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Multiscale Modeling of Clathrin-Mediated Endocytosis

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Abstract: Endocytosis is the process of uptake of cargo and fluid from the extracellular space to inside the cell; defects in endo- cytosis contribute to a wide spectrum of diseases including cancer, neurodegeneration, and heart disease. Clathrin- mediated endocytosis (CME) is an archetypal example of a membrane deformation process where multiple variables such as pre-existing membrane curvature, membrane bending due to the protein machinery, membrane tension regulation, and actin-mediated forces govern the progression of vesiculation. My group has been working for the past few years on deciphering the biophysical determinants of CME using multiscale modeling. We recently showed that membrane tension is a dynamic quantity that evolves over the progression of CME to modulate the energy barrier associated with vesiculation. Specifically, we identified that membrane tension governs CME through a snapthrough instability [1].

We then explored two ways by which the energy barrier associated with this instability can be overcome. First, we explored the role of actin cytoskeleton in force generation during CME. Our results show that a minimal branched actin network is sufficient to create sustained internalization of an endocytic pit against membrane tension. Furthermore, actin filament self-organization and bending, which arise from the spatial distribution of actin-coat attachment around the curved endocytic pit, allow the actin network to adapt to the changing load [2]. Second, we removed the restrictions of axisymmetric pit formation and showed that lower modes of symmetry naturally reduce the energy barrier associated with the constriction of a neck during CME [3]. Thus, we show that mechanical models of membrane bending and cytoskeletal organization can provide insight into the complex workings of CME.

Keywords: Clathrin-mediated endocytosis; membrane mechanics; actin dynamics; multiscale modeling

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