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Sterols Regulate the Activity of Phospholipid Scramblase by Interacting through Putative Cholesterol Binding Motif

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Abstract : Biological membranes are ordered association of lipids, proteins, and carbohydrates. Lipids except sterols possess asymmetric distribution across the bilayer. Eukaryotic membranes possess a group of lipid translocators called scramblases that disrupt phospholipid asymmetry. Their action is implicated in cell activation during wound healing and phagocytic clearance of apoptotic cells. Cholesterol is one of the major membrane lipids distributed evenly on both the leaflet and can directly influence the membrane fluidity through the ordering effect. The fluidity has an impact on the activity of several membrane proteins. The palmitoylated phospholipid scramblases localized to the lipid raft which is characterized by a higher number of sterols. Here we propose that cholesterol can interact with scramblases through putative CRAC motif and can modulate their activity. To prove this, we reconstituted phospholipid scramblase 1 of C. elegans (SCRM-1) in proteoliposomes containing different amounts of cholesterol (Liquid ordered/Lo). We noted that the presence of cholesterol reduced the scramblase activity of wild-type SCRM-1. The interaction between SCRM-1 and cholesterol was confirmed by fluorescence spectroscopy using NBD-Chol. Also, we observed loss of such interaction when one of I273 in the CRAC motif mutated to Asp. Interestingly, the point mutant has partially retained scramblase activity in Lo vesicles. The current study elucidated the important interaction between cholesterol and SCRM-1 to fine-tune its activity in artificial membranes.

Keywords : artificial membranes, CRAC motif, plasma membrane, PL scramblase
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