New insights into the mechanism underlying muscle hypertrophy during resistance training

Laboratory of Stem Cell Regeneration and Adaptation, Graduate School of Pharmaceutical Sciences

Professor So-ichiro Fukada

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Abstract

Skeletal muscle is mainly composed of multinucleated cells called myofibers. It has been established that skeletal muscle hypertrophy by resistance training requires an increased number of myonuclei provided by muscle satellite cells (MuSCs). Nevertheless, the mechanisms governing how MuSCs respond to the increased mechanical load during resistance training long remained elusive. Our research has unveiled that stromal cells in skeletal muscle (mesenchymal progenitors) perceive the increased mechanical load and subsequently secrete factors inducing MuSC proliferation.

Background & Results

Skeletal muscle consists of multinucleated cells called myofibers. Prolonged periods of disuse, such as being bedridden or immobilized in a cast induce muscle atrophy. Aging also causes skeletal muscle atrophy, increasing the risk of fractures resulting from falls, reducing overall activity levels, and ultimately decreasing healthy life expectancy. Skeletal muscle atrophy is thus a pressing global research concern that demands therapeutic approaches.

Conversely, skeletal muscles possess the ability to increase their size (hypertrophy) by training. Understanding the mechanism underlying skeletal muscle hypertrophy is a highly active area of research within the field of musculoskeletal studies, as it is likely to lead to the development of preventive and therapeutic methods for atrophy and innovative drugs to extend healthy life expectancy.

One of the mechanisms identified for muscle hypertrophy induced by muscle training is the increase in the number of myonuclei. It is well-established that MuSCs, which are stem cells specific to skeletal muscle, play a pivotal role in this increase of myonuclei number. However, the manner in which MuSCs proliferate in response to the physical forces generated during muscle training had remained elusive. While it had generally been assumed that MuSC proliferation is triggered by the breakdown of myofibers during muscle training, our previous study has revealed that MuSCs can proliferate independently death of myofibers. In the present study, our research group focused on mesenchymal progenitors and discovered that these cells secrete molecules necessary for the proliferation of MuSCs in response to the physical force exerted by muscle training.

Significance of the research and Future perspective

In recent years, stromal cells (fibroblasts) in various organs have garnered significant attention. It is becoming increasingly evident that stromal cells in different tissues possess unique characteristics. The stromal cells in skeletal muscle (mesenchymal progenitors) are highly differentiated into adipocytes, which cause scar formation. Intriguingly, mesenchymal progenitors also play a crucial role in maintaining skeletal muscle homeostasis and facilitating regeneration. Consequently, they have emerged as potential targets for addressing skeletal muscle diseases through pharmacological interventions. Our current study not only unveils novel insights into the biology of skeletal muscle mesenchymal progenitors but also underscores their relevance as therapeutic targets for muscle atrophy conditions. If the responses of mesenchymal progenitors observed during muscle training can be safely replicated through pharmaceutical interventions, our findings hold the promise of pioneering innovative anti-muscle atrophy medications.

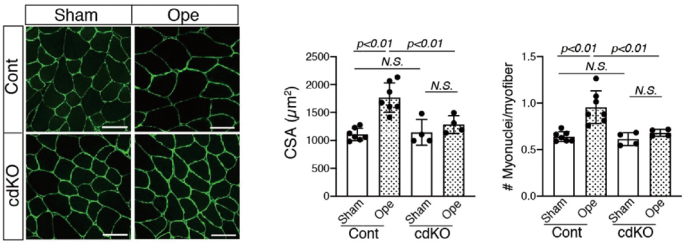

Figure 1 When YAP/TAZ, which migrate to the nucleus in a mechanical load-dependent manner, is eliminated in mesenchymal progenitors, myofiber size does not increase with mechanical load compared to controls. The increased number of myonuclei observed in Cont is also almost nonexistent in cKO.

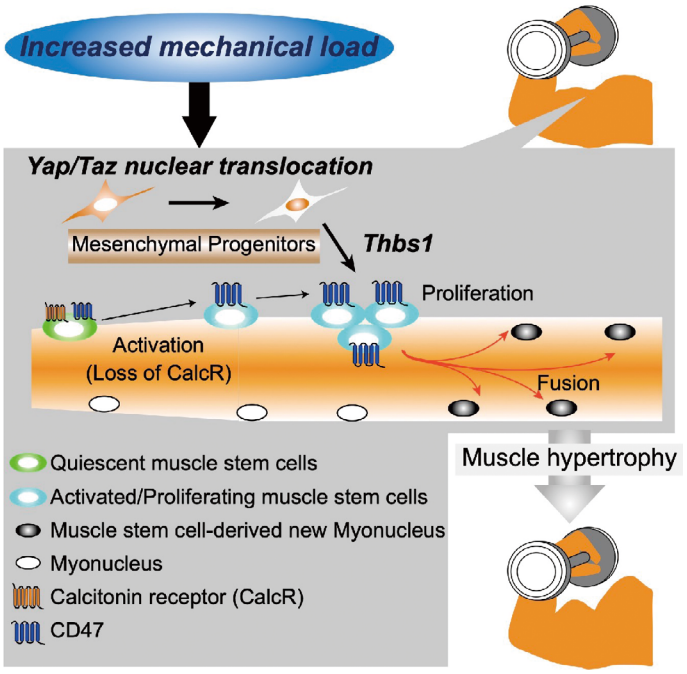

Figure 2 Increased mechanical load causes nuclear translocation of YAP/TAZ in mesenchymal progenitors, and then mesenchymal progenitors secrete thrombospondin 1. Satellite cells that have lost calcitonin receptor expression recognize the presence of thrombospondin 1 using CD47 and proliferate. The proliferating satellite cells eventually fuse with myofibers, becoming the nuclei of new myofibers and contributing the increase in muscle mass.

Patent

Treatise Kaneshige, Akihiro; Kaji, Takayuki; Zhang, Lidan et al. Relayed signaling between mesenchymal progenitors and muscle stem cells ensures adaptive stem cell response to increased mechanical load. Cell Stem Cell. 2022, 29(2):265-280.e6. doi: 10.1016/j.stem.2021.11.003
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URL

Keyword resistance training, mesenchymal progenitors, muscle satellite cells