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Helix-helix interactions in membrane domains of bitopic proteins: specificity and role of lipid environment

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ABSTRACT

Interaction between transmembrane helices often determines biological activity of membrane proteins. Bitopic proteins, a broad subclass of membrane proteins, form dimers containing two membrane-spanning helices. Some aspects of their structure-function relationship cannot be fully understood without considering the protein-lipid interaction, which can determine the protein conformational ensemble. Experimental and computer modeling data concerning transmembrane parts of bitopic proteins are reviewed in the present paper. They highlight the importance of lipid-protein interactions and resolve certain paradoxes in the behavior of such proteins. Besides, some properties of membrane organization provided a clue to understanding of allosteric interactions between distant parts of proteins. Interactions of these kinds appear to underlie a signaling mechanism, which could be widely employed in the functioning of many membrane proteins. Treatment of membrane proteins as parts of integrated fine-tuned proteolipid system promises new insights into biological function mechanisms and approaches to drug design.

Highlights

1. Activation of bitopic proteins is described with a focus on the membrane domain role
2. Structural data on the dimeric membrane domains of bitopic proteins is reviewed
3. Effects of membrane environment on the activation of bitopic proteins are discussed
4. Bitopic protein signaling and allostery can be modulated by protein-lipid interaction

Keywords: bitopic membrane protein; receptor tyrosine kinase; transmembrane domain; protein-lipid and protein-protein interactions; lipid density fluctuations; signal transduction.

Abbreviations: BP, bitopic protein; RTK, receptor tyrosine kinase; TMD, transmembrane domain; JM, juxtamembrane; ECD, extracellular domain; ICD, intracellular domain; NMR, nuclear magnetic resonance; MD, molecular dynamics; LID "ligand-induced dimerization" mechanism; LIR, "ligand-induced rotation" mechanism.