Regulation of TGF-β signaling by a ubiquitin ligase Arkadia

ユビキチンリガーゼ Arkadia による TGF-βシグナルの調節機構

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Abstract

Transforming growth factor-β (TGF-β) is a member of the TGF-β family, which has diverse activities including cell growth and differentiation. Aberration of TGF-β signaling has been believed to cause various diseases such as cancer and fibrosis. Thus, analysis of the regulatory mechanism of TGF-β signal transduction in detail is important to understand the process of many diseases related to aberrant TGF-β signaling. TGF-β signal is transduced through receptor kinases and their downstream effectors, Smad proteins. Activated Smad complex translocates into the nucleus to regulate transcription of target genes. TGF-β signaling is controlled by a variety of regulators that target either signaling receptors or activated Smad complexes. Among negative regulators, Smad7, a negative feedback regulator, antagonizes TGF-β signaling mainly through targeting the signaling receptors, whereas SnoN and c-Ski repress signaling at the transcriptional level through inactivation of Smad complexes.

Koinuma *et al* previously found that Arkadia is a positive regulator of TGF-β signaling which induces ubiquitin-dependent degradation of Smad7 through its C-terminal RING domain. I report here that Arkadia induces degradation of SnoN and c-Ski in addition to Smad7.

Arkadia interacts with SnoN and c-Ski and colocalizes with them in the nucleus.

Arkadia mediates ubiquitylation of SnoN and c-Ski and accelerates their turnover through its RING domain. Consistently, levels of expression of SnoN protein are higher in *Arkadia*$^{-/-}$ ES cells than in wild-type ES cells, and c-Ski protein accumulates in Arkadia-knocked down cell lines. In addition, Arkadia interacts with SnoN and c-Ski in their free forms as well as in the forms bound to Smad proteins, suggesting that Arkadia may constitutively down-regulate levels of expression of SnoN and c-Ski. Arkadia thus appears to effectively enhance TGF-β signaling through simultaneous down-regulation of two distinct types of negative regulators, Smad7 and SnoN/c-Ski, and may play an important role in determining the intensity of TGF-β signaling in target cells (Fig. 1).

Increased expression of SnoN and c-Ski has been reported in several tumors, but expression of Arkadia in tumors has not been examined yet. I also report that Arkadia is expressed in various tumor cell lines, whereas expression levels of SnoN and c-Ski are variable. In addition, Arkadia may not be functional in some tumor cell lines, since c-Ski protein does not accumulate in some Arkadia-silenced tumor cells. Elucidating the roles of Arkadia in tumor cells will be an important task in the near future.

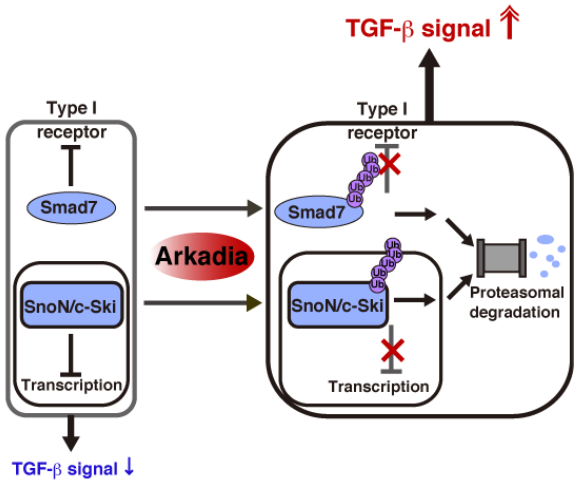

Fig. 1 A model of enhancement of TGF-β signaling by Arkadia