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Author: Prof.Dr. xiaoping chen
China Astronaut Research and Training Center, China

Mr. Peng Zhang
China Astronaut Research and Training Center, China

ER STRESS IS ACTIVATED AND INVOLVED IN DISUSE-INDUCED MUSCLE ATROPHY

Abstract

Background: Muscle atrophy resulting from disuse conditions (such as microgravity or bedrest) represents a serious medical complication that decreases life quality and even increases morbidity and mortality. The accumulation of misfolded/unfolded protein disrupts endoplasmic reticulum (ER) homeostasis and thus causes ER stress. Growing evidence indicates that ER stress plays an essential role in skeletal muscle remodeling under various physiological or pathophysiological conditions. However, whether ER stress is involved in disuse-induced muscle atrophy still remains unclear. Methods: To induce muscle atrophyeight-week-old C57BL/6 male mice were subjected to 3, 7 or 14 days of HU, rhesus macaques (Macaca mulatta) were subjected to 10 head-down tilted bed rest (HDBR) for 6 weeks. Taurourdodeoxycholic acid (500mg/kg/d) was oral administrated to mice during HU to inhibit ER stress. qRT-PCR, Western blotting and immunohistochemistry examinations were conducted to evaluate gene, protein and structural changes. Results: ER stress marker genes were rapidly induced by hindlimb unloading (HU) in a similar trend to that observed with atrophy-related genes such as Atrogin-1, MuRF1 and MUSA1. Inhibition of ER stress with tauroursodeoxycholicacid (TUDCA), a pan-ER stress inhibitor, attenuated HU-induced muscle atrophy and the upregulation of ubiquitin ligases via the AKT/Foxo3a pathway. In addition, the oxidative-to-glycolytic myofiber type transition caused by HU was also inhibited by TUDCA treatment. ER stress activation was also confirmed in head-down tilted bed rest (HDBR)-induced rhesus soleus muscle atrophy. Conclusions: The strong positive correlation between ER stress activation and both HU- and HDBR-induced muscle atrophy indicates that ER stress activation is ubiquitously involved in disuse-induced muscle atrophy, regardless of species. Inhibiting ER stress may be an effective therapeutic strategy to prevent muscle atrophy during disuse.