Temporal and Spatial Control of Receptor Tyrosine Kinase Signaling.

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Extracellular information received by plasma membrane receptors, such as G-protein coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs), is processed and encoded into complex temporal and spatial patterns of phosphorylation and topological relocation of signaling proteins. Our quantitative experimental monitoring and computational modeling of epidermal growth factor (EGF)-induced signaling revealed kinetic and molecular factors that control the time course of phosphorylation responses, such as transient versus sustained activation patterns and oscillations in protein phosphorylation state. Integration and processing signaling information through mitogen activated protein kinase (MAPK) cascades leads to important cellular decisions ranging from proliferation to growth arrest, differentiation or apoptosis.

Modeling of the spatial aspects of GPCR- and RTK-induced signaling emphasizes the importance of receptor-mediated membrane relocation of signaling proteins. We demonstrated that the spatial separation of kinases and phosphatases in MAPK cascades may cause precipitous spatial gradients of activated kinases (MEK and ERK) resulting in a strong attenuation of the signal towards the nucleus. The results suggest that there are additional (besides simple diffusion) molecular mechanisms that facilitate passing of signals from the plasma membrane to transcription factors in the nucleus. They may involve phospho-protein trafficking within endocytic vesicles, scaffolding and active transport of signaling complexes by molecular motors. We also discuss long-range signaling within a cell, such as survival signaling in neurons. We hypothesize that ligand-independent waves of receptor activation or/and traveling waves of phosphorylated kinases emerge to spread the signals over long distances.

In addition to a mechanistic modeling, a novel integrative (top-down) approach to inferring the structure of cellular regulatory networks was developed. Rapid advances in genomics and proteomics have enabled the acquisition of data on the expression of thousands of genes and the functional state of hundreds of proteins. However, there are no methods capable of providing quantitative interpretations of genomics and proteomics data sets in a manner that unravels the wiring of cellular machinery. Here, we propose a novel strategy of unraveling functional interactions in cellular signaling and gene networks. We demonstrate how dynamic connections leading to a particular module (e.g., an individual gene/protein or a cluster) can be retrieved from experimentally measured network responses to perturbations influencing other modules.

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