COMMENTARY

Anti-aging therapeutics for the musculoskeletal and cardiovascular systems: The role of regular exercise

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In the recent issue of *Nature*, the Molecular Transducers of Physical Activity Consortium (MoTrPAC) Study Group identified thousands of tissue-specific molecular alterations from a multi-omics perspective. This study provides significant biological insights into adaptive responses to endurance training.[1] And this commentary represents a significant step forward in our understanding of how exercise-induced molecular changes impact various tissues, with important implications for anti-aging therapeutics related to the musculoskeletal and cardiovascular systems (Figure 1).

It is well-established that regular exercise helps reduce the incidence of degenerative diseases, such as osteoporosis and cardiovascular disease. Exercise offers broad health benefits by increasing mitochondrial content and enhancing mitochondrial activity, leading to improved skeletal muscle performance and cardiac metabolism. However, the lack of regular exercise among many individuals, compounded by unhealthy lifestyle habits, negatively affects physical health and quality of life. The global rise in aging populations further exacerbates issues such as skeletal muscle loss and cardiovascular

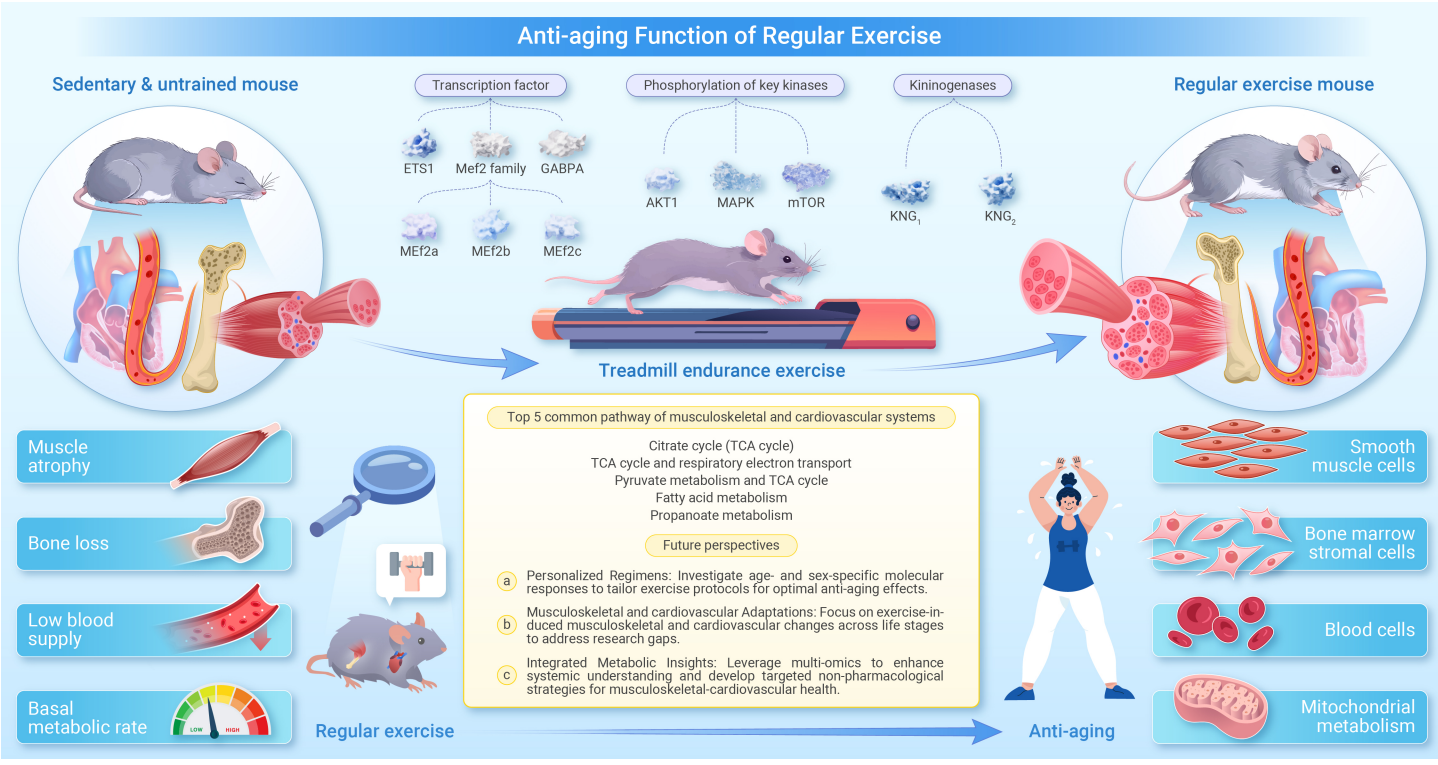

Figure 1. Anti-aging function of regular exercise (Left) The manifestations in the cardiovascular and muscular systems of rats that have been sedentary or untrained for a long period include: muscle atrophy, bone loss, low blood supply, and limited basal metabolic rate. (Middle) During the regular treadmill endurance training process, we have discovered that the heart and skeletal muscle share common signaling pathways, including the citric acid cycle and respiratory electron transport chain, fatty acid metabolism, pyruvate metabolism and so on. (Right) After long-term regular training, the performance of the cardiovascular and musculoskeletal systems in rats includes: the enhancement of smooth muscle cells, increased bone marrow stromal cell, and growing blood cells, as well as the strengthened mitochondrial metabolism.

system aging. As such, understanding the molecular response to exercise is increasingly essential for developing personalized exercise regimens and anti-aging interventions aimed at improving health outcomes. This understanding also informs public health initiatives promoting physical activity for healthier aging.

This commentary synthesizes the key findings from the MoTrPAC study, connecting molecular regulation induced by exercise to multi-tissue metabolic changes. These findings lay the groundwork for hypothesis-driven research into how exercise can enhance whole-body and tissue-specific health in the future. The positive effects of regular physical exercise on maintaining cardiovascular and skeletal muscle function are well documented. Studies at the population level consistently show that exercise reduces the risk of various systemic diseases, including heart disease, diabetes, metabolic syndrome, osteoporosis, and depression. However, the specific cellular and molecular mechanisms underlying these protective effects remain incompletely understood. Research has shown that exercise exerts beneficial

effects at the molecular level in various organs. For instance, in aged cardiac cells, long-term exercise increases the expression of SIRT1, PGC-1α, and AMPK, promoting metabolic adaptation, reducing pro-inflammatory mediators, and mitigating hypertrophic changes associated with aging.[2] Aerobic exercise has also been linked to increased expression of telomere repeat-binding factor 2 in the aorta and reduced expression of apoptosis regulators. In this study, the MoTrPAC Study Group applied comprehensive multi-omics to analyze molecular changes in male and female rats following endurance exercise training across 19 tissues using 25 distinct molecular platforms.

Exercise is a cornerstone intervention for managing chronic diseases, including non-alcoholic fatty liver disease, diabetes, cardiovascular conditions, and obesity.[3] The MoTrPAC Study Group conducted a comprehensive analysis of gene expression changes in response to exercise training, focusing on six tissues with the most detailed molecular profiles: gastrocnemius, heart, liver, white adipose tissue, lung, and kidney. Pathway enrichment analysis demonstrated that endurance training induced similar molecular responses across both male and female rats, with notable upregulation in mitochondrial metabolism, biogenesis, protein translation, and cellular responses to thermal stress. This study provides crucial insights into the systemic effects of regular exercise on immunity, metabolism, stress responses, and mitochondrial function, serving as a valuable resource for further exploration of endurance training's multi-tissue molecular impacts. Moreover, varying types of graded exercise in disease model mice will contribute to the development of personalized strategies for health improvement, aiding individuals in reaching their targeted health goals. In addition, this article highlights previously unidentified molecular targets associated with exercise-induced protection against myocardial oxidative stress. For instance, phosphorylation of the SRC target, GJA1 at site pY265, showed a marked increase following training. This phosphorylation event serves as a key sensor of cardiac electrical conductivity, suggesting that SRC signaling may regulate extracellular remodeling in the heart. Such findings could enhance our understanding of cardiovascular disease mechanisms and shed light on the protective effects of exercise on various organs, informing future disease prevention efforts and the development of targeted therapies. However, a significant gap in the article is the lack of systematic research on skeletal adaptations, which play critical roles in overall metabolic processes. Recent studies show that mice exercising during their early active phase achieve greater increases in bone length and mass through enhanced oxidative phosphorylation, emphasizing the importance of optimal timing in physical activity.[4] Therefore, we recommend employing multi-omics approaches to investigate skeletal changes in mice across various age groups, exercise intensities, and timing.

Moreover, both the heart and gastrocnemius exhibited significant enrichment in mitochondrial metabolic pathways. Transcriptomic and proteomic analyses further revealed enrichment of hematopoietic transcription factors such as GABPA, ETS1, KLF3, and ZNF143 in the cardiovascular system. Future studies should investigate how regular exercise modulates molecular responses in metabolically compromised mice, particularly under extreme environmental conditions, to assess the potential benefits of environmental factors in exercise-mediated disease prevention. Such research could help optimize exercise protocols and deepen our understanding of metabolic shifts in hormone and enzyme activities during exercis.

Consequently, regular exercise induced similar molecular and cellular changes in both the musculoskeletal and cardiovascular systems, such as the upregulation of mitochondrial metabolic pathways, biogenesis, and translation. These changes also included the activation of common Mef2 family transcription factor motifs and cellular responses to heat stress. There was an increase in the abundance of enzymes involved in the glycolysis-gluconeogenesis pathway, as well as enrichment in oxidative phosphorylation. Pathway enrichment revealed consistent regulation of carbon metabolism, amino acid synthesis, and fatty acid metabolism across the heart and skeletal muscles. Moreover, the regulation of kininogenases KNG1 and KNG2, which are involved in lowering blood pressure, suggested that similar molecular responses occur in both systems. These shared signaling pathways and transcription factors are closely related to known anti-aging pathways. For instance, the activation of mitochondrial biogenesis pathways, such as those involving PGC-1α, is linked to potential anti-aging effects. Enhanced carbon metabolism improves cellular energy production, which may help delay cellular aging caused by energy deficits. Furthermore, fatty acid metabolites' antioxidant capacity helps protect against oxidative damage from reactive oxygen species and reduces chronic inflammation, contributing to delayed cellular and tissue aging.[5] Key kinase phosphorylation events, including those involving AKT1, mTOR, and MAPK, were associated with cellular anti-aging effects in the heart, providing a theoretical basis for developing non-pharmacological anti-aging therapies for the musculoskeletal-cardiovascular axis, such as regular exercise. Additionally, sex-specific differences in Cyclin-Dependent Kinase 2 (CDK2) activity were observed in skeletal muscle. This suggests that factors such as sex hormone levels, sex chromosomes, and sex-specific metabolic pathways could play a role, potentially impacting exercise program design and muscle health. From a tissue differentiation and physiological standpoint, regular exercise induced anti-aging effects in both the musculoskeletal and cardiovascular systems in mice, primarily through pathways such as the citric acid cycle, fatty acid metabolism, and activation of key phosphorylated kinases like AKT1, mTOR, and MAPK, as well as transcription factors like the Mef2 family.

Overall, regular exercise can promote anti-aging pathways, primarily by maintaining muscle function and positively influencing both skeletal and cardiac muscle. These findings offer insights into the fundamental molecular mechanisms underlying exercise, emphasizing the link between exercise-induced molecular regulation and tissue metabolism. They have established a theoretical foundation for future research on how exercise improves overall health and offers non-pharmacological anti-aging strategies. Further exploration is needed to understand the molecular biological responses of various tissues and organs under different exercise intensities, particularly skeletal system changes. Notably, previous studies have generally overlooked the long-term effects of regular exercise on multiple tissues and organs in both sexes. However, the MoTrPAC Study Group has provided the first comprehensive biomolecular map illustrating the time-dependent effects of endurance exercise training in male and female rats, offering a valuable multi-omics data resource.

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AUTHOR CONTRIBUTIONS

Z.L, Y.H., and H.Z. provided the conception, revision and supervision. W.Z. and W.Z. conducted the literature research and wrote the initial manuscript and made the figure. All authors have read and approved to publish the article.

DECLARATION OF INTERESTS

The authors declare no competing interests.