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RNA-binding domain disorder modulates the RNA destabilizing activity in the TTP family of proteins

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Despite the importance of RNA-binding proteins to gene regulation, our understanding of how their structure and dynamics contribute to their biological activity is limited. In this study, we focus on two related RNA-binding proteins—TTP and TIS11d—that regulate the stability of mRNA transcripts encoding key cancer-related proteins, such as tumor necrosis factor- α and vascular endothelial growth factor. These two proteins display differential folding propensity in the absence of RNA, despite sharing a high sequence identity. We identified three residues located at the C-terminal end of an α -helix that determine the folding propensity of the RNA-binding domain in the apo state. We also showed that stabilization of the structure of the RNA-binding domain is associated with differences in RNA-binding activity *in vitro* and increased RNA-destabilizing activity in the cell. Phylogenetic analysis indicates that this family of proteins has only recently evolved to be able to modulate its biological activity through its dynamic structure. To investigate how three residues determine the folding and stability of the TZF domain we used molecular dynamics and NMR spectroscopy. We observed that a π - π stacking between the side chains of a conserved phenylalanine and the zinc coordinating histidine is essential to maintain the correct tetrahedral geometry between the three cysteines, the histidine and the zinc ion. A hydrogen bond in the C-terminal zinc finger of TIS11d is important to keep the phenylalanine in proximity of the imidazole ring of the zinc coordinating histidine in a conformation that allows for stacking of the side chains. Lack of this hydrogen bond in TTP is responsible for the reduced zinc affinity of the C-terminal zinc finger. Sequence alignment shows that this phenylalanine residue is highly conserved. These results suggest that most CCCH-type zinc finger proteins employ π - π interactions to stabilize the structure of the TZF domain.

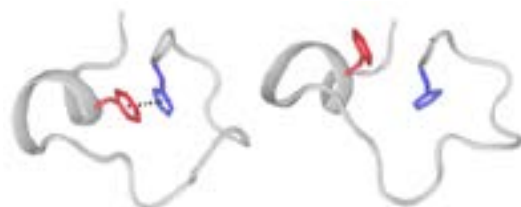


Figure1: The stacking of the aromatic rings of the conserved Phe and of the zinc coordinating His stabilizes conformation of the His in a rotameric state compatible for zinc-binding.

Biography

Francesca Massi is an Associate Professor in the Department of Biochemistry and Molecular Pharmacology at the University of Massachusetts Medical School. She received her Ph.D. in Chemistry with John E. Straub from Boston University and was a postdoctoral fellow with Arthur G. Palmer at Columbia University. Her research interests include protein function and dynamics studied with NMR spin relaxation experiments and computer simulations.

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