

INVITED LECTURE T3

Intrinsically disordered proteins: function, folding, and flexibility

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A significant proportion of gene sequences code not for folded globular proteins but for proteins that are intrinsically disordered. Numerous proteins that are highly flexible and lack intrinsic globular structure under physiological conditions have now been recognized. Such proteins participate in important regulatory functions in the cell, including transcription, translation, the cell cycle, and numerous signal transduction events. Disordered proteins often undergo coupled folding and binding transitions upon interaction with their cellular targets. The lack of stable globular structure confers numerous functional advantages, but not without cost; many disordered proteins are associated with amyloid disease and with chromosomal translocations in cancer. NMR is unique in being able to provide detailed insights into the intrinsic conformational preferences and dynamics of unfolded and partly folded proteins. Intrinsically disordered proteins occupy a continuum of “conformational space”, ranging from highly unstructured, through molten globule, to local disorder within an otherwise folded domain. NMR also provides detailed insights into the coupled folding and binding processes that mediate the physiological functions of disordered proteins. Applications of NMR to elucidate the function of intrinsically unstructured protein domains in transcriptional regulation will be described, with particular reference to the transcriptional adapter proteins CBP (CREB binding protein) and p300.