

# Kinetic Simulations of the EGFR Signaling Network

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## ABSTRACT

The cells of all living organisms sense their environment and respond to environmental stimuli. Signaling mechanisms of the cells govern how the information received by the cells from their environment are decoded, processed, and transferred to the appropriate locations within the cell. Signaling through the receptor tyrosine kinase (RTK) family of receptors, particularly the epidermal growth factor receptor (EGFR), is probably the most investigated and best understood receptor signaling system [1,2]. Signaling pathways of various RTK's have common underlying features such as the phosphorylation of the receptor and its interaction with the signal transducing molecules containing the src homology domain or the phosphotyrosine binding domains. The signal from the receptor is transmitted to the nucleus through a series of protein-protein interactions, and the MAP kinase cascade and ERK activation controls the final product, which is gene expression. Although participating cellular components depend on the pathway, different members of the RTK receptor family use simple variations of this basic network.

Following binding of any of its ligands, the EGFR is rapidly internalized by a mechanism (endocytosis) that requires intrinsic receptor kinase activity and specific motifs in the carboxy terminus domain of the receptor. The multiple ligands that bind to the EGFR are different in their ability to bind to the receptor as a function of the receptor microenvironment, such as intravesicular pH and localization within cells. Because of the potential effect of receptor microenvironment on receptor activity, receptor trafficking is believed to play a role in the diverse action of the ligands and may function as a mechanism to "decode" the information unique to each ligand. Therefore, ligand-receptor interactions control receptor trafficking, which in turn can control receptor activity. It has been shown that [3], similar to their surface membrane counterparts, internalized receptors can stay active and contribute to the cellular response. Why the cells internalize the receptors and the overall role of endocytosis in receptor signaling is not well understood.

Following internalization into early endosomal vesicles, the EGF receptors are exposed to the first stage of sorting and are either shuttled back to the plasma membrane or transported into late or multi-vesicular endosomes. The receptors in the late endosomes are further sorted by either targeting them to lysosomes for degradation or by recycling them back to the cell surface [4]. The endosomal sorting mechanism does not seem to require receptor kinase activity [5], and sorting nexins control the amount of receptor that is sent to the lysosome from the endosomes for degradation [6].

Earlier theoretical investigation of the EGFR signaling networks mainly followed two complementary approaches. Several groups,

particularly the group led by Lauffenburger and Wiley, concentrated their efforts on the trafficking aspects of the ligand-induced down-regulation of the EGFR [7]. This type of approach mainly focuses on the role of endocytosis and does not include how the signal gets transmitted to downstream elements such as Ras or MAP kinases. It, therefore, does not explicitly consider if there are differences in the response behavior of the plasma membrane bound receptors and the receptors in the endosomes. In contrast, other approaches have concentrated on the short-time response characteristics of the EGFR, i.e. the transmission of the signal from the receptor to the downstream elements on the signaling path. A particularly noteworthy effort is the development of a network model for EGFR signaling by Kholodenko and co-workers to study the signal transduction from the receptor to the Ras GTPase [8]. Although very useful, these approaches lack the trafficking aspects of the signaling network. It is believed that the internalization patterns of the receptors are the most essential factors in the regulation of the EGFR signaling.

It is obvious that a complete approach would have to combine these two complementary modeling efforts. To fill the gap between these complementary earlier approaches, we have been developing a quantitative model for the EGFR signaling network that incorporates the trafficking and the down-stream signal transduction aspects of the signaling pathway. Starting with our network model, we make use of quantitative kinetic simulations and semi-quantitative analysis methods to analyze the signaling network of the EGF receptor.

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