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Mesenchymal stem cells in autoimmune disease: A systematic review and meta-analysis of pre-clinical studies

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ABSTRACT

Mesenchymal Stem Cells (MSCs) are of interest in the clinic because of their immunomodulation capabilities, capacity to act upstream of inflammation, and ability to sense metabolic environments. In standard physiologic conditions, they play a role in maintaining the homeostasis of tissues and organs; however, there is evidence that they can contribute to some autoimmune diseases. Gaining a deeper understanding of the factors that transition MSCs from their physiological function to a pathological role in their native environment, and elucidating mechanisms that reduce their therapeutic relevance in regenerative medicine, is essential. We conducted a Systematic Review and Meta-Analysis of human MSCs in preclinical studies of autoimmune disease, evaluating 60 studies that included 845 patient samples and 571 control samples. MSCs from any tissue source were included, and the study was limited to four autoimmune diseases: multiple sclerosis, rheumatoid arthritis, systemic sclerosis, and lupus. We developed a novel Risk of Bias tool to determine study quality for *in vitro* studies. Using the International Society for Cell & Gene Therapy's criteria to define an MSC, most studies reported no difference in morphology, adhesion, cell surface markers, or differentiation into bone, fat, or cartilage when comparing control and autoimmune MSCs. However, there were reported differences in proliferation. Additionally, 308 biomolecules were differentially expressed, and the abilities to migrate, invade, and form capillaries were decreased. The findings from this study could help to explain the pathogenic mechanisms of autoimmune disease and potentially lead to improved MSC-based therapeutic applications.

1. Introduction

1.1. Mesenchymal stem cells

Mesenchymal stem cells, also known as marrow stromal cells or medicinal signaling cells, are commonly denoted by the term MSCs [1–4]. Over 50 years ago, MSCs were initially isolated from the adherent portion of the bone marrow aspirate. Currently, the International Society for Cell and Gene Therapy (ISCT) recommends that MSCs meet minimum criteria, including: adherence to plastic; ability to self-replicate; present a spindle-shaped/fibroblast appearance; differentiate into bone, fat, and cartilage cells; and express (>95 %) surface markers CD73, CD90, and CD105, and have an absence (<2 %) of surface markers CD34, CD45, CD11b or CD14, CD79α or CD 19, and HLA Class II molecules [5,6].

1.1.1. Sources of MSCs

Initially identified in bone marrow, MSCs are now sourced from additional tissues, including peripheral blood, dental pulp, umbilical cord tissue and blood, dermal tissue, adipose tissue, and synovial fluid [7–10]. Despite the source, MSCs have been shown to be therapeutic, migrate to damaged tissue, stimulate angiogenesis, engraft into target tissue, and regulate immune responses [8,11,12]. MSCs can secrete factors that help dampen inflammation associated with autoimmune diseases, creating an environment that supports immune regulation and tissue repair [13–15]. However, it is unclear if the source of MSC impacts this immunomodulatory effect, as well as the differentiation potential and therapeutic efficacy [16–19]. The inconsistency of these results in the literature

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Abbreviations

AD	Autoimmune disease
AD-MSCs	Autoimmune disease-derived mesenchymal stem cells
ASCs	Adipose-derived mesenchymal stem cells
BMSCs	Bone marrow-derived mesenchymal stem cells
d-MSCs	Dermal-derived mesenchymal stem cells
CLIP	Clinical Indication Prediction
DNR	Did not report
HC-MSCs	Healthy control-derived mesenchymal stem cells
IFATS	International Federation of Adipose Therapeutics and Sciences
ISCT	International Society for Cell Therapy
IVAT	*In vitro* assessment tool
MS	Multiple sclerosis
ND	No difference
RA	Rheumatoid arthritis
s-MSCs	Synovial-derived mesenchymal stem cells
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis
PPMS	Primary progressive multiple sclerosis
RRMS	Relapsing remittance multiple sclerosis
SPMS	Secondary progressive multiple sclerosis

could be due to variations in MSC gene expression patterns or the microenvironment of the tissue of origin.

1.1.1.1. Bone marrow-derived MSCs. Bone marrow-derived MSCs (BMSCs), still the most common source of MSCs used in clinical trials, are typically isolated from the iliac crest or other bones by aspiration and separation with a ficoll gradient [20–22]. This is an invasive harvest, which can carry more risk for patients with chronic health disorders, advanced age, or obesity [23]. The yield of MSCs from bone marrow can be relatively low, requiring *in vitro* expansion to obtain sufficient cell numbers [24]. Furthermore, compared to other sources, BMSCs are considered to have a moderate proliferation rate, taking longer to expand in culture than MSCs from other sources [25]. However, they have been shown to have robust osteogenic, chondrogenic, and adipogenic differentiation capabilities. Additionally, they have been extensively studied for their immunomodulatory capabilities. They can suppress excessive immune responses by inhibiting the proliferation and function of immune cells, such as T cells, B cells, and macrophages [26,27]. This immunosuppressive effect makes them potentially beneficial for autoimmune diseases where immune system dysfunction plays a role. BMSCs have been extensively investigated in clinical trials for various conditions, including bone and cartilage defects, hematological disorders, and autoimmune diseases [7,28–31].

1.1.1.2. Adipose derived MSCs. Adipose-derived MSCs (ASCs) are extracted from subcutaneous fat, which is more accessible than bone marrow, even in patients with chronic health disorders or advanced age [32,33]. The liposuction or surgical resection of adipose tissue is processed, and ASCs are isolated from the stromal vascular fraction. This less-invasive harvest typically provides a more significant number of cells than the harvest of BMSCs [34–36]. Additionally, ASCs have a higher proliferative capacity, reducing the time and need for *in vitro* expansion. Like BMSCs, they express CD73, CD90, and CD105 but may exhibit a higher expression of CD36 and CD44 [32]. ASCs possess osteogenic and chondrogenic differentiation capacity, but they demonstrate a higher adipogenic potential than other sources, making them particularly suitable for studies related to adipose tissue engineering. ASCs also possess immunomodulatory properties, although they may exhibit differences in their immune response compared to BMSCs. ASCs, for instance, have been reported to secrete higher levels of anti-inflammatory and angiogenic factors than BMSCs [16,37]. Overall, ASCs have a similar therapeutic effect to BMSCs and have applications in tissue engineering, wound healing, osteoarthritis, cardiovascular disease, and cosmetic procedures.

1.1.1.3. Synovial derived MSCs. Synovial-derived MSCs (s-MSCs) are collected from the synovial fluid of hip or knee joints, the synovial tissue, or they can be incidentally harvested from popliteal cyst medical waste [38–40]. In most cases, this is typically considered a minimally invasive procedure and is done with arthrocentesis, which involves aspirating synovial fluid from the joint space with a needle [41]. The quantity of MSCs in synovial fluid is generally lower than in bone marrow or adipose tissue. However, s-MSCs have been reported to be able to be expanded *in vitro* for prolonged periods with limited cell senescence. Regardless of donor age or serial passage, they can also be consistently induced into multilineage differentiation pathways [24,42,43]. This may be due to a lack of telomerase activity [24,43]. Their surface marker expression profile is less well-defined compared to BMSCs or ASCs. They commonly express CD73, CD90, and CD105, but the presence of other markers may vary [38,44,45]. Compared to BMSCs, s-MSCs have been shown to have increased chondrogenic and osteogenic potential; however, their adipogenic potential appears to be lower [38,44,46]. They may exhibit a unique secretome, potentially influencing the immunomodulatory and regenerative properties specific to the joint microenvironment [47]. The immunomodulatory characteristics of s-MSCs have been less extensively studied than those of BMSCs or ASCs. Their clinical applications are still being explored, particularly in joint-related disorders, autoimmune diseases affecting the joints, and cartilage regeneration [48].

1.1.1.4. Dermal derived MSCs. Another source of MSCs is the dermis (d-MSCs), usually from a skin biopsy or discarded foreskin [49–51]. The quantity of MSCs in dermal tissue is generally lower than in adipose tissue, and they typically have a lower proliferative capacity [17,52]. Expression markers of d-MSCs include CD90, CD73, CD29, and CD26 but vary depending on the isolation and culture methods used [53]. Like other sources of MSCs, d-MSCs have been reported to promote anti-inflammatory effects, possess wound-healing properties, and can differentiate into both neural and mesodermal cells [54]. They particularly have a high propensity to differentiate into cells related to the skin, such as fibroblasts. Consequently, d-MSCs have been studied for their role in promoting wound healing, skin regeneration, and treating disorders such as ulcers and cutaneous fibrosis [51,55].

1.1.2. Therapeutic efficacy

MSCs were initially of clinical interest because of their ability to self-renew and replace damaged or diseased tissue by differentiating into multiple lineages, such as osteocytes, chondrocytes, and adipocytes [6,22,23]. The paradigm has shifted, and MSCs are now considered helpful in clinical applications because of their non-immunogenic and immune-modulatory properties and their secretome, which can activate and support endogenous cells [10,39–43]. Because of these therapeutic attributes, MSCs have been studied in over 950 clinical trials worldwide and have exhibited excellent safety in patients [7,56,57].

Despite the therapeutic potential MSCs have for many diseases

and injuries, clinical trial outcomes have been inconsistent or subdued compared to results *in vitro* or with preclinical animal models [58–63]. Although many factors may contribute to these suboptimal outcomes, increased attention has been given to the quality of MSC donors. For example, MSCs harvested from people with autoimmune disease (AD) can expand *in vitro*, can differentiate, and have been shown to have the expected cell surface phenotype [64–67]. However, there are discrepancies in the literature on if they can proliferate and differentiate at the same magnitude as MSCs from healthy persons [14,15,68]. Additionally, MSCs from AD patients have been shown to be less therapeutic, causing some groups to pre-treat autologous cells from AD patients to increase their therapeutic efficacy [69].

The local niche in AD may influence MSCs, resulting in intrinsic differences related to donor selection [56]. Furthermore, the disease duration and severity variation between patients of the same AD may give rise to the broad quality disparity with donor-to-donor variation. This could cause a problem when using autologous cells for stem-cell treatments that have been exposed to disease microenvironments found in the MSC niche of AD patients [70]. Although clinical trials show an increasing use of allogeneic MSCs, most of those trials are investigating the safety of autologous vs allogeneic MSCs [15]. There is still a need to examine the efficacy of autologous vs. allogeneic MSC treatment in AD. Though preclinical studies show that both autologous and allogeneic sources can produce large numbers of MSCs, studies evaluating the molecular and phenotypic differences between MSCs from AD patients and healthy persons are conflicting and remain a gap of knowledge in the field [7,70]. Understanding the effects of AD on MSC quality could give valuable insight into result disparities and donor selection in stem cell treatment.

1.2. Autoimmune disease

An AD is typically a chronic illness that can be systemic or organ specific. Difficult to treat, approximately 8–10 % of the global population suffers from one of over 80 identified autoimmune diseases [14,71,72]. The severity and the pathophysiological manifestations of these disorders depend on the immune system and the type of immune response (innate, humoral, or cellular) involved. Having phenotypic variability, AD presents with variable symptoms and severity from patient to patient [73–75]. Current treatment options for AD are limited, with some patients not responding well to existing treatments. MSCs are being investigated as a treatment option for multiple ADs, including multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc) [14,63,68,76].

1.2.1. Multiple sclerosis

MS is a chronic, neuroinflammatory, autoimmune disease affecting approximately 2.3 million people worldwide [65,66]. Most cases present between the ages of 20 and 40, with women being affected 2.5 times more often than men [77,78]. Symptoms include limb paralysis, partial or complete loss of central vision, fatigue, dizziness, and depression [78,79]. MS is categorized into different phenotypes including primary progressives (PPMS), relapsing-remitting (RRMS), and secondary progressive (SPMS) [28,80]. The progressive phase is characterized by continuous and irreversible neurodegeneration and axon damage [81]. PPMS is characterized by worsening neurological function without early relapses or remissions. RRMS is the most common type of MS. It involves paroxysmal relapses with worsened symptoms, followed by a plateau of symptoms that is worse than before the relapse. Each relapse can potentially be more intense than previous relapses [77]. SPMS is a stage that comes after relapsing-remitting MS for many people. This type of MS gets steadily worse with little to no relapses.

The primary target of immune cells in MS are the myelin sheaths in the white matter of the central nervous system. Auto-reactive myelin-specific $CD4^+$ T helper (Th) cells, stimulated by either self-reactive or cross-reactive antigens and macrophages, infiltrate the central nervous system and propagate an autoimmune response against oligodendrocytes, which form the myelin sheath [82,83]. This results in the formation of CNS plaques composed of inflammatory cells and their products, demyelination, and transected axons, resulting in axonal loss, astrogliosis in both white and grey matter, and eventual damage of CNS signals [78,82–84].

MSCs have been shown to improve preclinical outcomes of murine models of MS with reduced inflammatory cell infiltration and reduced demyelination in the spinal cord [85,86]. Clinical trials in treating MS with MSCs have included MSCs from different sources, autologous and allogenic transplants, cell products and direct cell treatment, different injection routes, differing number of treatments, and multiple phenotypes of MS. The results of these trials vary, but overall, they have shown safety and some efficacy in phase I and II trials [87–95].

1.2.2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a widespread chronic autoimmune disease that affects joints and other connective tissue [96]. It is the most common inflammatory arthritis and is a consequential cause of morbidity and mortality in the U.S [14]. The pathologies of RA are diverse, with patients suffering from inflammation, joint stiffness, swelling, pain, loss of mobility, and co-morbidities with vascular, metabolic, and skeletal systems [73].

The primary target of autoimmunity in RA is the synovium membrane. The onset of RA is related to unbalanced immune homeostasis, most considerably between Th17 and Tregs cells [14]. This leads to the activation of autoreactive immune cells, which attack collagen-rich joint regions. With dysfunction in adaptive and innate immune responses, autoantibodies, most notably rheumatoid factors, are produced [97]. Additionally, the cytokine network becomes dysregulated, resulting in inflammation, which progressively destroys the synovial tissue of joints, cartilage, and bone and, less frequently, of extra-articular sites [97–102].

In animal models of RA, MSCs have been shown to ameliorate the severity of symptoms, including bone loss [102]. Clinical trials of MSCs for RA have mainly focused on the safety of MSC transplantation, with most Phase I/II trials showing no serious side effects or adverse effects with moderate intensity [103–105]. MSC treatment was shown to reduce the number of Th17 cells, increase the number of regulatory T cells, and decrease inflammatory cytokines in serum [104,106,107]. Disease activity was reduced in most clinical trials, but results were transient [103,104,106]. Though preclinical studies showed that allogeneic MSCs were more beneficial than autologous MSCs, autologous MSC treatment did reduce disease activity in a clinical trial reported by Ghoryani et al. [28,102,106,108].

1.2.3. Systemic sclerosis

Systemic Sclerosis (SSc), also known as scleroderma, is a complex and heterogeneous autoimmune disease characterized by progressive organ fibrosis, especially in the skin. The pathology of SSc is complex and involves the interplay of immune system dysfunction, vascular abnormalities, inflammation, fibrosis, and damage to various organ systems. SSc is associated with significant morbidity and mortality, primarily due to complications related to internal organ involvement, such as lung disease and cardiac issues [109]. Mortality rates vary depending on disease severity and organ involvement. There are two main types of SSc with various clinical

subtypes [110,111]. Limited Cutaneous SSc (lcSSc) primarily affects the skin of the face, hands, and feet. It often presents with distinct features such as Raynaud's phenomenon (cold-induced color changes in the fingers and toes), skin thickening, and the presence of specific autoantibodies like anticentromere antibodies. Diffuse Cutaneous SSc (dcSSc) has more widespread skin involvement, including the trunk and limbs. It is associated with a higher risk of internal organ involvement and may progress more rapidly.

While the precise origins of SSc remain unclear, it is widely believed that a combination of genetic markers and environmental factors are linked to a heightened susceptibility in the development of the condition [109,111]. SSc can impact people of all age groups, although it is typically identified more frequently in individuals aged 30 to 60 [111,112]. It predominantly affects women and is more common in specific populations, including individuals of African American and Native American descent [110,113–115]. SSc is associated with various co-morbidities, including pulmonary hypertension, interstitial lung disease, and gastrointestinal disease [114,116]. The prevalence of these co-morbidities can also vary among SSc patients.

The primary target of the immune system in SSc is the connective tissues in the skin and internal organs, especially the lungs, heart, kidneys, and gastrointestinal tract. SSc often begins with abnormalities in the small blood vessels, causing ischemia in distal tissues [114,115]. Dysfunctional endothelial cells in the microvasculature then contribute to the release of pro-inflammatory and pro-fibrotic factors. Fibroblasts are a principal etiologic agent in SSc and produce excessive collagen and other extracellular matrix proteins, resulting in fibrosis, which is the thickening and hardening of connective tissue. Keratinocytes and myofibroblasts are also affected in SSc and may produce pro-inflammatory and pro-fibrotic cytokines. The prominent factor contributing to the pathogenesis of SSc is an aberrant immune response [117]. Monocytes, macrophages, dendritic cells, mast cells, and T-cells accumulate in the skin [118]. B-cells become activated and produce autoantibodies, including antinuclear antibodies (ANA), anticentromere antibodies, and anti-Scl-70 antibodies. T cells and macrophages also exhibit an activated phenotype, indicating their critical role.

MSCs from different sources have been investigated in several animal models of SSc and showed that MSC treatment can reduce inflammation, skin fibrosis, and lung fibrosis [109]. For mechanisms, MSCs were shown to impede the infiltration of macrophages and neutrophils, but results on T-cell infiltration were conflicting [118]. In the clinic, autologous MSCs have been shown to be safe but have had conflicting results on improving symptoms and slowing down disease progression [109]. Allogenic MSC treatment resulted in regression of skin fibrosis, reduced skin ulcers, increased circulation in the extremities, and improved lung function [109].

1.2.4. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE), commonly referred to as lupus, is a chronic autoimmune disease that affects almost every organ system. The specific tissues and organs targeted in SLE vary from person to person but typically include skin, joints, kidneys, the cardiovascular system, and the central nervous system [119]. Because of this considerable variation in affected tissues, the pathology of SLE is complex and varies between patients, even at different times in the same patient [120,121]. The wide range of symptoms includes fatigue, joint pain and swelling, skin rashes, fever, Raynaud's phenomenon, hair loss, chest pain, kidney dysfunction, photosensitivity, neurological symptoms (headaches, seizures, and cognitive difficulties), and gastrointestinal symptoms (abdominal pain, nausea, vomiting, and diarrhea). It is also associated with various co-morbidities, including kidney disease (lupus nephritis), cardiovascular disease, and an increased risk of infections [122,123]. SLE is more common in specific populations, including individuals of African, Asian, Hispanic, and Native American descent [124,125]. SLE disproportionally affects women and is more frequently diagnosed in women of childbearing age, particularly those between 15 and 45 years old [126,127]. However, it can also occur in children, older adults, and males.

The exact cause of SLE is not fully understood, with the prevalence and incidence influenced by genetic, environmental, and socioeconomic factors. Like all autoimmune diseases, the immune system plays a central role in the pathogenesis of SLE, and multiple types of immune cells are implicated in the disease process. B cells produce autoantibodies that target a wide range of self-antigens, including antinuclear antibodies (ANA), anti-dsDNA antibodies, anti-smith antibodies, anti-phospholipid antibodies, or anti-ribosomal P antibodies [128–130]. Tregs are impaired, the differentiation of $CD4^+$ T cells is dysregulated, and there is an imbalance between Th1/Th2 and Th17/Tregs subsets with a skewing towards Th1 and Th17 [73,131]. Dendritic cells, macrophages, neutrophils, NK cells, and plasma cells are additional immune cells implicated in developing SLE.

Several SLE preclinical studies have studied the beneficial effects of MSC treatment [73,132,133]. MSCs were shown to release anti-inflammatory factors that dampen the immune response, potentially reducing tissue inflammation. MSCs were also shown to suppress the activity of immune cells, including autoreactive T cells and B cells that play a role in SLE pathogenesis [134]. Furthermore, MSCs helped to reduce the production of autoantibodies [123]. Additionally, some studies showed that MSCs offered protection against common co-morbidities, including atherosclerosis and lupus nephritis, a common complication involving kidney inflammation [122,132]. A limited number of clinical trials have investigated using MSCs in SLE treatment. These trials have primarily focused on refractory or severe cases of SLE that do not respond well to conventional therapies [123,135]. Results have shown that MSC therapy for SLE is generally considered safe, with no significant safety concerns reported [136,137]. Outcomes, however, have been mixed. While some trials have reported positive outcomes, including decreased disease activity and improved clinical symptoms, others have reported more modest advantages [138,139]. The outcome variation may be due to differences in patient populations, treatment protocols, and the source of MSCs.

1.3. Present study

Many studies have shown no difference between MSCs from AD patients and healthy donors [65,67,140,141]. However, we hypothesize that MSCs derived from AD patients are not as therapeutic as MSCs from normal, healthy individuals, partially giving rise to the discrepancies in clinical trials. Over 34 % of clinical trials using MSCs target autoimmune diseases, making it essential to determine if autologous MSCs exposed to disease microenvironments from AD patients are less therapeutic [22]. To test our hypothesis, we did a Systematic Review and Meta-Analysis of the current literature involving MSCs in AD. We included MSCs from any tissue and focused on four chronic ADs with dysregulation of innate and adaptive immune responses: MS, SLE, RA, and SSc.

2. Materials and methods

2.1. Search strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Registration # CRD42022345083) guidelines [142]. It is based on the approach developed by Arksey and O'Malley that includes five essential

steps: 1) identification of the research question; 2) identification of appropriate studies; 3) selection of studies; 4) tracking of data; and 5) collection, summarization, and reporting of results [143]. This systematic literature search was performed by three independent investigators using Scopus and PubMed from inception until submission. The following search terms were utilized in each database: ("mesenchymal stem cell" OR "mesenchymal stromal cell" OR "MSCs" OR "ASCs") AND ("Scleroderma" OR "Multiple sclerosis" OR "Systemic sclerosis" OR "Rheumatoid arthritis" OR "SLE"). Weekly updates were provided from Google Scholar, PubMed, and Scopus for any newly published studies that matched the search terms. We also manually reviewed the references cited within the included articles.

2.2. Eligible criteria

Eligibility criteria were determined prior to beginning the searches and applied to studies during abstract and title screening and during the full-text assessment. Studies were included if: 1) there was a comparison between MSCs that were isolated from healthy individuals and MSCs isolated from individuals with one of the four AD listed in the search terms; 2) studies were published and accessible in English; 3) studies included MSCs from any tissue source; and 4) studies were peer-reviewed. Studies were excluded if: 1) MSCs were derived from non-human species; 2) MSCs were treated with any pharmaceutical agent or biomaterial; or 3) the article was a review, conference proceeding, or retracted study.

2.3. Study selection

Three independent investigators recorded the number of results produced by each search term. Duplicates between the results of each search were removed. Results between the databases (Scopus and PubMed) were then combined, and duplicates between the databases were also removed. Investigators independently screened titles and abstracts for eligible studies utilizing the predetermined inclusion and exclusion criteria. Eligible studies were then forwarded to a fourth investigator who removed duplicates between investigators. Eligible studies were subjected to a full-text assessment utilizing the same exclusion criteria used during the titles and abstract screening. Two investigators completed a full-text assessment, and any discrepancies were discussed.

2.4. Quality assessment

We developed the *In Vitro* Assessment Tool (IVAT) method to determine each study's quality and Risk of Bias (Supp Table 1). Parameters of IVAT include 1) selection bias, 2) performance bias, 3) detection bias, and 4) reporting bias. Questions were applied to each study, and responses were recorded in a standardized spreadsheet (Supp Table 2). Once all studies were assessed, points were totaled, and studies were assigned a Risk of Bias category based on their score falling into a predetermined range. Scores of 21–30 demonstrated a low risk of bias, scores of 11–20 showed a moderate risk of bias, and scores of 0–10 were classified as a high risk of bias.

2.5. Data extraction

Two investigators extracted relevant data using a standardized collection form, which consisted of (1) donor demographics (number of patients/controls, age, BMI, disease duration, race, and gender); (2) cell demographics (cell source, isolation location, and passage); (3) proliferation (type of proliferation assay, duration of experiment, and results); (4) differentiation (type of differentiation assay, duration of experiment, and results); (5) surface antigens (positive markers, negative markers, and thresholds); (6) cell morphology and plastic adherence; and (7) other assays evaluated in the study (Supp Table 3). Once data was extracted from all included studies, a third investigator combined both Excel files and compared data. Any discrepancies were discussed. For missing or unclear data, an attempt was made to contact the authors for clarification.

2.6. Primary outcomes

The group identified the research question and determined the research strategy at the initial meeting. The research question was: "Are there differences between HC-MSCs and AD-MSCs, and, if so, are those differences similar between ADs?". The primary study outcomes included differentiation, proliferation, morphology, differential expression of biomarkers, and variation in phenotype.

2.7. Differentiation analysis

ImageJ/Fiji was used to quantify differentiation images obtained as JPGs from included studies [144]. The percent area that showed differentiation was calculated for each image and recorded in an Excel spreadsheet with other relevant data, including the magnification of images, the stain used, the cell source, and the assay duration. The index was calculated by setting the HC-MSC image for each study to "1" and dividing that by the results from the AD-MSC image. The indexes for each image were then averaged and graphed based on differentiation lineage, cell source, and disease.

2.8. Statistics analysis

All statistical analyses were performed using Minitab® Statistical Software (State College, Pennsylvania). The data were reported as the mean ± standard deviation. The statistical differences among two or more groups were determined by ANOVA, followed by Tukey's *post hoc* test. The statistical significance was set at $P < 0.05$.

3. Results

3.1. Study selection

The primary literature searches produced 26,939 potential studies (Fig. 1). With these studies, 7033 studied MS, 8445 reviewed SLE, 7286 studied RA, and 4175 studied SSc. Duplicates between search terms and search engines were removed, resulting in 14,097 studies subjected to abstract and title screening. There were 13,428 studies excluded due to the screening, resulting in 669 studies sent to the primary investigator. Duplicates between independent investigators were removed, resulting in 228 studies again screened against inclusion/exclusion criteria. This resulted in 168 studies being excluded (98 did not compare HC-ASCs to AD-MSCS, seven were treated with a pharmaceutical or biomaterial, 52 were review articles, conference proceedings, or retracted, and 11 were not in English), and 60 studies that met the inclusion criteria for further qualitative analysis.

3.2. Study quality

The IVAT was used to determine the quality of studies and any Risk of Bias (Supp Table 2). Most studies produced a moderate to high-quality score, with 52 studies classified as high quality (scores 21–30) and eight studies classified as moderate (scores 11–20; Fig. 2A). All bias categories had low percentages of poor-quality studies (Fig. 2B). Selection, detection, and reporting biases all had

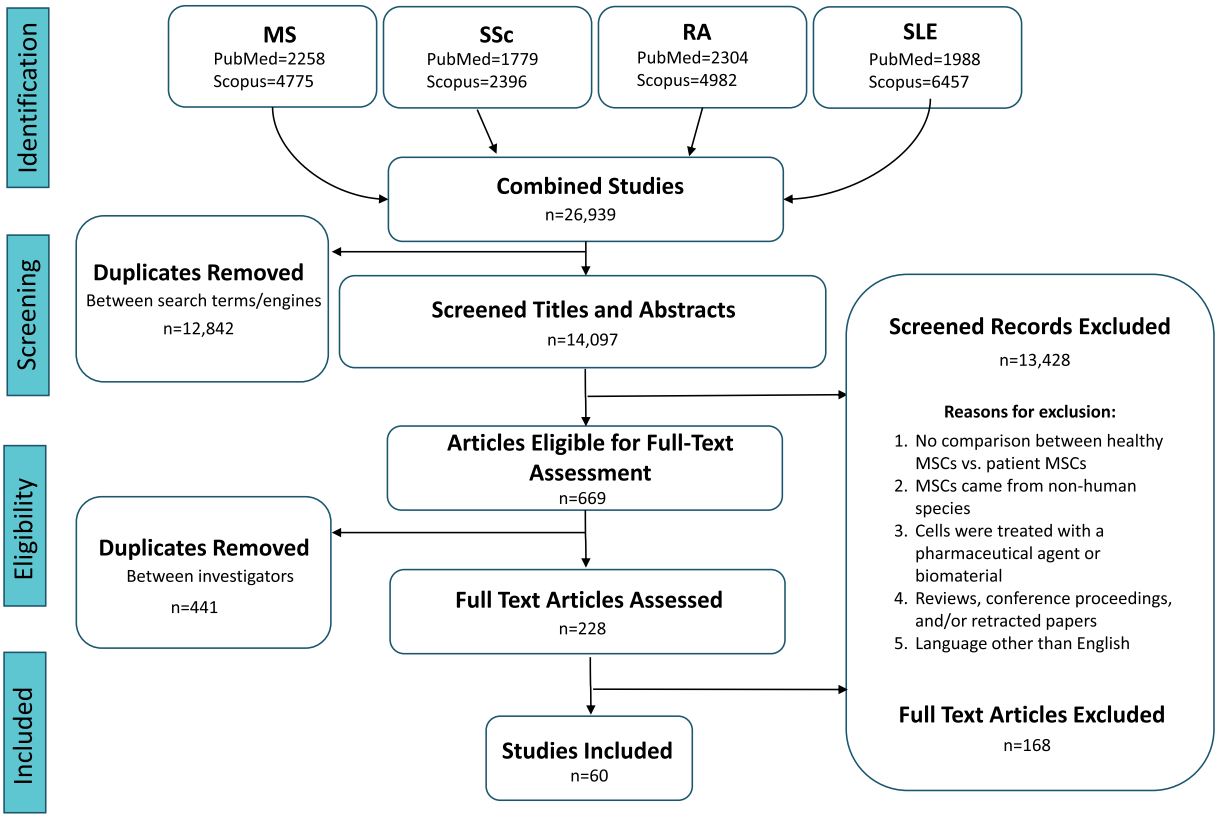

Fig. 1. Study Selection Flow Chart: Schematic of study search and selection protocol. A total of 60 studies met inclusion criteria.

high percentages of good quality (87.6 %, 98.9 %, 100 %, respectively). Performance bias had a slightly lower percentage of good quality and a higher percentage of unknowns (78.0 % and 20.9 %, respectively). This lower score was mainly due to not recording if experiments were performed in triplicate, which 49.2 % of studies did not report. However, in many of these cases, researchers conducted a microarray or other assay commonly performed with a single replicate due to cost and time. Half of the individual questions on the IVAT demonstrated some levels of poor quality (Fig. 2C), but these percentages of poor quality were relatively low. Because all studies received a score in the moderate (IVAT score 11–20) to low (IVAT score 21–30) risk of bias, no studies were removed following the quality assessment.

3.3. Study demographics

About 1/3 of the included studies analyzed MSCs from SSc patients; another 1/3 came from SLE patients; the rest were divided between RA and MS patients (Fig. 3A). Four studies examined MSCs from both SLE and SSc patients concurrently. All studies were published between 2000 and 2022, with most published in 2013 or later (Fig. 3B). The age and gender of patients were commonly reported throughout studies (93 % and 88 %, respectively), but only a small percentage of studies (<7 %) reported the BMI or race of their patients (Fig. 3C).

Over 71 % of patient samples were acquired from female patients (Fig. 3D), while less than 50 % of control cells were reported from females. Many studies did not report the gender of controls or listed them as “sex matched.” To keep our study rigorous, we included “sex-matched” with “did not report,” as there may have been some variation in matching and not precisely the same ratio of males to females. SLE studies isolated their samples predominantly from female patients, except for one study (Supp Table 3) [134]. The other three diseases were isolated from both males and females.

Of the few studies that did report BMI, they each studied ASCs. The average BMI of the samples was 24.8, and the controls were 25.9. Of those who reported race, 22 samples were isolated from Caucasians, four from African American/West Indies Black, and one who identified as Middle Eastern. One study reported controls as race matched to Caucasians, but no other study reported the race of controls [135].

3.4. Sample characteristics

Across all included studies, 845 patient samples were analyzed and compared to 571 control samples. Samples were mostly (98 %) obtained internally (Fig. 4A), with 2 % obtained as gifts from other labs. Controls were also primarily obtained internally (82 %) but also came from vendors (11 %), with Lonza being the most common. Approximately 5 % of studies did not report where controls came from, and like patient samples, 2 % were received as gifts from other labs.

Most patient samples and control cells were derived from bone marrow (68 % and 71 %, respectively; Fig. 4B). BMSCs were most commonly isolated from the iliac crest, followed by not reporting the location, then the femur, then the sternum, and then trabecular bone chips (Fig. 4E). Adipose tissue was the next most common source of MSCs, representing 23 % of the patient samples and 16 % of the control cells. ASCs were predominantly isolated from the abdomen, with four coming from the medial knee, and the rest were not reported. Synovial MSCs accounted for 8 % of samples and 10 % of control cells. About an equal number of cells came from the suprapatellar pouch as from an unreported location. The knee accounted for ~17 % of s-MSCs samples. Only one study evaluated d-

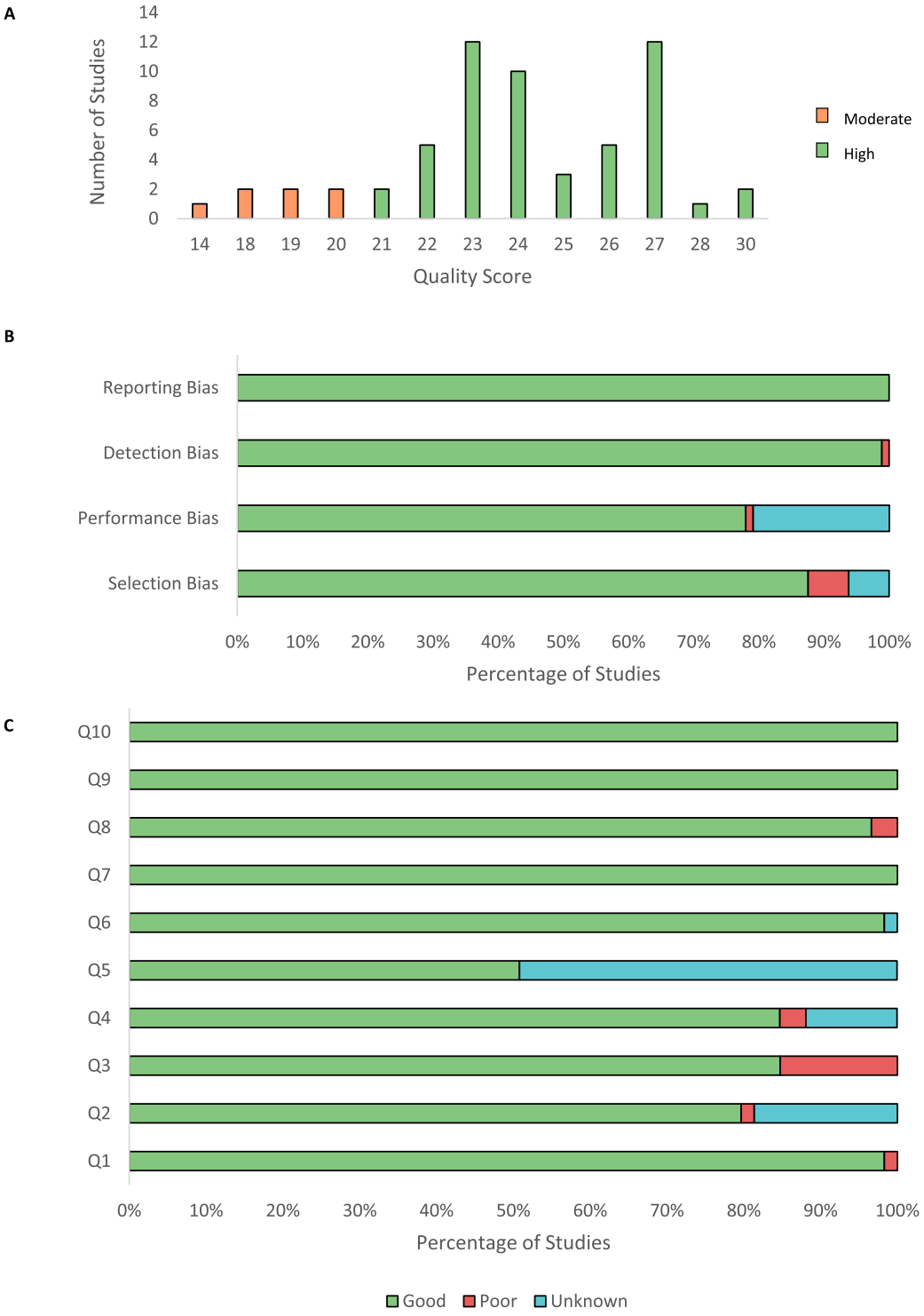

Fig. 2. Study Quality. Quality scores from IVAT including overall study (A), per bias category (B), and per question (C).

MSCs, with all the samples and controls isolated from the forearm.

Studies investigating MS solely evaluated BMSCs (Fig. 4C), RA and SLE evaluated two sources of MSCs, and SSc evaluated three. BMSCs were the only MSC source to be evaluated in all four diseases, ASCs were assessed in two diseases, d-MSCs were evaluated only in SSc, and s-MSCs were assessed only in RA (Fig. 4D).

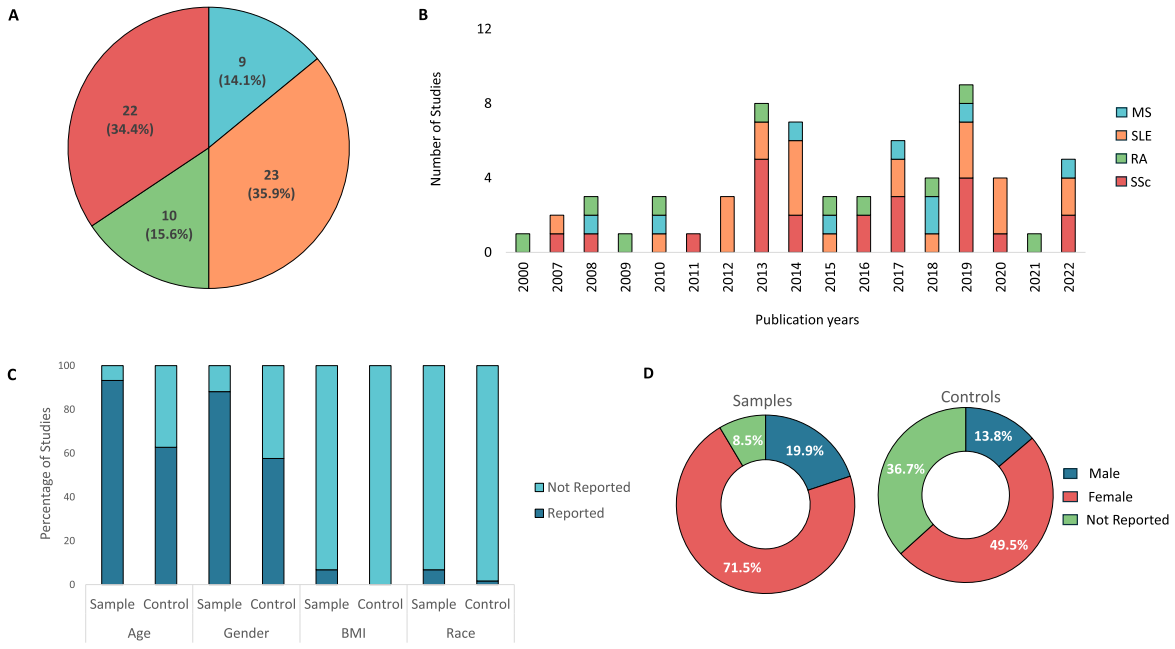

Fig. 3. Characteristics of Cell Donors. The number of studies for each disease with percentage of studies in parenthesize (A) and for each year (B). The percentage of studies that reported demographics of cell donors (C) and the gender of donors (D).

3.5. Reporting of ISCT criteria

As our study aims to compare AD-MSCs to HC-MSCs, it is essential to verify the identity of all samples as MSCs. The ISCT states that for an MSC to be considered an MSC, it must meet five criteria: adhere to plastic, have a fibroblast-like appearance, self-replicate, have appropriate surface antigens, and differentiate into bone, fat, and cartilage [5]. Therefore, the first step in our analysis was to verify each study against the ISCT criteria.

Only 6.7 % of studies reported all five ISCT criteria (Fig. 5A), while 23 % of studies did not report against any criteria. In some cases, the study referenced an earlier study from the same group. However, when following cited papers, we could only sometimes find the five ISCT criteria analyzed or be assured they were the same donors per study. Therefore, we recorded them as not reporting ISCT criteria, even though they could have evaluated their donors in an earlier study.

Of the ISCT criteria, surface antigens were the most reported, while plastic adherence was the least (71 % and 7 %, respectively; Fig. 5B). However, adhesion to plastic was inherent among assays in each study, so this ISCT criterion was met by default even though it was not reported. The ISCT criteria of tri-lineage differentiation into bone, fat, and cartilage was reported in 18 % of studies (Fig. 5B). An additional 23 % of studies evaluated differentiation into at least two lineages, most commonly adipocytes and osteocytes.

ISCT guidance says MSCs must be positive for CD105, CD73, and CD90 and negative for CD45, CD34, CD14/CD11b, CD79α/CD19, and HLA-DR [5]. While only 8 % of our included studies reported on each of these surface antigens, an additional 63 % of studies reported some of those antigens (Fig. 5B–D). Approximately 62 % of studies reported at least five or more of the ISCT recommended surface antigens (Fig. 5D). The most common surface antigens reported was CD45, but over half of the studies reported CD90, CD105, and CD34 (Fig. 5C). The least reported surface antigen was CD19/CD79α (15 % of studies), which are biomarkers for B-cell differentiation. They are expressed from the earliest stages of B cell development until plasma cell terminal differentiation when expression is lost [145,146]. The ISCT also sets criteria for negative and positive cut-offs of surface antigens, with positive being ≥95 % and negative ≤2 %. However, in our evaluated studies, cutoffs varied markedly between studies. Negative cutoffs ranged from <0.1 % to <9 % and positive cutoffs ranged from >10 % to >95 %, with many studies not mentioning their cutoff values.

Some of the variation in surface antigen reporting may be due to the source of MSCs. For example, the International Federation of Adipose Therapeutics and Sciences (IFATS) issued a joint statement with ISCT for guidelines on defining an ASC [36]. In addition to being positive for CD73, CD90, and CD105, they must also show positivity for CD13, CD29, and CD44. Negative markers include CD31, CD45, and CD235a. Many of these markers were reported in the included studies, potentially instead of the ISCT criteria.

3.6. Cell morphology

Cell morphology was reported in 45 % of the studies. Within those reports, 74 % of studies said there were no differences in appearance between AD-MSCs and HC-MSCs (Fig. 5E), with both populations presenting a fibroblast-like morphology. The passage evaluated may have contributed to the discrepancies in results between studies. One study noted that P3 MS-MSCs looked as senescent as P8 HC-MSCs [147].

Of the studies that reported abnormal morphologies in AD-MSCs, the cells were larger, appeared flatter, had visible stress fibers, and had longer podia. Some studies further evaluated morphological differences by examining the cell structure and cytoskeleton [148–150]. AD- MSCs were shown to have disorganized cell structure with dilated and distorted ER, swollen mitochondria, condensation of chromatin, increased protein aggregates in the ER, apoptotic features, and irregular actin distribution, which was disorganized and condensed on the edge of the cytoplasm [148–150]. Unsurprisingly, abnormal morphology was associated with senescence, increased cell size, and cytoplasmic granularity

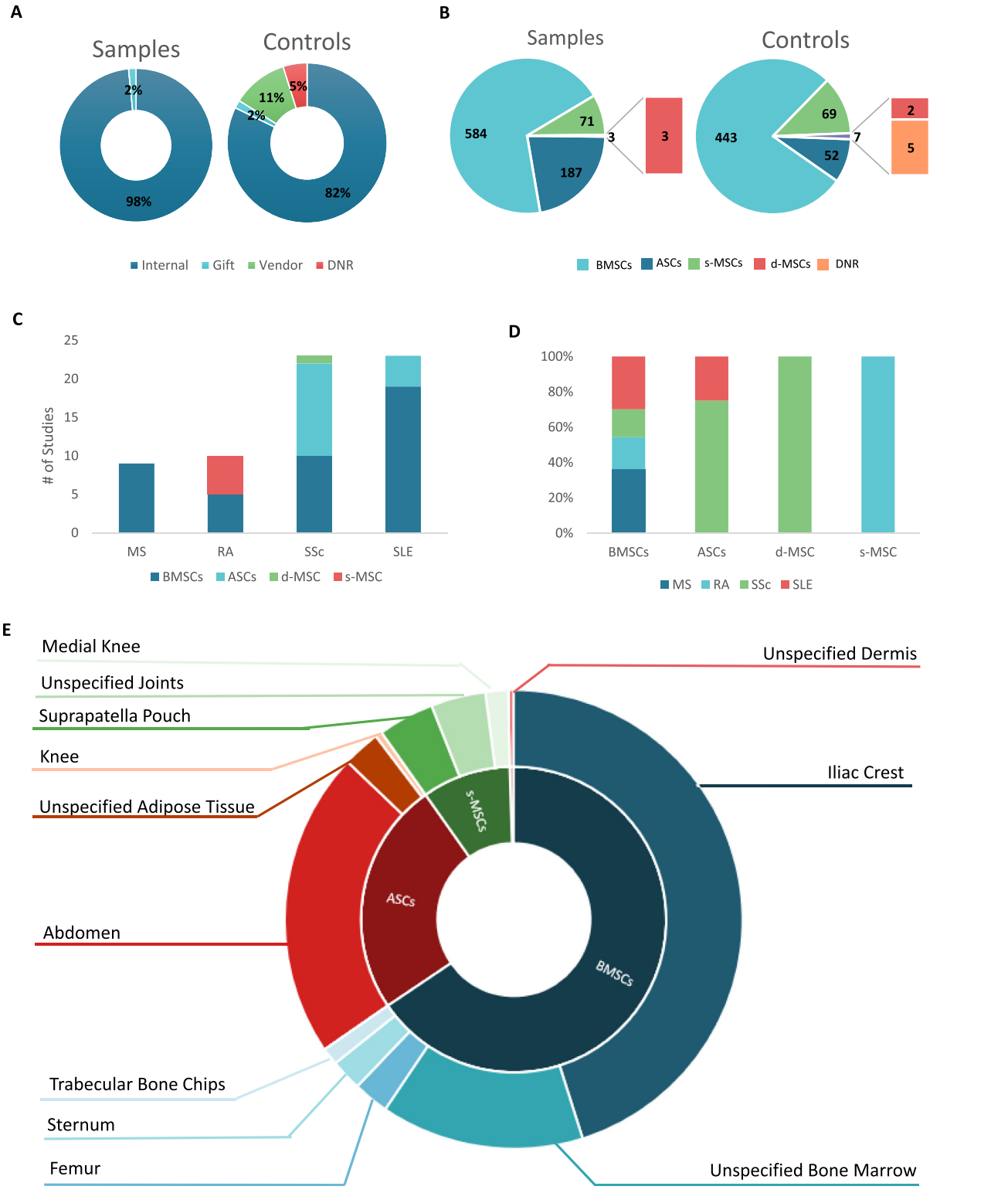

Fig. 4. Characteristics of Cells. The source (A) and tissue location (B) of cells. Tissue source of cells from each disease (C). Diseases per tissue source of MSCs (D). Specific tissue location of MSCs (E).

with increased passages of P5–P7 [151,152].

3.7. Proliferation

The 37 % of studies that reported proliferation utilized various methods and time courses (Fig. 6A and B). Most studies (54.3 %) measured cell growth, mainly evaluated by population doublings and trypan blue. Other assays included colony-forming units (CFUs) and enzymatic assays (MTT and CCK-8 kits). If reported, the most common duration of these experiments was 12–15 days, with 18+

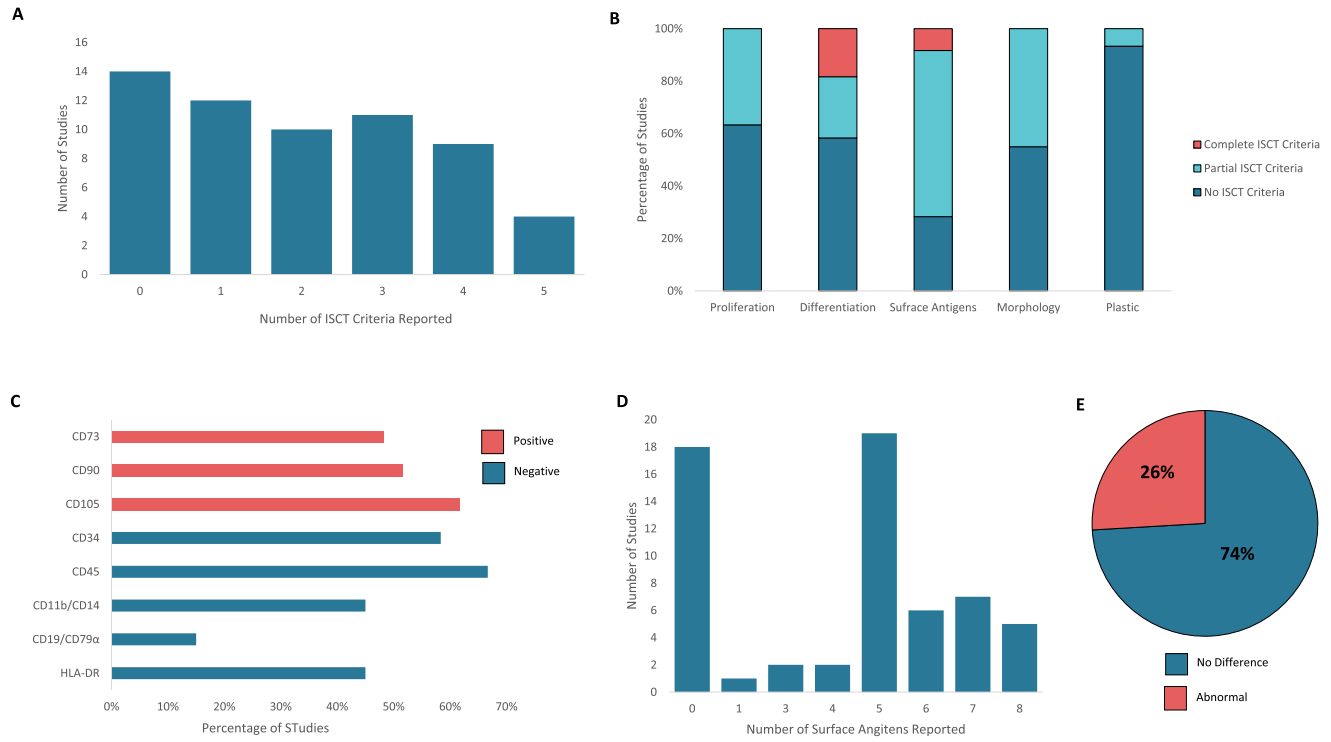

Fig. 5. Reporting of ISCT Criteria. The number of studies that reported ISCT recommended criteria (A), and the percentage of studies that reported each criteria (B) with red representing the full ISCT criteria was reported, light blue represents the ISCT criteria was reported in part, and dark blue shows that ISCT criteria was not reported. The percentage of studies that reported ISCT recommended surface antigens (C) with red = positive antigens and blue = negative antigens. The amount of ISCT recommended surface antigens reported in each study (D). Reported morphological features of cells (E).

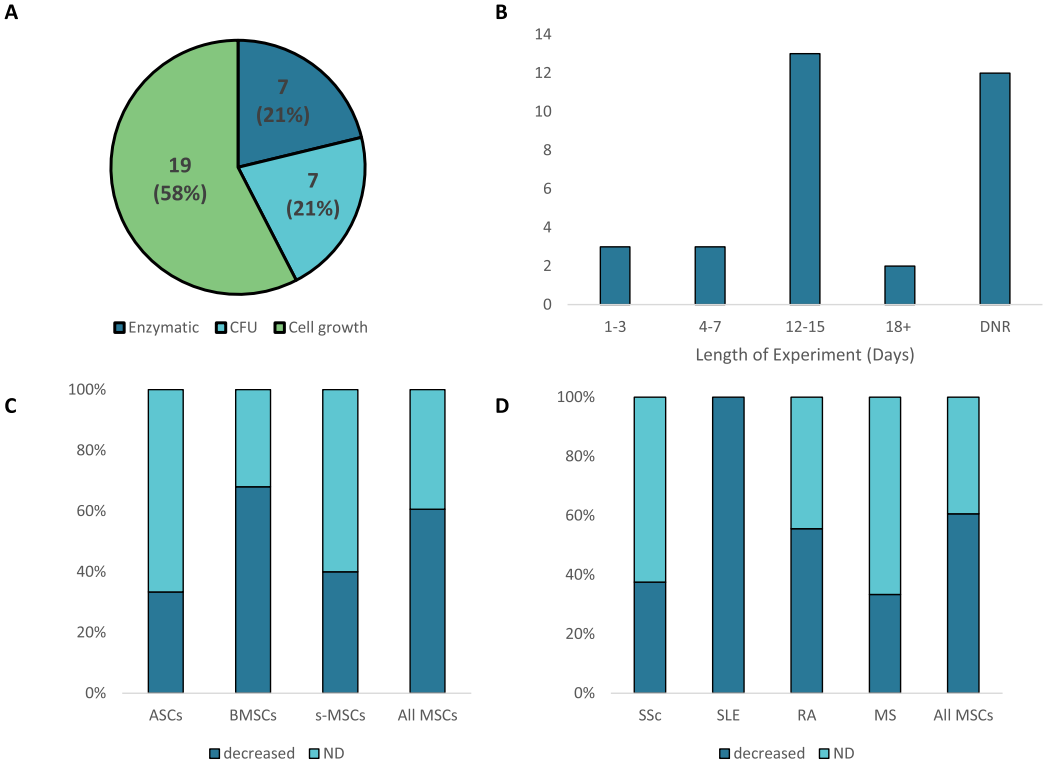

Fig. 6. Comparison of Proliferation Ability Between AD-MSCs and HC-MSCs. The type (A) and length (B) of proliferation assays used. Differentiation results by cell source (C) and by disease (D).

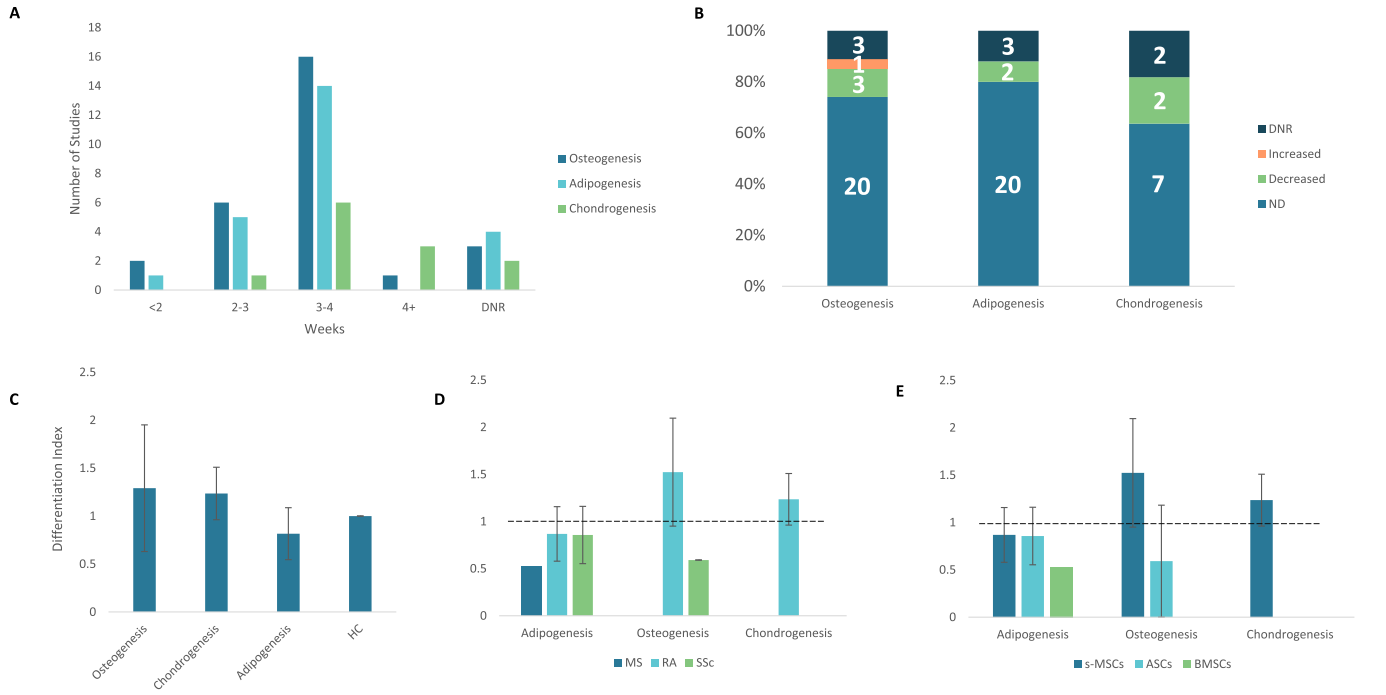

Fig. 7. Comparison of Differentiation Ability Between AD-MSCs and HC-MSCs. The length of differentiation assays (A). Differentiation results, with numbers representing the number of studies per result (B). Our analysis of differentiation using published figures and Fiji software (C). Our analysis stratified by disease type (D) and cell source (E). For C-E, the differentiation of HC-MSCs was set to "1"; values are mean ± SD.

days occurring the least (Fig. 6B).

Of those that did report proliferation, most studies (60.6 %) showed that AD-MSCs had a decreased proliferative ability, while the rest said there was no difference. The source of MSC had no significant effect on results, with all sources of MSCs reported in both categories (Fig. 6C). However, there were differences between types of AD (Fig. 6D). Interestingly, all SLE studies reported a decrease in proliferation rate, and RA reported a greater decrease than no difference. However, both MS and SSc reported more no difference than decreased. Even when accounting for the donor's age and the passage number of cell cultures using a Tukey post hoc test, there was an independent effect of the presence of an AD niche on the ability of MSCs to proliferate (not shown). Redondo et al. stated that the proliferation of AD-MSCs was influenced by the duration of progressive MS [152].

In addition to the proliferation assays, senescence was evaluated, typically with β-galactosidase staining. While Velier et al. reported no difference between AD-MSCs and HC-MSCs, ten other studies reported that AD-MSCs experienced an accelerated or increased senescence *in vitro* [151–162]. Furthermore, multiple studies from SLE demonstrated that AD-MSCs were restricted in the G1 phase of the cell cycle [158–161]. Some studies also evaluated apoptosis, with increased apoptosis in AD-MSCs cultures [67,149,157].

There were also discrepancies in other assays measuring cellular health and division. Though Nie et al. reported that AD-MSCs have telomerase activity, others showed that AD-MSCs had an inactive telomerase and shortened telomeres [67,151–153,156,163]. While Sun et al., 2007 showed that AD- MSCs had a normal karyotype, others showed that AD- MSCs had more DNA double-stranded breaks and a more significant percentage of DNA damage in the DNA tail compared to HC-MSCs [164–166]. Studies also found that AD-MSCs presented dysfunctional mitochondria and altered cellular bioenergetics [157,167].

3.8. Differentiation

Approximately 41 % of included studies compared differentiation abilities of AD-MSCs to HC-MSCs (Supp Table 3). Tri-lineage differentiation was evaluated in 18 % of studies, while the other 23 % evaluated one or two lineages, with osteogenesis being the most common. Similar to proliferation assays, there were variations in the assay type and the length of the assay. Regardless of the lineage being examined, the most used timeframe was 3–4 weeks (Fig. 7A). Twelve studies used multiple methods to evaluate differentiation along the same lineage (i.e., alkaline phosphatase and Alizarin Red; Supp Table 3).

Across the three lineages evaluated, most studies indicated no statistical difference between AD-MSCs and HC-MSCs (Fig. 7B). However, for many studies, the results were qualitative with no quantification. The authors reported "no difference" if AD-MSCs could differentiate in any capacity. Therefore, a result of "no difference" does not always indicate that AD-MSCs and HC-MSCs differentiated at the same magnitude.

For adipogenesis, 82.6 % of studies used Oil Red O, which all reported no difference. Interestingly, of the two studies that reported a decreased ability of AD-MSCs to differentiate into adipocytes, they both evaluated FABP4 expression. These two studies used different time points (10 and 21 days), evaluated different diseases (SSc and RA), and examined different sources of MSCs (s-MSCs and ASCs). Chondrogenesis had more variation in detection methods, with eight studies using alacian blue, two using toluidine blue, and two evaluating collagen II expression. Like adipogenesis, two outliers showed a reduced differentiation, while all others reported no difference. The outliers evaluated their samples at 21 days but used different detection methods and tissue sources for their MSCs. Osteogenesis also had variations in detection methods, with 16 studies using alizarin red, eight studies using alkaline phosphates, and 3 using Von Kassa. One study that evaluated

Table 1
Molecules differentially expressed in AD-MSCs. Twenty two differentially expressed molecules were evaluated in two more diseases. MS: multiple sclerosis; SSc: systemic sclerosis; RA: rheumatoid arthritis; SLE: systemic sclerosis; MSCs: mesenchymal stem cells; ASCs: adipose derived MSCs; BMSCs: bone marrow derived MSCs; s-MSCs: synovial derived MSCs, d-MSCs: dermal derived MSCs; ND: no difference.

Molecule	Function	Change of Expression	AD Type	MSC Source	Assay Used	Citation	Citation
IL6	regulates acute and chronic inflammation	↑	RA	s-MSCs	RT-PCR	212	Hou et al. 2016
		↑	RA	BMSCs	PCR	211	Feng et al. 2018
		↑	MS	BMSCs	microarray	140	De Oliveira et al. 2015
		↑	SSc	BMSCs	RT-PCR/ELISA	225	Cipriani et al. 2013
		↑	SLE	BMSCs	RT-PCR/WB	234	Geng et al. 2020
		↑	SLE	BMSCs	ELISA	158	Gao et al. 2017
		↓	SLE	BMSCs	RT-PCR	157	Sun et al. 2007
TGF -β	regulates cell proliferation and differentiation	↑	RA	BMSCs	microarray	55	Kastrinaki et al. 2008
		↑	SSc	BMSCs	RT-PCR	225; 231	Cipriani et al. 2013; Vanneaux et al. 2013
		↑	SSc	BMSCs	WB	223	Cipriana et al. 2014
		↑	SSc	BMSCs	RT-PCR / ELISA	225	Cipriani et al. 2013
		ND	SSc	ASCs	RT-PCR	148	Velier et al. 2019
		ND	SSc	BMSCs	RT-PCR	223	Cipriana et al. 2014
		↓	MS	BMSCs	microarray	140	De Oliveira et al. 2015
		↓	SLE	BMSCs	ELISA	158	Gao et al. 2017
		↓	SLE	BMSCs	ELISA	154	Gu et al. 2012
p21	regulates cell cycle progression at G1	↑	RA	BMSCs	WB	216	Sun et al. 2015
		↑	SSc	BMSCs	WB	225	Cipriani et al. 2013
		↑	SLE	BMSCs	RT-PCR	152	Gu et al. 2013
		↑	SLE	BMSCs	WB	153	Gu et al. 2014
VEGF	induces proliferation and migration of endothelial cells	↑	SSc	BMSCs	RT-PCR	223	Cipriana et al. 2014
		↑	SSc	BMSCs	RT-PCR/ELISA	227	Guiducci et al. 2011
		↑	SSc	BMSCs	ELISA	223	Cipriana et al. 2014
		↓	SSc	ASCs	RT-PCR	148	Velier et al. 2019
		↓	RA	BMSCs	RT-PCR	216	Sun et al. 2015
HGF	regulates cell growth, motility, and morphogenesis	↓	MS	BMSCs	microarray	140	De Oliveira et al. 2015
		ND	SSc	ASCs	RT-PCR	148	Velier et al. 2019
CCL2	invovled in immunoregulatory and inflammatory processes	↓	RA	BMSCs	RT-PCR	216	Sun et al. 2015
		↓	SLE	BMSCs	WB	232	Che et al. 2014
Bax	pro-apoptotic regualtors	↑	SLE	BMSCs	WB	142	Guo et al. 2015
		↓	RA	s-MSCs	PCR	149	Lee et al. 2021
BCL-2	anti-apoptotic	↓	RA	s-MSCs	PCR	149	Lee et al. 2021
		↓	SLE	BMSCs	RT-PCR	150, 142	Li et al. 2012; Guo et al. 2015
		↓	RA	BMSCs	WB	142	Guo e tal 2015
SDF-1 (CXCL12)	plays a role in inflammation response and metastasis	↑	RA	s-MSCs	RT-PCR	212	Hou et al. 2016
		↑	SSc	BMSCs	RT-PCR/ELISA	227	Guiducci et al. 2011
Cyclin D	regulate cell cycle	ND	SLE	BMSCs	RT-PCR/ELISA	141	Tang et al. 2012
		↓	RA	BMSCs	microarray	55	Kastrinaki et al. 2008
galectin-3	role in apoptosis, innate immunity, cell adhesion, and T-cell regulation	↓	SLE	ASCs	ELISA	219	Kuca-Warnawin et al. 2019
		↓	SSc	ASCs	ELISA	220	Kuca-Warnawin et al. 2020
GM-CSF	controls production, differentiation, and function of granulocytes and macrophages	↑	SSc	ASCs	RT-PCR	143	Virzi et al. 2017
		↑	SLE	BMSCs	ELISA	158	Gao et al. 2017
IL-1Ra	inflammation, particularly in acute phase	↑	SLE	ASCs	ELISA	219	Kuca-Warnawin et al. 2019
		↑	SSc	ASCs	ELISA	220	Kuca-Warnawin et al. 2020
Nanog	role in pluripotency	↑	SSc	d-MSCs	RT-PCR	137	Orciani et al. 2013
		↓	RA	s-MSCs	PCR	149	Lee et al. 2021
OCN	regulates bone remodeling and energy metabolism	↓	RA	s-MSCs	PCR	149	Lee et al. 2021
		↓	SLE	BMCs	RT-PCR/ WB	237	Tang et al. 2013
PDGF-R	role in development of cardio system and actin cytoskeletion	↑	SSc	BMCs	WB	223	Cipriana et al. 2014
		↑	SSc	BMCs	RT-PCR	225	Cipriani et al. 2013
		↑	RA	s-MSCs	RT-PCR	212	Hou et al. 2016
		ND	SSc	BMCs	RT-PCR	223	Cipriana et al. 2014
Sox2	role in pluripotency	↑	SSc	d-MSCs	RT-PCR	137	Orciani et al. 2013
		↓	RA	s-MSCs	PCR	149	Lee et al. 2021
TSG-6	invovled in ECM stability, cell migration, and inflammation	↑	SLE	ASCs	ELISA	219	Kuca-Warnawin et al. 2019
		↑	SSc	ASCs	ELISA	220	Kuca-Warnawin et al. 2020
Kynurenine	mitochondria function	↓	SLE	ASCs	ELISA	219	Kuca-Warnawin et al. 2019
		↓	SSc	ASCs	ELISA	220	Kuca-Warnawin et al. 2020
Oct3/4	invovled in ECM stability, cell migration, and inflammation	↑	SSc	d-MSCs	RT-PCR	137	Orciani et al. 2013
		↓	RA	s-MSCs	PCR	149	Lee et al. 2021
Smad 2/3	regulates cell proliferation, apoptosis, and differentiation	↑	RA	BMSCs	microarray	55	Kastrinaki et al. 2008
		ND	SSc	BMSCs	RT-PCR	231	Vanneaux et al. 2013
COL2	component of the extracellular matrix	↓	RA	s-MSC	PCR	149	Lee et al. 2021
		↓	SLE	BMSCs	RT-PCR/ WB	237	Tang et al. 2013
		↓	SSc	d-MSC	RT-PCR	137	Orciani et al. 2013

BMSCs in SLE reported a decreased osteogenic ability, while all other studies reported no differences, regardless of different methods, time courses, and cell sources.

Despite some differentiation images appearing different to us, our analysis of 13 published images also confirmed no significant differences (Fig. 7C). However, we did detect differences when stratifying based on cell source and disease type. MS and SSc had decreased differentiation, while RA had mixed results (Fig. 7D). Similarly, ASCs and BMSCs had reduced differentiation, while s-MSCs had mixed results (Fig. 7E). The mixed results of RA and s-MSCs may indicate that the cell source or disease state is associated with intrinsic differences in their MSCs, affecting their use in the clinic. The difference between our analysis and what was reported may be due to the limitation of only having one representative picture per study for us to analyze or investigators reporting on the ability to differentiate at any capacity and not comparing AD-MSCs quantitively to HC-MSCs.

3.9. Other phenomenon

Compared to healthy controls, AD-MSCs exhibited a decreased ability for migration and invasion as well as a decreased ability to form capillaries [155,165,168,169]. Regarding clinical efficacy, only one study made an *in vivo* comparison between AD-MSCs and HC-MSCs. This study, conducted using a murine model of RA, found that human AD-MSCs did not provide any therapeutic advantage, especially compared to human MSCs from healthy persons. In fact, symptoms worsened after human AD-MSC administration [156].

3.10. Biomolecules

AD-MSCs were found to have 308 differentially expressed molecules that consisted of genes, proteins, and miRNAs. Of those, 22 were evaluated in two or more diseases (Table 1). Two molecules were assessed in all four diseases, IL-6 and TGF- β. IL-6, a pro-inflammatory cytokine that plays a role in chronic inflammation and autoimmunity, was found to be upregulated in AD-MSCs in six studies while downregulated in one study. One of these studies evaluated s-MSCs, while all others examined BMSCs, and multiple detection methods were used. TGF-β, which regulates cell proliferation and differentiation, was also examined across all four diseases in ten studies. However, the results were mixed. One molecule, p21, which regulates cell cycle progression, was unanimously verified as upregulated in AD-MSCs in all four studies that examined it across three different diseases. All these cells were BMSCs, and their TGF- β levels were evaluated by RT-PCR or Western blot. Of the other 19 molecules found in at least two diseases, four were consistently reported as upregulated (TSG-6, IL-1Ra, SDF-1 (CXCL12), and GM-CSF), five were consistently reported as downregulated (BCL-2, Galectin-3, OCN, Kynurenine, and CoL2), and 10 had mixed results.

4. Discussion

Much of the scientific literature on MSCs is directed towards their potential for treating AD and inflammation. In clinical trials of AD, they have been demonstrated to be safe, but they have shown underwhelming therapeutic outcomes [170]. A Systematic Review and Meta-Analysis of MSCs in AD was necessary. Our study analyzed 845 patient samples from 60 studies, showing many disparities between results. In addition to the variables we recorded and analyzed, other techniques were highly variable or not reported among labs, including media used, initial and working cell-plating densities, and cell confluency at the time of assays. The variability in assays and reporting was a limitation in our analysis. Given the considerable variability, it is essential to compare AD-MSCs to HC-MSCs in parallel with different disease models and assays, to quantify both *in vivo* and *in vitro* results, and to submit raw data to repositories and databases, such as Gene Expression Omnibus (GEO) Database [171].

After being proposed two decades ago, the minimalistic ISCT criteria used to define an MSC are still being used [7]. Many groups have tried to modify that criteria by identifying an MSC biomarker, or a panel of biomarkers, that could be used to predict therapeutic efficacy in the clinic [7,61]. Some have suggested a need for phenotypical or functional studies, such as the Clinical Indication Prediction (CLIP) scale [172]. Our results identified a handful of biomolecules, and some functional assays that warrant further investigation.

IL-6 was found to be upregulated in MSCs across all four diseases evaluated. IL-6 has a diverse biological activity, contributing to homeostasis, embryonic development, bone metabolism, and acute-phase immune responses [173]. However, it is also critical to pathogenesis during periods of excessive production and uncontrolled IL-6 receptor signaling. Within MSCs, IL-6 has been observed to influence both proliferation and the immunosuppressive capacity of these cells [27]. Due to IL-6's involvement in numerous activities, it may pose challenges as a viable biomarker. However, just as the CLIP scale utilizes TWIST1 levels to gauge clinical effectiveness, correlating IL-6 levels to MSC pathogenesis could be a potential avenue for exploration.

Three diseases showed an upregulation of p21, while its expression in the fourth was not assessed. Also known as Cip1, p21 is upregulated by p53-dependent transcription and binds to and inhibits the kinase activity of the cyclin-dependent kinases Cdk2 and Cdk1, inducing cell cycle arrest and other biological responses. The upregulation of p21 has allowed cells to survive under nutrient-stress conditions [174]. In pathogenesis, p21 contributes to autoimmune disease, and in the context of MSCs specifically, p21 has been shown to contribute to MSC senescence in SLE [159,175].

TSG-6, IL-1Ra, SDF-1, and GM-CSF were upregulated in MSCs from two diseases and not assessed in the other two. However, they are found in the literature to be upregulated in other autoimmune diseases [176–178]. All four molecules are currently associated with playing a role in the pathogenesis of AD, especially the four focused on in this study [179–187]. Each of these molecules plays a different role in each autoimmune disease, making it more challenging to identify therapeutic targets [179,187]. For example, in the serum of SSc patients, SDF-1 can be found upregulated, downregulated, and comparable to normal levels. However, it is consistently upregulated in the skin and kidneys. Meanwhile, in RA, SDF-1 is upregulated in joint tissues, which has a role in synovial inflammation, bone erosion, cartilage degradation, and increased bone turnover.

Despite these roles in the pathogenesis of AD, these four molecules are commonly associated with desired outcomes in MSC-based therapies. SDF-1 and GM-CSF are required for MSC migration, resulting in many groups trying to enhance their expression [188,189]. IL-Ra has a role in the immunomodulatory abilities of MSCs and their ability to heal lung and eye injuries [190]. Within MSCs, TSG-6 has roles in extracellular matrix remodeling, anti-fibrotic effects, angiogenesis, immunomodulation, and anti-inflammation [191].

Galectin-3, BCL-2, OCN, Kynurenine, and Col2 were downregulated in two diseases and not evaluated in the other two. Kynurenine, a metabolite produced during the breakdown of tryptophan, has been shown to reverse autoimmune disease [192–194]. In the context of MSCs, kynurenine has been shown to be a link between metabolism and immunomodulatory properties [195,196]. The secretion of galectin-3 by MSCs is correlated with

immunosuppressive potential and has been suggested as a possible biomarker for their therapeutic efficiency [197]. Although our results show that galectin-3 is downregulated in MSCs from AD, other studies have shown that it is elevated in autoimmune diseases [198–201]. It has even been suggested as a biomarker for identifying patients with high mortality risk in SSc [198–201]. It could be tissue-specific, like SDF-1. Type II collagen is secreted by MSCs and is the basis for hyaline cartilage. Similar to galectin-3, our results showed a decrease in expression from MSCs of multiple AD's, while the literature shows an increase in AD, particularly RA [202]. TGF-β has pro-inflammatory, anti-inflammatory, and immunosuppressive activities; it is also involved in numerous MSC functions, including differentiation and immunomodulation. Like the others, it has also contributed to the pathogenesis of AD [203–207].

Though most studies reported no difference in the morphology of AD-MSCs, some did show irregular actin distribution [148–150]. Actin is a protein crucial in maintaining MSC shape, providing structural support to the cell, and facilitating various cellular processes, including movement, division, and intracellular transport [208,209]. Actin remodeling has been suggested as a biomarker in other disease pathologies, such as cancer [210].

Most studies showed a reduced proliferation in AD-MSCs, which matches results from other physiological states, such as aging [211]. With a decreased ability to proliferate, AD-MSCs cannot self-replicate or make daughter cells. Thus, they will have limited replacement of damaged cells, significantly impairing their capacity to regenerate and repair damaged tissue. Consequently, when using autologous transplants in these cases, cells must be pre-treated with cytokines or hypoxic conditions [212,213]. A comprehensive evaluation of differentially expressed molecules associated with MSC proliferation may provide novel insight for a therapeutic biomarker.

Although overall differentiation into bone, fat, and cartilage lineages was not statistically significant, differences were observed once stratified by disease and MSC cell source. Due to the limitation of a small sample size within each group, it is essential to explore further the differences in the differentiation capabilities between AD-MSCs and HC-MSCs. This exploration should encompass both quantifiable methods and the quality of differentiation. The Bern scoring system has been used to evaluate the quality of bone in tissue-engineered constructs and may be suitable for cell culture studies [214].

By developing a Risk of Bias assessment for *in vitro* studies, the IVAT, this study was able to compare over 800 patient samples to over 500 control samples with transparency and increased rigor. However, this study was limited by inconsistency: MS only evaluated BMCs, SSc was the only disease to evaluate d-MSCs, assays, and molecules was not evaluated across all diseases, and variable methods were used for every assay analyzed. With our methodology, we were able to simultaneously assess multiple AD. This enabled us to observe that AD-MSCs exhibited no variation from HC-MSCs in terms of morphology, the presence of recommended ISCT cell surface markers, or adherence to plastic. However, AD-MSCs exhibited higher levels of IL-6, diminished migration and invasion capabilities, and a reduced capacity for capillary formation. Overall, there were no differences in differentiation and proliferation between AD-MSCs and HC-MSCs. Nevertheless, while distinctions were noted between AD with differentiation and proliferation, the limited sample size necessitates further investigation. Furthermore, our study successfully identified 22 molecules for potential biomarker investigation in AD-MSCs.

5. Conclusion

MSCs can keep tissues and organs in homeostasis, or they can contribute to the development of different pathologies. This balance between the two outcomes needs to be explored further. Identifying the molecular and cellular changes, their interactions, and the pathways impacted could provide targets to mitigate MSC dysfunction, their involvement in disease pathology and progression, their anticipated normal physiological function, and their likely mechanisms of action.

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Data availability statement

The datasets generated during the current study are available from the corresponding author with reasonable request.

AI statement

Artificial intelligence (AI) and AI-assisted technologies were not used in the writing or editing of any part of this manuscript.

CRediT authorship contribution statement

Hailey N. Swain: Conceptualization, Data curation, Formal analysis, Methodology. **Parker D. Boyce:** Data curation, Methodology, Writing – review & editing. **Bradley A. Bromet:** Data curation, Formal analysis. **Kaiden Barozinksy:** Data curation, Investigation. **Lacy Hance:** Data curation, Investigation. **Dakota Shields:** Formal analysis. **Gayla R. Olbricht:** Formal analysis. **Julie A. Semon:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.biochi.2024.04.009.

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