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THE EFFECTS OF EXERCISE ON INFLAMMATION AND CELLULAR SENESCENCE: MECHANISMS AND IMPLICATIONS FOR HEALTHY AGEING

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Abstract

Ageing is accompanied by a progressive accumulation of senescent cells and a chronic, low grade inflammatory state often termed inflammation, both of which contribute to the onset of age related disease and functional decline. Physical exercise has emerged as one of the most accessible and effective non pharmacological interventions capable of modulating these processes. This review synthesizes evidence on the relationship between exercise, inflammation, and cellular senescence, with particular attention to the mechanisms through which acute and chronic exercise influence the senescence associated secretory phenotype, immune cell ageing, and tissue level senescent cell burden. The review considers the paradoxical role of exercise induced acute inflammation as a beneficial signal that promotes adaptive remodeling and senescent cell clearance, in contrast with the deleterious effects of unresolved chronic inflammation. It further examines emerging evidence on high intensity interval training, resistance exercise, and hypoxic exercise as modulators of senescence markers such as p16INK4a and p21CIP1, and considers the implications of these findings for the prevention of sarcopenia, cardiovascular ageing, and neurodegeneration. The review concludes that structured exercise interventions represent a promising senomorphic and senolytic adjunct strategy and identifies priority areas for future research, including dose response relationships and the translation of mechanistic findings into clinical exercise prescription for older adults.

Keywords: *exercise, inflammation, cellular senescence, inflammaging, senescence associated secretory phenotype, healthy ageing*

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INTRODUCTION

Cellular senescence is a stable state of cell cycle arrest triggered by diverse stressors, including DNA damage, telomere attrition, oxidative stress, and mitochondrial dysfunction, and is now recognised as one of the principal hallmarks of biological ageing (Chen et al., 2022; Huang et al., 2024). Senescent cells accumulate progressively with age across multiple tissues and secrete a complex mixture of proinflammatory cytokines, chemokines, and proteases collectively known as the senescence associated secretory phenotype, or SASP, which propagates chronic low grade inflammation throughout the body, a phenomenon widely described as inflammaging (Ferrucci & Fabbri, 2018; Zhang et al., 2024). This persistent inflammatory milieu accelerates tissue dysfunction and is implicated in the pathogenesis of numerous age related conditions, including sarcopenia, atherosclerosis, neurodegeneration, and frailty (Sato et al., 2024).

Physical exercise has long been recognised as a powerful modulator of immune and inflammatory function, yet its relationship with cellular senescence has only recently received sustained scientific attention. Importantly, exercise exerts a dual and apparently paradoxical influence on inflammation: acute bouts of exercise transiently elevate circulating inflammatory mediators, while regular exercise training reduces systemic chronic inflammation over time (Duggal et al., 2019). Emerging evidence suggests that this acute inflammatory response is not incidental but functionally necessary, contributing

directly to the clearance of senescent cells from skeletal muscle and other tissues (Moro et al., 2024). This review examines the mechanisms underlying the effects of exercise on inflammation and cellular senescence, drawing on literature published between 2015 and 2025, and considers the implications of these mechanisms for promoting healthy ageing.

Cellular Senescence and Inflammaging as Drivers of Ageing

Senescent cells differ from quiescent or terminally differentiated cells in that they remain metabolically active while permanently exiting the cell cycle, and they resist apoptosis through upregulation of antiapoptotic pathways (Huang et al., 2024). Hallmark molecular markers of senescence include elevated expression of the cyclin dependent kinase inhibitors p16INK4a and p21CIP1, increased senescence associated beta galactosidase activity, and persistent DNA damage signalling (Sato et al., 2024). Through the SASP, senescent cells secrete interleukin 6, interleukin 8, tumour necrosis factor alpha, and matrix metalloproteinases, which not only sustain local inflammation but can also induce paracrine senescence in neighbouring healthy cells, thereby amplifying tissue level dysfunction over time (Moiseeva et al., 2023, as cited in Huang et al., 2024).

In skeletal muscle, senescent cell accumulation within the regenerative niche disrupts the function of muscle satellite cells and impairs regenerative capacity, contributing to the progressive loss of muscle mass and strength characteristic of sarcopenia (Moiseeva et al., 2023). Similar senescence related dysfunction has been documented in vascular endothelial and smooth muscle cells, where senescent cell burden promotes arterial stiffening, endothelial dysfunction, and atherosclerotic plaque instability, establishing cellular senescence as a central mechanism in cardiovascular ageing (Liu et al., 2025). At the immune system level, repeated antigenic stimulation and chronic low grade inflammation drive immunosenescence, a process characterised by thymic involution, reduced naive T cell output, and a shift toward proinflammatory effector memory phenotypes, which in turn exacerbates systemic inflammaging in a self reinforcing cycle (Ross et al., 2024; Wang et al., 2025).

Acute Exercise, Inflammation, and Senescent Cell Clearance

A growing body of evidence indicates that the acute inflammatory response elicited by vigorous exercise plays a constructive role in tissue remodelling rather than representing simple collateral tissue damage. Following a single bout of high intensity exercise, transient increases in circulating cytokines and immune cell infiltration into skeletal muscle have been associated with the selective clearance of senescent cells, suggesting that acute inflammation acts as an immunosurveillance mechanism that targets and removes dysfunctional cells (Moro et al., 2024). Notably, experimental suppression of this acute inflammatory response, whether through nonsteroidal anti-inflammatory drugs, cold water immersion, antihistamines, or antioxidant supplementation, has been shown to blunt the beneficial reduction in senescence markers normally observed after exercise, indicating that the inflammatory signal itself is mechanistically required for senescent cell clearance and for downstream adaptations such as enhanced mitochondrial biogenesis and muscle hypertrophy (Moro et al., 2024).

High intensity interval training in particular has demonstrated pronounced effects on senescence markers. Reviews of recent trial data report that high intensity interval training significantly reduces circulating and tissue resident markers of cellular senescence, with the magnitude of benefit appearing greatest among individuals presenting with elevated baseline senescent cell burden, consistent with a homeostatic, threshold dependent mode of action (Moro et al., 2024). These findings position acute, intensity dependent inflammatory signalling as a key mechanistic link between exercise and senescent cell turnover, challenging the conventional assumption that all exercise induced inflammation should be minimised or suppressed.

Chronic Exercise Training, Systemic Inflammation, and Senomorphic Effects

In contrast to the transient inflammatory spike that follows a single exercise session, regular exercise training over weeks and months produces a net reduction in resting systemic inflammation, often described as an anti-inflammatory training effect (Duggal et al., 2019). This adaptation is thought to arise from repeated cycles of controlled inflammatory stress followed by resolution, which progressively recalibrate immune cell function, reduce circulating levels of interleukin 6 and C reactive protein, and enhance regulatory immune cell populations (Duggal et al., 2019; Wang et al., 2025).

Rather than eliminating senescent cells outright, chronic training appears in many tissues to exert a senomorphic effect, suppressing the secretory output of the SASP without necessarily eliminating the senescent cells themselves, thereby reducing the inflammatory burden propagated to surrounding tissue (Liu et al., 2025).

Resistance exercise training has shown particular promise for skeletal muscle, with longitudinal studies reporting reductions in p16INK4a positive cell populations within muscle biopsies following structured strength training programmes in older adults, alongside improvements in satellite cell function and fibre regeneration capacity (Sato et al., 2024). Hypoxic exercise, in which training is performed under conditions of reduced oxygen availability, has also been examined as a means of amplifying mitochondrial and antioxidant adaptations; a recent systematic review concluded that hypoxic exercise may further reduce senescence markers relative to normoxic training, although the evidence base remains limited and heterogeneous in methodology (Huang et al., 2024). Collectively, these findings suggest that different exercise modalities may engage distinct but complementary mechanisms in modulating senescence and its inflammatory consequences.

Molecular Mechanisms Linking Exercise, Inflammation, and Senescence

Several converging molecular pathways have been proposed to explain how exercise modulates cellular senescence. First, exercise enhances mitochondrial biogenesis and quality control through pathways involving peroxisome proliferator activated receptor gamma coactivator 1 alpha, reducing the mitochondrial dysfunction and excessive reactive oxygen species production that are well established triggers of cellular senescence (Sato et al., 2024). Second, exercise upregulates autophagic flux, facilitating the clearance of damaged organelles and proteins that would otherwise accumulate and contribute to senescence associated cellular stress (Zhang et al., 2024). Third, exercise modulates iron and lipid metabolism, restoring redox homeostasis and reducing the lipid peroxidation associated with ferroptosis, a regulated form of cell death increasingly implicated as a downstream consequence of senescence in neurodegenerative contexts (Yu & Chen, 2026).

Fourth, immune mediated surveillance appears central to exercise induced senescent cell clearance, with natural killer cells and macrophages recruited during the acute postexercise period implicated in the recognition and removal of senescent cells from skeletal muscle (Moro et al., 2024). Fifth, at the systemic level, exercise influences communication along the muscle, liver, and gut axes, modulating circulating myokines and metabolic signals that exert remote anti-inflammatory and antisenescent effects on distal organs, including the brain (Yu & Chen, 2026). Together, these mechanisms indicate that exercise acts simultaneously at the cellular, tissue, and systemic levels to counteract the drivers of senescence and chronic inflammation.

Implications for Healthy Ageing and Disease Prevention

The accumulating mechanistic evidence linking exercise, inflammation, and senescence carries substantial implications for the prevention of age related disease. Given the central role of senescent cell accumulation in sarcopenia, structured resistance and aerobic exercise programmes may serve as accessible, low cost interventions for preserving muscle mass and function in older adults, potentially delaying the need for pharmacological senolytic therapies (Sato et al., 2024). In the cardiovascular domain, regular exercise mediated reductions in vascular senescent cell burden may help to delay arterial stiffening and reduce cardiovascular event risk among ageing populations (Liu et al., 2025).

Exercise also holds promise in the context of neurodegenerative disease prevention, with recent mechanistic work suggesting that exercise counteracts senescence driven ferroptotic pathways implicated in Alzheimer's disease progression, in part through restoring iron homeostasis and reactivating antioxidant defences such as glutathione peroxidase 4 (Yu & Chen, 2026). Nonetheless, translating these mechanistic insights into standardised clinical exercise prescriptions remains challenging, given considerable heterogeneity across studies in exercise modality, intensity, duration, and population characteristics. Future research should prioritise well powered randomised controlled trials examining dose response relationships between exercise variables and senescence outcomes, alongside investigation of whether combining exercise with emerging senolytic or senomorphic pharmacological agents yields synergistic benefits for healthy ageing (Liu et al., 2025; Wang et al., 2025).

CONCLUSION

Exercise represents one of the most promising non pharmacological strategies for modulating the interconnected processes of inflammation and cellular senescence that underlie biological ageing. The literature reviewed here demonstrates that acute exercise induced inflammation functions as a necessary signal for senescent cell clearance, while chronic exercise training exerts complementary senomorphic effects that reduce systemic inflammaging over time. Mechanistically, these benefits arise through enhanced mitochondrial function, autophagy, immune surveillance, and favourable systemic signalling across multiple organ systems. As the global population continues to age, structured exercise interventions tailored to individual capacity and health status warrant greater integration into public health strategies aimed at extending healthspan and reducing the burden of age related disease.

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