Dynamics and function of the NF-kappaB signalling system

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It is increasingly important to quantify the dynamic molecular processes that underlie cell-fate decisions in single cells. Early signalling events often occur within seconds of stimulation, whereas intracellular signalling and transcriptional changes may take minutes or hours. Cell-fate decisions can take many hours or days. Multi-parameter experimental and computational approaches to integrate quantitative measurements and mathematical simulations are required in order to understand the highly dynamic mechanisms that control cell fate (Spiller et al., (2010) Nature **465**, 736).

Work on the NF-kappa B signalling system that has indicated a key role for dynamic processes in signal transduction through this key pathway. We used live cell imaging to show that NF-kappa B oscillates between the cytoplasm and nucleus in TNF-alpha stimulated cells (Nelson *et al*., (2004) *Science* **306**: 705) and obtained evidence for the hypothesis that the frequency of these oscillations can control the pattern of downstream target gene expression (Ashall *et al*., *Science*, (2009) **324**: 242). Cellular heterogeneity in the oscillations may be regulated and advantageous (Paszek *et al*., (2010) *PNAS* **107**: 11644).

I will discuss recent work on quantification of the processes that underlie NF-kappaB signalling. In particular I will discuss recent data derived from transgenic mice expressing human bacterial artificial chromosomes expressing IkappaBalpha-EGFP or p65-DsRedxp. These data suggest that oscillatory dynamics occur in primary cells and that the timing of these responses can be modified by a variety of stimuli and perturbations, We have also identified a mechanistic and functional link between the E2F system that controls the integration of the processes of G1/S progression in the cell cycle with NF-kappaB signalling. This suggests coordination of gene expression in response to NF-κB and E2F1 at G1/S and shows that NF-kappaB responses are inhibited in S-phase. Such studies suggest that coupled oscillatory processes may act together to control cellular transcription and cell fate decisions.