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Oscillations and feedback regulation in the NF-B signalling

Time-lapse cell imaging showed that in response to Tumour Necrosis Factor alpha (TNF) Nuclear Factor kappa B (NF-B) transcription factor oscillates between the cytoplasm and nucleus (Nelson et al., (2004) Science 306: 704). Treatment with repeat pulses of TNF at different intervals enabled frequency-dependent encoding of target gene expression (Ashall et al., (2009) Science 324: 242). Development of a highly constrained mathematical model suggested that cellular variation in NF-B dynamics arises from a dual-delayed negative feedback motif (involving stochastic transcription of IB and IB). We suggest that this feedback motif enables NF-B signalling to generate robust single cell oscillations by reducing sensitivity to key parameter perturbations. Enhanced cell heterogeneity may represent a mechanism that controls the overall coordination and stability of cell population responses by decreasing temporal fluctuations of paracrine signalling (Paszek et al., (2010) PNAS 107: 11644). We have also shown that the cell to cell heterogeneity is profoundly increased following low-dose stimulation. Low doses of TNF resulted in stochastic delays in single cells, but once the first translocation occurs the typical 100 min period was maintained (Turner, et al., (2010) J. Cell Sci. 15: 2834). Our analyses demonstrate a fundamental role of oscillatory dynamics in control of inflammatory signalling at different levels of cellular organisation.