SPACE LIFE SCIENCES SYMPOSIUM (A1)
Biology in Space (7)

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# DYSTROPHIN INVOLVED IN THE ATROPHIC RESPONSE OF SLOW MUSCLES TO HINDLIMB UNLOADING VIA CONCOMITANT ACTIVATION OF TGF-BETA1/SMAD3 SIGNALING AND UBIQUITIN-PROTEASOME DEGRADATION IN MICE

**Abstract**

Purpose: Dystrophin, which constitutes an important link between the cytoskeleton and the extracellular matrix, is believed to be involved in mechanically stabilizing skeletal muscle and in force generation. Thus, this study aims to investigate whether dystrophi is engaged in the hindlimb unloading (HU)-induced muscular atrophy. Methodology: Groups of 10-week-old wild type control mice (C57BL/10 Scott Snells) and dystrophin-deficient mdx mice were subjected to 0(groud-based control groups) or 14 days of HU. At the end of the experimental periods, soleus muscles were collected for RNA isolation, protein extraction or embedded with OCT compound for subsequent analyses. Results: Here we show that after a 14-day HU in C57BL/10 mice the expression of dystrophin is significantly down-regulated in fast twitch myofibers while up-regulated in slow twitch myofibers. To investigate the role of dystrophin in HU susceptibility, we focus on the slow twitch soleus muscle in dystrophin-deficient mdx mice and find that they display decreased susceptibility to HU comparing to the wild type (WT) animal, manifested by less reduction of muscle mass and myofiber cross-sectional area. Meanwhile, two ubiquitin ligases (MuRF1, Atrogin-1), which play a crucial role in the muscular ubiquitin-proteasome degradation, are significantly down-regulated in soleus muscle of mdx mice after HU, in contrast to that of WT. Transforming growth factor $\beta$(TGF-$\beta$1)/Smad3 signaling is inhibited in mdx in this course whereas activated in WT mice. Correspondingly, the expression of four myosin heavy chain (MyHC) subtypes and troponin I after HU in mdx mice indicates an inhibited or delayed slow-to-fast transition. Conclusions: In summary, our results suggest that dystrophin exerts a intermediate positive role in disuse atrophy of slow twitch muscles, and its effect is mediated through activation of TGF-$\beta$1/Smad3 signaling and downstream ubiquitin-proteasome pathway.