Protein Structure, Dynamics and Interactions at Atomic Resolution from Solution NMR Spectroscopy

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Pioneering work in the 1980s has established NMR spectroscopy as a routine method for protein structure determination with spatial resolution rivaling X-ray crystallography, and recent technological and methodological advances have significantly widened the scope and practical applicability of protein NMR. Understanding protein folding and function obviously requires knowledge not only of static structures but also of the conformational dynamics. Because the spectral parameters are sensitive to dynamics on all time-scales from picoseconds to real time, NMR spectroscopy is a particularly powerful tool for studying protein folding, intrinsically disordered regions, protein-protein and protein-ligand interactions, enzyme catalysis and other dynamic processes under native solution conditions, uniquely combining high spatial and temporal resolution. Following an introduction into the principles of NMR spectroscopy and an overview over various techniques in the state-of-the-art protein NMR “toolbox” with their advantages and limitations, the elucidation of the folding pathway of the Fyn SH3 A39V/N53P/V55L domain at high spatial and temporal resolution is presented as an example. This domain folds into its native conformation via a low-populated transient intermediate with a lifetime in the millisecond range. Folding intermediates have long been implicated in amyloid fibril formation involved in neurodegenerative disorders but the structural mechanisms have remained largely elusive. The intermediate of the Fyn SH3 A39V/N53P/V55L exposes an aggregation-prone beta-strand and mutants mimicking the intermediate spontaneously form fibrillar aggregates. This study provides detailed insight into how non-native interactions can derail folding and initiate amyloid fibril formation.