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Interaction of the Ubiquitin Ligase CHIP with Smad3 Regulates TGF- β Signal Transduction

Smad3 is a major mediator of TGF- β -induced gene expression. The regulation of the protein level of Smad3 can play a critical role in control of TGF- β function. Here we report a novel mechanism of regulation of TGF- β signaling, by which Smad3 protein levels are modulated through CHIP, a U-box-dependent E3 ubiquitin ligase as well as a co-chaperon protein. We demonstrate that CHIP interacts with Smad3 *in vitro* and *in vivo*. The TPR domain in CHIP and the MH2 domain in Smad3 are necessary for the interaction between the two proteins. Furthermore, we demonstrate that the co-expression of Smad3 and CHIP proteins results in the degradation of Smad3 through a ubiquitin-mediated process. Consistent with the observation that CHIP induces Smad degradation, we have shown that CHIP expression could inhibit the transcriptional activities of Smad3/4, which is the complex induced by TGF- β . Using RNAi to knock-down CHIP expression, we observed an increase in TGF- β - signaling. In contrast, stably expressing CHIP blocks the TGF- β -mediated Jun-B gene expression and abolishes the cell growth inhibitory action of TGF- β . Thus, our results indicate that CHIP interacts with Smad3 and blocks TGF- β signal transduction through ubiquitin-mediated degradation of Smad3, demonstrating a novel role of CHIP as a negative regulator of TGF- β signaling.

Date: 21 Feb 2003, Friday
Time: 4 - 5pm
Venue: LT 20
Host: Prof Hew Choy Leong

All are welcome