576a Implications of Spatial Organization of Epidermal Growth Factor Receptors

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The epidermal growth factor (EGF) receptor (EGFR) belongs to the family of receptor tyrosine kinases, also called as ErbB receptors. These receptors trigger a rich network of signaling pathways and regulate cell functions, such as proliferation, differentiation and migration, and can play a key role in the genesis of several tumors. Since EGF binding represents the initial step for activating EGFR, considerable work has been devoted to elucidating the mechanisms of ligand binding and dimerization. However, the influence of spatial features of plasma membrane on ligand binding and receptor dimerization are not as well understood. Herein, we describe a spatially distributed Monte Carlo based simulation framework to enable the multiscale simulation of in vivo receptor diffusion and dimerization, and to bridge the spatial and temporal resolution of various microscopy techniques. We hypothesize that the spatial organization of membrane EGFRs exerts influence on the response of signaling events by modulating the amount and mechanism of EGF binding. We present equilibrium and kinetic analyses to study the effect of plasma membrane heterogeneity on spatial organization of EGF receptors. Our study, based on the Scatchard plot and spatiotemporal dynamic Monte Carlo (MC) simulations, focuses on receptor localization and variation in mobility that may arise in lipid rafts and other microdomains. We find significant influence of plasma membrane heterogeneity and cell type on the EGFR dimerization dynamics. For example, we have been able to explain the concave up shape of the Scatchard plot using a heterogeneous biologically relevant model. MC simulations are in agreement with single particle tracking microscopy and biochemical data. Finally, it is demonstrated that a synergistic integration of biophysical, biochemical and imaging data is required for understanding of signaling events.