Surface Dynamics of Epidermal Growth Factor Receptors: Study of Ligand Binding and Oligomerization Events

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Signaling mechanisms of the cell to sense its extracellular environment can be divided into extracellular sensing machinery, which senses the extracellular cues and transfers the signal inside the cell, and intracellular machinery, which translates this transferred into a biological response. Efforts to comprehend the complexity associated with the signaling pathways have been endeavored at various computational and experimental levels. The epidermal growth factor receptor (EGFR) signaling pathway has been of interest, not only to understand the biological signaling mechanisms, but also because of its crucial implications in cancer. EGFR has been identified as a rational drug target for cancer therapy because of its availability to extracellular manipulation. Understanding the transients of extracellular signaling events can have important implications in designing selective anticancer drugs with higher therapeutic index and lower toxic levels as compared to currently available cancer treatments.

There exists a substantial amount of information enabling studies of various aspects of receptor-ligand and receptor-receptor interactions of the EGFR signaling network. To assemble and organize the molecular level interactions in a systematic

manner, there is a need to develop suitable mathematical models so that the underlying biological phenomena can be understood. Herein, we develop a reaction-diffusion type of model by incorporating molecular level interactions in order to understand the short-time signaling events of ligand binding and oligomerization. The importance of these events stems from their triggering intracellular activation of various signaling proteins resulting in the phosphorylation of mitogen activated protein (MAP) kinase to carry the proliferation message to the nucleus. We have examined the transients of the ligand binding, dimerization and oligomerization (formation of higher-mers) to understand the predominant sequence of events that result in the final state of the receptor population. Furthermore, model predictions have been compared with experiments to elucidate the ligand binding and dimerization events at shorter times (<1 min). We show that the sequence of events leading to the ligand bound dimerized receptor depends on the ligand concentration. Our simulations show that the high affinity subclass of receptors on unstimulted human epithelioid carcinoma cells (A-431) are present in a predimerized state, which is responsible for the early binding of EGF. The ligand independent dimer formation appears to be an important step particularly at ligand low concentrations. Finally, we have found that the kinetic and transport parameters of extracellular dynamics of receptor-ligand and receptor-receptor interactions play an important role leading to diverse intracellular activities.