

Itch E3 ligase-mediated regulation of TGF- β signaling by modulating Smad2 phosphorylation

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Transforming growth factor- β (TGF- β) is a multifunctional cytokine regulating diverse biological processes such as cell proliferation, differentiation, and apoptosis. E3 ubiquitin ligases like Smurf1 and Smurf2 have been implicated in the intracellular biochemical events transduced by TGF- β receptor via different mechanisms including the degradation of Smads or their binding proteins. Here we show that loss of Itch E3 ligase in mouse embryonic fibroblasts (MEFs) results in reduced susceptibility of TGF- β -induced cell growth arrest. The phosphorylation of Smad2 is decreased, without apparent alteration in protein levels for Smad2, Smad4, and Smad7 in Itch^{-/-} MEFs. Itch promotes ubiquitination of Smad2 and augments Smad2 phosphorylation that requires an intact ligase activity of Itch. Moreover, Itch facilitates the complex formation between TGF- β receptor and Smad2 and enhances TGF- β -induced transcription. This study reveals a previously unrecognized positive TGF- β signaling pathway via proteolysis-independent ubiquitination.