

# TIA-1 RRM23 binding and recognition of target oligonucleotides

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TIA-1 is an RNA-binding protein involved in splicing and translational repression. It mainly interacts with RNA via its second and third RNA recognition motifs (RRM2 and RRM3, respectively), with specificity for U-rich sequences directed by RRM2. It has recently been shown that RRM3 also contributes to binding, with preferential binding to C-rich sequences. In this work, we designed UC-rich and CU-rich 10-nt sequences for engagement of both RRM2 and RRM3 and demonstrated that the TIA-1 RRM23 construct preferentially binds the UC-rich RNA ligand (5'-UUUUUACUCC-3'). Interestingly, this binding depends on the presence of Lys274, located at the C-terminus of RRM3, and binding to equivalent DNA sequences occurs with similar affinity. Small-angle X-ray scattering was used to demonstrate that, upon complex formation with target RNA or DNA, TIA-1 RRM23 adopts a compact structure, showing that both RRM3s engage with the target 10-nt sequences to form the complex. We also report the crystal structure of TIA-1 RRM2 in complex with DNA to 2.3 Å resolution, providing the first atomic resolution structure of any TIA protein RRM in complex with oligonucleotide. Altogether, our data support a specific mode of TIA-1 RRM23 interaction with target oligonucleotides consistent with the role of TIA-1 in binding RNA to regulate gene expression.

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