Dynamic modeling of NF-κB signaling system in B cell

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Introduction

In systems biology, mathematical modeling and simulation has become a standard technique to predict and understand the dynamics of complex biochemical systems. Signaling systems transmit extra-cellular information to intra-cellular transcription factors, inducing gene expression and driving cell fate decisions such as cell proliferation, differentiation and apoptosis. The nuclear factor-kappa B (NF-κB) is a transcriptional factor and regulates expression of various genes which play important roles in biological process. The NF-κB transcriptional activity shows switch-like, while showing oscillating behavior. This oscillation dynamics is a result of negative feedback regulation from IκB to NF-κB [1, 2]. However, a regulatory mechanism of switch-like behavior of NF-κB activity is not known. To shed a light on the regulation of the NF-κB signaling system, we quantitatively analyzed the NF-κB system by using experiments and mathematical modeling. In this work, we focus on the CARMA1-TAK1-IKKβ module, which is an upstream of NF-κB, and investigate how this module affects the IκB-NF-κB activity.

Method

Experiments

Time courses and dose responses of TAK1, IKKβ and NF-κB activities in B cell were measured. Moreover, some knockdown experiments were examined.

Dynamic model

First, we constructed a mathematical model of CARMA1-TAK1-IKKβ module and optimized the kinetic parameters to the experimental data using evolutionary algorithm [3]. Sensitivity analysis for the model was examined. Then, we expanded it to the model with IκB-NF-κB.

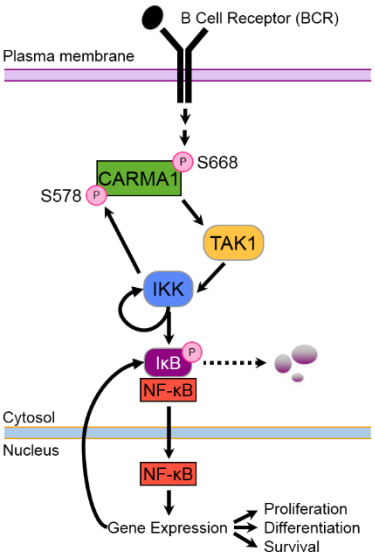

Fig.1 Illustration of NF-κB system

Results and Discussions

CARMA1, which functions as a scaffold protein, phosphorylates and activates TAK1 and IKK through their complex formation [4]. We revealed that this module forms a positive feedback loop, in which IKK activates TAK1 via phosphorylation of CARMA1. Furthermore, the experimental results indicated that the positive feedback loop enhances and prolongs signaling activities and changes the switch-like response of NF- κ B. Simulations of TAK1 and IKK corresponded to the experimental data very well (Fig.2A). The sensitivity analysis indicated that the positive feedback from IKK to TAK1 controls the amplitude of second peak for TAK1 activity (Fig.2B) and the auto-positive feedback of IKK determines the presence or absence or timing of these late activities (Fig.2C). Moreover, simulation of the expanded model with IκB-NF-κB indicated that the activity of NF-κB is dynamically operated by both a positive and a negative feedback loop. The results show that the switch-like behavior of NF-κB activity is at least regulated by the CARMA1-TAK1-IKKβ module.

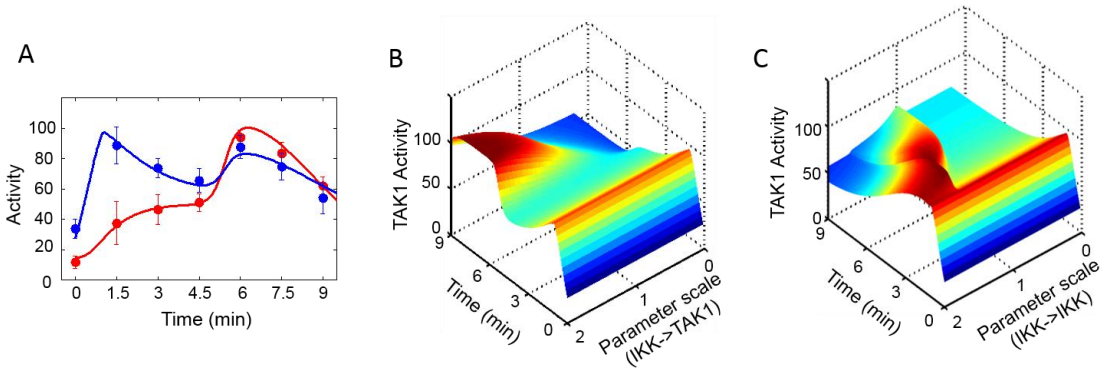

Fig.2 Simulations and experimental values for TAK1 and IKK (A) and sensitivity analysis for TAK1 (B, C). (A) Circles and lines are experimental values and simulation values, respectively. (TAK1: blue, IKK: red) (B) Change of TAK1 activity to change of the positive feedback parameter from IKK to TAK1. (C) Change of TAK1 activity to change of the auto-positive feedback parameter for IKK.

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