

Lipid selectivity of bovine α -lactalbumin binding to membranes: interplay of negatively charged lipids and cholesterol

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Many soluble proteins are known to interact with membranes and the mechanism of such interactions in cellular processes is beginning to be understood. *Apo*-bovine α -lactalbumin (BLA), a soluble protein, specifically interacts with negatively charged membranes and the membrane-bound protein exhibits a molten globule conformation. We report the novel observation that *apo*-BLA has an enhanced binding to negatively charged membranes in the presence of cholesterol. Interestingly, we observed that BLA has cholesterol recognition/interaction amino acid consensus (CRAC), a motif recognized for preferential association with cholesterol in many proteins. Tryptophans in BLA exhibit lower red edge excitation shift (REES) upon binding to negatively charged membranes, as opposed to zwitterionic membranes, implying enhanced solvent relaxation around the tryptophans in molten globule condition. Our results utilizing depth analysis by the parallax approach further support differential organization and dynamics of membrane-bound BLA forms. In addition, dipole potential measurements upon BLA binding to membranes and docking studies of BLA with cholesterol and phosphatidylglycerol headgroup provide useful insight into the lipid selectivity of BLA binding to membranes.