

SPATIAL AND TEMPORAL INFORMATION CODING BY THE NF- κ B SYSTEM

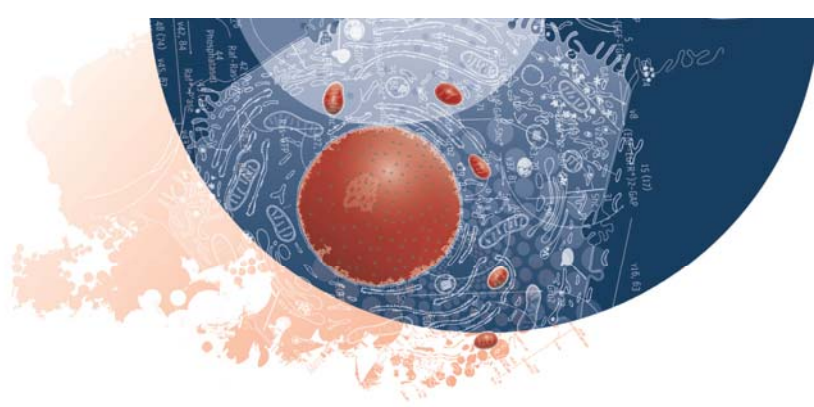
Mike White

School of Biological Science, University of Liverpool, UK

The Nuclear Factor kappa B (NF- κ B) transcription factor regulates cellular stress responses and the immune response to infection. NF- κ B activation results in oscillations in nuclear NF- κ B abundance [1]. We treated cells with repeated short pulses of tumor necrosis factor alpha (TNF α) at various intervals to mimic pulsatile inflammatory signals to show that altering the stimulation frequency gave different patterns of NF- κ B-dependent gene expression, supporting a functional role for oscillation frequency [2].

We applied single cell imaging to investigate dynamic responses to different Tumour Necrosis Factor alpha (TNF α) doses. Lower doses activated fewer cells and those responding showed an increasingly variable delay in the initial NF- κ B nuclear translocation and associated I κ B α degradation. Robust 100 minute nuclear:cytoplasmic NF- κ B oscillations were observed over a wide range of TNF α concentrations. The result is supported by computational analyses which identified a limit cycle in the system with stable 100 minute period over a range of stimuli and indicated no co-operativity in the pathway activation. These results suggest that a stochastic threshold controls functional all-or-nothing responses in individual cells. Deterministic and stochastic models simulated the experimentally observed activation threshold and gave rise to new predictions about the structure of the system and open the way for better mechanistic understanding of physiological TNF α activation of inflammatory responses in cells and tissues.

Heterogeneity between individual cells is a common feature of dynamic cellular processes, including signaling, transcription and cell fate; yet the overall tissue level physiological phenotype needs to be carefully controlled to avoid fluctuations. The precise timing of a dual-delayed negative feedback motif (involving stochastic transcription of Inhibitor kappaB (I κ B) - alpha and -epsilon) is optimized to induce heterogeneous timing of NF- κ B oscillations between individual cells. We suggest that this dual-delayed negative feedback motif enables NF- κ B signaling to generate robust single cell oscillations by reducing sensitivity to key parameter perturbations. Simultaneously, enhanced cell heterogeneity may represent a mechanism that



controls the overall coordination and stability of cell population responses by decreasing temporal fluctuations of paracrine signaling. It has often been thought that dynamic biological systems may have evolved to maximize robustness through cell to cell coordination and homogeneity. Our analyses suggest in contrast, that this cellular variation might be advantageous and subject to evolutionary selection [3].

The NF- κ B system is just one of a number of biological cycles that have been discovered. Other examples include calcium signalling, transcription cycles, p53, the segmentation clock, the circadian clock, the cell cycle and seasonal rhythms. We have identified significant functional and dynamic cross-talk between NF- κ B and the cell cycle via an interaction with E2F-1.

References

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