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# A NOVEL ROLE OF MEMBRANE RECEPTOR HEMOJUVELIN IN UNLOADED MUSCULAR ATROPHY AND ITS MECHANISM

**Abstract**

Transforming growth factor-$\beta$1 (TGF-$\beta$1) contributes to unloading muscle atrophy, inhibition of TGF-$\beta$1 signaling is a promising therapeutic strategy for the muscle atrophy. Hemojuvelin (HJV or Hjv as the murine homolog) is a membrane-bound protein that is highly expressed in skeletal muscle, heart and liver. In hepatic cells, Hjv acts as a co-receptor for bone morphogenetic protein (BMP), a TGF-$\beta$ subfamily member. The aim of this study was to investigate whether Hjv plays an essential role in unloading muscle atrophy by acting as a co-receptor for T$\beta$ R2 in TGF-$\beta$1 signaling. In the present study, we demonstrated that HJV was significantly downregulated during the hindlimb unloading-induced muscle atrophy of mice compared to their controls. Overexpression of Hjv rescued the dystrophic effects. Unlike its function in hepatic cells, the BMP downstream phosphorylated p-Smad1/5/8 signaling pathway was unchanged, but TGF-$\beta$1, TGF-$\beta$ receptor2 (T$\beta$R2 ), and p-Smad2/3 expression were increased in Hjv-deficient muscles. Mechanistically, loss of Hjv promoted activation of Smad3 signaling induced by TGF-$\beta$1, whereas Hjv overexpression inhibited TGF-$\beta$1/Smad3 signaling by directly interacting with T$\beta$R2 on the muscle membrane. Our findings identify an unrecognized role of Hjv in skeletal muscle by regulating TGF-$\beta$1/Smad3 signaling as a coreceptor for T$\beta$R2. Unlike the TGF-$\beta$1/Smad3 pathway, 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.

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