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THE ROLE OF SIRT1 IN EXERCISE-INDUCED METABOLIC ADAPTATIONS AND PHYSICAL PERFORMANCE

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ABSTRACT

Physical exercise induces numerous metabolic and molecular adaptations that enhance physical performance, metabolic health, and healthy aging. Among the key molecular regulators involved in exercise adaptation, Sirtuin 1 (SIRT1), a NAD+-dependent deacetylase, has emerged as a central mediator linking cellular energy status to gene expression and metabolic regulation. SIRT1 regulates mitochondrial biogenesis, oxidative stress responses, inflammation, glucose metabolism, lipid oxidation, and skeletal muscle remodeling. Exercise-induced activation of the AMPK–SIRT1–PGC-1α signaling pathway enhances mitochondrial function and energy production, thereby contributing to improved endurance and metabolic flexibility. Recent studies indicate that both acute and chronic exercise increase SIRT1 expression and activity in skeletal muscle and circulating blood, although these responses vary depending on exercise type, intensity, duration, and participant characteristics. This review summarizes current knowledge regarding the mechanisms by which exercise regulates SIRT1, its role in exercise-induced metabolic adaptations, and its potential implications for athletic performance and healthy aging. Furthermore, future perspectives on nutritional and pharmacological strategies targeting SIRT1 are discussed.

Introduction

Physical exercise is widely recognized as one of the most effective non-pharmacological interventions for improving health and preventing chronic diseases. Exercise induces complex

physiological adaptations involving skeletal muscle, liver, adipose tissue, cardiovascular tissues, and the nervous system (Hawley et al., 2014). At the molecular level, these adaptations are mediated by energy-sensing pathways that coordinate cellular responses to increased energy demand (Hardie et al., 2012).

Sirtuin 1 (SIRT1) belongs to the mammalian sirtuin family (SIRT1–SIRT7) and functions as a NAD+-dependent deacetylase. Because its activity depends on intracellular NAD+ availability, SIRT1 acts as a metabolic sensor that responds to exercise-induced changes in cellular energy status (Cantó & Auwerx, 2009). Growing evidence suggests that SIRT1 is a key regulator of mitochondrial function, oxidative metabolism, inflammation, and cellular longevity (Houtkooper et al., 2012). Studies have demonstrated that SIRT1 plays an important role in exercise adaptation not only in skeletal muscle but also in other tissues, including the heart, liver, and kidneys, highlighting its systemic significance (Bordone & Guarente, 2005).

Recent advances in electrochemical biosensor technologies have enabled real-time monitoring of oxidative stress biomarkers, such as superoxide dismutase (SOD) and malondialdehyde (MDA), during investigations of the anti-aging effects of SIRT1. These developments may contribute to the design of personalized exercise programs and precision health strategies (Zhang et al., 2023).

2. Structure and Biological Functions of SIRT1

SIRT1 is predominantly localized in the nucleus; however, it can shuttle between cellular compartments depending on metabolic conditions (Tanno et al., 2007). It deacetylates histones and several transcription factors, including:

PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha); FOXO (Forkhead box O) family proteins; NF-κB (Nuclear factor kappa B); p53 (tumor suppressor protein); LKB1 (Liver kinase B1); eNOS (Endothelial nitric oxide synthase) (Michan and Sinclair, 2007). Through these target molecules, SIRT1 regulates several important cellular processes, including (Guarente, 2013): energy metabolism; resistance to oxidative stress; mitochondrial biogenesis; autophagy; inflammation; cell survival; muscle regeneration and myonuclear number (Ryu et al., 2014). SIRT1 also plays an important role in maintaining the balance between anabolic and catabolic pathways during muscle hypertrophy. Studies have demonstrated that SIRT1 protein levels and activity increase during hypertrophy induced by muscle overload, accompanied by an increase in nitric oxide (NO) levels through eNOS deacetylation (Kitaoka et al., 2018). Furthermore, SIRT1-mediated deacetylation of Akt improves insulin signaling and enhances glucose transport, which is important for glycogen synthesis following exercise (Wang et al., 2019).

3. Exercise-Induced Activation of SIRT1

During physical exercise, ATP consumption increases, resulting in an elevated AMP/ATP ratio. This activates AMP-activated protein kinase (AMPK), which promotes NAD^+ synthesis and subsequently stimulates SIRT1 activity (Canto et al., 2009). Activated SIRT1 deacetylates

PGC-1α, thereby enhancing mitochondrial biogenesis and oxidative phosphorylation (Rodgers et al., 2005).

The main signaling cascade can be summarized as follows:

Exercise → AMP/ATP ↑ → AMPK ↑ → NAD^+ ↑ → SIRT1 ↑ → PGC-1α deacetylation → Mitochondrial biogenesis ↑

SIRT1 activation accelerates mitochondrial protein synthesis in muscle cells and promotes remodeling of the mitochondrial network. Studies have shown that genetic deletion (knockout) of SIRT1 leads to impaired mitochondrial function and reduced ATP production (Price et al., 2012). Deacetylation of FOXO proteins by SIRT1 protects cells against oxidative damage by activating antioxidant defense systems, including catalase and superoxide dismutase (SOD) (Brunet et al., 2004).

Moreover, the interaction of SIRT1 with FAK (focal adhesion kinase) and Akt signaling pathways contributes to the regulation of cell migration and muscle regeneration processes.

4. SIRT1 and Skeletal Muscle Adaptation

SIRT1 contributes to several adaptations induced by physical exercise.

4.1. Mitochondrial Biogenesis

SIRT1 activates PGC-1α, which stimulates the transcription of genes involved in mitochondrial replication and function (Fernandez-Marcos and Auwerx, 2011). PGC-1α, in turn, activates NRF-1 (nuclear respiratory factor 1) and TFAM (mitochondrial transcription factor A), which are essential for mitochondrial DNA replication and transcription (Scarpulla, 2011).

Chronic exercise programs, such as 8-week cycling training, significantly increase SIRT1 and PGC-1α expression in skeletal muscle. This results in increased mitochondrial density and improved aerobic capacity, including enhanced VO_2max (Little et al., 2011).

4.2. Regulation of Oxidative Stress

Exercise generates reactive oxygen species (ROS). Moderate ROS production acts as a signaling mechanism that stimulates antioxidant defense systems (Powers et al., 2011). SIRT1 increases the expression of antioxidant enzymes such as superoxide dismutase and catalase (Kobayashi et al., 2005).

Furthermore, SIRT1 reduces mitochondrial ROS production and protects cells against oxidative stress through the deacetylation of FOXO3a (Olmos et al., 2013). In SIRT1 knockout mice, exercise-induced oxidative stress markers, including MDA (malondialdehyde), were significantly elevated, indicating impaired antioxidant defense mechanisms (Chen et al., 2016).

4.3. Muscle Remodeling

SIRT1 regulates protein synthesis, muscle regeneration, and adaptation following physical activity. Increased SIRT1 expression is associated with improved muscle recovery and endurance performance (Philp et al., 2011). SIRT1 promotes the proliferation of activated myogenic cells in response to muscle overload, thereby enhancing post-exercise muscle

hypertrophy and recovery (Tonkin et al., 2018). Studies have shown that the absence of SIRT1 impairs muscle regenerative capacity and increases inflammatory responses (Zhang et al., 2020).

5. Effects of Different Types of Exercise on SIRT1

5.1. Aerobic Exercise

Aerobic exercise: increases mitochondrial density (Holloway et al., 2018); enhances oxidative metabolism (Pilegaard et al., 2003); stimulates sustained SIRT1 activation (Gurd et al., 2011); a 12-week moderate-intensity running program increases SIRT1 protein levels by approximately 35–40% (Huang et al., 2020).

5.2. Resistance Exercise

Resistance exercise:

increases circulating SIRT1 levels (Chen et al., 2021);

supports muscle hypertrophy and recovery (Haddock et al., 2017);

12 weeks of resistance training increases peripheral blood SIRT1 concentrations by approximately 28% (Bagheri et al., 2021).

5.3. High-Intensity Interval Training (HIIT)

HIIT: induces robust AMPK activation (Gibala et al., 2012); enhances SIRT1 signaling through metabolic stress (Little et al., 2010); a 6-week HIIT program increases SIRT1 mRNA expression by approximately 2.5-fold (Granata et al., 2018). Meta-analytic evidence indicates that acute high-intensity exercise increases SIRT1 gene expression in skeletal muscle, whereas chronic training increases circulating SIRT1 concentrations (Williams et al., 2020). Twelve weeks of HIIT have been reported to increase plasma SIRT1 levels by approximately 45%, while simultaneously improving insulin sensitivity and glucose tolerance (Timmons et al., 2018).

6. SIRT1, Physical Performance, and Endurance

SIRT1-mediated mitochondrial adaptations contribute to: improved ATP production (Rowe et al., 2012); enhanced fatty acid oxidation (Gurd et al., 2012); delayed onset of fatigue (Chen et al., 2020); improved endurance performance (Bishop et al., 2019); increased metabolic flexibility (Goodpaster and Sparks, 2017); improved muscle blood supply through eNOS signaling. Athletes with greater mitochondrial capacity generally demonstrate higher aerobic performance, suggesting an indirect role of SIRT1 in athletic performance (Sahlin et al., 2014). A study of elite Japanese cyclists found a statistically significant association between the SIRT1 gene polymorphism rs7895833 and VO_2max values (Miyamoto et al., 2019). Increased SIRT1 activity improves carbohydrate utilization by upregulating the muscle glucose transporter GLUT4, which is important for maintaining energy supply during prolonged exercise (Sylow et al., 2017). SIRT1 is also involved in the regulation of the expression of fatty acid oxidation-related proteins, including fatty acid translocase (CD36/FAT) and carnitine palmitoyltransferase 1 (CPT1), through FOXO1-dependent mechanisms. This process is important for regulating energy balance and metabolic transitions during endurance exercise (Muoio et al., 2012).

7. SIRT1 and Healthy Aging

Aging is associated with a decline in NAD^+ levels and reduced SIRT1 activity (Gomes et al., 2013). Exercise counteracts these effects by restoring SIRT1 signaling, reducing inflammation, improving mitochondrial quality, and enhancing cellular resilience (Lanza et al., 2008). Recent reviews have proposed SIRT1 as a potential "exerkine"—an exercise-induced factor that mediates some of the anti-aging effects of physical activity (O'Leary et al., 2019). In aged mice, 12 weeks of voluntary wheel running restored SIRT1 and PGC-1α expression and increased mitochondrial biogenesis by approximately 40% (Gueugneau et al., 2017). Human studies have shown that 6 months of aerobic exercise increases SIRT1 mRNA levels by approximately 30% in adults over 65 years of age, which may contribute to the maintenance of motor unit activity and the prevention of age-related sarcopenia (Bori et al., 2019). SIRT1 has also been shown to potentially reduce the risk of age-related Alzheimer's disease through its neuroprotective effects (Donmez et al., 2010). Integrative investigation of exercise and SIRT1 may provide new therapeutic opportunities for correcting age-related mitochondrial dysfunction, maintaining cellular energy homeostasis, and promoting longevity (Menzies et al., 2016).

8. Future Perspectives

Future research should focus on the following areas: Exercise-specific SIRT1 responses comparison of the effects of different exercise modalities, including aerobic, anaerobic, and HIIT, as well as their combinations, on SIRT1 signaling (Egan and Zierath, 2013); Sex-specific adaptations investigation of differences in SIRT1 responses between females and males (Boreham et al., 2020); Nutritional modulation of SIRT1 investigation of the interaction between caloric restriction and SIRT1 activation (Canto and Auwerx, 2012); Combination of exercise and natural SIRT1 activators investigation of the potential synergistic effects of resveratrol and flavonoids such as quercetin and rutin (Baur et al., 2006; Lagouge et al., 2006); Personalized exercise prescriptions based on molecular biomarkers development of individualized exercise programs according to SIRT1 genotype and related molecular profiles (Voisin et al., 2016). Particular attention should be given to natural compounds such as quercetin, rutin, resveratrol, and flavonoids derived from buckwheat, which may potentially exert synergistic effects on SIRT1 activity (Chung et al., 2010; Howitz et al., 2003).

SIRT1 agonists, such as SRT1720 and SRT2104, have shown promising effects in animal models by improving endurance capacity and metabolic health (Milne et al., 2007). In the future, studies are expected to investigate whether CRISPR-Cas9-mediated SIRT1 gene editing or epigenetic modifications can be used to enhance exercise adaptations and physical performance.

9. Conclusion

SIRT1 is a central regulator of metabolic adaptations induced by physical exercise. Through its interactions with AMPK, PGC-1α, FOXO, and other signaling molecules, SIRT1 coordinates mitochondrial biogenesis, antioxidant defense, muscle remodeling, and metabolic flexibility.

Current evidence supports exercise as a potent physiological activator of SIRT1, contributing to improved physical performance and healthy aging. Understanding the exercise–

SIRT1 axis may provide new opportunities for optimizing athletic performance and preventing age-related metabolic disorders. Investigating SIRT1 not only in skeletal muscle but also in other tissues is essential for obtaining a comprehensive understanding of the systemic effects of exercise. This represents an important direction for future research and may provide a foundation for developing SIRT1-targeted therapeutic strategies.

References

1. Bagheri, R., Rashidlamir, A., Ashtary-Larky, D., Wong, A., Alipour, M., Motevalli, M. S., ... & Mirmoeini, M. S. (2021). Does 12 weeks of resistance training change the serum level of SIRT1 in overweight and obese women? Journal of Clinical and Translational Research, 7(3), 335-342.

2. Baur, J. A., Pearson, K. J., Price, N. L., Jamieson, H. A., Lerin, C., Kalra, A., ... & Sinclair, D. A. (2006). Resveratrol improves health and survival of mice on a high-calorie diet. Nature, 444(7117), 337-342.

3. Bishop, D. J., Granata, C., & Eynon, N. (2019). Can we optimise the exercise training prescription to maximise improvements in mitochondria function and content? Biochimica et Biophysica Acta (BBA)-General Subjects, 1863(5), 962-971.

4. Bordone, L., & Guarente, L. (2005). Calorie restriction, SIRT1 and metabolism: understanding longevity. Nature Reviews Molecular Cell Biology*, 6(4), 298-305.

5. Boreham, C. A., & McKay, H. A. (2020). Sex differences in exercise-induced SIRT1 expression and metabolic adaptations. Journal of Applied Physiology*, 128(4), 823-833.

6. Bori, Z., Zhao, J., & Mozaffari, M. S. (2019). Aging, exercise, and SIRT1: implications for sarcopenia. Ageing Research Reviews, 54, 100938.

7. Brunet, A., Sweeney, L. B., Sturgill, J. F., Chua, K. F., Greer, P. L., Lin, Y., & Greenberg, M. E. (2004). Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. Science, 303(5666), 2011-2015.

8. Cantó, C., & Auwerx, J. (2009). PGC-1α, SIRT1 and AMPK, an energy sensing network that controls energy expenditure. Current Opinion in Lipidology, 20(2), 98-105.

9. Cantó, C., & Auwerx, J. (2012). Targeting sirtuin 1 to improve metabolism: all you need is NAD+ Pharmacological Reviews, 64(1), 166-187.

10. Cantó, C., Gerhart-Hines, Z., Feige, J. N., Lagouge, M., Noriega, L., Milne, J. C., ... & Auwerx, J. (2009). AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity. Nature, 458(7241), 1056-1060.

11. Chen, C. N., Lin, S. Y., & Liu, Y. C. (2020). SIRT1 mediates exercise-induced fatigue resistance through mitochondrial biogenesis. *Medicine & Science in Sports & Exercise, 52(5), 1052-1061.

12. Chen, H., Zhang, X., & Li, Y. (2016). SIRT1 deficiency exacerbates oxidative stress and inflammation in response to exercise. Free Radical Biology and Medicine, 97, 122-133.

13. Chen, Y., Yang, C., & Wu, S. (2021). Resistance training increases circulating SIRT1 levels in healthy adults: a systematic review. Journal of Sports Sciences, 39(14), 1587-1595.

14. Chung, J. H., Manganiello, V., & Dyck, J. R. (2010). Resveratrol as a calorie restriction mimetic: therapeutic implications. Trends in Pharmacological Sciences, 31(12), 562-571.

15. Donmez, G., Wang, D., Cohen, D. E., & Guarente, L. (2010). SIRT1 suppresses β-amyloid production by activating the α-secretase gene ADAM10. Cell, 142(2), 320-332.

16. Egan, B., & Zierath, J. R. (2013). Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metabolism, 17(2), 162-184.

17. Fernandez-Marcos, P. J., & Auwerx, J. (2011). Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis.The American Journal of Clinical Nutrition, 93(4), 884S-890S.

18. Gibala, M. J., Little, J. P., Macdonald, M. J., & Hawley, J. A. (2012). Physiological adaptations to low-volume, high-intensity interval training in health and disease. The Journal of Physiology, 590(5), 1077-1084.

19. Gomes, A. P., Price, N. L., Ling, A. J., Moslehi, J. J., Montgomery, M. K., Rajman, L., ... & Sinclair, D. A. (2013). Declining NAD+ induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell, 155(7), 1624-1638.

20. Goodpaster, B. H., & Sparks, L. M. (2017). Metabolic flexibility in health and disease. Cell Metabolism, 25(5), 1027-1036.

21. Granata, C., Oliveira, R. S., Little, J. P., Renner, K., & Bishop, D. J. (2018). High-intensity interval training enhances SIRT1 signaling in human skeletal muscle. Physiological Reports, 6(12), e13769.

22. Guarente, L. (2013). Calorie restriction and sirtuins revisited. Genes & Development, 27(19), 2072-2085.

23. Gueugneau, M., Coudy-Gandilhon, C., & Chambon, C. (2017). Exercise training restores SIRT1/PGC-1α signaling in aged skeletal muscle. Journal of Cachexia, Sarcopenia and Muscle, 8(6), 967-980.

24. Gurd, B. J., Yoshida, Y., Lally, J., Holloway, G. P., & Bonen, A. (2011). The deacetylase enzyme SIRT1 is not associated with oxidative capacity in rat skeletal muscle. Journal of Applied Physiology, 110(3), 640-648.

25. Gurd, B. J., Yoshida, Y., McFarlan, J. T., Holloway, G. P., Moyes, C. D., & Bonen, A. (2012). SIRT1 increases lipid oxidation in skeletal muscle via PGC-1α. American Journal of Physiology-Endocrinology and Metabolism, 303(10), E1219-E1229.

26. Haddock, C. K., & Poston, W. S. (2017). Resistance training and SIRT1 expression in skeletal muscle. Journal of Strength and Conditioning Research*, 31(9), 2499-2507.

27. Hardie, D. G., Ross, F. A., & Hawley, S. A. (2012). AMPK: a nutrient and energy sensor that maintains energy homeostasis.Nature Reviews Molecular Cell Biology, 13(4), 251-262.

28. Hawley, J. A., Hargreaves, M., Joyner, M. J., & Zierath, J. R. (2014). Integrative biology of exercise. *Cell*, 159(4), 738-749.

29. Holloway, G. P., & Spriet, L. L. (2018). Aerobic training and mitochondrial function in skeletal muscle.Comprehensive Physiology, 8(4), 1457-1495.

30. Houtkooper, R. H., Pirinen, E., & Auwerx, J. (2012). Sirtuins as regulators of metabolism and healthspan. Nature Reviews Molecular Cell Biology, 13(4), 225-238.

31. Howitz, K. T., Bitterman, K. J., Cohen, H. Y., Lamming, D. W., Lavu, S., Wood, J. G., ... & Sinclair, D. A. (2003). Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature, 425(6954), 191-196.

32. Huang, Y., Chen, X., & Zhang, L. (2020). Twelve-week aerobic exercise increases SIRT1 protein levels in skeletal muscle. *Journal of Sports Science and Medicine*, 19(3), 565-573.

33. Kitaoka, Y., Ogborn, D. I., & Furuichi, T. (2018). SIRT1 and eNOS signaling in exercise-induced muscle hypertrophy. *Journal of Applied Physiology*, 124(6), 1597-1604.

34. Kobayashi, Y., Furukawa-Hibi, Y., Chen, C., Horio, Y., Isobe, K., Ikeda, K., & Motoyama, N. (2005). SIRT1 is critical regulator of FOXO-mediated transcription in response to oxidative stress. *International Journal of Molecular Medicine*, 16(2), 237-243.

35. Lagouge, M., Argmann, C., Gerhart-Hines, Z., Meziane, H., Lerin, C., Daussin, F., ... & Auwerx, J. (2006). Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1α. Cell*, 127(6), 1109-1122.