Modeling the Dynamics of the RIG-I-MAVS/NF-κB/IRF3 Signaling Pathway

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Short Abstract — RIG-I-MAVS complex plays an active role in recognition of viral RNA, initiating a cascade of signaling pathways leading to the production of the cytokine Interferon-κB, and inflammatory response through the activation of NF-κB. We have performed experiments and developed a preliminary stochastic model of the dynamics of the pathway, which will allow us to predict the module’s response to a range of hypothetical experimental conditions.

Keywords — Innate immunity, Modeling, RIG-I-MAVS, IRF3, NF-κB.

I. PURPOSE

Double- and single-stranded viral RNAs bind to Cytoplasmic Retinoic acid-Inducible Gene 1 (RIG-I) inducing its ubiquitylation. This complex then binds to Mitochondrial Anti-Viral Signaling protein (MAVS; also known as IPS-1, VISA, and CARDIF). This oligomer, known as RIG-I-MAVS, recruits TNF Receptor-Associated Factors (TRAFs) 2, 3 and 6. The resulting complex generates divergent signaling pathways that control two potent transcription factors: NF-κB and IRF3 [1].

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a gene regulatory protein, or a transcription factor (TF). NF-κB is a key player in many stress-induced inflammatory and innate immune responses. In unstimulated cells, NF-κB is in a dormant state, sequestered in the cytoplasm by a family of inhibitors, mainly by the Inhibitor of κB (IκB). When an external stimulus of (IκB)κB of the RIG-I-MAVS pathway. Based on Smieja et al. [3]. 4) NF-κB signaling pathway that produces inflammatory response (Groβ protein) and auto-regulatory proteins IkBα and A20, where the latter also down-regulates the RIG-I-MAVS pathway. Based on Lipniacki and Kimmel [4].

III. EXPERIMENTS

Experiments, using cells directly infected with viral RNA and dsRNA, are under way. Time series of measurements, in 11 time points - from 0 to 36 hours post infection of mRNA transcript concentration of the IFNβ, RIG-I, IκBα, A20, and Groβ genes are being performed in Brasier laboratory (UTMB). The mRNA series are being followed by similar time series of protein concentration for RIG-I, TRAF3, TRAF2/6, IKKγ-WT, IKKγIκB, IRF3, and IRF3p and the complexes IKK -TBK1, IKKγ-WT-A20, IKKγΔ-A20. This will allow us to fine tune the parameters and validate the structure of the network proposed. In addition, we plan a range of knock-out experiments to separate the submodules of the RIG-I-MAVS pathway.

REFERENCES