NF-κB and IRF: cross-regulation between two major pathways

Marta Iwanaszko[1], Marek Kimmel[1,2]

***Short Abstract* — The NF-κB and IRF transcription factor families are major players in inflammation and antiviral response and act as two major effector arms of the innate immune response (IIR). Our *in silico* findings report that there is a cross-regulation between both pathways on level of gene transcription regulation, mediated by presence of transcription factor binding sites for both NF-κB and IRF families in essential dependent genes. These findings agree with recent experimental reports of crosstalk between pathways activated by RIG-I and TLR3 receptors in response to pathogens.**

***Keywords* — Gene regulation, innate immune response, cross-talk, NF-κB, IRF, promoter.**

I. Introduction

IDENTIFICATION of pathogen-associated molecular patterns, such as dual stranded RNA (dsRNA) and lipopolysaccharide (LPS), by host pattern recognition receptors (PRRs) is a critical step in innate immune response (IIR). Stimulation of TLRs by infecting pathogen induces activation of signal transduction cascades, which leads to translocation of nuclear factor-κB (NF-κB) to the nucleus [1], activation of interferon regulatory factor 3/7 (IRF3/7) which cooperate to induce transcription of various cytokines such as alpha/beta interferon (IFN-α/β) to dispose of infectious pathogens [2,3]. We analyze the cross-talk between two major signaling pathways in the IIR, namely NF-κB and IRF pathways. There is not enough data on how the activation of these two major signaling arms of the IIR is controlled or how they interact with each other. Recent experimental work by Brasier's group and others has shown that adapter molecules regulating the IRF3 signaling pathway is connected with that of NF-κB at multiple steps [4,5], but it is still not known how the NF-κB and IRF pathways interact with each other.

An attempt to the explanation of this interaction was made using mathematical modeling and other *in silico* methods, presented in Bertolusso et al. [6: 2013, in press]. Using computational methods and phylogenetic approach we analyzed promoters of genes coding for transcription factors, interacting in IRF and NF-κB pathways. In the first step of analysis we were looking for transcription factor binding sites (TFBSs) across given promoter region and in the second step we analyzed if these TFBS were conserved among species in conserved domains. Similar method TFBS analysis was used in Iwanaszko et al. [7].

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[1]Department of Automatic Control, Silesian University of Technology, Gliwice, Poland. E-mail: marta.iwanaszko@polsl.pl

[2]Department of Statistics, Rice University, Houston, TX, USA. E-mail: kimmel@rice.edu

II. Conclusion

Promoters of downstream genes in analyzed pathways, mainly coding for transcription factors, contain one or few transcription factor binding sites for IRF transcription factors and usually more binding sites for NF-κB family. Another finding is that IRF family genes regulation may be more sensitive to the direct NF-κB family activity, rather than IRF family itself, and some other unknown transcription agent could be involved. This may be supported by research on NF-κB-deficient cells, which has shown that the initial kinetics of the type I interferon (IFN) response is dependent on concurrent NF-κB activation [6]. Absence of NF-κB is the cause of blunted IFNβ expression, which result in reduced propagation of anti-viral signals in the mucosal surface. NF-κB also controls expression of the downstream IFN auto-amplification loop through STAT1, IRF-1, -5, and -7 transcription factors. Research indicate that the two NF-κB and IRF3 signaling arms are highly interconnected and that these interconnections influence the kinetics of the IIR. Knowledge about this crosstalk may be crucial for determining the outcome of viral infection.

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