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THE NOVEL ROLE OF SKELETAL MUSCLE MEMBRANE RECEPTOR COMPLEX HJV/TBRII IN UNLOADED MUSCULAR ATROPHY AND ITS MECHANISM

Abstract

Transforming growth factor-β1 (TGF-β1) contributes to unloaded muscular atrophy, inhibition of TGF-β1 signaling is a promising therapeutic strategy for the muscle atrophy. Hemojuvelin (HJV) is a membrane-bound protein that is highly expressed in skeletal muscle, heart and liver. In hepatic cells, HJV acts as a co-receptor for bone morphogenetic protein (BMP), a TGF-β subfamily member. The aim of this study was to investigate whether HJV/TβRII complex plays an essential role in unloading muscle atrophy and its mechanism. In the present study, we demonstrated that HJV was significantly downregulated during the hindlimb unloading-induced muscular atrophy of mice compared to their controls. Overexpression of HJV rescued the dystrophic effects. Unlike its function in hepatic cells, the BMP downstream phosphorylated p-Smad1/5/8 signaling pathway was unchanged, but TGF-β1, TGF-β receptor II (TβRII), and p-Smad2/3 expression were increased in HJV-deficient muscles. Mechanistically, loss of HJV promoted activation of Smad3 signaling induced by TGF-β1, whereas HJV overexpression inhibited TGF-β1/Smad3 signaling by directly interacting with TβRII on the muscle membrane. Our findings identify an unrecognized role of HJV/TβRII complex on skeletal muscle membrane in regulating unloaded muscular atrophy via TGF-β1/Smad3 signaling. Notably, unlike the TGF-β1/Smad3 pathway and its TβRII, HJV could be a reliable drug target as its expression is not widespread. Novel therapeutic strategies could potentially be devised to interfere only with the muscle function of HJV to treat unloading muscle atrophy in spaceflight.

Key words: Hemojuvelin; TβRII; TGF-β1; Hindlimb Unloading; Muscular Atrophy

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