

MBNL1-RNA Interactions: Binding-Induced RNA Conformational Changes

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The muscleblind-like protein 1 (MBNL1) is an RNA binding protein that regulates mRNA alternative splicing. It is implicated to be involved in myotonic dystrophy, an inherited multisystem disease, through interacting with poly(CUG) or poly(CCUG) RNA. In the disease state, MBNL1 is abnormally expressed and translocated, which leads to many mis-splicing events. MBNL1 can bind various RNA substrates, most of which share a stem-loop structure containing 5'YGCY3'(Y=U or C) motifs. Using FRET together with a combination of stopped-flow kinetic fluorescence measurements and gel shift assays, we have investigated the relationship between MBNL1-RNA interactions and RNA secondary structure. This work suggested that binding of MBNL1 destabilizes the RNA secondary structure and leads to a partial melting of the stem loop RNA. The RNA secondary structure stability is directly correlated with the kinetic and thermodynamic properties of the MBNL1-RNA complex. The data presented here provides insight into the role of RNA secondary structure in regulation of alternative splicing by MBNL1 and suggests new perspectives for drug development for myotonic dystrophy.

