Protein-lipid interactions in glycophorin-like dimerization motifs of transmembrane helices

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Receptor tyrosine kinases (RTK) are vital players in cell signaling governing growth and proliferation. These integral membrane proteins work only in dimeric states, so the conformation of transmembrane dimer determines the signal transferred into cell. Here, we used modern molecular modeling techniques to study details of protein-protein and protein-lipid interactions in model systems containing monomers and dimers of several receptor tyrosine kinases with glycophorin-like dimerization motifs. Comparison of structural and dynamic aspects of ErbB family members and glycophorin A (GpA) revealed similarities in their properties, especially, for ErbB1, ErbB2 and ErbB4 receptors utilizing the same GpA-like motif for dimerization in their basal state. We demonstrated that they all have similar organization of TM domain's molecular surface in terms of both relief, hydrophobic properties and lipid binding sites resembling GpA pattern studied before. All these RTKs strongly interact with lipid acyl chains, forming stable binding sites both in monomeric and dimeric states, and the most prominent binding areas are located in monomers on the future GpA-like dimerization interfaces. Then, lipids distribution changes upon dimer formation. This is not the case for alternative packing geometries observed for the second state of ErbB1 and, especially, ErbB3. We found higher numbers of immobilized lipids near C-terminus in ErbB1 and ErbB2 active dimers, thus assuming that the existing structure of ErbB3 is also active. However, there is non-functional GpA-like motif in ErbB3 with some bound lipids present near the N-terminus, suspecting another structure for inactive receptor. However, despite considerable similarities, these RTKs have different hydrophobicity distributions along helices, that can be important in terms of preferable lipid environment.
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