

Protein Folding Intermediates: Who Are They?... And What Are They Hiding?

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Proteins 'pose' well for us in X-ray and NMR structures, but in biological systems, they don't just sit there and look pretty. To carry out their function, they must undergo specific, thermally driven structural fluctuations, i.e. conformational dynamics. Don't believe me? Try getting your favourite hyperthermophile enzyme to turn over at room temperature. It'll fold up nicely, but without sufficient thermal energy to access functionally relevant dynamic modes, it'll just sit there, bricklike and generally uncatalytic. Conformational dynamics are also crucial to regulation of the protein interaction network within the cell (proteostasis). Thus, when a protein starts to exhibit non-native dynamic behaviour (due to mutation, oxidation, misprocessing, or mislabelling), the consequences can be severe: Transient, pathogenic protein structures are generated that disregulate normal protein-protein interactions, leading ultimately to cytotoxicity and the formation of large protein aggregates. The result is a 'conformational disease' which encompasses a growing list of illnesses including many neurodegenerative disorders such as Alzheimer's, Parkinson's, Lou Gehrig's. Our lab is interested in protein dynamics, function and aggregation at the molecular level. We aim to uncover specifically the chemical and structural features of conformational disease-associated proteins that makes them prone to non-native dynamics and aggregation. To address the analytical challenges of studying protein conformations that are transient, weakly populated at equilibrium and spectroscopically equivalent to the ground-state, we also develop our own analytical tools that combine Time-resolved Electrospray Mass Spectrometry, Microfluidics and Hydrogen/Deuterium Exchange, in addition to biophysical NMR approaches.