Transfer of Dynamically Encoded Information in the NF-κB Signaling Network

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***Short Abstract* — Nuclear Factor Kappa B is a family of transcription factors activated by a variety of extracellular signals. Despite the fact that these pathways all share a significant number of components, most of them are capable of eliciting stimulus-specific genetic responses. It has been reported that this ability in part relies on different stimuli causing characteristic temporal patterns of NF-κB activity, suggesting the notion of "dynamic encoding" of specificity. A key question is how is this encoding performed and what are the constraints on pathway components necessary for this information to propagate effectively. Here we begin to address these questions through a computational analysis of the capacity the postulated NF-κB regulatory mechanisms have for performing the observed dynamical encoding of specificity**.

***Keywords* — Signaling, Dynamics, Specificity, NF-κB, IKK**

I. Background

Nuclear Factor KappaB (NF-κB) is an important family of transcription factors that play fundamental roles in the immune system, organ development, response to stress, and the regulation of apoptosis among others. NF-κB signaling is a key link between inflammation and cancer, since it can upregulate genes with pro-tumor activity in response to immune signals [1]. NF-κB activity is triggered by signaling pathways that respond to a variety of stimuli including cytokines such as Tumor Necrosis Factor (TNF) and interleukins (IL), cellular stress, as well as pathogen components such as bacterial wall lipo-polysaccharides (LPS). Interestingly, many of these pathways converging on NF-κB manage to elicit stimulus-specific genetic responses in conjunction with a core group of common genes. Because aberrant NF-κB activity is an important factor in many diseases, much effort is being devoted to find specific drugs capable of attenuating the expression of pernicious NF-κB target genes. However, due to the importance of NF-κB mediated signaling during immune processes, such therapeutic approaches need to be able to abrogate NF-κB signaling only in response to the offending stimulus while preserving the ability to signal in response to normal physiological signals or in the presence of pathogens. It is therefore of great clinical importance to understand the origin of the stimulus specificity observed in the NF-κB induced genetic responses.

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II. Approach and Results

It has been observed [2,3] that different stimuli produce characteristic temporal activity patterns in the NF-κB network, and that this dynamic component of the signals is important to determine their genetic outcome. In other words, information about the stimulus is "encoded" in the dynamics of the signals. Where in the pathway these signals originate is still unclear. In this work we analyze this question by focusing on the Inhibitor of IKK kinase (IKK), a complex that operates upstream of NF-κB and acts as hub for a number of pathways. We consider two non-exclusive possibilities; a) signal dynamics are determined at the receptor proximal level of each pathway and just pass through IKK, or b) each pathway impinges on IKK with different intensities (inputs) which in combination with postulated IKK regulatory mechanisms result in information about the stimulus being dynamically encoded in the output.

Our computational investigation of the IKK regulatory mechanisms demonstrates that this hub kinase has a very limited repertoire of possible dynamical output regimes in response to a variety of inputs. Furthermore, we show that in most of these regulatory regimes, IKK may severely restrict the dynamics of the output, filtering potentially diverse upstream signals into a few template responses.

III. Conclusion

Our analysis suggests that the mechanisms regulating IKK play a major role modulating the signals driving NF-kB activity and can drastically affect dynamically encoded information about the stimulus. It also predicts that only a subset of the regimes in which IKK can operate is conducive to the transfer of dynamically encoded signals.

References

[1] Lin, W. et al. (2007) A cytokine-mediated link between innate immunity, inflammation, and cancer. J. Clin. Invest. **117**, 1175-1183

[2] Werner, S. et al. (2005) Stimulus specificity of gene expression programs determined by temporal control of IKK activity. Science **309**, 1857-1861

[3] Hoffmann, A. et al. (2002) The IkB-NF-kB signaling module: temporal control and selective gene activation. Science **298**, 1241-1245