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HINDLIMB-UNLOADING INDUCES PSMAD3 TO TRIGGER A SHIFT OF SLOW-TO-FAST TWITCH MYOFIBER TYPE AND MUSCLE ATROPHY IN MICE

Abstract

Purpose: Muscle atrophy and weakness due to muscle disuse are common during bed rest, aging or space flight. Transforming Growth Factor-β(TGF-β) signaling plays an important role in the pathogenesis of myofibers atrophy and endomysial fibrosis. TGF-β deactivates inflammatory macrophages, while promoting myofibroblast differentiation and matrix synthesis through Smad3-dependent pathways. Thus, this study aims to investigate the effect of Smad3 on skeletal muscles atrophy induced by hindlimb unloading (HU) and its mechanisms. Methodology: Groups of 8-week-old wild-type or Smad3-deficiency (Smad3+/-) 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: We found that HU upregulated the mRNA and protein expression of Smad2 and Smad3, especially pSmad3, while TGF-β1 was upregulated by HU at 3 or 7 days of HU, and downregulated at day 14 of HU, suggesting that TGF-β1/pSmad3 may be involved in the HU-induced changes. HU induced muscle atrophy by decrease in muscle mass and fiber cross-sectional area, and increase in the mRNA and protein expression of Atrogin-1 and MuRF1 in wild-type mice, whereas Smad3+/- rescued them. Smad3+/- mice also protected from HU-induced downregulation of slow-twitch myofiber MHC-I, MHC-IIa and upregulation of fast-twitch myofiber MHC-IIb, which triggers slow-to-fast twitch myofiber type transition. Furthermore, HU-enhanced pSmad3 directly repressed MHC-IIa and promoted MHC-IIb transcription which was dependent on the presence of Smad3 binding sites in the promoter region of MHC-IIa and MHC-IIb. Conclusions: Therefore, the study provides a novel molecular mechanism of TGF-β1/pSmad3 signaling in myofiber type switch associated with muscle atrophy, and a decrease in Smad3 could be attractive therapeutic targets for pharmacological countermeasures.