Watching single helical membrane proteins fold

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Despite advances in resolving structures of multi-pass membrane proteins, little is known about the native folding pathways of these complex structures. Using single-molecule magnetic tweezers, we report a complete folding pathway of purified human glucose transporter 3 (GLUT3) reconstituted within lipid bilayers composed of synthetic lipids and detergents. The N-terminal major facilitator superfamily (MFS) fold strictly forms first, serving as structural templates for its C-terminal counterpart that defines most of the glucose binding site. Our data further reveal folding pathways for individual MFS folds, where polar residues comprising the membrane-embedded conduit for glucose molecules present major folding challenges. The ER membrane protein complex facilitates insertion of more hydrophilic TMHs, thrusting GLUT3's microstate sampling toward folded structures. Final assembly between the N- and C-terminal MFS folds depends on specific lipids that ease desolvation of lipid shells surrounding the domain interfaces. Sequence analysis suggests that this asymmetric folding propensity across the N- and C-terminal MFS folds may prevail for metazoan sugar porters, revealing evolutionary conflicts between foldability and functionality faced by many multi-pass membrane proteins.

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[Field of research] Single-molecule biophysics of membrane proteins, Development of high-throughput profiling tool for protein-protein interactions