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Membrane-mediated membrane protein interactions drive membrane protein organization

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The plasma membrane's main constituents, i.e. phospholipids and membrane proteins, are known to be organized in lipid-protein rafts, functional domains, and supercomplexes. No active process is known to establish such higher-order membrane protein organization. Thus, the interplay of thermal activation and the biophysical determinants of membrane-mediated membrane protein interactions must be understood to understand membrane organization. Here, we used high-speed atomic force microscopy (HS-AFM), kinetic analysis, and membrane elastic theory to investigate the behavior of a model membrane protein in oligomerization and assembly in controlled lipid environments. We formed membrane protein patches that contained only very little lipid and covered only a few percentages of the sample surface, and subsequently supplied vesicles of defined hydrophobic thickness for vesicle spreading and bilayer fusion until complete sample surface coverage, thus forming a continuous fluid lipid bilayer in which the membrane proteins diffused and interacted. We directly recorded thousands of membrane protein association/dissociation event dwell-times in bilayers of different thicknesses. We found that the membrane protein interaction energies scaled with the hydrophobic mismatch between protein and the lipid bilayers. These findings were rationalized in the framework of physical theories according to which elastic potential differences caused by membrane deformation energies determine the membrane-mediated interaction of two approaching molecules. The mismatch-dependent energy differences provide effective biases for membrane organization. In addition, we observed non-canonical oligomers of the model protein in lipids of protomer interface matching hydrophobic thickness, which suggests that energetics from membrane mismatch is also involved in stabilizing membrane protein oligomerization. Thus, we find that the membrane mismatch determines oligomerization, assembly energetics, and 2D-organization of membrane proteins. In summary, our experimental and theoretic frameworks reveal how membrane organization can emerge from Brownian diffusion and a set of physical properties of the membrane constituents.