Modular and Mechanistic Analyses of Cellular Networks: Can We Navigate Through Molecular Jungles?

Boris N. Kholodenko

Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, 1020 Locust St., Philadelphia, PA 19107, USA.

The deciphering of the genome has generated a list of the macromolecular parts of living cells. A challenge for systems biology is to understand how this "genetics parts" list gives raise to a space and time varying cellular behavior resulting from dynamic interactions within cellular signaling, metabolic, and gene networks. Advances in high-throughput genomics and proteomics analyses have enabled the acquisition of large data sets on the gene expression levels and activities of signaling proteins. However, these data do not reveal interactions between components of cellular networks. Recently, a novel strategy to infer the topology and the strength of network connections using steady-state responses to perturbations was proposed [1]. Here we extend this method by analyzing time-varying responses that provide more information than steady-state dependencies. Monitoring time series has an additional advantage because, in contrast with the steady-state case, not every network component has to be perturbed, although the number of independent perturbations has to be equal to the number of components [2].

External information received by plasma membrane receptors, such as G-protein coupled receptors and receptor tyrosine kinases is processed and encoded into complex temporal and spatial patterns of phosphorylation and topological relocation of signaling proteins. We quantify cellular signal transduction in terms of the sensitivity of a target (e.g., a transcription factor) to a signal (e.g., a growth factor or neurotransmitter). Our experimental monitoring and computational modeling of growth factor 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 [3]. We showed how the cellular response is controlled by the membrane translocation of signaling proteins upon receptor activation. The modeling of a 4D-organization of protein phosphorylation cascades demonstrates that the spatial separation of kinases and phosphatases may cause precipitous spatial gradients of activated kinases resulting in a strong attenuation of the signal towards the nucleus [4]. 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 [4]. 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 [5].

References.

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