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Modulation of the transmembrane helix insertion pathway by polar cargo DAYANJALI WIJESINGHE, ALEXANDER KARABADZHAK, Department of Physics, Univeristy of Rhode Island, VLADISLAV MARKIN, Department of Neurology, Univeristy of Texas Southwestern Medical Center, DONALD ENGELMAN, Department of Molecular Biophysics and Biochemistry, Yale University, OLEG ANDREEV, YANA RESHETNYAK, Department of Physics, Univeristy of Rhode Island — In an earlier study, we found a series of kinetic steps in the pH-triggered insertion of the pHLIP® (pH (Low) Insertion Peptide). In the present work we observe that the polarity of the inserting end, including its cargo, modulates the number of intermediates, and that insertion can be described as a two state process for a simple case. Each investigated pHLIP variant preserve the pH-dependent properties of surface binding to membrane at neutral pH and insertion at low pH to form a transmembrane helix. However, there are thermodynamic and kinetic properties that are determined by the degree of cargo polarity. The presence of a polar cargo at the peptide's inserting end leads to the appearance of two additional intermediate states on the insertion pathway of the pHLIP-2E peptide, which itself (when no cargo is attached) shows an all-or-none transition from the partially unstructured membrane-surface to the transmembrane state described well by the two-state model at 800 ms timescale. We discuss the utility of our observations for the design of new delivery agents for the direct translocation of polar therapeutic and diagnostic cargo molecules across cellular membranes. The work is supported by NIH grants CA133890 to OAA, DME, YRK.

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