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Probing Protein Fluctuations, Folding and Misfolding at Single-molecule Resolution

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The conformational fluctuations and folding of proteins are key for their function in cells and organisms. Conversely, misfolding and aggregation can cause disease, although amyloids with functional significance are also being identified. To better understand these aspects of protein biophysics, we utilize single-molecule fluorescence and complementary methods to directly study complex protein dynamics, structural distributions, and conformational transitions. In one example, we used these methods to investigate disorder and disorder-to-order transitions in intrinsically disordered proteins (IDPs). IDPs are an interesting class of proteins which are relatively unstructured in isolation, but can often fold by interacting with binding partners. These complex systems are increasingly found to play major roles in biology and disease. In one case, we used a combination of single-molecule FRET (smFRET), coincidence and correlation analyses to probe the native structural features of a yeast protein Sup35, whose amyloid state is believed to be used in a beneficial context in yeast. We find that the monomeric protein populates a compact and rapidly fluctuating ensemble of conformations. In another case, we studied the binding-coupled folding of the IDP alpha-synuclein, whose misfolding and aggregation have been linked to Parkinson's disease. Single-molecule measurements directly revealed a complex multi-state folding landscape for this protein. Observations of a transient folding intermediate using microfluidic mixing, and links to misfolding and aggregation will also be discussed. Our results highlight single-molecule methodology that is broadly applicable to map protein folding and misfolding landscapes.