

Modeling the Dynamics of the RIG-I-MAVS/ NF- κ B/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- β , and inflammatory response through the activation of NF- κ B. 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- κ B.

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- κ B and IRF3 [1].

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) is a gene regulatory protein, or a transcription factor (TF). NF- κ B is a key player in many stress-induced inflammatory and innate immune responses. In unstimulated cells, NF- κ B is in a dormant state, sequestered in the cytoplasm by a family of inhibitors, mainly by the Inhibitor of κ B α (I κ B α). When an external stimulus (such as Tumor Necrosis Factor α , or TNF α) activates specific receptors, the I κ B Kinase (IKK) becomes activated, subsequently phosphorylating I κ B α and leading to its degradation. The freed NF- κ B then enters the nucleus, activating a number of target genes. Among them, at least two are important for regulation of NF- κ B itself: A20 and I κ B α . A20 inactivates IKK, and I κ B α binds NF- κ B inhibiting its action.

Activated IRF3 migrates into the nucleus, where it forms and enhances with NF- κ B [2], activating the production of type I interferons (IFNs), which in turn generates potent up-regulation of RIG-I, which potentiates coordinated signaling

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by the NF- κ B and IRF3 innate signaling responses [1].

II. PROPOSED MODEL

The current version of the proposed model consists of 64 chemical species and 82 reactions. The model can be separated into four modules summarized below:

1) Single-stranded viral RNA recognition by RIG-I-MAVS and recruitment of proteins, creating the oligomers that drive the divergent signaling pathways of IRF3 and NF- κ B. Based on Liu et al. [1]. 2) IRF3 activation with resulting interferon production. Based on Liu et al. [1] and Ford and Thanos [2]. 3) RIG-I up-regulation as a response of interferon production. Based on Smieja et al. [3]. 4) NF- κ B signaling pathway that produces inflammatory response (Gro β protein) and auto-regulatory proteins I κ B α 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 IFN β , RIG-I, I κ B α , A20, and Gro β 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, IKK γ -WT, IKK γ Δ , IRF3, and IRF3pn and the complexes IKK -TBK1, IKK γ -WT-A20, IKK γ Δ -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.

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