Computational analysis of network motifs suggests simple strategy to study pathway cross-talks of cells under repetitive exposure to stimuli

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***Short Abstract* — Priming refers to that repetitive exposure to stimulants results in non-additive augmented cellular responses, especially for immune cells. By means of a computational search through the parameter space of a coarse-grained three-node network with a two-stage Metropolis sampling approach, we enumerated all the network topologies that can generate priming. The numerical analysis automatically reveals three major mechanisms (pathway synergy, suppressor deactivation, activator induction). We then applied the strategy suggested by the theoretical study to analyze the human macrophage microarray data, and revealed candidates for Inteferon-γ induced priming effects.**

***Keywords* — innate immunity, high throughput, pathway crosstalk**

I. BACKGROUND

CELLS are subject to fluctuating and multiple stimuli in their natural environment. The signaling pathways often crosstalk to each other and give rise to complex nonlinear dynamics. In this work we focus on the cellular priming effect (also called preconditioning and sensitization), which refers to a well-observed phenomenon that after being treated with a seemingly negligible concentration of stimulus, a cell may launch amplified responses upon a second exposure to the same stimulus at a higher concentration. Two such examples are lipopolysaccharide-mediated and Interferon-γ-mediated pro-inflammatory priming effects observed in innate immune cells such as monocytes and macrophages [1-2]. The phenomenon has important pathological and clinical significances with relation to various diseases such as diabetes, atherosclerosis, rheumatoid arthritis, hepatitis and multiple sclerosis. However, detailed molecular mechanisms for priming are often unclear.

II. RESULTS

The published observations and our own new experimental results have inspired us to look for all possible mechanisms for priming. To do this, we computationally searched the high-dimensional parameter space associated with a generic mathematical model of a three-node regulatory network. The search reveals only three mechanisms accounting for priming (pathway synergy, suppressor deactivation, activator induction). We then searched the database and literature and found that existing experimental results support the theoretical result.

The computational study also suggests a straightforward procedure to identify molecular candidates contributing to the priming effect and the corresponding mechanisms. The procedure involves time course measurements, e.g., gene expression levels, or protein activities under low, high, and low + high dose of stimulant, then computational analysis of the dynamics patterns, and identification of functional roles in the context of the regulatory network. We applied the procedure to a set of published microarray data on interferon-γ-mediated priming effect of human macrophages. The analysis identified a number of network motifs and molecular species possibly contributing to Interferon-γ priming. A separate detailed mathematical model analysis further reveals how combination of different mechanisms leads to the observed phosphorylated-STAT1 priming effect.

III. CONCLUSION

Based on *in silico* studies, we proposed a generic procedure to identify possible molecular candidates contributing to the priming effect through combined experimental time course measurement, subsequent data analysis and computational modeling. We demonstrated the procedure with microarray and other data on interferon-γ induced priming effects. This procedure is generally applicable to other similar problems. One may perform systematic screening using the proposed procedure combining with high throughput measurements, at both transcriptome and proteome levels.

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