Chapter 15

Clinical Perspectives on Mesenchymal Stem Cell-Based Regenerative Medicine: Source Diversity, Plasticity, Immunomodulation, and Therapeutic Mechanisms

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Abstract

MSCs[1] are multipotent stem cells derived from embryonic mesoderm and neural crest, capable of self-renewal and giving rise to several mesenchymal lineages, including osteoblasts, adipocytes, chondrocytes, myocytes, etc. Human MSCs were first identified in adult bone marrow as fibroblast-like cells and then were isolated from diverse sources, including adipose tissue, skin, UC[2], WJ[3], dental tissue, various biofluids such as amniotic fluid, synovial fluid, cerebrospinal fluid, breast milk, and urine. Each source provides unique benefits in terms of accessibility, proliferation, and regeneration potential. Even though UC MSCs exhibit higher stemness properties with prominent differentiation capacity. Although donor factors, tissue origin, and culture conditions all can affect

1. Mesenchymal stem cells
2. Umbilical cord
3. Wharton's jelly

the biological heterogeneity of MSCs, the isolated cells share characteristics such as plastic adherence, CD105, CD73, and CD90 expression, lack of hematopoietic markers, and trilineage differentiation in accordance with ISCT[1] criteria. Preclinical and clinical studies, including trials for multiple sclerosis, osteoarthritis, heart disease, and COVID-19[2], have demonstrated their efficacy in immune modulation and regeneration, though challenges like heterogeneity and optimal sourcing persist. Along with these descriptions, it is thought that MSCs hold immense promise for regenerative medicine, with exosomes emerging as safer alternatives.

Keywords: Mesenchymal stem cells; Regenerative medicine, Immunomodulation, Exosomes, Plasticity

1. Introduction

MSCs were first identified in 1970 by Friedenstein and colleagues as a population of non-phagocytic, plastic-adherent, fibroblast-like cells derived from the bone marrow of mice and pigs. These cells exhibited the ability to form colonies and differentiate into bone and reticular tissue [1-3]. Subsequent studies by Caplan demonstrated that these cells, in addition to forming bone tissue, are also capable of differentiating into adipose and cartilage cell lineages [4]. Eventually, Pittenger and colleagues showed that human bone marrow also contains a population of stromal cells that are, in fact, multipotent stem cells. These cells possess the ability to form individual colonies and differentiate into various mesenchymal lineages, including bone, cartilage, adipose tissue, tendon, and muscle [5].

MSCs are multipotent cells derived from the embryonic mesoderm and the neural crest [6, 7]. In addition to bone marrow, they can be isolated

[1]. International Society for Cell & Gene Therapy
[2]. Coronavirus disease 2019

from a wide range of tissues, including adipose tissue, umbilical cord, WJ, placenta, fetal liver, muscle, menstrual blood, endometrial polyps, dental tissues, dental pulp, synovial fluid, and cutaneous tissue [8-17]. MSCs possess self-renewal capacity and, beyond their ability to differentiate into mesodermal cell types such as osteoblasts, adipocytes, and chondrocytes, they are also capable—both *in vitro* and *in vivo*—of differentiating into endodermal-derived cells, including lung cells, muscle cells, and gastric epithelial cells, as well as ectodermal-derived cells such as neurons [18]. Studies on MSC donors, tissue sources, culture methods, and single cells within a clonal population indicate the heterogeneous nature of these cells. Besides their multipotent differentiation potential, MSCs possess unique immunomodulatory properties. Furthermore, over time and under varying environmental conditions, MSCs exhibit remarkable plasticity [19]. MSCs are a type of stem cell that are widely used in the treatment of various diseases, including bone disorders, due to their unique characteristics such as ease of isolation and collection, plasticity, and the ability to home to sites of injury [20]. With the biological studies, preclinical data, MSCs were first used clinically in 1995 [21].

2. MSC Sources

MSCs can be derived from a range of adult and fetal tissues, each offering distinct advantages in terms of accessibility, proliferation capacity, and regenerative potential [22]. These cells can be derived from a wide range of adult and fetal tissues, including bone marrow, adipose tissue, synovial membranes, tendons, skeletal muscle, peripheral blood, periosteum, UC blood, WJ, skin, and the nervous system (**Figure 1**) [23, 24]. Additionally, postnatal dental tissues serve as a rich source of MSCs,

with six well-characterized subtypes: DPSCs[1], PDLSCs[2], stem cells from SHED[3], SCAPs[4], DFSCs[5], and GMSCs[6] [25-27]. BMSCs[7], as the first identified source, are among the most extensively studied sources. They exhibit strong differentiation potential into osteogenic, chondrogenic, and adipogenic lineages [28, 29]. However, their extraction is invasive, requires anesthesia, and yields a limited number of cells [30]. In contrast, ASCs[8] are more accessible due to their abundance and minimally invasive collection via liposuction [31]. These cells demonstrate a high proliferative capacity, making them a promising alternative for regenerative applications [32]. Another source of MSCs, the UC and WJ, particularly those from WJ, offers a highly promising option for stem cell sourcing. These cells stand out due to their biologically young nature, enhanced ability to multiply, and greater potential to develop into various cell types when compared to MSCs from bone marrow or adipose tissue [33-35]. A key advantage is that UC-MSCs can be collected non-invasively at birth, providing a large quantity of stem cells without any risk or harm to the donors [36]. In addition, the amniotic fluid and amniotic membrane are abundant sources of MSCs that exhibit strong anti-inflammatory and regenerative properties [37, 38]. These characteristics make them especially valuable for treating a range of conditions, including tissue injuries and immune system disorders. Together, UC-derived sources present compelling alternatives for advancing regenerative medicine and

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1. Dental pulp stem cells
2. Periodontal ligament stem cells
3. Stem cells from the exfoliated deciduous teeth
4. Stem cells from the apical papilla
5. Dental follicle stem cells
6. Gingival mesenchymal stem cells
7. Bone marrow-derived MSCs
8. Adipose-derived MSCs

therapeutic applications [39, 40]. DT-MSCs[1] originate from different parts of the oral cavity, including the dental pulp, periodontal ligament, apical papilla, alveolar bone, and gingiva [41]. These cells are isolated using mechanical or enzymatic techniques and possess a high proliferative capacity, along with the ability to differentiate into various cell types, which makes them well-suited for applications in dental tissue regeneration, bone repair, neural therapies, and immune-related disorders [42, 43]. Additionally, synovial fluid and skeletal muscle contain MSCs that contribute to musculoskeletal regeneration [44, 45]. Synovial-derived MSCs are particularly relevant for joint repair and osteoarthritis treatment [46, 47], while skeletal muscle-derived MSCs hold potential for muscle regeneration and therapies targeting degenerative muscular diseases [48]. Each MSC source exhibits distinct characteristics in terms of proliferative capacity, immunomodulatory properties, and surface marker expression [49]. Notably, UC-MSCs demonstrate a higher proliferation rate, indicating their primitive and versatile nature. However, the optimal MSC source for clinical applications remains a subject of debate, as no definitive consensus has been reached [50]. Continuous research efforts aim to compare various MSC types to enhance their therapeutic efficacy in regenerative medicine and cell-based therapies [51]. While traditional sources such as bone marrow, adipose tissue, and UC blood have been extensively studied, emerging research has identified alternative, non-invasive sources, including cerebrospinal fluid, breast milk, and urine [52-54]. These unconventional sources not only offer ease of collection but also present unique biological properties that could enhance therapeutic applications. Cerebrospinal fluid-derived MSCs naturally home to the nervous system, showing strong healing abilities by reducing

[1]. Dental tissue-derived MSCs

inflammation, protecting neurons, and even turning into nerve-like cells. Their CNS origin makes them especially effective for treating neurodegenerative diseases like PD[1] and AD[2], spinal cord injuries, and multiple sclerosis [53, 55]. Breast milk is a non-invasive, rich source of multipotent stem cells with the ability to differentiate into various lineages. These cells support neonatal development by promoting immune maturation, tissue regeneration, and the formation of gastrointestinal and neural systems. Their secretion of bioactive factors further enhances immune defense, positioning them as promising candidates for neonatal and regenerative therapies [56, 57]. Likewise, USCs[3] show promise in treating psoriasis, repairing kidney and neural tissues, and managing conditions like arthritis and chronic wounds by promoting regeneration and reducing inflammation, offering a simple, noninvasive treatment option [52]. Despite the promise these alternative MSC sources hold, further research is required to fully elucidate their biological characteristics, therapeutic efficacy, and clinical safety. Optimizing isolation and expansion protocols, understanding their immunomodulatory effects, and assessing their scalability for widespread medical use are crucial steps in advancing their application. Nevertheless, these discoveries mark a significant expansion in stem cell research, offering innovative and more accessible avenues for regenerative therapies [58, 59].

[1]. Parkinson's disease
[2]. Alzheimer's disease
[3]. Urine-derived stem cells

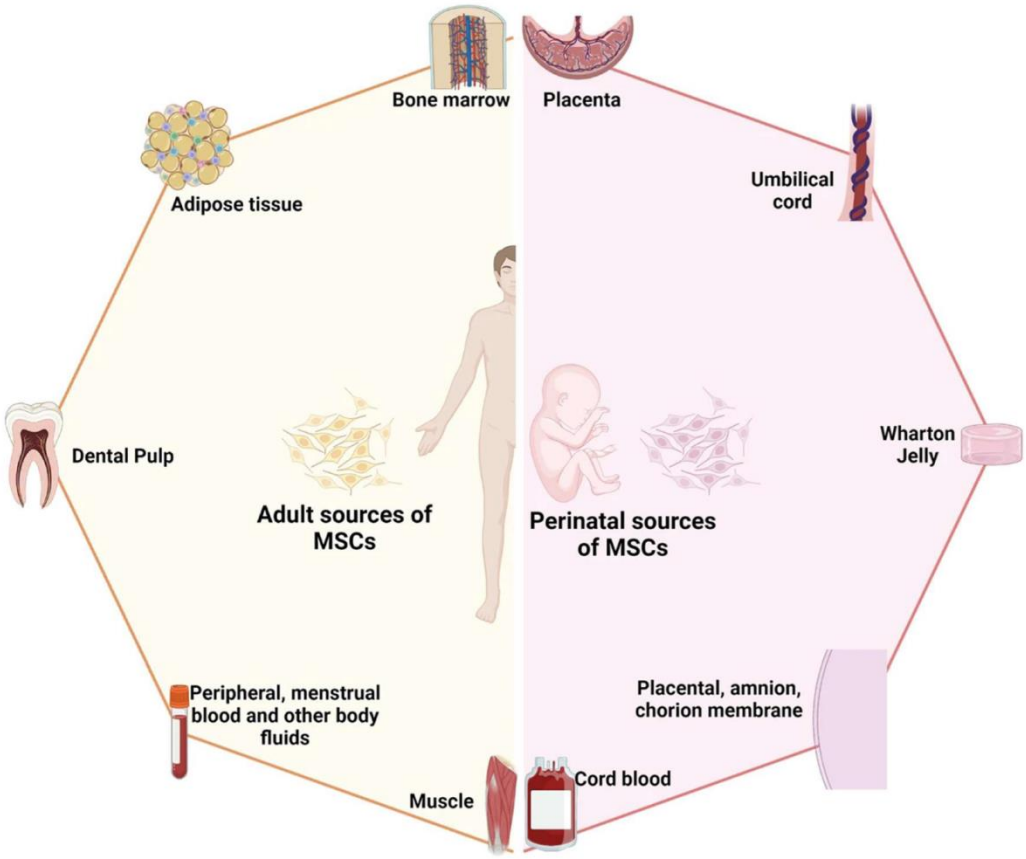

Figure 1. Tissue sources of MSCs. Reproduced with permission. [60]. Biomedicines 2024.

3. Biological properties and therapeutic mechanisms

MSCs are nonhematopoietic adult stem cells capable of self-renewal and differentiation into multiple cell lineages. MSCs are typically part of heterogeneous cell populations in initial cultures, including fibroblasts, myofibroblasts, and a small fraction of stem/progenitor cells, while lacking hematopoietic or ECs[1] [61, 62]. They vary in growth potential, differentiation capacity, and surface marker expression. Despite this

[1]. Endothelial cells

heterogeneity, confluent MSC cultures often display a uniform fibroblast-like morphology [63, 64]. Factors such as donor characteristics (age, sex, health status), tissue source, and isolation techniques (e.g., enzymes, culture media) contribute to MSC variability [65-67]. Still, MSCs share common traits, including fibroblast-like morphology, specific surface markers, proliferation ability, and multidirectional differentiation potential [68]. In 2006, the ISCT established minimal criteria for MSC identification: plastic adherence under standard conditions, expression of CD105, CD73, and CD90, absence of CD45, CD34, CD14, CD11b, CD79α, CD19, and HLA-DR,[1] and differentiation into osteoblasts, adipocytes, and chondroblasts *in vitro* [69]. Early studies on MSCs from humans, baboons, and mice demonstrated their immunosuppressive properties, inhibiting T lymphocyte activation and proliferation *in vitro* [70]. MSCs exhibit low immunogenicity and strong immunomodulatory effects, regulating innate and adaptive immune cells through direct contact and paracrine signaling (**Figure 2**) [71]. They interact with Tregs[2], DCs[3], NK[4] cells, and neutrophils to mediate therapeutic outcomes. Of note, MSCs enhance inflammation when the immune system is underactive and suppress it when overactive, maintaining balance [72, 73]. They downregulate effector T cells while boosting Tregs, suppressing CD4+ and CD8+ T-cell proliferation via TGF-β[5], IDO[6], and PGE2[7] [74, 75]. MSCs also arrest T cells in the G0 phase, reducing activation markers [76]. MSCs modulate DCs, particularly moDCs[8], by inhibiting maturation (reducing CD80, CD86, CD40, MHC II)

1. Human Leukocyte Antigen – DR
2. Regulatory T cells
3. Dendritic cells
4. Natural killer
5. Transforming growth factor beta
6. Indoleamine-2,3-dioxygenase
7. Prostaglandin E2
8. Monocyte-derived DCs

and promoting a tolerogenic state via IL-10[1]. They secrete PGE2, TGF-β[2], and IL-6 to maintain immature DCs and reduce pro-inflammatory cytokines such as IL-12 [77, 78]. MSCs influence macrophage polarization, shifting pro-inflammatory M1 to anti-inflammatory M2 subtypes through PGE2, IL-10, and CCL2, aiding tissue repair. MSC-derived EVs[3] further enhance M2 polarization and immune modulation [79, 80]. MSCs modulate the cytotoxic properties of NK cells by downregulating activation markers such as NKp30, NKG2D, and NKp44, inhibiting NK cell proliferation, and suppressing IFN-γ[4] production. MSCs specifically suppress cytokine production and cytotoxicity in freshly isolated NK cells, but not in activated NK cells. These effects are primarily mediated by IDO and PGE2 [81, 82]. MSCs regulate inflammation induced by neutrophils through the release of anti-inflammatory cytokines, namely IL-10 and TGF-β, which inhibit neutrophil aggregation at sites of inflammation. Furthermore, MSCs diminish the generation of ROS[5], suppress NADPH oxidase function, and presumably reduce NET[6] formation, while encouraging the development of an aged neutrophil phenotype marked by elevated CD24 levels and decreased chemotactic activity. Together, these actions promote inflammation resolution, highlighting the significant immunomodulatory potential of MSCs for therapeutic purposes [83-85]. DCs, monocytes, and macrophages play critical roles within the MPS[7], supporting both innate and adaptive immune responses. Monocytes, a diverse group of innate immune cells, travel through the bloodstream, relocate to sites of

1. Interleukin
2. Transforming growth factor-β
3. Extracellular vesicles
4. Interferon-gamma
5. Reactive oxygen species
6. Neutrophil extracellular trap
7. Mononuclear phagocyte system

inflammation, and possess the capacity to differentiate into either macrophages or dendritic cells [86, 87]. These cells play key roles in phagocytosis, antigen presentation, and cytokine production, helping regulate immune responses and maintain homeostasis [88]. MSCs can regulate immune responses by DCs, particularly moDCs[1]. They inhibit DC maturation by reducing surface markers (CD80, CD86, CD40, MHC II) and suppressing antigen presentation [89, 90]. MSCs also promote a tolerogenic DC state, increasing Treg development while reducing pro-inflammatory cytokines such as IL-12 [75, 91]. These immunosuppressive effects are mediated through paracrine signaling, direct cell contact, extracellular vesicles, and metabolic reprogramming. MSCs secrete soluble factors like PGE2, TGF-β, IL-6, and IL-10, preventing monocyte differentiation and keeping DCs in an immature state. Additionally, they reduce IL-12, TNF-α[2], and IL-6 production while enhancing IL-10 secretion, shifting DCs toward an anti-inflammatory profile [92, 93]. Moreover, MSCs influence DC function through IDO activity (leading to tryptophan depletion), Notch and STAT3 signaling, mitochondrial transfer, and phagocytosis modulation [94-96]. These mechanisms contribute to immune tolerance, making MSCs promising candidates for treating autoimmune diseases, transplant rejection, and inflammatory disorders [97]. Macrophages are classified into M1 (pro-inflammatory) and M2 (anti-inflammatory) subtypes. Polarization refers to the transition from an M1-like to an M2-like phenotype, playing a crucial role in both inflammation activation and resolution [98, 99]. MSCs play a vital role in regulating macrophage function by influencing their polarization, phagocytosis, and metabolism. They promote the transition from pro-inflammatory M1 to anti-

[1]. Monocyte-derived DCs
[2]. Tumor Necrosis Factor alpha

inflammatory M2 macrophages by secreting factors like PGE2, TGF-β, IL-10, and CCL2, which help suppress inflammation and support tissue repair [100, 101]. MSCs enhance macrophage phagocytosis, improving their ability to clear debris and pathogens, which is crucial for immune homeostasis. Additionally, MSC-derived EVs and MPs[1] contribute to immune modulation by inducing M2 polarization and reducing inflammatory cytokine production [102, 103]. In liver injury models, BM-MSCs protect hepatocytes by activating Hippo signaling and NLRP3, which facilitates M1-to-M2 conversion [104]. In another study, BM-MSCs were demonstrated to drive macrophages toward an anti-inflammatory M2 phenotype by activating the NF-κB and STAT3 signaling pathways, resulting in upregulated expression of M2 markers such as Arginase-1 and CD206 and simultaneous suppression of pro-inflammatory cytokines like TNF-α and IL-1β, highlighting the immunomodulatory capacity of BM-MSCs in controlling inflammation and promoting tissue repair [105]. Likewise, ASCs promote the production of IL-10, which improves M2 polarization. MSCs are phagocytosed by monocytes/macrophages following intravenous infusion, regardless of their state—viable, apoptotic, or dead—and affect immune responses through paracrine signaling. MSCs are intriguing candidates for the treatment of autoimmune illnesses, inflammatory conditions, and organ damage because they motivate macrophages into an anti-inflammatory, tissue-repairing phenotype through the release of regulatory chemicals [106, 107]. NK, a subset of ILCs[2], is vital in eliminating infected and cancerous cells without prior antigen exposure. They share features with ILC1s[3], as both secrete

[1]. Membrane particles
[2]. Innate lymphoid cells
[3]. Type 1 Innate lymphoid cells

cytokines like TNFα and IFN-γ and respond to IL-12, IL-15, and IL-18. However, unlike NK cells, most ILC1s lack cytotoxic activity, except in certain tissues like the liver [108-110]. Cytokines like IFN-γ, IL-2, IL-12, IL-15, and IL-18 can increase NK cell numbers and enhance their activation to target a broader range of cells, especially those unaffected by inactive NK cells. Activated NKCF[1], perforin, and various pro-inflammatory cytokines, leading to cytotoxic activity [111, 112]. MSCs regulate NK cell activity by suppressing their proliferation and cytokine production, primarily inhibiting IL-2, IL-15, and IFN-γ. While they do not affect the cytotoxicity of resting NK cells, MSCs reduce the killing ability of activated NK cells through direct contact and the release of immunosuppressive factors like IDO, PGE-2, TGF-β1, and HLA-G5 [113, 114]. Exposure to IFN-γ enhances MSC resistance to NK-mediated killing by upregulating HLA-I, downregulating ULBP-3, and increasing IDO and PGE-2 production. HLA-G isoforms also bind to inhibitory NK receptors, dampening IFN-γ secretion and cytotoxic activity [115-117]. Neutrophils are the most abundant circulating leukocytes and serve as first responders to injury and infection. These short-lived cells develop in the bone marrow through granulopoiesis and are released into the bloodstream in a chemokine-regulated, circadian manner [118, 119]. Various studies have shown that MSCs, as immunomodulator cells, can impact neutrophil function and viability by modulating their recruitment, activation, behavior, survival, reactive oxygen species generation, phagocytic capacity, and apoptosis [120]. MSCs regulate neutrophil function and survival by extending their lifespan, reducing apoptosis, and controlling ROS production. They achieve this by secreting factors like G-CSF, GM-CSF, IL-6, TGF-β, and PGE2, which activate anti-apoptotic pathways and prevent oxidative stress

[1]. NK cells secrete cytotoxic factors

[120, 121]. MSCs also enhance neutrophil phagocytosis through IL-17 and MIF, promote an aged, non-inflammatory phenotype via CD24, and inhibit neutrophil migration to inflamed tissues by releasing TSG-6, preventing excessive inflammation [85, 122].

Plasticity, a defining feature of MSCs, enables them to differentiate into diverse specialized cell types, making them highly valuable for regenerative medicine applications [68]. In addition to their capacity to differentiate into diverse cell types, MSCs exhibit remarkable functional plasticity. Beyond direct differentiation, they contribute to tissue repair by secreting growth factors, cytokines, and exosomes. These bioactive molecules help modulate the immune response, activate resident cells, and enhance regenerative processes, ultimately creating a favorable environment for tissue healing. The plasticity of MSCs is regulated by key signaling pathways that influence their differentiation and function in tissue repair [51, 123-125]. The TGF-β/SMAD pathway directs MSCs toward osteogenic, adipogenic, or chondrogenic lineages, while the Wnt/β-Catenin pathway helps maintain stemness and modulates differentiation [126, 127]. The Notch pathway supports cell communication and immune modulation, whereas the PI3K/Akt and MAPK/ERK pathways promote MSC survival, proliferation, and lineage commitment [128, 129]. Additionally, the Hippo/YAP pathway controls cell growth and differentiation, and the Hedgehog pathway regulates osteogenesis and chondrogenesis. These pathways work together, ensuring MSC adaptability in regenerative medicine and tissue healing [130].

The differentiation potential of MSCs refers to their remarkable ability to transform into diverse specialized cell types. They are primarily recognized for their capacity to develop into mesodermal-derived cells, including those that form bone, cartilage, and fat [131]. However, several in vitro and *in*

vivo studies indicate that under certain conditions, MSCs may also have the ability to differentiate into ectodermal and endodermal cell types, broadening their potential for therapeutic use [132, 133]. In terms of ectodermal differentiation, studies have shown that MSCs can acquire neuron-like properties when exposed to neurogenic culture conditions. These conditions typically involve the presence of specific growth factors such as NGF[1] and BDNF[2]. While these neuron-like cells can express neural markers and demonstrate some functional properties, their full functionality as mature neurons should be investigated by ongoing studies [134-136]. Apart from their neurogenic potential, MSCs have also shown that, under certain induction conditions using factors including bFGF[3], EGF[4], PDGF[5], and GDNF[6], they can develop into glial cells, such as astrocytes, oligodendrocytes, and Schwann-like cells [137]. These factors promote the expression of glial markers, including GFAP[7], MBP[8], and S100β[9], which are important for sustaining neuronal function and brain regeneration, particularly in the setting of neurodegenerative disease therapies. They also stimulate signaling pathways like PI3K/Akt, MAPK/ERK, and JAK/STAT [138, 139]. MSCs have shown impressive potential in endodermal differentiation, particularly in generating liver-like cells. When exposed to HGF[10]and FGF[11], MSCs can develop characteristics similar to liver cells, expressing specific markers and even

[1] . Nerve growth factor
[2] . Brain-derived neurotrophic factor
[3]. Basic fibroblast growth factor
[4]. Epidermal growth factor
[5]. Platelet-derived growth factor
[6]. Glial cell line-derived neurotrophic factor
[7]. Glial fibrillary acidic protein
[8]. Myelin Basic Protein
[9]. S100 Calcium Binding Protein B
[10]. Hepatocyte growth factor
[11]. Fibroblast growth factor

performing essential functions such as glycogen storage and albumin production. This makes them a promising option for liver regeneration therapies [140]. Additionally, MSCs have shown that they can differentiate into cells that resemble pancreatic islets, which may help treat diabetes by resuming the production of insulin. According to research, MSCs stimulate important pancreatic transcription factors, including PDX1[1], NGN3[2], and MafA[3], under particular induction procedures that include activin A, nicotinamide, and elevated glucose concentrations, promoting the development of insulin-producing cells, while also exhibiting immunomodulatory qualities by secreting substances such as TGF-β, PGE2, and IL-10, which shield beta-cells from autoimmune destruction and help regulate T cell activity. This is especially important in type 1 diabetes [141-144]. MSCs have been shown to be able to differentiate into intestinal and lung epithelial cells, thereby aiding in tissue repair in both IBD and pulmonary fibrosis [145-147]. In lung injury, MSCs migrate to inflammation sites and release Ang-1[4], KGF[5], and HGF to promote alveolar repair and reduce vascular leakage, as well as IL-1ra and TSG-6, which inhibit pro-fibrotic TGF-β signaling [148, 149]. In IBD[6], MSCs control immunity through IL-10 and TGF-β, and they promote mucosal healing by stimulating IL-22 production through ILC3 interaction These findings highlight the broad therapeutic potential of MSCs in regenerative medicine [150, 151]. The differentiation of MSCs is influenced by a captivating combination of biological signals, surrounding conditions, and genetic factors. These cells possess an extraordinary capacity to develop into

[1]. Pancreatic and duodenal homeobox 1
[2]. Neurogenin-3
[3]. Mast cell function-associated antigen
[4]. Angiopoietin 1
[5]. Keratinocyte growth factor
[6]. Inflammatory bowel disease

various cell types based on the signals they encounter [152, 153]. Growth factors are critical drivers of MSC differentiation. For example, proteins such as BMP-2[1], BMP-7, TGF-β, and FGF-2 are instrumental in guiding MSCs to differentiate into osteoblasts, which form bone. Conversely, exposure to TGF-β1 and IGF-1[2] steers these cells toward becoming chondrocytes, which produce cartilage [154-158]. PPARγ[3] and C/EBPs are key transcription factors that regulate adipogenic differentiation. Glucocorticoids, such as dexamethasone, enhance this process by inducing the expression of PPARγ and C/EBP family members (α, β, and δ). In 3T3-L1 preadipocytes, the expression of PPARγ and C/EBPα increases throughout adipogenesis, while C/EBPβ declines in the later stages [159, 160]. Similar to how MSCs are guided to differentiate into muscle cells by MyoD and IGF-1, they are guided to differentiate into neuron-like cells by EGF, bFGF, and retinoic acid [161]. Under some conditions, MSCs can also differentiate into endothelial cells, which, when triggered by VEGF[4] and angiopoietin signals, contribute to the creation of blood vessels [162]. Beyond these biochemical signals, the physical environment plays a crucial role in shaping MSC differentiation. For example, a stiff surface encourages bone formation, whereas a softer environment supports the development of fat or nerve cells [163, 164]. Mechanical forces like stretching can help MSCs turn into muscle or cartilage cells, while low oxygen levels (hypoxia) can steer them toward becoming vascular or neural cells [165]. MSC behavior can be influenced by extrinsic factors such as nutrition and drugs. For example, retinoic acid promotes brain growth, while dexamethasone improves bone and muscle

[1]. Bone Morphogenetic Protein
[2]. Insulin-like growth factor 1
[3]. Peroxisome proliferator-activated receptor gamma
[4]. Vascular endothelial growth factor

differentiation. While metabolic variables such as glucose and fatty acids also affect differentiation pathways, vitamin C is known to promote the production of both bone and cartilage [166-168]. Ultimately, MSC differentiation is a carefully controlled process that is impacted by a number of chemical, genetic, and mechanical factors. By understanding and altering these signals, researchers are making incredible advances in tissue engineering, regenerative medicine, and the development of new treatments for a variety of diseases. Preclinical studies highlight MSC-based therapies for various diseases, leveraging their natural tropism to migrate and home to injured sites under the influence of growth factors, chemokines, and cytokines. Migration allows them to travel through the bloodstream in response to signals from damaged areas, while homing enables them to attach, enter the tissue, and begin healing [169, 170]. MSCs are activated in response to injury or inflammation and, by releasing from their primary locations in tissues such as bone marrow or adipose tissue, enter the bloodstream and migrate towards the damaged areas. This multi-step and precise process is regulated by biochemical signals, cell receptors, and microenvironmental interactions [170, 171]. The migration of MSCs begins with the release of factors such as SDF-1[1], TNF-α, and VEGF[2] from damaged tissues. These molecules stimulate the migration of MSCs and facilitate their entry into the bloodstream [172]. Then, the cells are directed towards the site of injury with the help of receptors such as CXCR4 and other chemotactic receptors (like CCR1, CCR2, CXCR3, CXCR4). After approaching the target tissue, MSCs initially adhere to the blood vessel wall through molecules such as selectins. Subsequently, this attachment is strengthened by integrins

[1]. Stromal cell-derived factor 1
[2]. Vascular endothelial growth factor

(such as α4β1 or VLA4) and adhesive molecules like VCAM-1[1] and ICAM-1[2], facilitating their passage through the vessel wall (a process known as diapedesis or transmigration [173-175]. In this process, signaling pathways such as the CXCR4/SDF-1 and CCL2/CCR2 axes play a key role. To traverse the extracellular matrix, enzymes such as MMP-2[3] and MT1-MMP assist in tissue degradation. Upon entering damaged tissue, MSCs contribute to repair through two primary mechanisms: differentiating into specialized cells to replace damaged ones and secreting bioactive molecules that reduce inflammation, activate immune cells, enhance blood circulation, and promote tissue repair mechanisms [176-178]. MSCs release important cytokines such as TGF-β, which regulates inflammation and cell differentiation, IL-6, which stimulates angiogenesis and proliferation, TNF-α, which controls inflammation and tissue repair, and IL-10, which significantly lowers inflammation [83, 179]. In addition, chemokines such as SDF-1, CCL2 (MCP-1), and CXCL8 (IL-8) help attract immune cells, stimulate angiogenesis, and accelerate tissue clearance.
The growth factors secreted by MSCs also play a fundamental role in tissue regeneration [51, 180, 181]. The growth factors secreted by MSCs also play a fundamental role in tissue regeneration. VEGF promotes angiogenesis, IGF-1 enhances cell survival, FGF supports fibroblast proliferation for tissue repair, HGF aids in cell growth and differentiation, and PDGF regulates cell growth and intercellular communication [181, 182]. In addition, MSCs extend their therapeutic functions through the release of extracellular vesicles, particularly exosomes. These nanoparticles (with a size of 30 to 150 nanometers) contain proteins, lipids,

[1]. Vascular cell adhesion molecule-1
[2]. Intercellular adhesion molecule-1
[3]. Matrix metalloproteinase-2

and RNAs that, by affecting target cells, reduce oxidative stress, regulate immune response, stimulate regeneration, and support angiogenesis [183, 184]. Exosomes, due to their high safety, ability to cross biological barriers, ease of storage, and lack of tumorigenic risk, have been proposed as a suitable alternative to live cell therapy in regenerative medicine [185]. Although the use of biomaterials such as microgels can increase the survival of MSCs at the site, it may sometimes disrupt their function by blocking essential receptors for migration. For this reason, direct or local injection of MSCs near the damaged tissue is an effective strategy to enhance therapeutic efficacy [186, 187].

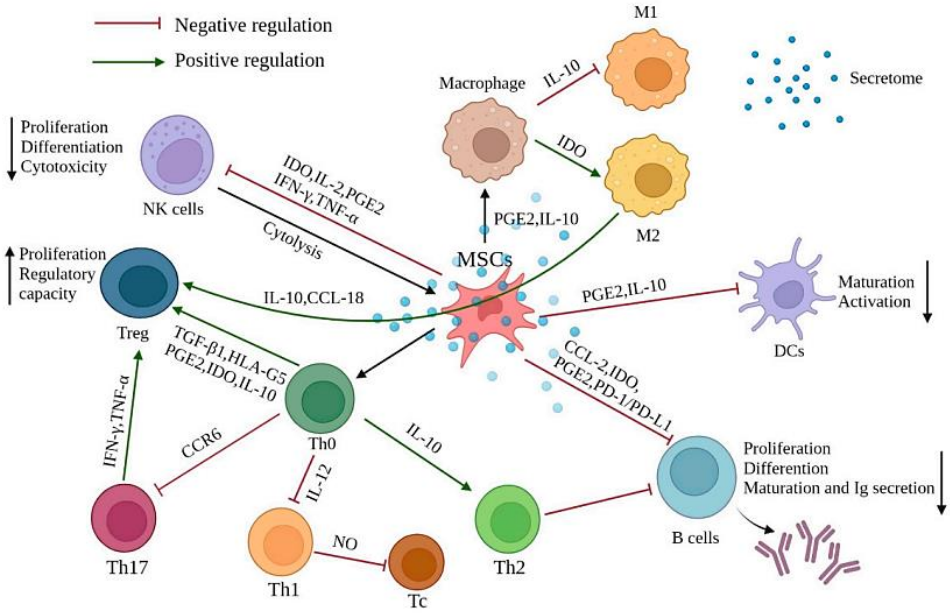

Figure 2. Immunomodulatory properties of MSCs. These cells can modulate innate and adaptive immune cells through the secretion of growth factors, interleukins, cytokines, and chemokines. This immune regulation enables effective treatment of various tissue injuries. Reproduced with permission. [188]. International Journal of Molecular Sciences. 2022.

4. MSC-based clinical studies

A summary of clinical trials investigating the therapeutic potential of MSCs in various diseases (**Table 1**). These studies highlight the diversity of MSC sources, delivery routes, and clinical outcomes observed across different trials.

Table 1. Overview of MSC-based clinical trials in treating various pathological conditions

Disease	Source	Administration Method	Phase	Outcomes	Trials NCT ID	Start Year	End Year/Status
Acute Kidney Injury	BM-MSCs	IV	I	Reduced kidney inflammation, improved function	NCT01275612	2010	2015
Cerebral Palsy	UC-MSCs	Intrathecal	II	Improved motor coordination, acceptable safety	NCT01929434	2013	Ongoing (2025)
Heart Disease (Post-MI)	BM-MSCs, ASCs	IV or IC	II/III	Enhanced heart function, reduced scar tissue	NCT02013674	2013	2021
Muscular Dystrophy	WJ-MSCs	IV or IM	I/II	Improved muscle strength, no significant side effects	NCT02814110	2016	2019
Osteoarthritis	ASCs, BM-MSCs	IA	II/III	Pain reduction, partial cartilage repair	NCT02958267	2016	2020
Crohn's Disease	ASCs, UC-MSCs	Local or IV	II	Reduced gut inflammation, symptom improvement	NCT03279081	2017	2020
MS	BM-MSCs, ASCs	IV or Intrathecal	I/II	Reduced inflammation, some neurological improvement	NCT03355365	2017	2021
Rheumatoid Arthritis	UC-MSCs, BM-MSCs	IA or IV	I/II	Reduced joint inflammation, improved function	NCT03618784	2018	2022
Skin Hyperpigmentation	ASCs-Exos	Topical Application	I	Reduced melanin levels, temporary improvement	NCT03661554	2018	2020
Stroke	BM-MSCs-Exos	IV	I	Enhanced neuroprotection, reduced infarct size	NCT03384433	2018	2022
Chronic Kidney Disease	UC-MSC-Exos	IV	I/II	Ameliorated progression, improved renal function	NCT04115345	2019	Ongoing (2025)
Type 1 Diabetes	UC-MSCs	IV	I//II	Immune modulation, reduced insulin needs	NCT03920397	2019	Ongoing (2025)

COVID-19 Pneumonia	ASC-Exos	Aerosol Inhalation	I	Improved lung function, reduced inflammation	NCT04276987	2020	2021
ARDS (e.g., COVID-19)	UC-MSCs	IV	I/II	Reduced cytokine storm, improved oxygenation	NCT04333368	2020	2022

Abbreviations: BM-MSCs: Bone marrow-derived mesenchymal stem cells, IV: Intravenous, hUC-MSCs: Human umbilical cord-derived mesenchymal stem cells, ASCs: Adipose-derived mesenchymal stem cells, ASC-Exos: ASC-derived exosomes, MS: Multiple Sclerosis, IC: Intracardiac, WJ: Wharton's jelly-derived mesenchymal stem cells, IA: Intra-articular, IM: Intramuscular, Exos: Exosomes, COVID-19: Coronavirus disease 2019, ARDS: Acute respiratory distress syndrome

5. Conclusion

During recent decades, various aspects related to MSC regenerative potential have been determined using numerous studies. These cells possess unique properties that can be used in human medicine. By direct commitment into target cell lineages and release of several cytokines, these cells can orchestrate the healing process a few weeks after being transplanted into the injured sites. These features make MSCs a valuable stem cell source for cell therapy, regenerative medicine, and tissue engineering modalities.

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