhatomy et al. on grade I-II PCL ruptures showed arthroscopic-guided intrasubstance PCL injection with allogeneic UC-MSC secretomes produced significant improvements at one-year final follow-up in IKDC, Modified Cincinnati, and Lysholm scores. Post-treatment MRI at one year showed 50% regained PCL continuity. 41.6% had near-normal PCL continuity and 8.3% regained PCL continuity, but had deformed outlines [232].

Exosomes and secretomes offer numerous advantages over MSCs: 1) secretomes represent a safer allogenic alternative since they do not involve the transfer of complete cells that could contain immunogenic components; 2) with a diameter generally between 30 and 150 nm, secretomes are notably smaller than MSCs, allowing for their efficient penetration and

migration through different tissues and organs; 3) secretomes are equipped with homing molecules on their surfaces which assist in directing them to specific target locations in the body; 4) the presence of surface proteins in secretomes allows them to display biological properties, similar to those of their host MSCs, which helps them avoid phagocytosis; 5) secretomes may offer advantages in preservation, as EVs can be kept at −20 ◦C in contrast to stem cells that need to be stored in liquid nitrogen to ensure their viability; and 6) priming and activating MSCs allows for the engineering of secretome and exosome contents, potentially resulting in a greater influence on specific targeted effects [233-243].

Exosomes are commonly created through the budding of Intraluminal Vesicles (ILVs) that reside in the luminal space of Multivesicular Bodies (MVBs). When MVBs connect with the cellular membrane, these ILVs are released as exosomes [244]. These exosomes serve as a paracrine mediator between MSCs and target cells [245,246]. Exosomes play a crucial role in intercellular communication by transporting proteins mRNA and miRNA to target cells. This process can initiate cascades that enhance tissue repair by sustaining and attracting endogenous stem cells facilitating immunomodulation, encouraging angiogenesis, and preventing apoptosis [247].

Exosomes are recognized for their significant contribution to osteoarthritis treatment by suppressing pro-inflammatory factors and pathways while simultaneously promoting the proliferation and migration of chondrocytes. This mechanism may involve the exosomes' ability to obstruct NFκB signaling through the inhibition of IκBα phosphorylation, leading to a reduction in TNF-α-induced COX2 expression, as well as interleukin and collagenase activity. Exosomes can also mitigate inflammation and enhance tissue regeneration through stimulating the shift of pro-inflmmatory M1 macrophages to anti-inflammatory M2 macrophages and reducing expression of IL-1β, TNF-α, and IL-6 (pro-inflammatory cytokines). Additionally, exosomes increase the expression of IL-10 chondrogenic genes SOX9 and WNT7A and promote the production of proteoglycan and type II collagen [248]. Exosomes have been demonstrated to enhance the proliferation and migration of chondrocytes, as well as diminish chondrocyte apoptosis. This is accomplished by downregulating various molecules, including ADATS5, ALPL, iNOS, MMP13, and the signaling pathways associated with PI3K/Akt, p38, TAK1, and IL-1β-activated pro-inflammatory Erk1/2 and NF-κB. Furthermore, exosomes promote the upregulation of genes like ACAN (aggrecan), BCL2, and PRG4 [249,250].

A single clinical study was identified that utilized exosomes for the treatment of an orthopaedic condition. In their study, Dordevic et al. explored the application of exosomes from BM-MSCs in managing osteoarthritis in various joints. Their six-month follow-up revealed notable improvements in the Brief Pain Inventory and Oswestry Disability Index, with scores increasing by 77% and 80% respectively. Furthermore, functional assessments for the upper and lower extremities demonstrated enhancements of 51% and 76% respectively [251].

Quantifying and Qualifying MSCs: Do They Reflect in Clinical Outcomes?

Other than overall concentration of MSCs from different sources, other practical methods and markers, such as Nucleated Cell Counts (NCC) and fibroblast Colony Forming Units (CFU-F), have been proposed to correlate MSC with BMA(C) or other harvest sources [13,252]. By analyzing different parameters, it was proposed that it may be possible to quantify the amount and quality of MSCs from various sources and characteristics of sources. Cavallo et al. [253] demonstrated that patient age could affect the quality of BMAC and correlations with MSCs as they showed significantly higher mononuclear cell counts in younger patients when compared to older patients ($3.8\pm1.8\times10^7$ vs. $1.2\pm0.8\times10^7$, $p<0.0005$). Donor sites were also shown to have significant impact on the quality of BMAC and quantity of MSC as samples taken from the iliac crest exhibited a significantly higher mean concentration of mononuclear cells per milliliter of BMAC than those sourced from the proximal tibia ($1.2\pm0.8\times10^7$ vs $0.3\pm0.2\times10^7$, $p=0.001$). These results also had comparable correlation with the CFU-F analysis, with the iliac crest BMAC samples showing significantly higher CFU-F counts compared to proximal tibia at multiple days of culture (15.9±19.4 vs 0.6±1.0, p=0.001 at day 10 and 21.7±23.0 vs 2.9±4.2, p=0.006 at day 20).

While there is evidence that younger patients and the iliac crest may have increased numbers of NCC and CFU-F, there is still no distinct evidence on whether these surrogate markers accurately estimate MSCs. As early as 2007 [254], Dr. Gobbi questioned the relationship between CFU-Fs as a biomarker to estimate MSCs and their effectiveness in BMAC [6]. He conducted a 10-year study investigating the correlation between the total number of CFU-Fs acting as an estimating marker on the quantity of MSCs and the clinical outcomes of patients treated for cartilage lesions using a hyaluronic acid-based scaffold combined with bone marrow aspirate concentrate (HA-BMAC) in their 10-year follow-up cohort study [254-256]. In this study, 25 participants (mean age 46.6±1.7 years) with chondral lesions (mean size 8.3±6.3 cm^2) underwent treatment using HA-BMAC. Total number CFU-Fs (mean 4018, range 1932 to 5700) were used to quantify the number of MSCs in the harvested BMAC. The majority of patients had lesions greater than 4 cm^2 (68.0%) and were older than 45 years old (60.0%). Secondary outcomes showed that there was no significant correlation between age at the time of surgery (greater or less than 45 years old) (Table 2) or lesion size (greater or less than 4 cm^2) (Table 3) and clinical outcomes (TEGNER, IKDC, VAS, MARX, KOOS, LYSHOLM) at short-term and long-term follow-up.

Cercone and Fortier conducted a study using bone marrow aspirated from the sternum of horses, correlating NCC and CFUs to MSCs. Their results showed no to a very weak correlation between NCC and MSCs (r=−0.34 95% CI=- 0.64-0.06 n=25, p=0.09) CFUs and MSCs (r=0.13 95% CI=- 0.27-0.5 n=25, p=0.50) and NCC and CFUs (r=0.08 95% CI= - 0.16-0.32 n=66, p=0.50). They arrived at a conclusion similar to that of Gobbi et al., asserting that neither NCC nor CFUs correlated with MSCs, thereby rendering them unsuitable as surrogate markers for quantifying MSCs in BMAC. Moreover, it is suggested that these markers may not be directly responsible for the therapeutic effects attributed to MSCs, but rather may indicate a different subset of bioactive factors. They suggested that laboratory-based methods, such as tri-lineage differentiation or flow cytometry, should still be used to characterize MSCs in BMAC until alternative biomarkers can be identified [257].

Table 2: Final Follow-up Clinical Outcomes by Age Group.

	Age		p value
	≤45 (n=10)	>45 (n=15)	
TEGNER	5.0 (1.0)	5.0 (2.0)	0.4093
IKDC Subjective	83.3 (23.0)	81.6 (20.9)	0.8903
IKDC Objective	1.0 (0.0)	1.0 (1.0)	0.4760
VAS	0.3 (2.0)	1.0 (1.8)	0.8615
MARX	8.0 (4.0)	10 (6.0)	0.4946
KOOS			
Pain	96 (8.0)	95 (15.0)	0.4055
Symptoms	89 (7.0)	93 (18.7)	0.5202
ADL	98.5 (7.0)	99 (17.5)	0.6017
Sport	75 (30.0)	80 (31.0)	0.9774
QOL	82.5 (25.0)	85 (18.5)	0.8440
LYSHOLM	92.5 (10.0)	80 (22.2)	0.5195

*Mann-Whitney U Test
*Data are expressed in median and interquartile range (IQR)

Table 3: Final Follow-up Clinical Outcome by Lesion Size.

	Lesion Size		p value
	≤4 cm²	>4 cm²	
TEGNER	4.5 (2.5)	5.0 (2.0)	0.4550
IKDC Subjective	83.9 (25.8)	80.5 (23.4)	0.7478
IKDC Objective	1.0 (0.5)	1.0 (1.0)	0.8223
VAS	0.5 (1.6)	0.3 (2.2)	0.7602
MARX	9.0 (4.0)	8.0 (6.0)	0.4372
KOOS			
Pain	96 (8.0)	95 (15.0)	0.5075
Symptoms	94 (6.5)	89 (13.8)	0.1064
ADL	99.5 (19.5)	97 (7.7)	0.9757
Sport	82.5 (24.5)	75 (35.0)	0.9526
QOL	85 (19.0)	81 (26.2)	0.6578
LYSHOLM	97 (18.0)	90 (17.7)	0.1262

*Mann-Whitney U Test
*Data are expressed in median and interquartile range (IQR)

While HA-BMAC was shown to be an effective treatment option for chondral lesions with significantly improved outcomes at 6 months, 12 months, 24 months, and at long term follow-ups beyond 10 and 14 years [6,19,24,27,31,33], Gobbi et al. concluded that CFU-Fs may not be an effective marker in determining the quantity of MSCs in BMAC as well as the effect of MSCs on clinical outcomes [254-256]. This could be due to the fact that MSCs do not act directly as progenitor cells or stem cells, but as signaling cells with immunomodulatory and trophic properties as described by Caplan [54]. Cercone and Fortier in 2021 conducted an animal study examining the relationship between NCC and CFUs in relation to MSCs, ultimately concluding in agreement with Gobbi et al. that neither NCC nor CFUs demonstrated a correlation with MSCs thus deeming them ineffective as surrogate markers for measuring MSCs in BMAC [257].

Gender also seemed to have no correlation to clinical outcomes (Table 4) as there was no significant difference amongst the male and female participants in the various outcome measures, except for LYSHOLM where significantly higher values were seen in the female population (mean LYSHOLM score 95 vs 80, p=0.0074).

Table 4: Final Follow-up Clinical Outcomes by Gender.

	Gender		p value
	Male (n=17)	Female (n=8)	
TEGNER	6.0 (2.0)	5.0 (1.0)	0.2319
IKDC Subjective	80.5 (20.2)	87.3 (23.0)	0.7478
IKDC Objective	1.0 (1.0)	1.0 (0.0)	0.2460
VAS	0 (2.2)	0.6 (1.5)	0.7141
MARX	8 (4.5)	11.0 (4.0)	0.2319
KOOS			
Pain	95 (15.0)	98.5 (9.0)	0.2782
Symptoms	90 (11.5)	89 (12.0)	0.9532
ADL	96 (9.2)	99.5 (16.5)	0.7840
Sport	75 (27.5)	95 (27.0)	0.2341
QOL	81 (19.0)	97 (22.0)	0.2042
LYSHOLM	80 (14.0)	97 (5.0)	0.0074

*Mann-Whitney U Test
*Data are expressed in median and interquartile range (IQR)

The primary outcome showed there was no correlation between the number of CFU-Fs and the clinical outcome at short-term and long-term follow-up. In addition to CFU-F count, age at the time of surgery and lesion size (except for KOOS symptoms, p=0.45) did not have significant correlation between the various outcome measures (TEGNER, IKDC, VAS, MARX, KOOS, LYSHOLM) at final follow up (Table 5).

Table 5: Correlation Between CFU-F, Lesion Size, and Age at Surgery to Outcome Measures at Final Follow-up in Patients with Chondral Lesions Treated with HA-BMAC.

	CFU-F		Lesion Size		Age at Surgery	
	Spearman r	p value	Spearman r	p value	Spearman r	p value
TEGNER	0.082	0.696	0.146	0.488	- 0.172	0.412
IKDC Subjective	0.188	0.367	- 0.127	0.545	- 0.283	0.171
IKDC Objective	- 0.329	0.109	0.019	0.930	0.291	0.158
VAS	- 0.250	0.228	0.109	0.604	0.222	0.287
MARX	- 0.281	0.173	- 0.093	0.660	0.016	0.941
KOOS						
Pain	- 0.061	0.773	- 0.281	0.173	- 0.343	0.094
Symptoms	0.031	0.883	- 0.405	**0.045**	- 0.037	0.862
ADL	0.137	0.512	- 0.150	0.474	- 0.268	0.196
Sport	0.048	0.818	- 0.227	0.275	- 0.296	0.151
QOL	- 0.148	0.481	- 0.290	0.160	- 0.210	0.314
LYSHOLM	- 0.088	0.677	- 0.323	0.115	- 0.283	0.170

**Spearman r correlation

The International Society for Cellular Therapy's Mesenchymal and Tissue Stem Cell Committee proposed criteria to define human MSCs [68] – 1) MSCs must be plastic-adherent in standard culture conditions, 2) MSCs must express CD73, CD90, and CD105, and lack expression of HLA-DR surface molecules CD34, CD45, CD14, or CD11b, CD79alpha, or CD19, 3) MSCs must differentiate to adipocytes, osteoblasts, and chondroblasts *in vitro*. Although this criterion successfully outlines the *in vitro* identification of MSCs, the *in vivo* identification of MSCs before culture has not been sufficiently established [258].

CD73 functions as an ecto-5'-nucleotidase facilitating the conversion of extracellular adenosine monophosphate into adenosine typically found in epithelial cells, endothelial cells, fibroblasts, lymphocytes, and smooth muscle cells [259-262]. CD90 is a protein that is anchored to the cell membrane by glycosylphosphatidylinositol and plays a crucial role in interactions between cells and the extracellular matrix frequently isolated in lymphatic and vascular endothelial cells, fibroblasts, hematopoietic cells, lymphocytes, and neurons [263-266]. CD105 is classified as a type I membrane glycoprotein and acts as a supplementary receptor for ligands within the TGF-β superfamily. This protein is expressed in chondrocytes, fibroblasts, hematopoietic progenitor cells, monocytes, synctiotrophoblasts, and vascular endothelial cells [267]. Although CD73, CD90, and CD105 are included in the minimum criteria for human MSCs, there is currently no evidence to suggest that any antibodies can specifically identify these proteins in vivo within MSCs.

One promising candidate for a biomarker that could enhance the quantification of MSCs, is CD271. While it is not recognized in the International Society for Cellular Therapy's guidelines for defining human MSCs studies have demonstrated that CD271 is one of the most specific markers associated with human BM-MSCs [267,269]. Not only is CD271 found in bone marrow, this biomarker can also be seen in adipose tissue, placental tissue, trabecular bone, and dermal tissue [270-275]. Although CD271 appears to be specific to MSCs from multiple tissue sources, it does not qualify as a universal marker for MSC identification as it is not consistently detectable in tissues like umbilical cord blood, Wharton's jelly, and peripheral blood [276-279]. Regardless, bone marrow and adipose tissue remain two of the most common sources for MSCs used in orthopaedic practice. Therefore, CD271 could potentially act as a biomarker that offers a more accurate representation of the quantity and quality of MSCs derived from these sources in comparison to NCC and CFUs.

Conclusion

As the use of MSCs in clinical practice expands, the necessity for a distinct marker or component of MSCs to enhance the prediction of clinical outcomes has become evident. This review concludes that the initially proposed markers of MSCs, namely CFUs and NCCs, have proven insufficient in predicting outcomes. However, by broadening our perspective beyond these markers, we might uncover a new marker that possesses greater predictive significance. Since the foundational studies conducted by Friedenstein and Caplan, there has been a remarkable surge in our knowledge and comprehension of MSCs. By utilizing the trophic and immunomodulatory properties inherent in MSCs, we seek to harness their regenerative abilities for the treatment of multiple diseases and conditions, either through the standalone application of MSCs or by integrating these cells with other technological solutions. The horizon for MSCs is bright, as innovative treatments and technologies like secretomes and exosomes provide new pathways to improve outcomes and fully exploit the regenerative potential of MSCs.

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