Mathematical modelling studies on crosstalk between canonical and noncanonical NF-κB signalling pathways

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2014BLZ8200

Abstract

The nuclear factor kappaB (NF-κB) family of dimeric transcription factors directs a range of biological processes, including immune activation, cell proliferation, and cell survival. These factors, the most prevalent being RelA:p50 and RelB:p52 heterodimers, are activated via the canonical and the noncanonical pathways. Microbial substances and inflammatory cytokines induce the canonical pathway, which generates a temporally controlled RelA NF-κB activity. The canonical pathway activates the expression of pro-inflammatory and pro-survival genes. On the other hand, immune-organogenic cues signal through the noncanonical pathway, which elicits a sustained RelB NF-κB activity. The RelB heterodimers induce the expression of genes involved in immune-differentiation. Biochemical studies also charted mutual interactions between components of the canonical and the non-canonical pathways. We asked if these molecular links provide for dynamical regulation of signal-induced NF-κB responses.

Reconstructing these NF-κB pathways in a mathematical model, I investigated how their crosstalk modulated NF-κB responses. Our study predicted that noncanonical signalling would prolong canonical RelA NF-κB responses in a stimulus- and cell type-specific manner. These predictions were experimentally substantiated. Conversely, canonical signalling triggered RelB NF-κB activity, which altered the dynamical control of the canonical NF-κB response, in a mutant system comprising a defective noncanonical module. Finally, we identified that this newly discovered NF-κB crosstalk might dampen the heterogeneity of signal-response of cells in a population. In sum, we characterised crosstalk between two NF-κB-activating pathways and charted its biological implications.