University of Massachusetts Medical School

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

BIOCHEMISTRY AND MOLECULAR PHARMACOLOGY

Ph.D. THESIS DEFENSE

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THURSDAY, 5/5/2016 10:00 a.m.
LRB 816

"CHARACTERIZING THE DISORDER IN TRISTETRAPROLIN AND ITS CONTRIBUTION TO POST-TRANSCRIPTIONAL GENE REGULATION"

RNA-binding proteins (RBPs) are important for a wide variety of biological processes involved in gene regulation. However, the structural and dynamic contributions to their biological activity are poorly understood. The tristetraprolin (TTP) family of RBPs, including TTP, TIS11b and TIS11d, regulate the stability of mRNA transcripts encoding for key cancer-related proteins, such as tumor necrosis factor-α and vascular endothelial growth factor. Biophysical studies have shown that the RNA binding domain, consisting of two CCCH zinc fingers (ZFs), is folded in the absence of RNA in TIS11d and TIS11b. In TTP, however, only ZF1 adopts a stable fold, while RNA is required to completely fold the tandem zinc finger (TZF). The focus of this research was to understand the origin and biological significance of the structural differences observed for the TZF domains of TTP and TIS11d. Three residues were shown to control the affinity for the structural Zn^{2+} and determine the folding of ZF2 in the absence of RNA. The partially-folded TZF domain of TTP has greater selectivity for RNA sequences than the fully folded TZF domain of TIS11d. The mRNA destabilizing activity of TTP was increased when the partially disordered RBD of TTP was replaced with the fully structured TZF domain of TIS11d. Disruption of the structure and/or dynamics of the TZF domain observed in the disease-associated mutations of TIS11d, P190L and D219E, results in aberrant cytoplasmic localization. This work demonstrates that the extent of RBD folding in the TTP family is important for differential RNA recognition, mRNA turnover, and protein localization *in vivo*.

Mentor(s)

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