Data-based modeling of signal-transcription network for cell fate control

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Signal transduction network is a system to sense, sort and transfer a variety of extracellular information to transcription factors in the nucleus to regulate gene expression for cell determination. Interestingly, signaling pathways often control these processes in a nonlinear manner and, in some cases, analogous graded doses of extracellular stimuli promote digital activation of transcription factors. Time and space-resolved context-dependent network plays an essential function to realize these types of responses. In this talk, the data-based modeling, as one of the methods for heterogeneous data integration, to explain digital activation mechanisms of two transcription factors, c-Fos and NF-κB, will be explored.

We show that prolonged ERK activation along with c-fos mRNA transcription and c-Fos protein stabilization by ERK forms a feedforward AND gate loop for full activation of c-Fos in growth factor-stimulated breast cancer cells. In this system, duration of ERK activity is a critical factor to determine the c-Fos response. Our analysis shows that different growth factors initially activate similar signaling pathways but the transcription response cascades switches after the timing of c-Fos activation. On the other hand, in antigen-stimulated BCR response, NF-κB activity is controlled by two positive feedback loops within the signaling pathway, from TAK1 to IKK and from IKK to IKK, to produce a switch-like activation of NF-κB. These feedback loops contribute to determine the threshold for NF-κB-mediated B cell proliferation, suggesting that the mechanism is important for B cell lineage commitment.

Digital activation of transcription factors may be more beneficial in a noisy cellular environment and for accurate control of gene expression for cell fate decision. Our studies suggest that cellular complexity might arise from combinatorial regulation of binary states of transcription factors.