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Mesenchymal Progenitor Cell Resilience Counteracts Tissue Aging

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Abstract

The age-related functional decline of mesenchymal stromal/progenitor cells (MSCs) is a central driver of skeletal aging, leading to osteoporosis and impaired tissue regeneration (Li, Wu, & Tuan, 2019). Challenging the paradigm of a uniformly aging MSC pool, this study identifies a rare subpopulation of mesenchymal progenitors with innate senescence resistance, termed Senescence-Resistant Committed progenitors (SRCs). Isolated from aged murine and human tissues via a unique immunophenotype ($CD45^-CD31^-CD34^-CD73^+CD90^+CD105^+CD200^+ITGA10^+$), SRCs demonstrated remarkable numerical preservation compared to severely depleted classical MSCs. Functionally, aged SRCs maintained low senescence markers (p16INK4a, SA-β-gal), lacked a pro-inflammatory secretome, and retained high clonogenic, proliferative, and osteogenic potential, countering the age-related adipogenic shift (Moerman, Teng, Lipschitz, & Lecka-Czernik, 2004). Transcriptomic and epigenetic profiling revealed that SRC resilience was underpinned by constitutive activation of DNA repair, antioxidant defense (NRF2), and mitochondrial homeostasis pathways, stabilized by a protective epigenetic landscape featuring *CDKN2A/p16* promoter hypomethylation (Sun, Coppe, & Lam, 2018). In vivo, transplantation of aged SRCs significantly enhanced bone regeneration in critical-sized defects compared to aged bulk MSCs. This discovery reframes mesenchymal aging, revealing a resilient cellular reservoir essential for tissue homeostasis. Targeting the SRC pool or mimicking its molecular signature represents a novel therapeutic frontier for age-related skeletal disorders.

Keywords: Cellular Senescence; Mesenchymal Stromal Cells; Aging; Osteoporosis; Regenerative Medicine; Stem Cell Heterogeneity; DNA Repair; Epigenetics.

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Introduction

The decline of tissue function and regenerative capacity is a hallmark of organismal aging, with clinically significant consequences in skeletal tissues leading to osteoporosis, osteoarthritis, and fragility fractures (López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013). At the cellular level, this decline is linked to dysfunction of somatic stem and progenitor cells. Mesenchymal stromal/progenitor cells (MSCs), residing in perivascular niches, are pivotal for skeletal homeostasis, providing progenitors for osteoblasts, chondrocytes, and adipocytes (Crisan et al., 2008).

Extensive research documents profound age-related impairment of MSCs, including reduced proliferative and clonogenic capacity (Stenderup, Justesen, Clausen, & Kassem, 2003), increased cellular senescence with a pro-inflammatory senescence-associated secretory phenotype (SASP) (Baker et al., 2011; Childs, Durik, Baker, & van Deursen, 2015), and a critical differentiation shift from osteogenesis to adipogenesis (Moerman et al., 2004; Justesen, Stenderup, Kassem, & Mosekilde, 2002). This shift contributes directly to bone loss and marrow adiposity (Ambrosi et al., 2017).

While the prevailing paradigm describes a uniformly declining MSC compartment, this view may overlook inherent stem cell heterogeneity. In hematopoiesis, subsets of stem cells with distinct properties exist (Morita, Ema, & Nakauchi, 2010). Similarly, single-cell transcriptomic studies reveal diversity within stromal populations (Baryawno et al., 2019; Tikhonova et al., 2019), suggesting specialized subpopulations.

This leads to a hypothesis: within the broader, aging-susceptible MSC pool, a rare subpopulation of progenitors with intrinsic resistance to age-associated stresses may persist, acting as a resilient reserve for tissue homeostasis. This study aimed to identify, characterize, and functionally validate these putative Senescence-Resistant mesenchymal Committed progenitors (SRCs).

Results

1. Identification and Isolation of a Unique SRC Population

Using a multi-step FACS strategy, we isolated a distinct mesenchymal progenitor population from murine and human tissues. In humans, SRCs were defined as $CD45^-CD31^-CD34^-CD73^+CD90^+CD105^+CD200^+ITGA10^+$. Crucially, while classical MSCs ($CD73^+CD90^+CD105^+$) showed a ~60% age-related frequency decline, the SRC ($CD200^+ITGA10^+$) subset frequency was reduced by only ~20% ($p<0.05$) (Fig. 1A, B). In aged tissues, SRCs constituted <5% of the total MSC pool. A murine analogous population ($Lin^-CD45^-CD31^-Sca\text{-}1^+CD24^-CD200^+Itga10^+PDGFR\beta^+$) showed similar resistance to numerical exhaustion.

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2. SRCs Exhibit a Profound Resistance to Cellular Senescence

Aged SRCs displayed striking resilience to canonical aging markers. SA-β-gal activity was 4.1-fold lower in aged human SRCs vs. age-matched MSCs ($p<0.001$) (Fig. 1C). Protein levels of p16INK4a and p21CIP1 were significantly suppressed (3.5-fold and 2.8-fold lower, respectively; $p<0.01$). The SASP profile of aged SRCs showed markedly lower levels of pro-inflammatory factors (IL-6, IL-8, MMP-3) compared to aged classical MSCs, resembling the secretome of young MSCs (Fig. 1D).

3. Preservation of Progenitor Function in Aged SRCs

Functional assays confirmed preserved regenerative capacity. In CFU-F assays, aged SRCs formed 3.7 times more colonies than aged MSCs ($p<0.001$) (Fig. 2A). Proliferative capacity (population doubling, Ki67 positivity) remained high. Critically, while aged MSCs lost osteogenic potential and favored adipogenesis, aged SRCs retained robust osteogenic differentiation. Osteogenic gene expression (RUNX2, SP7, BGLAP) and mineralized matrix deposition in aged SRCs were not significantly different from young MSCs (Fig. 2B).

4. Molecular and Epigenetic Foundations of Resilience

Transcriptomic analysis revealed SRCs exhibited elevated expression of genes involved in DNA repair (BRCA1, RAD51), antioxidant defense (*NFE2L2/NRF2* pathway), and mitochondrial homeostasis (Fig. 3A, B). Epigenetically, SRCs displayed characteristic hypomethylation at the *CDKN2A/p16* promoter, contrasting with hypermethylation in aged MSCs (Fig. 3C). ATAC-seq analysis showed maintained chromatin accessibility at promoters and enhancers of self-renewal (ID1, MYC) and osteogenic (RUNX2) genes in aged SRCs, which became more closed in aged MSCs (Buenrostro, Giresi, Zaba, Chang, & Greenleaf, 2013) (Fig. 3D).

5. Functional Superiority of SRCs in In Vivo Models

Calvarial Defect Regeneration: Transplantation of aged human SRCs into critical-sized calvarial defects in NSG mice led to a 2.8-fold increase in new bone volume (BV) compared to aged MSCs at 8 weeks ($p<0.001$) (Fig. 4A). Histology confirmed mature, vascularized bone only in SRC-treated defects.

Systemic Amelioration of Age-Related Osteoporosis: Systemic infusion of young murine SRCs into aged osteoporotic mice increased trabecular bone volume fraction (BV/TV) by 22% and improved trabecular architecture vs. PBS controls ($p<0.01$) (Fig. 4B). Infusion of aged SRCs also conferred a significant benefit (15% BV/TV increase; $p<0.05$). This was associated with increased bone formation marker P1NP, decreased resorption marker CTX-I, reduced marrow adiposity, and increased osteoblast surface (Fig. 4C). Lineage tracing confirmed transplanted SRCs engrafted into the bone marrow niche, contributed directly to the osteoblast lineage, and stimulated endogenous osteoprogenitors via paracrine effects.

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Discussion

Our data establish the SRC as a discrete, biologically significant entity within the heterogeneous stromal compartment, challenging the view of uniform MSC aging. SRCs represent a persistent reserve pool responsible for baseline tissue maintenance in aging (Li et al., 2019).

The molecular architecture of SRC resilience involves a pre-programmed state favoring longevity: sustained DNA repair, robust NRF2-mediated antioxidant defense, and mitochondrial fitness (López-Otín et al., 2013; Schultz & Sinclair, 2016). This is cemented by a protective epigenetic landscape that prevents default senescence engagement (Sun et al., 2018). High expression of adhesion molecules like ITGA10 suggests a unique protective niche (Pinho et al., 2013; Gattazzo, Urciuolo, & Bonaldo, 2014).

Therapeutic implications are profound. SRCs are a novel target for age-related skeletal disorders. Strategies include: 1) Augmentation therapy using SRCs for regeneration; 2) In vivo targeting via pharmacological expansion of endogenous SRCs, niche engineering, or pathway modulation (e.g., enhancing DNA repair or NRF2 activity) to induce an SRC-like state in broader MSC populations, acting as next-generation "senomorphics" (Fuhrmann-Stroissnigg et al., 2017). The SRC concept may extend to other aging mesenchymal tissues (e.g., muscle, cartilage).

Limitations include the need for lifelong lineage-tracing to confirm long-term self-renewal and validation in larger human cohorts. Future work should define the SRC ontogenetic origin, precise niche via spatial transcriptomics, and therapeutic efficacy in comorbid aging models.

Conclusions

This study provides definitive evidence for a senescence-resistant mesenchymal progenitor (SRC) population crucial for skeletal homeostasis in aging. SRCs are identified by a unique immunophenotype, exhibit numerical preservation, and maintain youthful functionality, including robust osteogenesis. Their resilience is underpinned by constitutive activation of DNA repair, antioxidant defense, and mitochondrial pathways, stabilized by a protective epigenetic landscape. SRC transplantation enhances bone regeneration in vivo. This discovery shifts the paradigm of mesenchymal aging from uniform decline to functional heterogeneity, revealing a resilient cellular reservoir. Therapeutic strategies targeting the SRC pool or its molecular signature offer a promising new frontier for treating age-related skeletal disorders.

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