News Release

Title

Exercise Restores Muscle Stem Cell Mobilization and Regenerative Capacity and Muscle Metabolic Alterations via Adiponectin/AdipoR1 Activation in SAMP10 mice

Key points:

- The stimulated BM-derived $CD34^+$/integrin-$\alpha7^+$ MuSC protection and mobilization and homing into injured musculature and proliferation, and it retarded the mitochondria damage and cell apoptosis via an AMPK-dependent mechanism that is mediated by the adiponectin/AdipoR1 axis in a senescence-accelerated mouse prone 10 (SAMP10) model.
- The ability of exercise training to restore the "young" muscle response can be recommended as a powerful strategy to prevent age-associated declines in muscle regeneration and function by recruiting and improving the delivery of MuSCs to the damaged muscle tissues.

Summary

Aiko Inoue (the first author; 4th PhD student, Department of Community Health & Geriatrics), Xian-Wu Cheng (Associate Professor, Institute of Innovation for Future Society and Department of Community Health & Geriatrics), Masafumi Kuzuya (Professor, Institute of Innovation for Future Society and Department of Community Health & Geriatrics), and his team from Nagoya University Graduate School of medicine (Dean: Masahide Takahashi, MD, PhD) found that exercise restores muscle stem cell mobilization and regenerative capacity and muscle metabolic alterations via adiponectin/its receptor1 activation in a senescence-accelerated mouse prone 10 (SAMP10) model.

Here we report that long-term exercise training improved the declines in muscle regeneration and performance via an AMP-activated protein kinase (AMPK)-dependent mechanism that is mediated by the adiponectin/AdipoR1 axis in a senescence-accelerated mouse prone 10 (SAMP10) model.

Research Background

Aging and metabolic disorders were observed to result in a decrease in plasma adipose tissue-derived adiponectin protein levels and tissue adiponectin receptor 1 (AdipoR1) levels. It has become clear that the function and the number of bone-marrow (BM)-derived stems cells are modified by pathological conditions such as aging and metabolic disorders. The ability of therapeutic strategies to improve the regenerative capacity of muscle stem cells (MuSCs) located in muscle fibers is likely to contribute to muscle repair under the changed systemic and local microenvironments associated

with aging. In addition, regular exercise training has been extensively studied because of its beneficial effects in restoring organ and tissue physical functions, thus preventing age-related diseases such as muscle atrophy and peripheral arterial disease, possibly by activating cellular metabolism and regeneration. Long-term exercise training alone or combined with diet or the use of an anti-oxidant drug was shown to alter the plasma or/and adipose tissue adiponectin levels in animals and humans. As is the case with vascular endothelial progenitor cells, a limited number of experimental and clinical studies have reported that bone-marrow MuSCs contributed to muscle homeostasis and regeneration in humans and animals that underwent an exercise intervention.

Research Results

1. The mice that underwent exercise training as early as at 24 weeks of age showed improved physical performance in contrast to aging-associated muscle wasting.
2. Here, at the molecular and cellular levels, the exercise enhanced not only the circulating adiponectin levels and muscle AdipoR1 gene expression but also the AMPK/PGC-1α-related mitochondrial biogenesis and Akt/mTOR-mediated protein synthesis and proliferation.
3. Simultaneously, the exercise training retarded the Akt/p-FoxO3-related atrogin-1 activation and Nox2-related oxidative stress production and restored the anti-apoptotic (Bcl-1 or/and Bcl-XL) molecule expression.
4. Adiponectin blocking diminished these beneficial intracellular actions and the muscle dysfunction improvement in the exercise training mice. Pharmacological interventions targeted toward AdipoR1 and AMPK also abrogated ET-related muscle beneficial actions in SAMP10 mice.
5. Moreover, recombinant mouse adiponectin resulted in increased levels of p-AMPKα, p-mTOR, and Bcl-2 in BM-derived integrin-α7$^+$ cells.
6. The exercise training stimulated BM-derived CD34$^+$/integrin-α7$^+$ MuSC protection and mobilization and homing into injured musculature and proliferation, and it retarded the mitochondria damage and cell apoptosis via an AMPK-dependent mechanism that is mediated by the adiponectin/AdipoR1 axis in SMAP10 mice.

Research Summary and Future Perspective

The present study's results indicate that aging-associated muscle wasting in SMAP10 mice can be ameliorated by exercise training via the improvement of adiponection-AdipoR1-dependent AMPK/Akt-mTOR signaling-mediated protein catabolic and anabolic responses, oxidative stress-related cell apoptosis, and adiponectin/PGC-1α activation-related biogenesis. The ability of exercise training to restore the "young" muscle response can be recommended as a powerful strategy to prevent age-associated declines in muscle regeneration and function by recruiting and improving the delivery of MuSCs to the damaged muscle tissues. This might also allow

the therapeutic use of nonpharmacological interventions, such as voluntary exercising, to complement pharmacological or cell therapies.

Publication

Aiko Inoue, Xian Wu Cheng Zhe Huang, Lina Hu, Ryosuke Kikuchi, Haiying Jiang, Limei Piao, Takeshi Sasaki, Kohji Itakura, Hongxian Wu, Guangxian Zhao, Yanna Lei, Guang Yang, Enbo Zhu, Xiang Li, Kohji Sato, Teruhiko Koike, Masafumi Kuzuya. Exercise Restores Muscle Stem Cell Mobilization and Regenerative Capacity and Muscle Metabolic Alterations via Adiponectin/AdipoR1 Activation in SAMP10 mice. The paper on the above result was published online (before print) in an English journal *Journal of Cachexia, Sarcopenia and Muscle* on November 29, 2016.
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Japanese ver.

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