PTBP1 Contains a Novel Regulatory Sequence, the rBH3, that Binds the Pro-Survival Protein MCL1

Christine Christine, Jia Cui,1 Alexus Acton,2 and William Placzek3

1Harvard Medical School/Boston Children’s Hospital; 2Univ of Alabama at Birmingham; and 3The Univ of Alabama at Birmingham

Abstract ID 15827

The maturation of RNA from its nascent transcription to ultimate translation or utilization in alternate biological processes (e.g. miR-mediated RNA silencing) is an intricately coordinated series of biochemical reactions. RNA binding proteins (RBPs) are the sites at which these biochemical reactions occur, and therefore serve as the effectors of RNA maturation and processing. Over the past several decades, there has been extensive effort to elucidate the biological factors that control the specificity and selectivity of RNA target binding and downstream function. Polypyrimidine tract binding protein 1 (PTBP1) is an RNA binding protein that is not only involved in all steps of RNA maturation but serves as a key regulator of alternative splicing of many cellular transcripts, therefore understanding its regulation is of critical biologic importance. While several mechanisms of RBP specificity have been proposed (e.g. cell- or tissue-specific expression of RBPs, secondary structure of target RNA), recently protein-protein interactions with individual domains of RBPs have been suggested to be important determinants of downstream function. Here we demonstrate a novel binding interaction between the first RNA recognition motif (RRM1) of PTBP1 and the pro-survival protein MCL1. Applying both in silico and in vitro analysis, we have demonstrated that MCL1 binds a novel regulatory sequence on RRM1 termed the rBH3. NMR spectroscopy reveals that this interaction allosterically perturbs key residues in the RNA binding interface of RRM1 and negatively impacts RRM1 association with target RNA. Pulldown of MCL1 by endogenous PTBP1 has verified that these proteins interact in an endogenous cellular environment, establishing the biological relevance of this binding event. Overall, the current study proposes a novel mechanism of regulation of PTBP1, in which a protein-protein interaction with a single RRM can impact RNA association.

This work was supported, in part, by funding from the National Institutes of Health Grants R01GM117391 (to W.J.P.) and National Institutes of Health Grants T32GM008361 (to T.Y.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.