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Clinical application of mesenchymal stem cells in immunosenescence: a qualitative review of their potential and challenges

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Abstract

Aging leads to a gradual decline in immune function, termed immunosenescence, which significantly elevates the susceptibility to infections, cancers, and other aging-related diseases. Recent advancements have shed light on the molecular underpinnings of immune aging and pioneered novel therapeutic interventions to counteract its effects. Mesenchymal stem cells (MSCs)-a type of multipotent stromal cells with regenerative potential, low immunogenicity, and strong immunomodulatory properties-are increasingly recognized as a promising therapeutic option to reverse or alleviate immunosenescence-related dysfunction. This review systematically summarizes recent discoveries on how MSCs counteract immune aging, particularly their ability to rejuvenate aged immune cells and restore immune homeostasis. It also addresses key challenges, such as variations in MSC sources, donor variability, and the lack of standardized protocols, while proposing future directions to enhance therapeutic precision. Although preclinical and clinical studies highlight the potential of MSC-based strategies for delaying immunosenescence, critical issues remain unresolved, including long-term safety and efficacy, optimizing cell delivery systems, and elucidating context-specific mechanisms. Addressing these challenges will accelerate the development of MSC-based therapies to combat aging-associated immune decline.

Keywords Adaptive immunity, Challenges, Inflammaging, Immunosenescence, Innate immunity, Mesenchymal stem cells

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Introduction

Aging is a natural yet complex biological process that remains incompletely understood. A central challenge in aging is immunosenescence-the gradual decline of immune function with age [1, 2]. This decline compromises the body's ability to fight infections, respond to vaccines, and maintain immune balance, which significantly heightens the vulnerability of the elderly to infections and chronic inflammatory diseases, such as rheumatoid arthritis, cancer, atherosclerosis, type 2 diabetes, and neurodegenerative diseases [3]. Recent breakthroughs have begun to unravel the molecular mechanisms driving aging, leading to innovative therapeutic approaches to delay or even reverse aging [4]. For example, senescent cell scavengers, dasatinib and quercetin, can selectively eliminate aged, dysfunctional cells, and have shown promise in delaying age-related conditions in preclinical studies [5, 6]. Among emerging therapies, mesenchymal stem cells (MSCs) stand out for their unique regenerative and immunomodulatory properties. MSCs can self-renew, differentiate into diverse cell types, and suppress harmful immune responses, making them a compelling candidate for rejuvenating the aging immune system [7].

This review explores the connections between aging, immunosenescence, and MSC-based therapies. We explain how aging disrupts the immune system's ability to fight threats while avoiding overreaction. We then elucidate the multifaceted roles that MSCs play in modulating immune responses—from mitigating excessive inflammation to fostering tissue repair and regeneration. Finally, we discuss the potential of MSC-based therapies to improve health span in aging populations and outline critical challenges that must be addressed to translate these findings into real-world treatments. By bridging current knowledge gaps, this work aims to provide insights that may inspire future research and contribute to the development of novel therapeutic strategies against aging-related immune decline.

Mechanisms of aging

Aging is marked by three pivotal hallmarks: telomere shortening, genomic instability, and cellular senescence. Initially characterized in 1961 [8], cellular senescence is described as the sustained cessation of cell division and resistance to programmed cell death. Cellular senescence arises due to the accumulation of diverse mechanisms, such as telomere shortening, DNA damage, oxidative stress, and prolonged exposure to inflammatory molecules [9, 10]. Given the absence of a distinct biomarker, cellular senescence is identified via a combination of diverse markers, including multiple DNA damage foci indicated by phosphorylated histone H2AX, increased lysosomal β-galactosidase (senescence-associated [SA] β-gal) activity, increased expression of cyclin-dependent kinase inhibitors ($p16^{INK4A}$ and $p21^{CIP1}$), senescence-related secretory phenotype (SASP) components (interleukin-6 [IL-6], IL-8, tumor necrosis factor-α [TNF-α], and CCL2), and increased anti-apoptotic protein expression. Furthermore, nuclear envelope alterations attributed to downregulated lamin B1 and augmented reactive oxygen species (ROS) generation contribute to mitochondrial dysfunction during cellular senescence [11]. In particular, senescent cells exhibit SASP, which is characterized by cytokines, chemokines, and proteases; this not only prompts the senescence of adjacent cells but also alters their microenvironments [12]. The SASP serves as a signaling mediator that enables communication between senescent cells and immunosenescence. Moreover, it plays a vital role in recruiting and activating immune cells, thereby facilitating the elimination of senescent cells and moderating inflammatory responses. However, inadequate clearance can lead to rapid accumulation of senescent cells; this exceeds the immune system's capacity and leads to the establishment of a chronic systemic state of senescence [13]. Thus, aging, as an inherent biological process, exerts profound effects on multiple physiological systems within the body, particularly the immune system, underscoring its complexity and significance as a societal and medical challenge [14, 15].

Characteristics of immunosenescence

Immunosenescence is an intricate process with an unclear specific mechanism that affects innate and adaptive immune cells to varying extents during aging (Fig. 1). Altered immune cell numbers and function impair their migration ability, antigen response, and killing potential, and lead to general inflammaging. The waning efficacy of the aging immune system in mounting responses against pathogens or cancer cells has been implicated in the pathogenesis of various diseases, such as rheumatoid arthritis, cancer, atherosclerosis, type 2 diabetes, and neurodegenerative diseases [16–20]. Chronic immune activation may precipitate premature, age-independent immunosenescence, thereby heightening vulnerability to disease and exacerbating morbidity and mortality among the elderly population [21, 22]. Defining immunosenescence-associated characteristics has implications for understanding aging-related disease progression and identifying therapeutic targets. Therefore, in the subsections below, we delve into the functions and senescence-related characteristics of various innate and adaptive immune cells.

Immunosenescence of innate immune cells

Compared to younger individuals, in the elderly, innate immune cells, including macrophages, neutrophils,

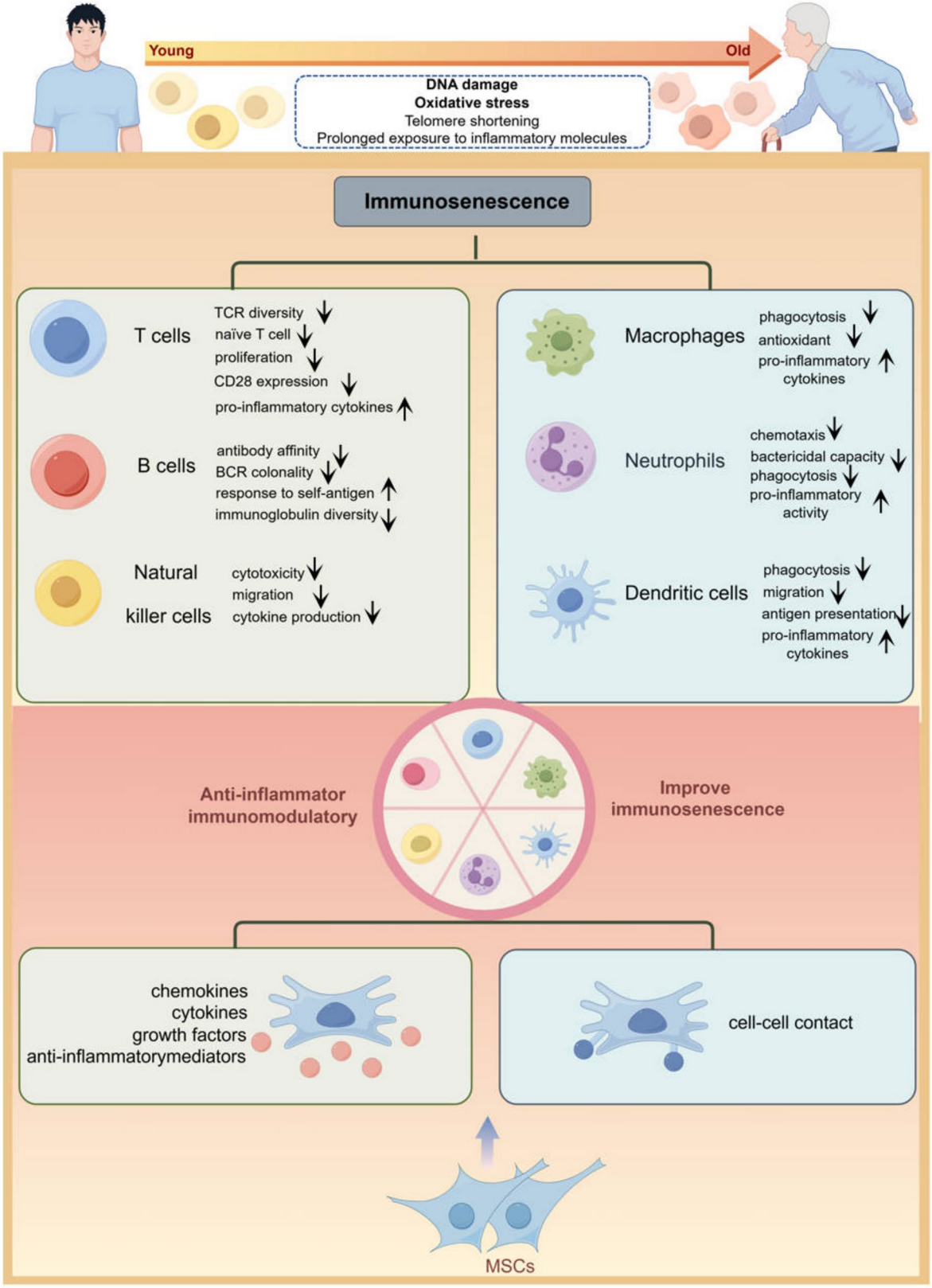

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Fig. 1 Characteristics of immunosenescence and effects of mesenchymal stem cells on immunosenescence. BCR, B-cell receptor; MSC, mesenchymal stem cell; TCR, T-cell receptor. Aging is a complex process driven by mechanisms such as telomere shortening, DNA damage, oxidative stress, and chronic inflammation, all of which contribute to immunosenescence. This decline affects both the quantity and function of innate and adaptive immune cells to varying degrees. MSCs exert anti-inflammatory and immunomodulatory effects through direct cell-cell interactions and indirect mechanisms that counteract immunosenescence.

dendritic cells (DCs), and natural killer (NK) cells, exhibit significant changes in both number and function. Studies have reported that aging is associated with an increase in the number of monocytes and NK cells; in contrast, the number of neutrophils remains constant or slightly elevated [23, 24]. The aging-related functional abnormalities in these cells encompass reduced clearance, phagocytosis, and chemotaxis, alongside impaired antigen presentation and cytotoxic abilities, coupled with an increase in pro-inflammatory cytokine production. Below, the functions and aging-related abnormalities for the major innate immune cells are described in detail.

Monocytes/Macrophages

Macrophages are key regulators in the maintenance of homeostasis, existing in two polarized forms: the pro-inflammatory M1 and anti-inflammatory M2 types. Increased endoplasmic reticulum stress and mitochondrial dysfunction drive the accumulation of M2-like macrophages during aging, which paradoxically exhibit a pro-inflammatory phenotype [25]. Senescent monocytes/macrophages have reduced phagocytic capacity and increased expression of pro-inflammatory cytokines, such as IL-6 and TNF-α. In addition, depletion of macrophages has also been observed in senescent mice, and macrophage depletion was found to ameliorate tissue dysfunction [26]. Macrophages are also pivotal in the chronic oxidative stress linked to aging, as evidenced by the concurrent decline in antioxidant capacity observed in old mice [27]. Accordingly, reduced synthesis of nicotinamide adenine dinucleotide (NAD)+, a known antioxidant factor, has been observed in senescent macrophages, and increasing NAD + synthesis was found to improve oxidative phosphorylation and immune function [28]. Decreased antioxidant capacity is linked with the development of various diseases, especially those whose incidence increases with age [29]. With regard to disease risk, D-galactose (D-gal)-induced senescent THP-1 monocytes were found to be susceptible to viral infection [30].

Neutrophils

Neutrophils are key components of the innate immune system that primarily provide protection against infections by phagocytosing and destroying pathogens, releasing antimicrobial substances, and regulating inflammatory responses. Defective neutrophil function is known to affect disease regression in the aging immune system. Elevated intra-neutrophil calcium concentrations and reduced ROS production that occur with aging lead to a decrease in chemotaxis and bactericidal capacity and increased pro-inflammatory activity in neutrophils [31, 32]. In addition, senescent neutrophils exhibit reduced phagocytic capacity [33]. Interestingly, while older individuals produce greater levels of neutrophil extracellular traps, these traps also exhibit structural changes that result in their dysfunction [34].

NK cells

NK cells serve as central effector cells of the innate immune system. Aging is accompanied by progressive impairment of NK cells in terms of their cytotoxicity, migration, and immune regulatory functions [35]. These aging-related dysfunctions contribute to a higher incidence of infections, reduced vaccine responses, and increased accumulation of senescent cells. In addition, an increase in NK cell numbers and a decline in NK cell activity are observed with aging; this may be associated the accumulation of long-lived NK cells in older adults [36]. Further, the decline in NK cell activity has also been associated with increased cancer susceptibility and metastasis. NK cells suppress cancer progression through multiple mechanisms, including the "missing-self" recognition, antibody-dependent cellular cytotoxicity, and the production of pro-inflammatory cytokines. Notably, NK cell cytotoxicity declines significantly with aging, whereas their antibody-dependent cellular cytotoxicity remains unaffected [37]. Recently, NK cell-based immunotherapies have shown promising efficacy in cancer treatment [38, 39].

DCs

Aging has little effect on DC numbers and subpopulations, but it impairs DC phagocytosis and migration [40]. DCs in elderly individuals exhibit elevated pro-inflammatory cytokine secretion and reduced release of anti-inflammatory and immunomodulatory cytokines [41, 42]. DCs are the main antigen-presenting cells responsible for interacting with naïve T cells. Aging decreases the antigen-presenting capacity of DCs and induces a shift to an inflammatory state, consequently affecting the activation of naïve $CD8^+$T cells and the subsequent generation of effector T cells [24, 32].

Immunosenescence of adaptive immune cells

Although aging has a detrimental effect on both innate and adaptive immunity, adaptive immune cells, notably T cells and B cells, undergo more profound functional deterioration than their innate counterparts. The aging of the adaptive immune system is mainly marked by reduced T and B cell receptor diversity, a decline in naïve lymphocytes accompanied by the accumulation of memory cells, diminished antigen clearance capacity, and increased secretion of pro-inflammatory cytokines.

B cells

B cells exert an immune response by secreting antibodies, presenting antigens, and regulating T cells. During aging, bone marrow microenvironmental factors reduce precursor B cell production and result in the loss of immunoglobulin diversity [43, 44]. The impaired antibody response reduces the affinity of B-cell antibodies [45]. The B-cell receptor (BCR) binds self-antigens and foreign antigens to determine B-cell differentiation and response. The frequencies of autoreactive B cells, characterized as B cells that recognize and bind to self-antigens, leading to potential autoimmune responses, increase during aging [46]. Aging-related reductions in BCR diversity and increases in clonal expansion are associated with a higher incidence of disease [47]. In elderly people, BCR changes reflect an age-related process of B cell selection and demonstrate the importance of BCR function for maintaining health during aging [48]. Immature transitional B cells are characterized by a $CD19^{+}CD24^{high}CD38^{high}$ phenotype and negatively regulate the immune response through IL-10 secretion. Aging individuals experience a decline in peripheral blood $CD19^{+}CD24^{high}CD38^{high}$ mononuclear cell frequency and quantity [49]. The proportion of late/exhausted memory B cells increases with age and is associated with the expression of SASP; importantly, aging-related decrease in these cells contributes to reduced vaccine response [50]. Further, germinal center responses and memory B-cell responses are defective in elderly people following vaccination [45].

T cells

Thymic degeneration is one of the main causes of T-cell senescence [51]. Senescent T cells exhibit diminished T-cell receptor (TCR) diversity, thus compromising immune responses in the elderly. This is accompanied by reduced naïve T-cell numbers and elevated memory T-cell counts. Prematurely senescent T cells exhibit telomere shortening, increased production of pro-inflammatory factors, and impaired DNA repair [52]. Telomerase activity, the proportion of naïve T cells, and health status influence the changes in T-cell telomere length that occur with aging [53]. Decreased T-cell telomerase expression is associated with decreased T-cell proliferative capacity. Senescent T cells lose CD28 and express CD57, a shift that correlates with diminished proliferative capacity [54]. $CD8^{+}$T cells are more likely to acquire an immunosenescent phenotype than $CD4^{+}$ T cells. In particular, unlike effector memory T cells ($CD45RA^{-}CD27^{-}$), effector memory $CD8^{+}$T cells with CD45RA reintroduction (CD8 T_{EMRA}) exhibit immunosenescence features, such as decreased proliferation, impaired mitochondrial function, and increased ROS levels and p38 MAPK activation [55]. CD8 T_{EMRA} cells secrete SASP, which is regulated by p38 MAPK [56]. Accordingly, inhibition of the p38 MAPK pathway was found to enhance CD8 T_{EMRA} proliferation and telomerase activity while suppressing TNF-α secretion [57]. Furthermore, removal of ROS was found to prevent telomere shortening [58]. These findings demonstrate the role of ROS, telomere shortening, and $CD8^{+}$T cells in the senescence process.

In vitro and in vivo effects of MSCs on immunosenescence

MSCs are pluripotent adult stem cells of mesodermal origin that were first discovered in the bone marrow [59] and later found to exist in various tissues throughout the human body, including the bone marrow, adipose tissue, umbilical cord blood, and placenta. MSCs can be induced to expand at high proliferation rates under in vitro conditions [60]. Under specific conditions, MSCs can differentiate into not only cells of mesodermal lineages, such as adipocytes, chondrocytes, and osteoblasts, but also cells of the ectodermal or endodermal cell lineages [61]. In addition, MSCs can secrete various biofactors and extracellular vesicles (EVs) to induce an effect on the microenvironment to support hematopoiesis and modulation of immune responses. Thus, MSCs possess the capacity of self-renewal, multipotent differentiation, and immunomodulation, which make them a promising therapeutic option. Currently, MSCs are emerging as promising therapeutic candidates for various autoimmune disorders, such as primary biliary cholangitis [62], systemic lupus erythematosus [63], and rheumatoid arthritis [64]. With regard to their specific immune targets, MSCs can suppress the activation of T cells, B cells, and NK cells, while promoting the differentiation of regulatory T cells (Tregs) and M2 macrophages, thereby restoring immune homeostasis. Among these immune cells, T cells have been the major focus of research on the effects of MSCs on immunosenescence [65]. We have summarized the relevant findings of in vivo and clinical studies on the ability of MSCs transplantation for conditions associated with immunosenescence in Table 1.

In terms of their mechanisms of action, MSCs exert their immunoregulatory function through direct cell–cell contact and indirect secretome (e.g., cytokines, chemokines, and growth factors)- or EV-mediated

Table 1 In vivo and clinical studies of mesenchymal stem cell transplantation for conditions associated with immunosenescence. BMSCs, bone marrow mesenchymal stem cells; CRP, C-reactive protein; D-gal, D-galactose; Exo, exosome; hPMSCs, human placenta mesenchymal stem cells; MSC, mesenchymal stem cell; NK cells, natural killer cells; ROS, reactive oxygen species; SA-β-gal, senescence-associated β-galactosidase; SASP, senescence-related secretory phenotype; TNFα, tumor necrosis factor-α; 8-OH-dG, 8-Hydroxy-2′-deoxyguanosine

Subjects	Number of subjects	MSC dose and method of administration	Results	Reference
20-month-old BALB/c mice	5	A single dose of 1×10^7 allogenic BMSCs administered via caudal vein injection	increased proportion of $CD8^+CD28^+$T cells; decreased p16 expression and enhanced AUF1 expression	[70]
D-gal induced C57BL/6 mice	10	1×10^6 hPMSCs administered once per week for three weeks (during weeks 5–7) via caudal vein injection	decreased levels of ROS and senescence-related markers (p16, p21, and SASP) in senescent $CD4^+$T cells	[72]
D-gal induced C57BL/6 mice	10	100 μg/week hPMSCs-Exo administered for two weeks via caudal vein injection	decreased oxidative stress damage (ROS and 8-OH-dG), SA-β-gal positive cell numbers, and senescence related markers (p16, p21, and SASP) in senescent $CD4^+$T cells	[73]
Aging patients with frailty, average age of 78.4 ± 4.7 years	5 per group	a single administration of 2×10^7, 1×10^8, or 2×10^8 allogenic BMSCs administered via intravenous infusion	reduced levels of TNF-α; optimal dose is 100 million cells	[75]
Aging patients with frailty, average age of 75.5 ± 7.3 years	10 per group	a single administration of 1×10^8 or 2×10^8 allogenic BMSCs administered via intravenous infusion	reduced serum and B cell intracellular levels of TNF-α; a significant decline in $CD8^+$T cells	[76]
COVID-19 patients aged 45–65 years	7	a single administration of 1×10^6 BMSCs per kilogram of weight administered via intravenous drip	decreased neutrophil/lymphocyte ratio, CRP, and TNF-α;disappearance of over-activated cytokine-secreting T and NK cells	[79]

signal transduction [65–67]. Further, MSCs can interact directly with immune cells through cell surface receptors, thus modulating their activation and differentiation. MSCs primarily exert their therapeutic effects through the paracrine secretome, via factors such as transforming growth factor (TGF)-β, prostaglandin E2, indoleamine 2,3-dioxygenase, hepatocyte growth factor, nitric oxide, interferon-γ, IL-2, and IL-10, to modulate immune cell proliferation, differentiation, and cytotoxicity. For example, MSCs inhibit T helper 1 differentiation and promote Treg development by secreting TGF-β through the STAT6 pathway [68]. Further, MSCs have been found to induce T-cell apoptosis via the expression and secretion of FasL and PD-L1 [69].

One study reported the effects of exogenous administration of MSCs on the proportions of $CD8^+CD28^+$ T cells in senescent model mice. In the study, 17-month-old BALB/c mice were found to have a lower proportion of $CD8^+CD28^+$ T cells in the spleen than 2-month-old mice, which is indicative of premature senescence of proliferative T cells [70]. Further, aged mice showed a decrease in the frequency of $CD8^+CD44^{low}CD62L^{high}$ T cells and an increase in the population of $CD8^+CD44^{low}CD62L^{high}Sca\text{-}1^+$ stem-like memory T cells, with Wnt signaling implicated in the induction of Sca-1 expression [70, 71]. These changes were reversed following administration of 1×10^7 allogeneic bone marrow-derived mesenchymal stem cells (BMSCs) from C57BL/6 mice into the caudal vein, and this was attributed to the activation of Wnt expression associated with stem cell genes or the restoration of BMSC stemness [70]. Comparable findings were obtained in a mouse model with chemically triggered immunosenescence. Senescence was induced in 8-week-old C57BL/6 mice for 7 weeks using D-gal, and 1×10^6 human placenta-derived MSCs (hPMSCs) were administered via the caudal vein once per week for three weeks (during weeks 5–7). $CD4^+$ T cells in the D-gal-induced mice had notably increased ROS levels and substantially reduced antioxidant marker activity (antioxidant enzymes: superoxide dismutase, glutathione peroxidase, and catalase). Further, they exhibited senescent phenotypes, characterized by markedly increased SA-β-gal activity, SASP component secretion (e.g., IL-6), and increased p21 and p16 expression. Administration of hPMSCs alleviated the changes and attenuated $CD4^+$ T cell senescence via activation of the Akt–GSK-3β–Fyn pathway to inhibit the Fyn-mediated degradation of nuclear factor erythroid-2-related factor 2 (Nrf2). This led to an increase in the levels of Nrf2, a crucial cellular antioxidant regulator. Furthermore, in vitro experiments demonstrated that hPMSCs attenuated the replicative senescence of human naïve T cells [72]. Overall, the findings of these studies imply that MSCs can delay or reverse immunosenescence via two mechanisms: (1) enhancing antioxidant capacity and mitigating oxidative stress damage in $CD4^+$ T cells and (2) regulating the populations of $CD8^+$ $CD28^+$ T cells.

MSC-derived exosomes are another emerging therapeutic option for addressing senescence. For example, administering 100 μg of hPMSC-derived exosomes through the caudal vein every week for 2 weeks was found to markedly inhibit $CD4^+$ T cell senescence. This inhibitory effect was attributed to the transportation of microRNA-21 and the activation of an exogenous antioxidant defense pathway mediated by the PTEN–PI3K–Nrf2 axis [73]. While treatment with MSCs or MSC-derived exosomes (MSC-Exos) has been found to improve immunosenescence in spontaneous and chemically induced senescent mouse models, it has also been reported that the ameliorative effects of MSCs were transient and required multiple infusions [74]. Therefore, the long-term effects of MSCs on immunosenescence and the specific mechanisms involved require further research.

MSC-based therapy in immunosenescence-related disease

MSCs have shown significant potential in treating conditions linked to immune aging, such as age-related frailty and COVID-19, and research has uncovered valuable insights into their potential for mitigating age-related immune decline. The safety and potential effectiveness of human donor bone marrow–derived allogeneic hMSCs (allo-hMSCs) for treating elderly frailty patients (mean age: 78.4 ± 4.7 years) were assessed in a non-randomized, dose-escalation study [75] in which the patients received a single intravenous infusion of 20 million, 100 million, or 200 million allo-hMSCs. The level of the chronic inflammatory marker TNF-α, which is associated with aging and increased mortality in elderly people [7], was significantly reduced at 6 months in both the 100- and 200-million dose groups. However, the patients' C-reactive protein (CRP), IL-6, fibrinogen, and D-dimer levels, as well as their white blood cell counts were unchanged. Treatment with the 100-million dose was the most effective, with the patients in the group exhibiting substantially enhanced SF-36 physical component scores across all assessment time points [75]. These findings are supported by another phase II randomized, double-blind, placebo-controlled study on human donor bone marrow–derived allo-MSC transplantation in a group of aged frailty patients (mean age: 75.5 ± 7.3 years) that reported the same results [76]. Regarding the outcomes, no treatment-emergent serious adverse events occurred 1 month after treatment, and after 6 months, the patients displayed improved physical performance and reduced levels of frailty-associated inflammatory markers. Specifically, the serum TNF-α levels were reduced after 6-month MSC treatment, along with reduced intracellular TNF-α levels in B cells. Furthermore, the population of $CD8^+$ T cells, whose expansion is a critical hallmark of aging, was significantly decreased [76]. While immunologic improvements were observed in the 100- and 200-million groups, enhanced physical performance was exclusive to the 100-million group. These findings imply that allo-hMSC transplantation therapy is safe and immunologically tolerable in aging frailty patients. Importantly, allo-hMSC administration improved clinical symptoms and immune characteristics, thus supporting the clinical application of MSC-based therapy for senescence.

Chronic infections, senescent cells, and SASP cause inflammaging—a significant risk factor for numerous age-related degenerative diseases [77]. Immunosenescence and inflammaging significantly affect the immune response to COVID-19 infection in older people [78]. As a result, elderly people with COVID-19 face increased susceptibility to developing severe illnesses that lead to higher hospitalization and mortality risk. Administration of BMSCs (via intravenous drip, at 1×10^6 per kg body weight) in patients with COVID-19 aged 45–65 years was found to significantly alleviate symptoms, inflammation, and immune response in seven patients after 14 days of treatment, with no adverse effects. Furthermore, MSC transplantation led to an increase in the population of peripheral blood lymphocytes and a decrease in the neutrophil–lymphocyte ratio, CRP, and TNF-α, as well as resulted in the elimination of the overactivated cytokine-secreting $CXCR3^+CD4^+$ T cells, $CXCR3^+CD8^+$ T cells, and $CXCR3^+$ NK cells. COVID-19 tends to disproportionately affect elderly people with comorbidities, potentially leading to severe or even fatal respiratory diseases. Additionally, older individuals may be more susceptible to the effects of immunosenescence. Thus, intravenous MSC transplantation appears to be a safe and effective intervention for treating COVID-19 pneumonia, particularly severe cases [79]. Importantly, MSC administration appears to ameliorate the severe immune responses caused by immunosenescence and inflammaging and could be a promising tool for the treatment of infectious diseases. Below, we will discuss this possibility in more detail by discussing the challenges and limitations associated with the clinical application of MSC treatments, as well as future prospects in terms of clinical research and applications.

Challenges and future perspectives in the clinical application of MSCs

The potential of MSCs to delay aging and mitigate aging-related diseases is widely recognized. Furthermore, MSC transplantation has demonstrated great promise for improving conditions associated with immunosenescence. While various potential applications of MSCs have come to light, the path ahead is fraught with both opportunities and challenges (Fig. 2).

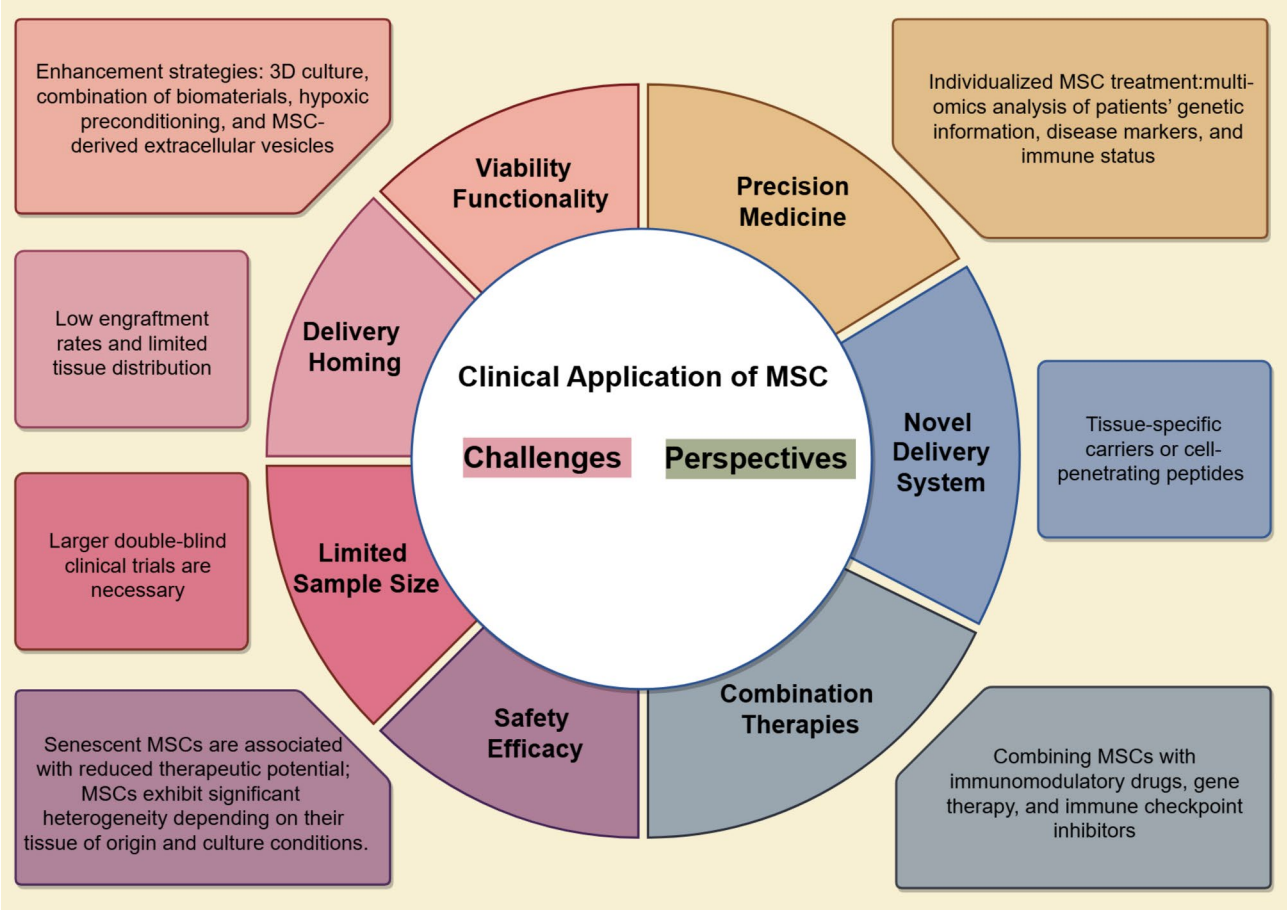

Fig. 2 Challenges and future perspectives in the clinical application of mesenchymal stem cells (MSCs)

Challenges

Safety and efficacy

Safety and efficacy are the foremost concerns with the utilization of MSCs as a novel therapeutic approach. Mouse model research has yielded relatively satisfactory results in this regard, but clinical trials investigating MSC transplantation efficacy and safety for improving immunosenescence are limited. Specifically, while three clinical studies supported the safety and feasibility of MSC-based therapy for improving immunosenescence [75, 76, 79], one study reported that MSCs are also subject to replicative senescence during in vitro expansion, with old donor-derived MSCs exhibiting cellular senescence features [80]. This increase in the senescent MSC population is associated with reduced therapeutic potential and might even exert a detrimental effect to potentially promote disease progression [81, 82]. Consequently, maintaining MSCs in a healthy state is of utmost importance when considering their clinical application. The strategies explored to address cellular senescence and restore MSCs to a youthful state include removal (elimination of senescent or damaged cells), rejuvenation (reversing aging-related cellular dysfunction), and replacement (transplantation of young or genetically modified MSCs) [7]. In addition, inflammaging negatively affects MSC immunomodulatory function and leads to their deterioration; thus, the use of allogenic MSCs from younger donors is considered a potential solution to improve the safety and efficacy of MSC-based therapies. Another limitation is that MSCs exhibit significant heterogeneity in their biological properties, depending on their tissue of origin and culture conditions. This heterogeneity can affect their therapeutic potential and necessitates standardization of MSC isolation, expansion, and characterization protocols. Thus, while MSCs have shown promising results in preclinical and clinical studies, their long-term safety and efficacy in treating immune senescence remain to be fully elucidated.

Delivery and homing

Efficient delivery and homing of MSCs to target tissues are critical for their therapeutic efficacy. However, current delivery methods, such as intravenous injection, often result in low engraftment rates and limited tissue distribution. Furthermore, the absence of standardized guidelines regarding the MSC infusion route and

dosage complicates their application. Standardization of administration protocols is difficult due to the absence of consistent results regarding the optimal dosage. For example, two clinical trials reported that the 100-million dose resulted in substantially enhanced age-related physiological and immunological indicators, whereas the 200-million dose only exerted beneficial immunomodulatory effects. However, the reason for the inverse dose–effect relationship remains unclear [75, 76]. It is possible that the efficacy of MSC-based therapy in ameliorating immunosenescence is not contingent on MSC infusion quantity, but rather, on cellular functionality. This needs to be further explored to obtain viable data based on which MSC dosage regimens can be standardized. There has been a recent surge in research on enhancing MSC viability and functionality to augment their therapeutic effects, with strategies such as hypoxic preconditioning, 3D culture, and combination of biomaterials currently being explored [83]. Another promising option is MSC-derived EVs, as they have shown the ability to delay aging and age-related diseases. Studies have shown that various factors secreted by extracellular vesicles (particularly exosomes) determine the primary therapeutic effects of MSC treatment. As a cell-free option, exosomes offer higher safety due to their nanoscale size, which effectively reduces adverse effects (e.g., infusion-related toxicity). Exosomes serve as key mediators of intercellular communication by carrying a diverse array of bioactive molecules, including proteins, lipids, and RNAs, that play essential roles in immune modulation, inflammation reduction, and tissue regeneration [84–86]. Moreover, they protect molecules from degradation and can be modified on their surface to achieve highly selective targeted delivery. In preclinical and clinical studies, exosomes have demonstrated significant therapeutic potential in areas such as immunomodulation, regenerative medicine, and gene delivery [87].

Limited sample size

The three clinical studies on MSC treatment of immunosenescence published so far reported that the treatment did not influence all immunosenescence-associated inflammatory markers [75, 76, 79]. However, their findings are limited by their small sample size, as the number of patients treated was only 5, 10 or 7. Therefore, larger double-blind clinical trials are necessary to explore the molecular mechanisms of MSCs in the improvement of immunosenescence, as this would enhance our understanding of MSC efficacy. Improving immunosenescence via MSC-based therapy might facilitate early disease intervention or treatment, improve patients' quality of life, and prolong their lifespan.

Future perspectives

Potential of combination therapies

Combining MSCs with other therapeutic modalities, such as drugs and gene therapy, may enhance their therapeutic effects in immunosenescence and immunosenescence-related diseases while addressing some of the current challenges. In particular, combining MSCs with immunomodulatory drugs, anti-inflammatory agents, and specific targeted drugs may have a synergistic effect and enhance the overall therapeutic effects [88, 89]. For instance, co-administration with immunosuppressants may reduce immune rejection of MSCs while promoting immune system reconstruction and balance [90]. With regard to integrating MSCs with immune checkpoint inhibitors, based on the ability of these inhibitors to release the immune system's brakes, the combination could enhance anti-tumor immune responses by simultaneously promoting immune reconstruction and strengthening control over tumors and other immune-related diseases [91]. Moreover, MSC-based gene therapy is an emerging therapeutic strategy that integrates stem cell technology with genetic engineering. These approaches have been explored under in vitro settings and involve gene editing of MSCs through tools such as the CRISPR-Cas9 system to enable precise integration of therapeutic genes into MSCs while maintaining their proliferative and differentiation potential [92]. For instance, in immunosenescence-associated disorders, transplantation of IL-10-overexpressing human amniotic MSCs attenuates arthritis progression by expanding Tregs while suppressing Th17 cell activation, thereby reducing inflammatory infiltration in joint tissues and downregulating the expression of pro-inflammatory factors including IL-1β, IL-6, monocyte chemoattractant protein-1, and TNF-α [93]. Furthermore, CRISPR/dCas9- engineered MSCs with Sox9 activation and RelA inhibition ameliorate cartilage degradation and significantly attenuate inflammatory responses in osteoarthritis models. This anti-inflammatory therapeutic effect correlates with reduced macrophage infiltration in synovial tissues, decreased IL-1β levels in the joint, and downregulation of NF-κB-related genes in synovial cells [94]. For other aging related diseases, VEGF-engineered MSCs enhance angiogenesis and cardiac repair in the ischemic myocardium [95]. Aging related cardiovascular dysfunction is exacerbated by the functional decline of cardiac progenitor cells which may stem from upregulation of SASPs, including matrix metalloproteinase-3, granulocyte-macrophage colony-stimulating factor, IL-1β, IL-6, and IL-8 [7]. Further, aging-associated musculoskeletal alterations, including muscle weakness, osteopenia, and increased bone fragility. MSCs transduced with the BMP2 or RUNX2 genes can enhance osteogenesis and accelerate bone regeneration [96]. In addition, by

utilizing MSCs as vectors for gene therapy, therapeutic genes can be directly delivered to the disease site [97, 98]. This strategy holds particular promise in genetic diseases or immune aging-related conditions requiring long-term gene expression regulation.

Precision medicine

Advances in genomics, proteomics, and metabolomics would enable the application of precision medicine principles to the development of personalized MSC therapies tailored to individual patients' genetic backgrounds and disease states. By analyzing patients' genetic information, disease markers, and immune status, individualized MSC treatment plans can be developed, thus enhancing treatment targeting and efficacy [99]. The personalization of MSC-based therapies is based on considerations of patient-specific variables, disease-specific variables, and product-specific variables. For patient-specific variables, the source (autologous or allogenic) and dose (adjusted based on disease severity, body weight, and metabolic activity) of MSCs are the foremost factors to be considered. For disease-specific variables, the CRISPR-mediated correction of disease-causing mutations (e.g., *COL1A1* in osteogenesis imperfecta) or insertion of therapeutic genes (e.g., *IL-10* for Crohn's disease) based on genetic profiling are alternatives according to specific diseases [100–102]. For product-specific variables, 3D-cultured, pre-treated MSCs, or MSC exosomes may serve as candidate-specific choices.

Novel delivery systems

The development of novel delivery systems, such as tissue-specific carriers or cell-penetrating peptides (CPPs), may improve MSC homing and engraftment and, thereby, enhance their therapeutic potential. That is, carriers that specifically recognize and target damaged tissues or organs, such as nanoparticles modified with tissue-specific antibodies or ligands, can be developed to enhance the efficiency of MSCs [103]. An example of such a carrier is CPPs, which are small molecular peptides that efficiently traverse cell membranes. Conjugating CPPs with MSCs can facilitate their passage through physiological barriers, such as the blood-brain barrier, to reach disease sites inaccessible with traditional methods [104, 105].

Summary

The rapid growth of the elderly population represents a major societal challenge. With aging, the occurrence of immunosenescence and the consequent development of chronic inflammation is inevitable. Immunosenescence renders elderly individuals more susceptible to infections, reduces vaccine responsiveness, and increases reactivity to self-antigens. Moreover, aging decreases stem cell production or activity, leading to impaired physiological function and inflammaging [106]. Currently, there is no effective treatment for immunosenescence. There is evidence to suggest that replenishing or restoring the microenvironment by intravenous MSC infusion might aid the amelioration of aging and aging-related diseases. In fact, in recent years, MSCs have emerged as a promising therapeutic option and have shown efficacy in mouse models of senescence and in the treatment of immunosenescence-related diseases. However, the long-term safety and efficacy of MSCs require further validation through larger clinical trials. In particular, the limited homing ability and activity of MSCs have constrained their further clinical application. Recent strategies, such as genetic modification of MSCs and their combination with drug therapy and novel delivery systems, have been employed to enhance therapeutic outcomes. Overall, MSCs hold potential for ameliorating immunosenescence, reducing inflammatory responses, and restoring immune balance, and warrant future investigation.

Abbreviations

MSCs	Mesenchymal stem cells
SASP	Senescence-related secretory phenotype
IL	Interleukin
TNFα	Tumor necrosis factor-α
ROS	Reactive oxygen species
DCs	Dendritic cells
NK cells	Natural killer cells
NAD	Nicotinamide adenine dinucleotide
IFN	Interferon
BCR	B-cell receptor
TCR	T-cell receptor
EVs	Extracellular vesicles
Tregs	Regulatory T cells
TGFβ	Transforming growth factor-β
hPMSCs	Human placenta mesenchymal stem cells
CPPs	Cell-penetrating peptides

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Author contributions

YY, LW and FZ conceived the project. XW, DG, CH, XX, and YW collected the data. YY and XW wrote and revised the manuscript. YY, LW and FZ provided guidelines and edited the manuscript. All authors read and approved the final manuscript.

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Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

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