**TGF-β requires the activation of canonical and non-canonical signalling pathways to induce skeletal muscle atrophy**


**Abstract**

The transforming growth factor type-beta (TGF-β) induces skeletal muscle atrophy characterised by a decrease in the fibre’s diameter and levels of myosin heavy chain (MHC), also as an increase of MuRF-1 expression. In addition, TGF-β induces muscle atrophy by a mechanism dependent on reactive oxygen species (ROS). TGF-β signals by activating both canonical Smad-dependent, and non-canonical signalling pathways such as ERK1/2, JNK1/2, and p38 MAPKs. However, the participation of canonical and non-canonical signalling pathways in the TGF-β atrophic effect on skeletal muscle is unknown. We evaluate the impact of Smad and MAPK signalling pathways on the TGF-β-induced atrophic effect in C2C12 myotubes. The results indicate that TGF-β activates Smad2/3, ERK1/2 and JNK1/2, but not p38 in myotubes. The pharmacological inhibition of Smad3, ERK1/2 and JNK1/2 activation completely abolished the atrophic effect of TGF-β. Finally, the inhibition of these canonical and non-canonical pathways did not decrease the ROS increment, while the inhibition of ROS production entirely abolished the phosphorylation of Smad3, ERK1/2 and JNK1/2. These results suggest that TGF-β requires Smad3, ERK1/2 and JNK1/2 activation to produce skeletal muscle atrophy. Moreover, the induction of ROS by TGF-β is an upstream event to canonical and non-canonical pathways.

**Keywords**

MAPK; MuRF-1; Muscle atrophy; Reactive oxygen species; Smad