Non-self RNA rewires IFNβ signaling: A model of the innate immune response

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***Short Abstract* — Type I interferons (IFNs) coordinate the innate immune response to viral infection. Through activation of STATs in bystander cells they induce the expression of IFN-stimulated genes (ISGs). We show, however, that in cells transfected with an analog of viral RNA, poly(I:C), transcriptional activity of STATs is terminated. Two poly(I:C)-activated ISGs, RNase L (degrading RNAs) and PKR (inhibiting translation), are responsible for termination of STATs activity and enhanced activation of IRF3 and NF-κB, which trigger IFNβ expression. We incorporated these findings into a comprehensive mathematical model of innate immunity. The model explains how non-self RNA turns cells from IFNβ-responders to IFNβ-producers.**

***Keywords* — regulatory pathways, cell fate decisions, parameter identifiability.**

I. Background

THE antiviral innate immune response is coordinated by interferon signaling. Through autocrine and paracrine signaling, mediating, respectively, positive feedback and feedforward loops [1] IFNs promote expression of ISGs to enhance the innate immune response to viral RNA. In a physiologically realistic scenario, at low multiplicity of infection, there are three distinct subpopulations of cells: (*i*) primary infected cells that may produce IFNβ, (*ii*) not-yet-infected cells that respond to IFNβ, and (*iii*) IFNβ-primed cells that become infected due to infection spread. We consider the behavior of the IFN-primed subpopulation of cells to be of crucial importance for shaping the kinetics of progression of viral infection.

II. Results

A. *Experiment*

Motivated by the role of priming with IFNβ, we investigated activation of the NF-κB/IRF3 pathways by an analog of viral RNA, poly(I:C), as well as activation of the STAT1/STAT2 pathway by IFNβ. Using an alveolar epithelial cell line, A549, we found that in IFNβ-primed cells, poly(I:C) terminates STAT signaling. Deactivation of STAT1/2 turned out to result from the depletion of the IFNβ receptor, IFNAR due to both translation inhibition by PKR-phosphorylated eIF2α and *IFNAR1* transcript degradation by RNase L. We also found that RNase L rapidly degrades STAT-regulated transcripts (including those of RNase L, PKR, RIG-I and OAS1/2/3), but does not affect transcripts of IFNβ and weakly impacts transcripts of interleukins 6 and 8, permitting propagation of paracrine signaling. Cells are thus turned from IFNβ-responders to IFNβ-producers

B. *Model*

These findings were used for construction of mathematical model coupling five regulatory modules: poly(I:C), NF-κB, IRF3, IFNβ and STAT, which are intertwined by positive and negative feedback loops ([2], Fig. 1). The main positive feedback loop augments paracrine IFNβ signaling such that IFNβ-primed cells upon stimulation with poly(I:C) become IFNβ producers. The main negative feedback causes that the STAT program is triggered only transiently in cells challenged with poly(I:C), and is terminated in IFNβ-primed cells upon poly(I:C) stimulation. The model parameters were constrained based on a set of experiments on WT and KO cells subjected to various time protocols, containing 2915 independent data points. By systematic simplifications we were able to reduce the number of parameters to 38 obtaining the first identifiable model of innate immunity.

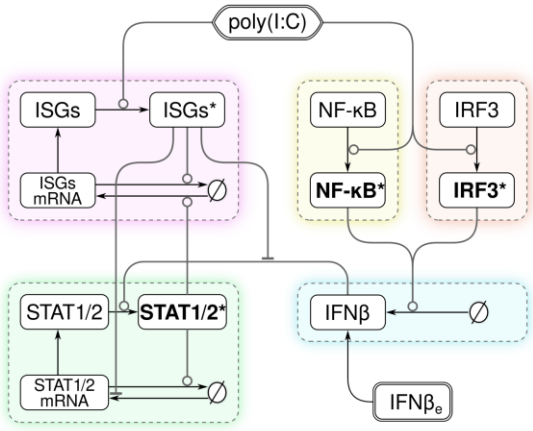

Fig. 1. Coarse grained scheme of the innate immunity model.

References

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