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Theory of Membrane Shaping and Remodeling by Proteins

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Cellular membranes are highly dynamic, undergoing both persistent and dynamic shape changes driven by specialized proteins. The observed membrane shaping can be simple deformations of existing shapes or membrane remodeling involving fission or fusion. I will describe the major mechanistic principles by which membrane shaping proteins act and address, specifically, the models for membrane fission by ESCRT-III proteins and N-BAR domains.

The N-BAR domain containing proteins, endophilin and amphiphysin, have been suggested to induce large membrane curvatures during endocytosis. We propose and substantiate by modeling that, in addition to curvature generation, the N-BAR domains are able to drive membrane fission and, hence, accomplish the whole transformation of flat membranes into separate transport intermediates. The model is based on the interplay and mutual frustration of two modes by which N-BAR domains can bend lipid membranes: the shallow insertion of amphipathic helices into the lipid bilayer matrix and the membrane scaffolding by the concave faces of BAR dimers. We use the elastic models of lipid bilayers and BAR dimers to show that increasing amounts of the membrane-bound N-BARs resulting in membrane bending also generate mechanical stresses which drive transformation of cylindrical or flat membranes into spherical vesicles, i.e., membrane fission. We analyze quantitatively the conditions of this transformation, demonstrate its biological feasibility and predict a difference in the abilities of endophilin and amphiphysin to induce membrane fission. We propose that the suggested principle is not limited to N-BAR domains but may underlie membrane remodeling by numerous proteins known to have a potential to bend membranes by both the hydrophobic insertion and scaffolding mechanisms.

ESCRT-III proteins catalyze membrane fission during multi vesicular body biogenesis, budding of some enveloped viruses and cell division. We propose that the ESCRT-III subunits, CHMP2 and CHMP3, self-assemble into hemi-spherical dome-like structures within the necks of the initial membrane buds generated by CHMP4 filaments. The dome formation is accompanied by the membrane attachment to the dome surface, which drives narrowing of the membrane neck and accumulation of the elastic stresses leading, ultimately, to the neck fission. Based on the bending elastic model of lipid bilayers, we determine the degree of the membrane attachment to the dome enabling the neck fission and compute the required values of the protein-membrane binding energy. We estimate the feasible values of this energy and predict a high efficiency for the CHMP2-CHMP3 complexes in mediating membrane fission. We support the computational model by electron tomography imaging of CHMP2-CHMP3 assemblies in vitro.