News Release

Title: Muscle-derived myonectin prevents sarcopenia through AMPK/PGC1α signaling.
～ It shed light on the development of sarcopenia therapy for healthy life expectancy ～

Key Points

- The development of sarcopenia therapy is an urgent health issue for promoting healthy life expectancy in an aging society.
- Myonectin improves skeletal muscle mass and function in various models of muscle atrophy.
- Myonectin could be involved in the effect of exercise on prevention of sarcopenia.
- Myoncetin could be a novel therapeutic target for various types of muscle atrophy, including aging, disuse atrophy and steroid-induced atrophy.

Summary

In this study, associate professor Koji Ohashi, professor Noriyuki Ouchi in Department of Molecular Medicine and Cardiology, Nagoya University Graduate School of Medicine and post graduate student Yuta Ozaki, assistant professor Katsuhiro Kato and professor Toyoaki Murohara in Department of Cardiology, Nagoya University Graduate School of Medicine, demonstrated the role of myonectin in various types of muscle atrophy including age-associated sarcopenia.

To maintain and restore skeletal muscle mass and function is essential for healthy life expectancy. We have found that myonectin acts as a cardioprotective myokine. Here, we investigated the effect of myonectin on skeletal muscle atrophy in various models of muscle atrophy. Myonectin knockout (Myo-KO) mice exhibited skeletal muscle atrophy in age-associated, sciatic denervation-induced or dexamethasone (DEX)-induced muscle atrophy models. Myo-KO mice also showed exacerbated mitochondrial dysfunction and reduced expression of mitochondrial biogenesis-associated genes including PGC1α in denervated muscle. Myonectin supplementation attenuated denervation-induced muscle atrophy via activation of AMPK. Myonectin also reversed DEX-induced atrophy of cultured myotubes through the AMPK/PGC1α signaling. Furthermore, myonectin treatment suppressed muscle atrophy in senescence-accelerated mouse prone (SAMP) 8 mouse model of accelerated aging or mdx mouse model of Duchenne muscular dystrophy. These data

indicate that myonectin can ameliorate skeletal muscle dysfunction through AMPK/PGC1α-dependent pathway, indicating that myonectin could represent a novel therapeutic target of muscle atrophy.

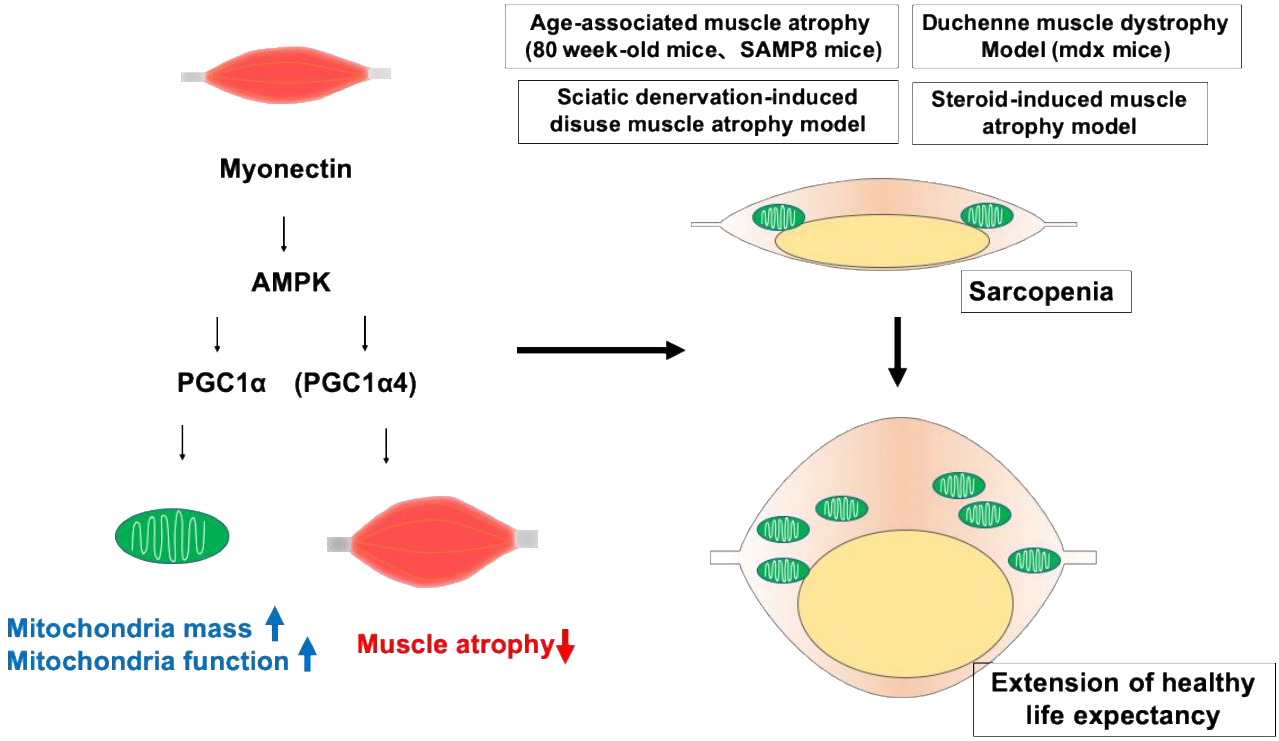
Research Background

According to advances in medical technology, average life expectancy continues to increase. However, there is a growing social problem due to the significant gap between healthy life expectancy and average life expectancy. Age-associatd sarcopenia is one of the serious health problems that contribute to this gap. Exercise training is an established treatment for sarcopenia, but there are no established drugs or therapies for bedridden patients who are unable to engage in physical activity.

In previous research, we reported that a muscle-derived myonectin has a protective effect on the heart during ischemia reperfusion injury. In this study, we investigated the role of myonectin in various mouse models of muscle atrophy.

Research Results

The expression of myonectin in skeletal muscle tissues was lower in 80-week-old (aged) wild-type (WT) mice than in 20-week-old (young) WT mice. To investigate whether reduced myonectin levels contribute to muscle atrophy during the aging process, aged-myonectin knockout (Myo-KO) and aged-WT mice were used for analyses. Aged-Myo-KO mice showed decreases in gastrocnemius and soleus muscle weights, and reduction of muscle strength and running distance compared with aged-WT mice. Myo-KO mice also showed severer muscle atrophy induced by sciatic denervation or dexamethasone (DEX)-treatment compared with WT mice. In addition, Myo-KO mice exhibited reduced expression levels of mitochondria biogenesis-associated genes including PGC1α, and exacerbated mitochondria dysfunction as well as reduced AMPK phosphorylation in denervated muscle compared with WT mice. Treatment of C2C12 myotubes with myonectin protein restored DEX-induced myofiber atrophy via activation of AMPK-dependent induction of PGC1α expression. Administration of myonectin protein into muscle ameliorated muscle atrophy after denervation through its ability to increase PGC1α expression via activation of AMPK. Furthermore, intramuscular injection of myonectin attenuated muscle atrophy in SAMP8 and mdx mice, which are models of accelerated aging and Duchenne muscle dystrophy, respectively.



Research Summary and Future Perspective

Myonectin prevents skeletal muscle atrophy by modulating mitochondrial function through the AMPK/PGC1α-dependent mechanism. Thus, myonectin could be a promising therapeutic target of cardiovascular disease and muscle atrophy in elderly people.

Publication

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Title: Myonectin protects against skeletal muscle dysfunction through activation of AMPK/PGC1α pathway.

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