Temporal gene expression patterns reveal mass conservation in TNF-α signaling

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1 Introduction

Tumor necrosis factor-α (TNF-α) is an important cytokine produced during the activation of innate immunity and is involved in numerous cellular functions such as growth, differentiation, apoptosis, etc. Recent high-throughput dataset on TNF-α stimulation shows three dynamical patterns (groups) arising from 180 up-regulated genes in murine embryonic fibroblasts (MEF). These groups were delineated based on the shape of their temporal activation profiles. [2] In group 1, the time of peak activation is early (~0.5h) and decays rapidly. In groups 2 and 3, the peak activation is delayed (~2h and ~12h, respectively) and the decay is very slow. These results were interpreted to arise due to the rate of instability of mRNA determined by the number of AU-rich element in the 3’ untranslated region (UTR). Here, using a computational model of TNF-α signaling, we show that the 3 temporal patterns of gene expressions can be reproduced using the law of mass conservation and mass-action kinetics. Next, in addition to the instability of mRNA, we show groups 1 and 2 genes are mainly activated by primary signaling with transcription factors AP.1 and NF.κB with differing kinetics and group 3 genes are induced by secondary signaling such as autocrine stimulations of IL.1 and IL.8. Here, we compared our model simulation with dynamical experimental data and suggested the dynamical patterns of gene expression in complex networks can be represented by simple physical rules.

2 Materials and Methods

We first performed literature survey to construct the TNF-α signaling pathway (Fig.1A). Based on this, we developed a dynamical model of TNF-α signaling pathway using E-Cell version 3. [3] Each signaling process was represented using mass-action kinetics based on the law of mass conservation. Recently 180 up-regulated genes after TNF-α stimulation are found to be distinguished based on the shape of their temporal activation profiles. In group 1, the time of peak activation is early (~0.5h) and decays rapidly. In groups 2 and 3, the peak activation is delayed (~2h and ~12h, respectively) and the decay is very slow. (Fig.1B) This time, we used these three types of temporal gene patterns for our computational model.

3 Results and Discussion

We simulated three types of gene activation in TNF-α signaling. We found that simulation results of group1 and group2 were comparable with the experimental results. (Fig.2A) However, for group3 genes did not match the experimental observation. (Fig.1B) For fitting our model with experimental data, we considered the secondary signaling or a novel pathway with delayed kinetics is needed to activate group3 genes. From these results, we show that group1 and 2 genes are activated by primary signaling with AP.1 and NF.κB with different kinetics and group3 genes are induced by secondary signaling such as autocrine stimulations of IL.1 and IL.8. (Fig.2B) Finally we concluded three temporal gene activation patterns can be reproduced using the law of mass conservation and mass-action kinetics and demonstrated simple physical rules can be governed in complex signaling networks. We hope our approach help to a better understanding of TNF-α induced complex mechanism such as switching mechanism between cell survival and apoptosis process.
Figure 1: Schematic representation of TNF-α signaling pathway. A) The pathway as depicted from current literatures. B) Temporal three gene expression patterns arisen from 180 up-regulated genes after TNF-α stimulation. [2]

Figure 2: Simulation results of three temporal gene expression. (A): Dot line indicates group1 gene, dashed line indicates group2 gene, and black line indicates group3 gene. (B): (*) indicates secondary signaling or a novel pathway with delayed kinetics.

4 References