Model Analysis of Helper T Cell Differentiation

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1 Introduction

Helper T (Th) cells regulate immune responses by producing various cytokines upon antigen stimulation. Helper T cells can be divided into two subsets, Th1 and Th2 [2]. The Th1 cells are responsible for defense against infectious intracellular microorganisms. The Th2 cells are responsible for defense against extracellular pathogens and the development of allergic immune reactions. The SOCS family was reported to regulate Th differentiation [3, 4]. In order to analyze the balance of Th1/Th2 differentiation and the role of SOCS family, we developed the model of Th0 cells containing IL-4, IL-12 and IFN-γ JAK/STAT signal transduction pathway, which simulates the first stage of Th1/Th2 differentiation.

2 Method and Results

Factors to determine development of either Th1 or Th2 are cytokines at the initial stage of activation through T cell receptor. IL-12 and IL-4 are responsible for the development of Th1 and Th2 cells, respectively. IFN-γ pathway is also included because it is an important cytokine for Th1 responses. The signals of these three cytokines are transduced by JAK/STAT pathways. The model shown in Figure 1-(1) simulates the first stage of Th1/Th2 differentiation in Th0 cells. The SOCS3 is induced by IL-4 signal, binds to IL-12 receptor, and inhibits IL-12 signal [4]. The SOCS5 is induced by IL-12 signal, inhibits IL-4 signal by binding to IL-4 receptor [3]. SOCS1 is induced by these three cytokines and inhibits all three signals. The models of these three cytokine signal transduction pathways are constructed based on JAK/STAT signal transduction pathway model for IFN-γ [5]. IL-4 activates STAT6, and STAT6 induces GATA3 synthesis. STAT6 and GATA3 induce IL-4 synthesis. IL-12 activates STAT4, and STAT4 induces T-bet and IL-12 receptor synthesis. STAT4 and T-bet induce IFN-γ synthesis. All chemical reactions were described in differential equations, and solved mathematically by using Runge-Kutta-Gill method as described previously [5].

Figure 1-(2), (3) shows the time course of STAT activation and cytokine synthesis. IL-4 induces STAT6 activation and IL-4 synthesis (left). IL-12 induces STAT4 activation and IFN-γ synthesis (center). Both cytokines activate both pathways, but more IFN-γ are synthesized. In the SOCS1 knock-out cells, both pathways are more activated than in normal cells, and IFN-γ is more synthesized than IL-4 (Figure 1-(3)), which was consistent with the results of SOCS1 knock-out cells. In the SOCS3 and SOCS5 knock-out cells, slightly more IL-12 and IL-4 pathway are activated, respectively (data not shown). From these results, SOCS1 is considered to be the most important negative regulator, and SOCS3 and SOCS5 are considered to be used to maintain Th2 and Th1 state, respectively. Since some polymorphisms in IL-4 receptors were reported for atopic disorders [1], the allergic disorder is

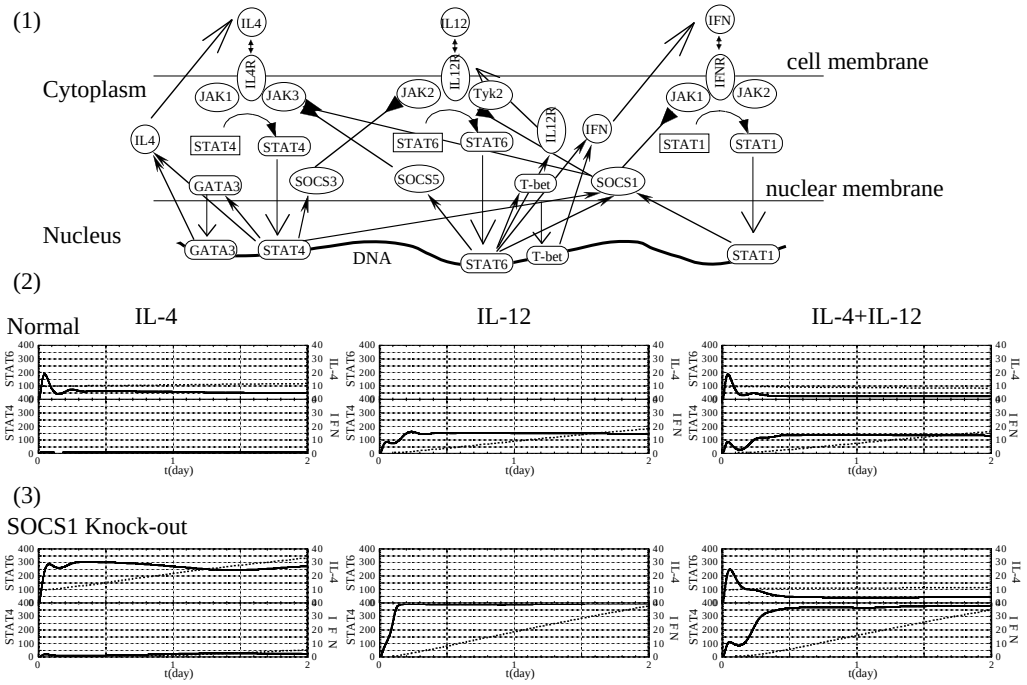

Figure 1: The model of Th0 cells and simulation results. (1) The model of Th0 cells, (2) the time courses of STAT6 phosphorylation, IL-4, STAT4 phosphorylation, and IFN-γ by the addition of IL-4 (left), IL-12 (center), and IL-4 and IL-12 (right) in the normal cells. Each graph shows the time course of phosphorylated STAT6 dimers in nucleus (solid line) and extracellular IL-4 (dotted line) (upper panel) and phosphorylated STAT4 dimers in nucleus (solid line) and extracellular IFN-γ (dotted line) (lower panel), (3) the time courses in the SOCS1 knock-out cells.

simulated by the model containing more IL-4 receptors, JAK1, and JAK3. In simulations of adding inhibitors to the allergic model, an inhibitor binding to JAK3 shows time course more similar to that in normal cells than inhibitors binding to IL-4R, JAK1, STAT6, or SOCS3 (data not shown).

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