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Membrane-associated peptide folding: pH triggered insertion and helical structure formation[1] ALEXANDER KARABADZHAK, Department of Molecular Biophysics and Biochemistry, Yale University, DHAMMIKA WEERAKKODY, MAK THAKUR, Physics Department, University of Rhode Island, DONALD ENGELMAN, Department of Molecular Biophysics and Biochemistry, Yale University, VLADISLAV MARKIN, Department of Neurology, University of Texas Southwestern Medical Center, OLEG ANDREEV, YANA RESHETNYAK, Physics Department, University of Rhode Island — We are interested in the molecular events that occur when a peptide inserts across a membrane or exits from it. pHLIP (pH (Low) Insertion Peptide) provides an opportunity to study membrane insertion/exit and folding/unfolding, since its insertion is modulated by pH and since it forms helical structure as it inserts. We found that pHLIP inserts across a POPC phospholipid bilayer in several steps: first is the rapid formation (100 ms) of an interfacial helix, which is then followed by a slow insertion pathway that contains several intermediates. We show that while the number of protonatable residues at the inserting end does not affect the formation of helical structure in the membrane, it correlates with the time for transmembrane insertion, the number of intermediate states on the folding pathway, and the rate of unfolding and exit. We conclude that particular intermediate states on the folding and unfolding pathways are not mandatory and, in the simple case of a polypeptide with a non-charged and non-polar inserting end, the folding and unfolding is well described as an all-or-none transition. A model for membrane-associated insertion/folding and exit/unfolding is proposed.

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