Nonself RNA rewires IFN-β signaling: A mathematical model of the innate immune response

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Type I interferons (IFNs) are key coordinators of the innate immune response to viral infection, which, through activation of the transcriptional regulators STAT1 and STAT2 in bystander cells, induce the expression of IFN-stimulated genes (ISGs). Contrary to bystander cells, cells producing IFN-β exhibit only short-lasted STAT1/2 activation.

To elucidate the molecular background causing cell population to split into IFN-β–secreting and IFN-β–responding cells and obtain a model of innate immunity in response to nonself RNA, we studied epithelial cell responses to IFN-β and nonself RNA analog, poly(I:C), both in isolation and in temporal combinations. We found that the transcriptional activity of STAT1/2 was terminated in response to, poly(I:C) because of depletion of the interferon IFN-β receptor, IFNAR. Comparing responses in wild-type and RNase L and PKR deficient cells, we demonstrated that activation of these two ISG-coded proteins not only hindered the replenishment of IFNAR (by transcript degradation and protein synthesis inhibition) but also suppressed negative regulators of IRF3 and NF-κB consequently promoting *IFNB* transcription. Additionally, we showed that RNase L preferentially degrades ISG transcripts and weakly degrades transcripts of IRF3 and NF-κB regulated cytokines, including *IFNB* [1].

We incorporated these findings into a mathematical model of innate immunity consisting of five regulatory modules, Fig. 1. The model consists of 53 variables and contains 38 independent parameters, but the large set of data allowed us to reach parameters identifiability.

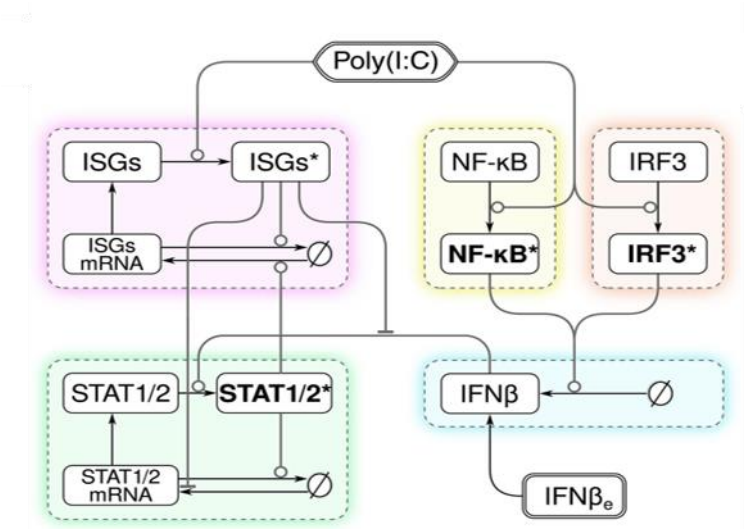

Fig. 1. Computational model of innate immune signaling. Coarse-grained scheme of the key interactions within and between the five regulatory modules. Asterisks denote the active form of proteins.

By coupling signaling through the IRF3–NF-κB and STAT1/2 pathways with the activities of RNase L and PKR, the model explains how poly(I:C) switches the transcriptional program from being STAT1/2 induced to being IRF3–NF-κB induced, which converts IFN-β–responding cells to IFN-β–secreting cells.

[1] Korwek et al. Science Signaling, 16(815), 2023.

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