Roberto Bertolusso
Rice University, Houston, TX, USA
e-mail: rbertolusso@rice.edu
Allan Brasier
University of Texas Medical Branch, Galveston, TX, USA
e-mail: arbrasie@utmb.edu
Marek Kimmel
Rice University, Houston, TX, USA
e-mail: kimmel@rice.edu
Tomasz Lipniacki
IPPT, Warszawa, PL
e-mail: tlipnia@ippt.gov.pl

IRF3 and NF-κB: Transcription factors acting in a coordinated way under double stranded RNA stimulation

Dynamics of innate immunity system under viral attack is still not understood in detail. However, new insights are emerging based both on novel experiments and on system modeling approach. We report a model of coordinated response of IRF3 and NF-κB transcription factors pathways in A549 lung cancer cells, under double stranded RNA (dsRNA) stimulation, itself a model for viral RNA. Viral infection leads to multiplication of viral RNA which is sensed by the innate immune system at a later stage. dsRNA, instead, rapidly activates the IRF3 and NF-κB pathways, leading to responses which are stronger and better localized in time.

dsRNA is sensed both by RIG-like family of helicases (RIG-I) and toll-like receptor 3 (TLR3). Activation of RIG-I leads, via multistep pathway, to the nuclear translocation of IRF3. In turn activation of TLR3 leads to phosphorylation and degradation of primary NF-κB inhibitor IκBα, freeing NF-κB which also translocates to the nucleus. IRF3 and NF-κB are independently and cooperatively responsible of the activation of a number of genes involved in innate immune and inflammatory responses, in particular both IRF3 and NF-κB are needed for the activation of the interferon β. In addtion NF-κB also activates a number of inhibitors, among them IκBα and A20, inhibiting both pathways or selectively one pathway.

Three kind of experiments were performed:

- Time series (0, 0.5, 1, 2, 4 and 6 hours) of key mRNAs induced by NFkB and IRF3 transcription factors.
- Time series of key phosphorylated proteins at same time points as above.
- Knock-down experiments using small interfering RNA (siRNA) on NF-κB, IRF3, RIG-I, and IKKγ with and without dsRNA stimulation.

The emerging deterministic mathematical model considers 87 species and 147 reaction. It seems to be the first aggregate model of dynamics of NF-κB and IRF3, and shows agreement with experimental data. In addition we carried out stochastic simulations of hypothetical single-cell experiments, which display bimodality of responses not visible in cell-population experiments.