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Effect of Protein-Induced Membrane Curvature on the Receptor-Ligand Binding Constant

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Abstract: Cell adhesion is a fundamental biological process involved in many crucial cellular activities such as tissue formation, immune response, and cell locomotion [1, 2]. The adhesion process is mediated by the specific binding of membrane-anchored receptor and ligand proteins, which is quantified by the two-dimensional binding equilibrium constant [3-5]. These adhesion proteins are associated with cell membranes either *via* transmembrane domains or *via* GPI anchors, and may very likely generate membrane curvature, which has been shown for a number of membrane proteins to play an important role in organelle shaping, vesicle trafficking, cell fusion and division as well as protein sorting [6-10]. An important question remains of whether the local membrane curvatures induced by the adhesion proteins affect their binding and of how to quantify this effect. Using Monte Carlo simulations of a mesoscopic model with biologically relevant parameters, we systematically investigated the impact of protein-induced membrane curvatures on the specific binding of receptors and ligands. We find that the binding constant increases or decreases with the protein-induced curvature depending on the signs of the curvatures. This is attributed to the change of (i) membrane deformations and (ii) protein-protein interactions due to the induced curvatures. We have presented a theory in which the above two factors are incorporated by taking into account the distribution of local membrane separation and effective protein concentrations. The theory agrees quantitatively with our simulation results and provides a useful route to calculate the binding constant for curvature-inducing receptors and ligands. Our work deepens our understanding the roles of protein-induced curvature in the receptor-ligand interactions, and suggests that the effect of induced curvature should be carefully considered in the experimental measurement of the binding constant.

Keywords: Membrane curvature; receptor-ligand interactions; binding constant

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