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Review article

Running on empty: Exploring stem cell exhaustion in geriatric musculoskeletal disease

Amy Lawton [a,b], Nicholas Tripodi [a,c], Jack Feehan [a,d,*]

[a] Institute for Health and Sport, Victoria University, Melbourne, Australia
[b] College of Sport, Health and Engineering, Victoria University, Melbourne, Australia
[c] First Year College, Victoria University, Melbourne, Australia
[d] School of Health and Biomedical Sciences, STEM College, RMIT, Melbourne, Australia

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ABSTRACT

Ageing populations globally are associated with increased musculoskeletal disease, including osteoporosis and sarcopenia. These conditions place a significant burden of disease on the individual, society and the economy. To address this, we need to understand the underpinning biological changes, including stem cell exhaustion, which plays a key role in the ageing of the musculoskeletal system. This review of the recent evidence provides an overview of the associated biological processes. The review utilised the PubMed/Medline, Science Direct, and Google Scholar databases. Mechanisms of ageing identified involve a reaction to the chronic inflammation and oxidative stress associated with ageing, resulting in progenitor cell senescence and adipogenic differentiation, leading to decreased mass and quality of both bone and muscle tissue. Although the mechanisms underpinning stem cell exhaustion are unclear, it remains a promising avenue through which to identify new strategies for prevention, detection and management.

1. Introduction

Ageing is a key risk factor for almost all chronic disease in humans, including cardiovascular disease, cancer, neurodegenerative disease, and musculoskeletal conditions [1]. Musculoskeletal diseases represent a substantial burden on older adults globally, significantly impacting their health and well-being. As populations age worldwide, the prevalence of musculoskeletal conditions such as osteoporosis, and sarcopenia rise dramatically. These conditions lead to reduced mobility, functional limitations, and diminished quality of life among older individuals. Globally, musculoskeletal disorders are among the leading causes of years lived with disability (YLDs), with older adults bearing a disproportionate share of this burden [2]. The economic impact of musculoskeletal diseases is also significant, with healthcare costs, lost productivity, and the need for long-term care placing a strain on healthcare systems and economies worldwide [3,4]. In the face of such significant impact, there is a need to understand the biological changes which occur in the ageing musculoskeletal system in order to identify new avenues for disease detection, treatment and prevention.

The modern field of geroscience attempts to unify the key biological changes which define physiological ageing and in turn drive the onset and progression of all chronic diseases, including musculoskeletal conditions [5]. Geroscience has currently identified the key physiological factors of inflammation, proteostasis, macromolecular damage, epigenetics, metabolism, and stem cell exhaustion [6]. While all of the physiologies identified by geroscience have an impact on bone, muscle and cartilage, stem cell exhaustion has gained particular attention in the field of musculoskeletal disease and regenerative medicine.

Stem cell exhaustion refers to the progressive loss of progenitor cell function and regenerative capacity over time, which leads to diminished tissue maintenance and repair [7]. As stem cells divide to replenish tissues throughout life, telomere shortening, accumulation of DNA damage, and alterations in the niche microenvironment in which they reside, all contribute to reduced proliferation and altered capacity for differentiation. Stem cell ageing has been more clearly defined in tissues with high turnover rates, such as the hematopoietic system, intestinal epithelium, and the skin, where small changes in function lead to large impacts [7]. While the stem cell and progenitor populations of musculoskeletal tissue do not proliferate as rapidly as epithelial tissues, their highly specialized differentiation physiology leaves them equally vulnerable to these changes [8]. Understanding the physiological impact of stem cell ageing on bone, and muscle is critical in identifying novel

* Corresponding author at: Victoria University, Australia.
E-mail address: jack.feehan@vu.edu.au (J. Feehan).

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means to diagnose and treat chronic musculoskeletal disease affecting older adults. Therefore, this review aims to synthesise recent evidence on the impact of stem cell ageing in older adults to identify future research directions for regenerative medicine in the field. Despite its notable impact on older adults, osteoarthritis has been excluded from the review. This decision was based on the uncertain role of stem cells to the pathophysiology of the disease, and a notable lack of research in the area, despite the rise in progenitor-based treatments.

2. Methods

To produce this review of the recent evidence a search was conducted utilising the PubMed/Medline, Science Direct, and Google Scholar databases. Searches were conducted using the terms 'stem cell', and 'progenitor' alongside 'ageing', 'exhaustion', and 'senescence', to find studies relevant to stem cell ageing and exhaustion. In addition, the keywords 'bone', 'muscle', 'musculoskeletal', 'mesenchymal', and 'mesodermal' were used to limit the search to musculoskeletal progenitor populations, with appropriate Boolean operators. Where relevant, both US and UK spellings were used. Articles that were published from 2010 to 2024 and written in English were included to provide a contemporary review on this rapidly evolving topic. Once duplicates were removed there were a total of 3092 articles remaining. From here the authors screened the pool of articles to identify studies directly relevant to ageing, with 42 articles being included in the final manuscript. In order to provide the most direct evidence on the impact of ageing on the musculoskeletal system, only studies which directly studied the effect were included, rather than animal knock-out or knock-in experiments, or other genetic manipulation studies.

2.1. Rejuvenation of the musculoskeletal system

Tissues of the musculoskeletal system undergo lifelong regeneration, repair, and adaptation to mechanical and chemical forces acting on them via the processes of mechano- and chemotransduction [9]. This process is orchestrated by a complex interaction between a number of tissue-specific progenitor cells, as well as the immune and endocrine systems. There are a number of specific progenitor populations involved in the regeneration of the musculoskeletal system, with the most well-known being the mesenchymal stem and progenitor cells (MPCs) found in the bone marrow, which differentiate into osteoblasts, chondrocytes, and adipocytes [10], as well as the muscle-specific satellite cell populations [11]. More recently, there have been novel populations of musculoskeletal progenitors found in blood [12], adipose [13], and other tissues, however, their roles in the maintenance of muscle and bone, as well as the impact of ageing on these cells largely remains unknown [14,15].

2.2. The ageing skeleton – the role of stem cell exhaustion in bone

Maintenance of bone health requires a dynamic balance between the anabolic osteoblast, and catabolic osteoclast, mediated by resident osteocytes embedded in the bone [16]. In a normal setting, the MPC population in the bone marrow responds to anabolic signaling from osteocytes and endocrine signals by proliferating and then differentiating into osteoblasts, which lay down and mineralize the osteoid. This is balanced by the fusion of monocyte derived osteoclast progenitors, forming multinucleate mature osteoclasts, which resorb bone, releasing calcium into the circulation. Ageing bone is characterized by increased osteoclastogenesis, and decreased osteoblast differentiation, which shifts the equilibrium toward bone resorption, resulting in decreased bone density and quality, which over time leads to the development of osteoporosis and an increased risk of fragility fracture [16]. The physiological root of this imbalance is multifactorial, including chronic inflammation-mediated acceleration of osteoclastogenesis, age-related decline in the availability of critical nutrients for bone formation (e.g. vitamin D, calcium, and protein), and exhaustion of the MPC pool (Fig. 1).

A decline in the proliferation capacity or MPCs, as well as dysfunction in their differentiation physiology, has significant impacts on the ageing skeleton. As an individual ages, an increasing proportion of MPCs become senescent, entering a stable period of cell cycle arrest, in which the cell ceases to proliferate. This is triggered by the accumulation of genetic damage, epigenetic change, and telomere shortening in the cells [8]. This process forms a major component of anti-tumor defense, however, accumulation of these cells across the lifespan leads to ongoing and advancing dysfunction in musculoskeletal regeneration. Importantly, these cells retain some secretory capacity, termed the senescence associated secretory phenotype (SASP), which is commonly pro-inflammatory and pro-oxidative, and can propagate senescence to neighboring cells.

Effective maintenance of bone by MPCs requires the cells to respond to anabolic or injury signaling by proliferating, migrating to the affected area, and differentiating into osteoblasts to deposit and mineralize the osteoid. Each of these physiological processes is disrupted by ageing, leading to advancing deficits in bone density and quality in older adults. With increasing age, the proportion of senescent MPCs in the pool grows, with the SASP triggering an inflammatory and oxidative environment in the bone marrow progenitor niche, driving further senescence. This increasing number of senescent cells leaves a smaller number of active proliferative cells in the bone marrow of older adults, limiting their capacity to regenerate the bone. Interestingly, treatment with the

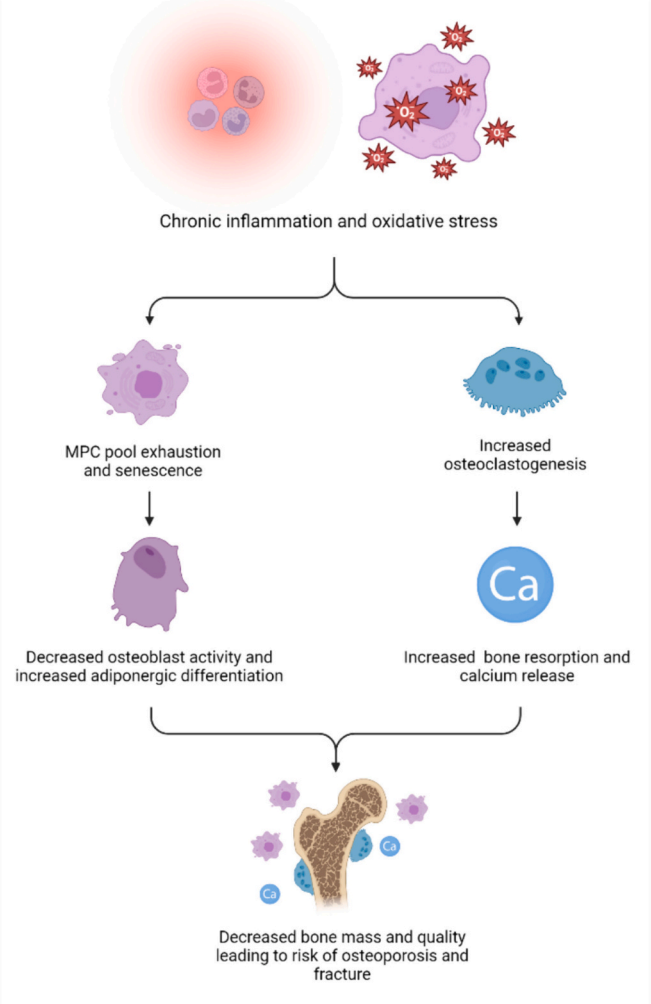

Fig. 1. The driving mechanisms of ageing bone. Created with BioRender.com.

common osteoporosis medication zoledronate restored proliferative function in MPCs, protecting them against genetic damage through inhibition of mammalian target of rapamycin (mTOR) signaling, potentially underpinning some of its anabolic effects [17]. In addition to restricted proliferation, ageing MPCs also have a reduced ability to migrate, with decreased expression of key cytokinetic markers such as C-X-C chemokine receptor type 4 (CXCR4) and 7 (CXCR7), which allow homing to sites of bone formation [18]. Finally, ageing MPCs also show an altered capacity for osteoblastic differentiation. Senescent MPCs in bone tend to differentiate toward an adipogenic lineage, rather than osteoblastic, leading to decreased bone formation and accumulation of adipose tissue in the bone marrow. A number of mechanisms, including oxidative stress and accumulation of reactive oxygen species (ROS), mammalian target of rapamycin (mTOR) signaling, and excessive exposure to insulin like growth factor 1 (IGF1) are all known mediators of pro-adipogenic differentiation in MPCs [19].

Excessive mTOR and IGF1 signaling are common in older adults, driven by glucometabolic changes, chronic hyperglycemia and hyperinsulinaemia, which in turn also drive oxidative stress in the bone marrow microenvironment [20]. Murine MPCs treated with IGF1 binding protein (IGF1BP) show decreased capacity for proliferation, which is restored following inhibition of this pathway [21]. MPCs isolated from the umbilical cord of females with gestational diabetes show limited proliferation and differentiation capacity and have a greater senescence phenotype [22] demonstrating the critical relationship between glucose control and progenitor function. The effect of ROS and oxidative stress on MPC function and bone health is widespread. Oxidative stress has been shown to cause significant changes to the immunomodulatory function of MPCs, driving increased inflammation, and reduced proliferation and differentiation [23]. This is exacerbated by the increase in osteoclast activity in settings of inflammatory and oxidative stress, leading to excess bone resorption, alongside decreased osteogenesis.

These changes collectively lead to an inability for the osteoblast and MPCs to collectively maintain bone mass in the face of ongoing and often accelerated osteoclast activity. This imbalance is a core component of the rapid increase in osteoporosis and osteopenia in later life and, subsequently, the enormous burden of fragility fractures in older adults. However, while the decrease in bone health plays a central role in this, it is also strongly contributed to by the age-related decline of skeletal muscle tissues, and the onset of sarcopenia, with associated increased risk of falling.

2.3. The role of stem cell exhaustion in the ageing muscular system

Adequate skeletal muscle mass and effective function is critical to healthy ageing, providing functional independence, cardiometabolic health, and preventing falls [24,25]. As with bone, skeletal muscle undergoes continuous remodeling, with resident adult stem cells, known as satellite cells, responding to injury and anabolic signaling, by differentiating into functional myocytes. In ageing, the capacity for regeneration declines, leading to both common acute injuries in older adults such as rotator cuff and biceps brachii rupture, and more widespread disease such as sarcopenia. This decline in regeneration is multifactorial but is strongly contributed to by the decline of satellite cell function secondary to immune system dysregulation and inflammation (Fig. 2).

Whether it be through the physiological microtrauma of resistance training, or gross injury such as muscle strain, a range of growth factors and inflammatory mediators trigger the proliferation, and differentiation of quiescent local satellite cells to form new muscle fibres. As with the MPC population in the bone marrow, ageing satellite cells are characterized by decreased autophagy, increased genetic damage and senescence, leading to a decrease in the number of active proliferating cells [26,27]. This results in a decreased capacity for ongoing tissue repair, as well as a reduction in the ability to respond to resistance training interventions. In addition to decreased proliferation, ageing

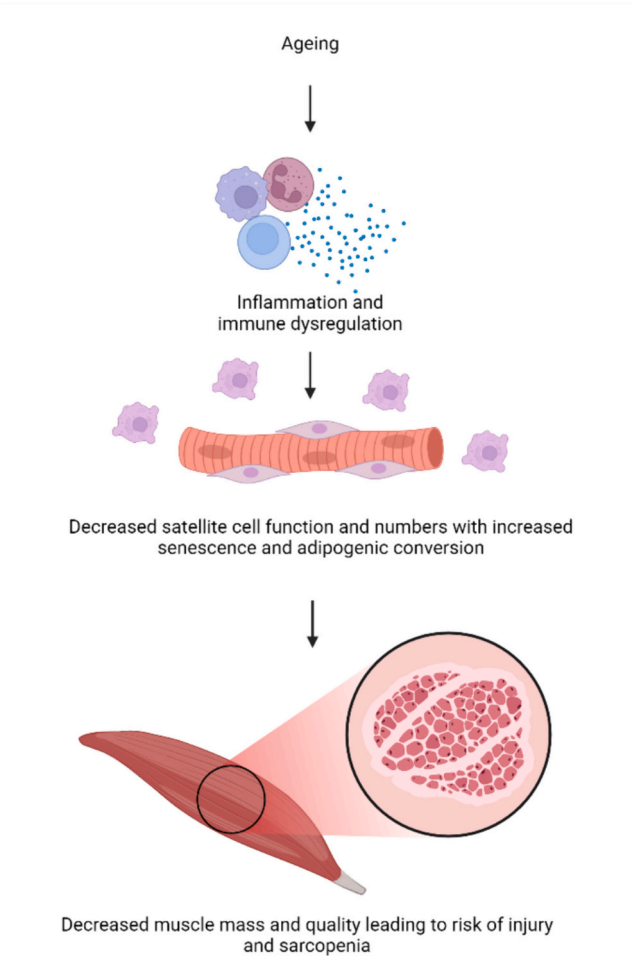

Fig. 2. The age-related changes that lead to sarcopenia. Created with BioRender.com.

muscle is characterized by a general loss of satellite cell numbers, which occurs with changes to the niche microenvironment [28]. Increased expression of factors such as fibroblast growth factor 2 (FGF2), and upregulated NOTCH signaling leads to cell cycle exit of satellite cells and population decline [28,29].

More so than MPCs, satellite cells require a close interaction with the immune system for optimal function [30]. Skeletal muscle maintains a dedicated immune presence throughout life, with specialized monocyte/macrophage populations differentiating into pro or anti-inflammatory phenotypes to respond to local conditions with contractile activity. In addition, these resident macrophages critically regulate the proliferation and differentiation of satellite cells [31]. Furthermore, resident regulatory T cells (Tregs) produce a number of factors, such as amphiregulin, and interleukin-33, which also trigger the proliferation and replenishment of satellite cell populations in muscle [32]. This interaction between the satellite cells and the immune system is commonly dysregulated with ageing, as immunosenescene leads to a prolonged and dysfunctional inflammatory state, particularly in persistent resident cells, such as macrophages and Tregs [33].

The process of differentiation from satellite cell to functional muscle fibre is complex, requiring sequential expression of several transcription factors, such as PAX7, Myf5, and MyoD [34]. Adding additional complexity, satellite cells self-regulate during proliferation, with Myf5+ satellite cells maintaining overall stem cell populations in the muscle [35], compounding the dysfunction seen in ageing muscle. In aged mice, PAX7 concentrations decline, likely leading to decreases in early differentiation [36], but also then reducing expression of the downstream

Myf5. This subsequently reduces maintenance of the quiescent stem cell pool and reduces capacity for ongoing renewal. In addition, ageing satellite cells are prone to undergo adipogenic conversion, leading to aggregation of intramuscular adipose tissue (IMAT), though other cell types can also contribute [35]. IMAT is a key feature of many chronic diseases, such as sarcopenia and metabolic syndrome, and leads to reduced functional capacity, and accelerated skeletal muscle loss. The pathways driving adipogenic conversion of satellite cells are poorly understood, however it seems likely that insulin/glucose signaling plays a strong role [37,38]. Skeletal muscle is an important reservoir for plasma glucose, and is highly sensitive to insulin and other incretin signals. Chronic exposure to nutrient sensing hormones and factors such as IGF1 and insulin, as well as their target pathways such a mTOR has been shown to induce adipogenesis in satellite cells in animal and cell culture models [39,40], however it has also been suggested that other terminally differentiated and progenitor cells can contribute to adipogenesis and deposition of IMAT [41,42].

2.4. Future directions

In recent years, there has been a rapid increase in focus on regenerative therapies and stem cell exhaustion as a therapeutic target in ageing research. However, before these approaches are able to be translated into use, there is a significant amount of research required to fully understand their roles in health and disease. The complex interplay between progenitor populations, the niche microenvironment, and the endocrine and immune systems, makes isolating a role for stem cells challenging. It is possible that many of the changes seen in adult stem cells from older adults are, in fact, a response to systemic factors such as ongoing inflammation, oxidative stress, and changes to glucometabolism. This would likely make interventions directed at the progenitors themselves less effective. However, these interactions could also help identify new or repurposed therapeutic targets, with molecules that modulate these signaling pathways, potentially providing greater therapeutic effects. Novel mechanisms, such as the deficiency of the anti-ageing hormone klotho, have emerged in recent years [43], providing key areas of future research interest. The emergence of other broad therapeutics aimed at removing, or restoring senescent cells is also an emerging area of interest in regenerative and progenitor cell therapies. These treatments, commonly referred to as senolytics, hold particular hope for stem cell populations, due to their demand for proliferative activity, and their complex secretory networks. However, the tolerability and safety of these treatments in stem cells are yet to be established in humans, so much work remains before they can be translated. There have however, been successful early human trials of senolytics in other disease areas, such as pulmonary fibrosis [44], providing hope for future progress in this area. Geroprotective diets, such as the Mediterranean, caloric restriction and anti-oxidant varieties, have been shown to reduce cell senescence in both mouse and human tissues [45,46]. Caloric restriction in particular, has been found to regulate several gene and signaling pathways involved in musculoskeletal fragility [47]. Other functional micronutrients including the polyphenol resveratrol, found in grape skins and red wine, could act as a caloric restriction mimetic, potentially reducing possible side-effects of restricting calories in the older person [48]. Further research is needed to fully understand the effects of these potentially promising therapeutic pathways.

3. Conclusion

Stem cell exhaustion is a key mechanic influencing a number of musculoskeletal diseases of older age, and has the potential for therapeutic use. Over the lifespan, stem cells become senescent, limiting their differentiation and proliferation capacity, and altering their differentiation, commonly shifting toward adipogenic fate. This leads to a breakdown in the rejuvenation of bone and skeletal muscle, and contributes to the development of osteoporosis and sarcopenia. Future studies are required to isolate the primary stem cell effects, from the systemic changes which regulate the progenitor niches in the muscle and bone marrow, to allow for the development of targeted therapies with strong potential for clinical translation.

Contributors

Amy Lawton contributed to the literature search and analysis, and drafted the manuscript.

Nicholas Tripodi contributed to interpreting the data and critical revision of the manuscript.

Jack Feehan contributed to the literature search and analysis, and drafted the manuscript.

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Declaration of competing interest

The authors declare that they have no competing interest.

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