

# Modulation of NF- $\kappa$ B Oscillatory Patterns Mediated by $\beta$ -TrCP

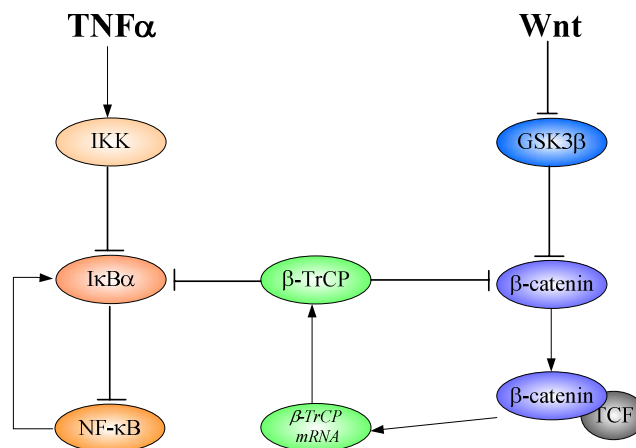
Dongkwan Shin<sup>1</sup> and Kwang-Hyun Cho<sup>1\*</sup>

1. Department of Bio and Brain Engineering and Institute for the BioCentury,  
Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea

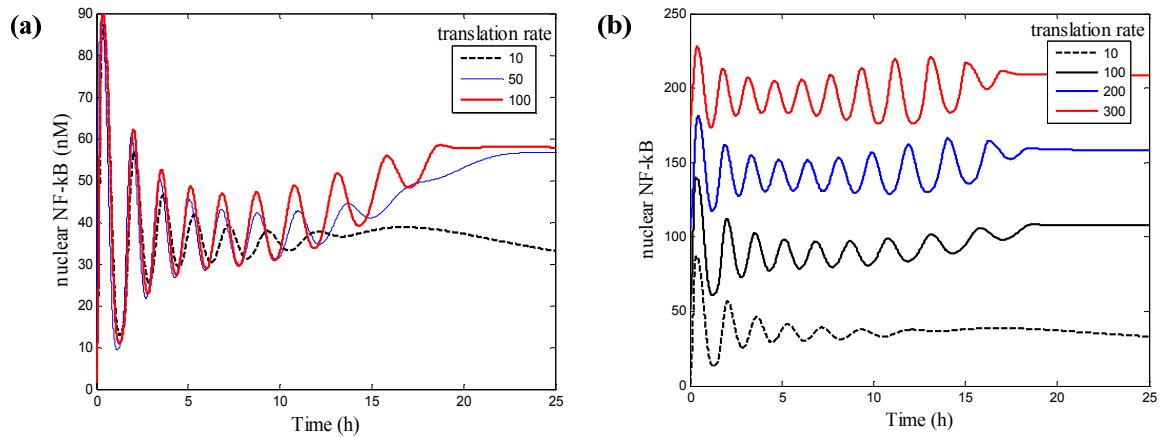
\*email: ckh@kaist.edu

There have been some recent reports on the crosstalk between Wnt/ $\beta$ -catenin and NF- $\kappa$ B pathways through  $\beta$ -transducin repeat-containing protein ( $\beta$ -TrCP) which is the ubiquitin ligase complex component targeting both  $\beta$ -catenin and I $\kappa$ B $\alpha$  (Fig. 1).  $\beta$ -TrCP induces ubiquitination and subsequent degradation. Hence, it acts as a negative regulator of Wnt/ $\beta$ -catenin signaling while acts as a positive regulator of NF- $\kappa$ B signaling (1-3). Interestingly,  $\beta$ -TrCP is induced by Wnt/ $\beta$ -catenin signaling which is involved with various differentiation events during embryonic development and tumor formation when aberrantly activated. Considering that I $\kappa$ B degradation is an essential step for the nuclear translocation of NF- $\kappa$ B and its transcriptional activity, we expect that  $\beta$ -TrCP may play a significant role in regulating the expressions of NF- $\kappa$ B target genes during tumorigenesis.

In this study, we have constructed a mathematical model representing the NF- $\kappa$ B signaling pathway, the Wnt/ $\beta$ -catenin signaling pathway, and their crosstalk through  $\beta$ -TrCP based on previous experimental results and available part lists (4, 5). From simulation of this model, we found that  $\beta$ -TrCP positively regulates the NF- $\kappa$ B activity and thereby modulates the oscillation pattern of the nuclear NF- $\kappa$ B protein level (Fig. 2).



**Figure 1.** A schematic diagram representing the crosstalk through  $\beta$ -TrCP.



**Figure 2.** Oscillatory patterns of the nuclear NF- $\kappa$ B for different translation rates. (a) Stabilization of  $\beta$ -TrCP increases the duration of NF- $\kappa$ B oscillations as well as their steady state levels. (b) Overexpression of  $\beta$ -TrCP by increasing the translation rate decreases the frequency of NF- $\kappa$ B oscillation. Note that NF- $\kappa$ B levels were vertically shifted in this figure for easier comparison.

Recently, Noubissi *et al.* have demonstrated that the RNA-binding protein CRD-BP (coding region determinant-binding protein), a target of  $\beta$ -catenin/TCF transcription factor, stabilizes  $\beta$ -TrCP mRNA and elevates  $\beta$ -TrCP levels, which gives rise to the accelerated degradation of  $I\kappa$ B $\alpha$  (6). Based on this experimental finding, we assumed various translation rates of  $\beta$ -TrCP for simulation and observed oscillatory patterns of nuclear NF- $\kappa$ B as follows: First, the stabilization of  $\beta$ -TrCP increases the time duration expressing oscillatory behavior of NF- $\kappa$ B as well as its steady state level (Fig. 2(a)). Secondly, the overexpression of  $\beta$ -TrCP by an increased translation rate decreases the frequency of NF- $\kappa$ B oscillation (Fig. 2(b)). Recently, there have been some studies focusing on the NF- $\kappa$ B oscillations mediated by  $I\kappa$ B $\alpha$  isoforms (7, 8), but not by a crosstalk. Here, we suggest that the crosstalk between NF- $\kappa$ B and Wnt/ $\beta$ -catenin signaling pathways through  $\beta$ -TrCP modulates the oscillatory pattern of NF- $\kappa$ B localizations and thereby such a crosstalk may play a crucial role in determining the NF- $\kappa$ B-dependent gene expressions according to the time duration and frequency of NF- $\kappa$ B oscillation.

NF- $\kappa$ B is well known for its dual functioning in tumorigenesis. In other words, NF- $\kappa$ B behaves as a tumor promoter under certain circumstances while it also works as a tumor suppressor under other conditions (9). However, the underlying mechanisms behind such dual roles of NF- $\kappa$ B have not been well understood. In this study, we examined that the

crosstalk through  $\beta$ -TrCP acts as a modulator of NF- $\kappa$ B oscillations and revealed that various oscillation patterns might be associated with the contradictory roles of NF- $\kappa$ B in tumorigenesis.

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