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CLIC1 interaction with Model Membranes

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Sterols have been reported to modulate conformation and hence function of several membrane proteins. One such group is the Chloride Intracellular Ion Channel (CLIC) family of proteins. These largely soluble proteins can spontaneously insert into phospholipid bilayers to form integral membrane ion channels [1]. To date, the structure of their membrane-bound form and factors influencing their auto-insertion remains largely unknown. We have performed Langmuir-film, X-ray, and neutron reflectivity experiments to study the interaction of wild-type or mutant versions of CLIC1 with monolayers prepared with mixtures of different phospholipids and sterol molecules. We investigated the regulatory role of different membrane lipid combinations on the spontaneous membrane insertion of CLICs and elucidated the structural features of the CLIC1 membrane-bound form within these lipid monolayers.

We have shown that CLIC1, in cholesterol containing lipid monolayers, showed significant interaction into the acyl chain region, whereas when cholesterol was absent insertion was limited to the head-group region only. CLIC1 membrane insertion, a pre-cursor to forming functional ion channels is therefore cholesterol dependent [2].

We have also demonstrated for the first time that the GXXXG motif in CLIC1 acts as the cholesterol-binding site for the initial recognition and binding to membrane cholesterol [3]. Further experiments with a variety of sterols confirmed that the interaction between CLIC1 and sterols is dependent on an intact 3β-OH group in the sterol ring. Modification of the sterol structure by the introduction of additional hydroxyl groups and methylation of the sterol alkyl chain was shown to increase membrane insertion of the protein within the phospholipid monolayer [4]. These findings provide clear evidence for the important role of sterols in the regulation of CLIC1 membrane interactions and a putative mechanism for its initial binding and membrane integration.

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3. Hossain, K., et al., *A conserved GXXXG motif in the transmembrane domain of CLIC proteins is essential for their cholesterol-dependant membrane interaction.* Biochim Biophys Acta Gen Subj., 2019. 1863(8): p. 1243-1253.
4. Hossain, K., et al., *Sterol Structural Features' Impact on the Spontaneous Membrane Insertion of CLIC1 into Artificial Lipid Membranes.* Langmuir., 2023. 39(9): p. 3286-3300.

Topics

Biological Systems and Soft Matter

Primary author(s) : HOSSAIN, Khondker Rufaka (University of Technology Sydney)

Co-author(s) : HOLT, Stephen (Australian Nuclear Science and Technology Organisation); Dr VALENZUELA, Stella (University of Technology Sydney)

Presenter(s) : HOSSAIN, Khondker Rufaka (University of Technology Sydney)

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