PriMera Scientific Surgical
Research and Practice
Volume 7 Issue 1 January 2026
DOI: 10.56831/PSSRP-07-234
ISSN: 2836-0028

PriMera Scientific Publications

Age-Related Decline in Mesenchymal Stem Cells: Implications for Degenerative Disease Burden and Regenerative Medicine Strategies

Type: Research Article
Received: November 21, 2025
Published: December 18, 2025

Citation:
Gordon Slater., et al. "Age-Related Decline in Mesenchymal Stem Cells: Implications for Degenerative Disease Burden and Regenerative Medicine Strategies". PriMera Scientific Surgical Research and Practice 7.1 (2026): 02-09.

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Abstract

Mesenchymal stem/stromal cells (MSCs) exhibit the most dramatic age-related decline among adult stem cell populations, decreasing 100-to 1,000-fold in frequency and suffering profound functional impairment in proliferation, differentiation, immunomodulation, and paracrine activity. Normalized epidemiological data reveal a striking inverse relationship across the human lifespan: as MSC levels plummet between the third and sixth decades, the incidence and prevalence of major degenerative diseases; osteoarthritis requiring total knee/hip replacement, cardiovascular disease, and cancer, rise exponentially (Figure 1). Unlike hematopoietic, neural, muscle, or intestinal stem cells, which primarily undergo qualitative deterioration or protective quiescence while preserving cell numbers, MSCs experience both quantitative depletion and senescence without compensatory mechanisms. Their primary physiological role is not direct lineage replenishment but orchestration of tissue repair through secreted growth factors, anti-inflammatory mediators, and extracellular vesicles that support resident progenitor cells and resolve chronic inflammation. Many clinical trials now demonstrate that administration of culture-expanded autologous or allogeneic MSCs, particularly from younger donors, safely reduces pain and improves function in knee osteoarthritis, modestly enhances cardiac performance post-infarction, and induces remission in steroid-refractory inflammatory diseases, with effect size correlating with donor age and cell dose. These findings strongly suggest that the precipitous loss of functional MSCs constitutes a pivotal, upstream bottleneck in endogenous regenerative capacity and a rational cross-disease therapeutic target. Strategies to restore youthful MSC activity via allogeneic cells from perinatal sources, pharmacological mobilisation, exosome-based therapeutics, or rejuvenation of autologous cells hold promise for mitigating the escalating burden of age-related degenerative pathology and warrant prioritisation in late-stage clinical investigation.

Keywords: Regenerative Medicine; Osteoarthritis; Stem Cells; Mesenchymal Stem Cells

Introduction

Stem cells are defined by two cardinal properties: the capacity for prolonged self-renewal and the ability to differentiate into specialized cell types [1]. In adult mammals, tissue-resident stem cell populations maintain homeostasis by replacing lost or damaged cells throughout life [2]. Well-characterized examples include hematopoietic stem cells (HSCs) that generate all blood lineages [3], neural stem cells in the subventricular zone and dentate gyrus [4], muscle satellite cells [5], and intestinal crypt stem cells [6].

Mesenchymal stem/stromal cells (MSCs) constitute a distinct adult stem cell population originally identified in bone marrow by Friedenstein and colleagues in the 1960s-1970s as plastic-adherent, colony-forming cells capable of osteogenic, adipogenic, and chondrogenic differentiation [7, 8]. The International Society for Cellular Therapy (ISCT) established minimal criteria in 2006: adherence to plastic, expression of CD105, CD73, and CD90 with absence of CD45, CD34, CD14/CD11b, CD79α/CD19, and HLA-DR, and tri-lineage mesenchymal differentiation potential in vitro [9]. MSCs are present at low frequency in virtually all postnatal organs and tissues, with the highest concentrations in bone marrow, adipose tissue, umbilical cord, and dental pulp [10].

Importantly, MSCs differ fundamentally from most tissue-specific stem cells in their primary mechanism of action. Whereas HSCs, neural stem cells, and satellite cells directly generate mature progeny of their respective lineages, MSCs rarely contribute substantial numbers of differentiated parenchymal cells after transplantation in adults [11, 12]. Instead, they function as medicinal signaling cells that orchestrate regeneration through secretion of growth factors, cytokines, extracellular matrix components, and extracellular vesicles [13]. This paracrine/trophic activity underlies their profound immunomodulatory, anti-fibrotic, and pro-regenerative effects across diverse injury models [14].

The progressive increase in life expectancy over the past century has been accompanied by a dramatic rise in chronic degenerative diseases that now dominate morbidity and mortality in individuals over 60 years [15, 16]. Although multifactorial, a unifying biological hallmark is the decline in endogenous repair capacity [17]. Among adult stem cell compartments, MSCs exhibit the steepest quantitative and qualitative deterioration with age [18]. This review examines the magnitude and mechanisms of MSC aging, contrasts it with other stem cell populations, and evaluates evidence that MSC decline contributes causally to the escalating burden of osteoarthritis, cardiovascular disease, cancer, and other age-related pathologies.

Age-Dependent Decline of Mesenchymal Stem/Stromal Cells

The decline in mesenchymal stem/stromal cell (MSC) number and function with advancing age is one of the most dramatic and consistent phenomena observed across adult stem cell compartments. In human bone marrow, the archetypal MSC niche, the frequency of colony-forming unit-fibroblasts (CFU-F); the standard functional assay for MSCs, decreases dramatically. Newborn bone marrow contains roughly 1 MSC per 10,000 nucleated cells, whereas in individuals over 80 years of age the frequency falls to 1 in 1-2 million. Similar age-related depletion occurs in adipose tissue, umbilical cord blood, and peripheral blood mobilizable MSC-like populations [19].

Beyond absolute numbers, aged MSCs exhibit pro-found qualitative impairment. Proliferative capacity, measured by population doubling time and CFU-F efficiency, declines markedly [20]. Telomere length shortens progressively, accumulation of DNA damage and reactive oxygen species increases, and mitochondrial function deteriorates with reduced membrane potential and ATP production [21]. Senescence-associated β-galactosidase activity and expression of p16INK4a, p21, and p53 rise significantly [22].

Differentiation potential is also compromised in a lineage-specific manner. Osteogenic capacity is most severely affected, with aged MSCs showing reduced expression of RUNX2, osteocalcin, and alkaline phosphatase, and diminished mineralized matrix formation [23]. Chondrogenic differentiation is similarly impaired, with lower deposition of aggrecan and type II collagen [24]. Adipogenesis, conversely, is often pre-served or even enhanced, reflecting a shift toward senescence-associated secretory phenotype (SASP)-driven metabolic dysfunction [23].

Immunomodulatory and paracrine functions, now recognized as the primary therapeutic mechanisms of MSCs, are significantly attenuated with age. Secretion of anti-inflammatory mediators such as TSG-6, PGE2, and IL-1RA decreases, while pro-inflammatory cytokines increase [25]. The ability to polarize macrophages toward an M2 anti-inflammatory phenotype and to suppress T-cell proliferation is reduced in MSCs from elderly donors compared with young donors [26, 27].

Epigenetic drift plays a central role. Aged MSCs display global DNA hypermethylation at pluripotency and developmental genes (OCT4, NANOG, SOX2) and hypomethylation at senescence and inflammatory loci [28, 29]. Histone modifications shift toward repressive H3K27me3 marks, and chromatin accessibility at regenerative gene enhancers is lost [30].

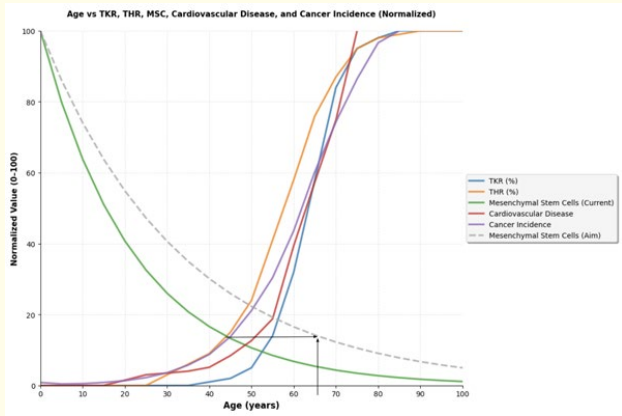

Figure 1

Fig. 1: Age-dependent normalisation of clinical prevalence and incidence rates. Data represent normalized values (0-100 scale) for total knee replacement (TKR), total hip replacement (THR) [31], mesenchymal stem cell frequency [19], cardiovascular disease prevalence [32], and cancer incidence [33] across the human lifespan. Normalization enables comparative analysis of age-related trajectories despite differing measurement scales and units. An estimated aim of projected MSC levels is indicated by a grey dotted line, where a higher msc level could skew mentioned prevalence and incidence rates.

This temporal congruence, while not proof of causality, strongly supports the hypothesis that loss of functional MSCs constitutes a critical upstream driver of systemic regenerative failure in aging.

Comparative Aging of Adult Stem Cell Compartments

Adult stem cell populations exhibit diverse aging trajectories, reflecting their distinct physiological roles and niche dependencies. Hematopoietic stem cells (HSCs) provide the clearest contrast to MSCs [34]. In humans and mice, HSC numbers remain stable or even increase modestly with age, yet functional quality deteriorates through accumulated DNA mutations, replication stress, and lineage bias toward myeloid output at the expense of lymphoid and erythroid potential [35, 36]. Despite these defects, the HSC compartment never undergoes the catastrophic numerical depletion characteristic of MSCs.

Muscle satellite cells (MuSCs), the principal stem cells for skeletal muscle regeneration, show a different pattern: their absolute number is largely preserved throughout life, but they transition into a state of prolonged, often irreversible quiescence termed “gerogenic quiescence” [37]. This is driven by upregulation of p16INK4a, increased FGF signaling, and stiffness of the aged extracellular matrix, resulting in dramatically reduced regenerative capacity after injury [38, 39].

Neural stem cells (NSCs) in the subventricular zone and subgranular zone of the hippocampus also decline in activity, with a decrease in absolute number with age [40]. Neurogenesis falls sharply after middle age due to depletion of the quiescent NSC pool, exhaustion of transit-amplifying progenitors, and a pro-inflammatory, pro-fibrotic niche microenvironment [41, 42]. Systemic factors such as CCL11/eotaxin further suppress NSC proliferation in aged individuals [43].

In marked contrast, MSCs are unique among adult stem cells in displaying both a steep quantitative decline and simultaneous qualitative senescence without compensatory hyperplasia or prolonged protective quiescence [19, 44]. This dual loss likely reflects their primary evolutionary role not as direct lineage progenitors, but as orchestrators of the perivascular niche and modulators of inflammation and repair [46]. When MSC support wanes, tissue-resident stem cells, even if numerically intact; lose critical trophic, anti-inflammatory, and anti-fibrotic cues, accelerating systemic degenerative failure [47]. The distinctive aging pattern of MSCs therefore positions their decline as a pivotal upstream bottleneck in multi-organ dysfunction during aging.

Mechanisms of MSC-Mediated tissue Regeneration

Contemporary understanding of mesenchymal stem/stromal cell (MSC) function has moved decisively away from the early hypothesis of direct cellular replacement and toward recognition of predominantly paracrine, trophic, and immunomodulatory mechanisms. Extensive preclinical and clinical biodistribution studies consistently show that fewer than 5% of administered MSCs (whether delivered intravenously, intra-arterially, or locally) remain detectable at the target site beyond 7-14 days, with a study showing most MSCs delivered to the kidney intravenously disappearing after 2 days [48].

Instead, MSCs act as transient "medicinal signaling factories" [49]. Their therapeutic effects are mediated by a complex secretome that includes soluble growth factors (VEGF, HGF, IGF-1, FGF-2) [50], anti-inflammatory and pro-resolving mediators (IL-10, TGF-β1, TSG-6, PGE2, IDO-1), anti-fibrotic molecules, and large numbers of extracellular vesicles (exosomes and microvesicles) carrying proteins, mRNA, miRNA, and lipids [51]. These secreted factors exert multiple synergistic actions: (i) direct trophic support that prevents apoptosis and stimulates proliferation of resident tissue progenitors via PI3K/Akt and MAPK pathways [52]; (ii) potent immunomodulation through inhibition of pro-inflammatory T-cell and macrophage responses, induction of regulatory T cells, and polarization of macrophages toward an anti-inflammatory M2 phenotype [53]; (iii) reduction of pathological fibrosis by antagonizing TGF-β/Smad signaling [54]; and (iv) promotion of neo-angiogenesis and vascular stabilization [55].

Critically, MSCs do not directly expand or replenish other stem-cell populations such as HSCs, satellite cells, or neural progenitors. Rather, they create a regenerative microenvironment that enables endogenous tissue-specific stem and progenitor cells to function more effectively. This "supporting-cast" rather than "lead-actor" role explains both the remarkably broad efficacy of MSC therapy across seemingly unrelated degenerative diseases and the emerging success of cell-free MSC-derived exosome preparations as next-generation therapeutics.

Clinical Evidence of MSC Therapy in Degenerative Diseases

In knee osteoarthritis, multiple meta-analyses of randomised controlled trials (RCTs) involving autologous or allogeneic bone marrow-and adipose-derived MSCs report significant reductions in pain (WOMAC and VAS scores) and improvement in cartilage volume and quality on MRI at 12-24 months, with effect sizes superior to hyaluronic acid or placebo [56]. Trials using younger allogeneic donors or higher doses (≥40-100 × 10^6 cells) show the largest benefits, indirectly supporting the age-related functional decline hypothesis [57].

For cardiovascular disease, phase II/III studies of intramyocardial or intracoronary MSC delivery after acute myocardial infarction or in chronic ischemic cardiomyopathy modestly improve left ventricular ejection fraction (3-6 %), reduce scar size, and decrease major adverse cardiac events [58].

In steroid-refractory graft-versus-host disease, Crohn's fistulae, systemic sclerosis, and multiple sclerosis, allogeneic MSC products (including the approved remestemcel-L) achieve response rates of 50-75 % where conventional therapy fails, primarily through im-

munomodulatory mechanisms [59]. Early-phase trials in frailty and sarcopenia further demonstrate improved physical performance, reduced inflammatory markers, and enhanced quality of life in elderly recipients of young allogeneic MSCs [45]. These clinical outcomes strongly reinforce the concept that restoring youthful MSC activity can meaningfully counteract age-associated degenerative pathology.

Discussion

The data presented in this review, particularly the striking inverse mirror-image trajectories shown in Figure 1, provide compelling circumstantial evidence that the steep age-related decline in mesenchymal stem/stromal cell (MSC) frequency and function represents a critical upstream driver of the exponential rise in degenerative disease burden after middle age. The temporal alignment is remarkable: the most rapid drop in MSC numbers occurs between the third and sixth decades, precisely when total joint replacement rates, cardiovascular disease prevalence, and cancer incidence begin their steep ascent. Although correlation does not prove causation, this pattern is consistent with extensive preclinical evidence. Human observational studies similarly associate higher circulating MSC-like populations or younger donor MSC therapy with reduced cardiovascular events, better postoperative recovery, and lower systemic inflammatory markers [45].

The unique biology of MSCs explains why their decline may have system-wide consequences disproportionate to their low baseline frequency. Unlike hematopoietic, neural, muscle, or intestinal stem cells, which primarily serve lineage-restricted replacement. MSCs evolved as perivascular orchestrators of the regenerative microenvironment. Their loss therefore deprives multiple tissue-resident stem cell compartments of essential trophic, anti-inflammatory, and anti-fibrotic support, even when those compartments remain numerically intact. This "supporting-cast" model accounts for the surprisingly broad efficacy of MSC-based interventions across seemingly unrelated degenerative conditions, from osteoarthritis to ischemic cardiomyopathy to steroid-refractory autoimmunity.

Current limitations of MSC therapy are well recognised: autologous cells from elderly patients exhibit reduced potency, allogeneic products face donor-to-donor variability and logistical challenges, and optimal dose, route, and timing remain incompletely standardised. Nevertheless, the consistent finding that younger donor age and higher cell dose predict superior clinical outcomes strongly reinforces the central thesis that age-related MSC dysfunction is biologically meaningful and clinically reversible.

Emerging strategies including cytokine/hypoxia priming, use of perinatal tissues, pharmacological mobilisation of endogenous MSCs, and cell-free exosome therapeutics offer realistic paths toward overcoming these hurdles [60, 61].

Conclusions

In conclusion, the pronounced and distinctive aging of the MSC compartment represents a rational, cross-disease therapeutic target for the burgeoning epidemic of age-related degenerative pathology. Appropriately powered clinical trials using optimised, youth-associated MSC products or their bioactive derivatives are now justified to determine whether partial restoration of MSC activity can meaningfully compress morbidity and extend health span in the aging population.

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