Hierarchical membrane compartmentalization stabilizes IFN receptor dynamics

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Short Abstract — **Nanoscale compartmentalization of the plasma membrane caused by the actin meshwork or membrane microdomains has been speculated to play an important role for the assembly and stability of signaling complexes. Here we present results from a recent experimental and computational study quantifying the role of membrane compartmentalization in regulating the stability and the dynamics of type I interferon receptor complexes. Re-association of individual receptor dimers is promoted in a highly specific manner, ensuring maintenance of signaling complexes beyond their molecular lifetime.**

Keywords — **Receptor dynamics, plasma membrane compartmentalization, spatial-stochastic model.**

I. Introduction

Transport and communication across the plasma membrane frequently involves the association of transmembrane proteins into dimeric or oligomeric complexes. Two-dimensional association and dissociation rate constants determine the interaction dynamics within these complexes. Nano-scale confinement of the interaction partners by the actin meshwork and micro-domains in the plasma membrane has been speculated to play an important role for the dynamics of such protein complexes [1-6]. We recently combined experimental and computational methods to quantify the effects of plasma membrane compartmentalization on the assembly dynamics of type I interferon receptor complexes [7]. Such complexes are relatively long-lived, which makes them ideally suited to study compartmentalization effects.

II. Results

A detailed computer model of the membrane compartmentalization was developed, which was built entirely on experimentally obtained parameters. Simulation results of receptor dynamics were compared with those obtained from single molecule fluorescence microscopy experiments employing dual-color quantum-dot (QD) labeling of receptor subunits. The integration of model building and experiments let to the discovery that a two-tiered compartmentalization was involved in regulating receptor stability.

High-resolution spatial stochastic simulations of receptor hop diffusion in our model membrane further confirmed that confinement enables rapid re-association of dissociated signaling complexes in time frames similar to those of QD experiments. Our computer simulations also reproduced key control experiments.

III. Conclusions

Receptor dimers in the plasma membrane are stabilized beyond the molecular ligand-receptor interactions. Our spatial-stochastic model of a two-tiered MSK faithfully reproduces diffusion and interaction properties in the plasma membrane. The hierarchical organization was found to be critical for explaining the experimentally observed signaling complex stability. Moreover, our spatial-stochastic model enabled us to identify a crucial role of the association rate constant in complex stabilization. We found that efficient stabilization is achieved only beyond a threshold, which corresponds to typical 'on-rates' of protein complexes. Thus, specificity towards stabilization of protein complexes with high 'on-rates' is ensured.

In summary, our findings reveal the important role of plasma membrane compartmentalization for the assembly and stability of the signaling complex.

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