News Release

Title

Cathepsin K Activity Controls Cardiotoxin-Induced Skeletal Muscle Repair in Mice

Key Points

○ Pharmacological and genetic reduction of Cathepsin K activity suppressed skeletal muscle loss and fibrosis in response to cardiotoxin injury, possibly via a reduction of inflammation and cell apoptosis.

○ The intervention with regulating Cathepsin K activity can be recommended a novel therapeutic strategy for the control of the skeletal muscle diseases such as sarcopenia and frail.

Summary

Shinyu Ogasawara (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 found that cathepsin K (CatK) activity controls cardiotoxin-induced skeletal muscle repair.

Although cysteine protease-cathepsin K has been shown to be involved in cardiovascular and bone remodeling, the role of CatK in the muscle disease is largely unknown. Prior to the world, this study suggested that Pharmacological or genetic reduction of Cathepsin K activity suppressed skeletal muscle loss and fibrosis in response to cardiotoxin injury, possibly via a reduction of inflammation and cell apoptosis.

Therefore, our findings suggest that CatK might be a new therapeutic target for the injury-related muscle disease including sarcopenia and frailty.

Research Background

The age-related loss of skeletal muscle mass and function can results in ultimate consequences such as decreased quality of life. The causes of age-associated muscle disease (e.g., sarcopenia, frailty, etc.) are multifactorial and included biological and environmental factors.Various injuries to skeletal muscles have been shown to contribute to muscle weakness and dysfunction in aged animal and humans.

On the other hand, we have reported that CatK, a cysteine protease that acts as a scavenger in lysosomes, suppressed apoptosis, inflammation and remodeling in the cardiovascular system. However, the role of CatK in skeletal muscles is still unclear.

Here, we hypothesized that ablation of CatK mitigates injury-related skeletal muscle

remodeling and fibrosis in mice with special focus on inflammation and cell apoptosis.

Research Results

- On post-injection day 14, CatK deletion ameliorated muscle interstitial fibrosis and remodeling and performance.
- At an early time point (day 3), $CatK^{-/-}$ reduced the lesion macrophage and leukocyte contents and cell apoptosis, the mRNA levels of monocyte chemoattractant protein-1, toll-like receptor-2, and toll-like receptor-4, and the gelatinolytic activity related to matrix metalloproteinase-2/-9.
- CatK deletion also restored the protein levels of caspase-3 and cleaved caspase-8 and the ratio of the BAX to the BCL-2. Moreover, CatK deficiency protected muscle fiber laminin and desmin disorder in response to CTX injury.
- These beneficial muscle effects were mimicked by CatK-specific inhibitor treatment.
- In vitro experiments demonstrated that pharmacological CatK inhibition reduced the apoptosis of C2C12 mouse myoblasts and the levels of BAX and caspase-3 proteins induced by CTX.

Research Summary and Future Perspective

Token together, present findings show that CatK plays an essential role in skeletal muscle loss and fibrosis in response to CTX injury, possibly via a reduction of inflammation and cell apoptosis, suggesting a novel therapeutic strategy for the control of skeletal muscle diseases by regulating CatK activity.

Publication

Shinyu Ogasawara, Xian Wu Cheng, Aiko Inoue, Lina Hu, Limei Piao, Chenglin Yu, Hiroki Goto, Wenhu Xu, Guangxian Zhao, Yanna Lei, Guang Yang, Kaoru Kimura, Hiroyuki Umegaki, Guo-Ping Shi, Masafumi Kuzuya. Cathepsin K Activity Controls Cardiotoxin-Induced Skeletal Muscle Repair in Mice. The paper on the above results was published online (before print) in an English journal: Journal of Cachexia, Sarcopenia and Muscle on Oct. 23, 2017.
DOI: 10.1002/jcsm.12248

Japanese ver.

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