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Protein Folding, Structure and Function Studied by Mass Spectrometry

Proteins are biological nano-machines that carry out a myriad of functions inside living organisms. In order to perform these tasks, the linear amino acid chain of each protein has to fold into a highly specific three-dimensional structure. Once a protein has reached this native state, conformational dynamics play a key role for energy transduction, signaling, enzyme catalysis and many other processes. Electrospray ionization (ESI) mass spectrometry (MS) provides a number of exquisitely sensitive strategies for exploring protein structure and dynamics. Our laboratory employs a combination of "native" ESI-MS, on-line rapid mixing, H/D exchange (HDX), as well as covalent labeling for studies in this area. For example, insights into the mechanism of bacterial signal transduction can be obtained by using "bottom-up" HDX experiments, whereas "top-down" HDX with electron capture dissociation (ECD) represents a novel approach for exploring the structures of short-lived folding intermediates. Exciting new developments in microsecond hydroxyl radical labeling provide insights into the folding mechanisms of water-soluble and membrane proteins. The information gained using these techniques is complementary to that obtainable with traditional structural biology tools such as NMR and X-ray crystallography. This presentation will also highlight some of our recent work on the mechanism of the electrospray process.