Commentary

Exercise Under the Microscope: How Physical Activity Reshapes Aging Muscle Biology

Exercice sous la loupe: comment l'activité physique remodele la biologie musculaire du vieillissement

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Abstract | Résumé

Sarcopenia is an age-related musculoskeletal disease characterized by the progressive loss of skeletal muscle mass, strength, and regenerative capacity, contributing to frailty, impaired mobility, and reduced independence in older adults. While pharmacological therapies targeting muscle degeneration continue to emerge, exercise remains one of the most effective and accessible interventions for preserving musculoskeletal health during aging. This commentary discusses the study by Liu et al., which used single-cell transcriptomic analyses to demonstrate that exercise modulates aging tissue biology through both direct and indirect mechanisms. Exercise directly influenced inflammatory signaling, stem cell communication, and regenerative pathways while indirectly improving broader physiological processes associated with healthy aging and functional recovery. By reducing inflammatory signatures and restoring intercellular communication within aged skeletal muscle, exercise may improve tissue regeneration beyond its effects on muscle mass alone. These findings emphasize the growing importance of rehabilitation-based strategies for preserving mobility, improving recovery, and maintaining functional independence in aging populations.

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La sarcopénie est une maladie musculosquelettique liée à l'âge caractérisée par une perte progressive de masse musculaire squelettique, de force et de capacité régénératrice, contribuant à la fragilité, à la mobilité réduite et à une diminution de l'indépendance chez les personnes âgées. Bien que les thérapies pharmacologiques ciblant la dégénérescence musculaire continuent d'émerger, l'exercice reste l'une des interventions les plus efficaces et accessibles pour préserver la santé musculosquelettique au fil du vieillissement. Ce commentaire aborde l'étude de Liu et al., qui a utilisé des analyses transcriptomiques unicellulaires pour démontrer que l'exercice module la biologie tissulaire vieillissante par des mécanismes directs et indirects. L'exercice a directement influencé la signalisation inflammatoire, la communication avec les cellules souches et les voies régénératrices tout en améliorant indirectement les processus physiologiques plus larges associés au vieillissement sain et à la récupération fonctionnelle. En réduisant les signatures inflammatoires et en restaurant la communication intercellulaire au sein des muscles squelettiques vieillissants, l'exercice peut améliorer la régénération tissulaire au-delà de ses seuls effets sur la masse musculaire. Ces résultats soulignent l'importance croissante des stratégies basées sur la rééducation pour préserver la mobilité, améliorer la récupération et maintenir l'indépendance fonctionnelle des populations vieillissantes.

Keywords: Aging, sarcopenia, exercise, skeletal muscle regeneration, rehabilitation, inflammaging, inflammation, muscle stem cells, tissue homeostasis.

Introduction

Aging is associated with a progressive decline in skeletal muscle mass, strength, and regenerative capacity, contributing to impaired mobility, increased risk of falls, frailty, and reduced quality of life(1, 2). Sarcopenia is a musculoskeletal disease characterized by the age-associated decline in skeletal muscle tissue and affects approximately 10–16% of the aging population and represents an increasing burden on healthcare and rehabilitation systems (3–5). While muscle degeneration has traditionally been associated with the loss of muscle mass alone, aging also impairs the ability of skeletal muscle to effectively regenerate following injury or physiological stress (4). Reduced regenerative capacity contributes not only to muscle weakness, but also to prolonged recovery following injury, illness, or hospitalization, increasing the risk of long-term dependence in older adults (6, 7). As populations continue to age, there is growing interest in identifying therapeutic strategies capable of preserving muscle and improving regeneration to maintain functional independence in older adults.

Current therapeutic approaches aimed at combating age-related muscle degeneration include physical, nutritional and pharmacological interventions (8). Drug-based methods target specific molecular pathways such as PI3K/Akt/mTOR and myostatin signalling, involved in inflammation, protein turnover,

and muscle growth (9–11). Myostatin inhibitors, for example, aim to increase muscle mass by blocking negative regulators of muscle hypertrophy (10, 12). However, despite significant research efforts, there are currently no United States Food and Drug Administration (FDA)-approved drugs specifically for the treatment of sarcopenia (8). Furthermore, many of these pharmacological therapies focus on isolated mechanisms and may fail to address the broader physiological and regenerative changes that occur during aging. On the other hand, exercise remains the most effective strategy and is capable of simultaneously influencing multiple biological processes associated with muscle health, including inflammatory signalling, stem cell activity, metabolism, vascularization, and tissue remodelling (13). Beyond its effects on muscle mass and strength, exercise may act as a biologically active regulator of tissue regeneration and healthy aging (11). Furthermore, understanding the molecular pathways through which exercise promotes regeneration may also contribute to the development of exercise mimetics for individuals unable to participate in regular physical activity. Addressing functional decline through rehabilitation, and preventative strategies is therefore crucial for preventing the effects of aging, preserving independence, and reducing long-term strain on healthcare and rehabilitation systems (14).

The recent study by Liu et al. provides important mechanistic insight into how exercise reshapes aging stem cell environments and improves tissue homeostasis across multiple organ systems (15). Unlike previous studies that primarily examined exercise-induced changes in muscle mass or bulk tissue signalling, this study provides cell-type specific insight into how exercise remodels aged stem cell niches across multiple tissues. Using integrative single-cell transcriptomic analyses, the authors examined over 435,000 single cells collected from skeletal muscle, neural stem cell compartments, hematopoietic stem and progenitor cells, and peripheral immune cells in both young and aged mice subjected to voluntary exercise. Their findings demonstrate that exercise significantly reduces inflammatory signalling across multiple stem cell compartments while restoring more youthful intercellular signalling within aged skeletal muscle. This work suggests that exercise has both direct and indirect effects, as it not only preserves muscle tissue superficially but also alters the regenerative landscape of aging tissue at the molecular and cellular levels. The use of single-cell transcriptomics allows for a more comprehensive understanding of how exercise influences intercellular communication and inflammatory signalling during aging. In this context, studies such as Liu et al. are valuable because they not only reinforce the importance of exercise in promoting regeneration but also provide mechanistic insight into the signalling pathways and intercellular communication networks involved, potentially helping identify targets that could mimic the regenerative effects of exercise.

Results

One of the most significant findings of this study is the observation that exercise reverses several age-associated inflammatory changes. Research shows aging is commonly characterized by chronic low-grade inflammation, often referred to as “inflammaging,” which contributes to impaired stem cell function and reduced regenerative capacity (16). In this paper, increased inflammatory signalling pathways involving interferon gamma (IFNγ), interferon alpha (IFNα), interleukin-6 (IL-6), and tumour necrosis factor alpha (TNFα) were observed across multiple aged cell populations. Exercise reduced the expression of many of these pathways, although these effects varied between cell types, suggesting that physical activity may partially restore a more regenerative environment within aged tissue by reducing inflammation.

Since chronic inflammation can disrupt communication between regenerative cell populations, these findings are particularly relevant in the context of skeletal muscle regeneration. Effective muscle repair depends not only on muscle stem cells (MuSCs), also known as satellite cells, but also on the surrounding stem cell niche and communication between neighbouring cell populations (17). Aging disrupts this cellular communication network, impairing the coordinated signalling required for efficient tissue repair (18). Liu et al. showed that exercise restored several of these disrupted communication pathways, particularly interactions involving monocytes, macrophages, fibro-adipogenic progenitors (FAPs), and myofibers. The restoration of these networks suggests that exercise may improve regeneration by reshaping the broader regenerative landscape rather than acting only on muscle fibers themselves.

This concept shows one of the major advantages of exercise-based interventions compared to many pharmacological therapies. Rather than targeting a single pathway, exercise influences multiple interconnected biological systems at the same time. In this sense, exercise may be viewed not simply as a method of maintaining physical fitness, but as a form of regenerative rehabilitation capable of modifying the biological processes underlying aging itself.

Moving Forward

The broader implications of these findings extend beyond skeletal muscle biology alone. Exercise-induced reductions in inflammatory signalling were also observed within neural stem cell compartments and hematopoietic tissues, supporting the idea that exercise promotes systemic tissue homeostasis during aging. Liu et al. also showed changes within hematopoietic stem cell niches, suggesting that exercise may influence regeneration through broader immune-related mechanisms. This may be particularly relevant in the context of sarcopenia, as immune aging contributes to chronic low-grade inflammation and altered immune signalling that can impair muscle stem cell function and regenerative capacity (19). These findings support the idea that the benefits of exercise extend beyond muscle growth and cardiovascular fitness, influencing regenerative processes throughout the body. Understanding how exercise modulates these interconnected systems may help identify future therapeutic

targets that mimic or enhance the regenerative benefits of physical activity.

Importantly, the findings presented by Liu et al. also emphasize the importance of rehabilitation-based approaches in aging populations. Preservation of mobility and functional independence remains one of the primary goals of geriatric healthcare and rehabilitation. Exercise-based rehabilitation strategies not only improve strength and balance but may also directly influence the molecular mechanisms responsible for tissue maintenance and repair. By improving regenerative capacity and reducing chronic inflammation, exercise may help delay frailty, reduce fall risk, and improve recovery following injury or illness in older adults.

Despite these promising findings, limitations and challenges remain. Exercise responsiveness varies considerably between individuals and may be a less suitable option in older populations with advanced frailty or chronic disease (20). Adherence to long-term exercise programs may also present difficulties due to mobility limitations, pain, or comorbidities (21). Furthermore, while exercise improves regenerative signaling, it may not fully reverse all age-associated declines in muscle function.

Additional limitations arise from the translational nature of the study itself. Many of the reported findings are based on transcriptomic changes observed in murine models, which may not fully reflect functional outcomes in humans. Although altered gene expression profiles suggest improved regenerative potential, transcriptional changes do not always directly translate into enhanced tissue repair, mobility, or sustained functional recovery. Furthermore, because the mice engaged in voluntary exercise, exercise levels varied and may not accurately represent exercise behavior in aging human populations. Future research should therefore build on this paper's findings to focus on identifying clinically effective exercise regimens and exploring how exercise-based rehabilitation strategies may be integrated with pharmacological or regenerative therapies to optimize recovery outcomes in older adults.

Overall, the study by Liu et al. provides important molecular insight into how exercise modulates aging tissue biology. Using single-cell transcriptomic analyses, the authors demonstrated that exercise reduces inflammatory signaling, restores intercellular communication, and improves stem cell niche environments across multiple aged tissues. These findings suggest that exercise promotes regeneration both directly and indirectly: directly by influencing molecular pathways involved in inflammation, stem cell function, and tissue repair, and indirectly by improving broader physiological processes associated with healthy aging and functional recovery. Understanding how exercise influences these signaling networks may help guide the development of more effective rehabilitation and pharmacological strategies for preserving mobility, improving recovery, and maintaining functional independence in aging populations.

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