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Molecular Interactions Driving RNA Binding to hnRNPA1 Implicated in Neurodegeneration

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Abstract : Heteronuclear ribonucleoprotein (hnRNPA1 or A1) is associated with the pathology of different diseases, including neurological disorders and cancers. In particular, the aggregation and dysfunction of A1 have been identified as a critical driver for neurodegeneration (NDG) in Multiple Sclerosis (MS). Structurally, A1 includes a low-complexity domain (LCD) and two RNA-recognition motifs (RRMs), and their interdomain coordination may play a crucial role in A1 aggregation. Previous studies propose that RNA-inhibitors or nucleoside analogs that bind to RRMs can potentially prevent A1 self-association. Therefore, molecular-level understanding of the structures, dynamics, and nucleotide interactions with A1 RRMs can be useful for developing therapeutics for NDG in MS. In this work, a combination of computational modelling and biochemical experiments were employed to analyze a set of RNA-A1 RRM complexes. Initially, the atomistic models of RNA-RRM complexes were constructed by modifying known crystal structures (e.g., PDBs: 4YOE and 5MPG), and through molecular docking calculations. The complexes were optimized using molecular dynamics simulations (200-400 ns), and their binding free energies were computed. The binding affinities of the selected complexes were validated using a thermal shift assay. Further, the most important molecular interactions that contributed to the overall stability of the RNA-A1 RRM complexes were deduced. The results highlight that adenine and guanine are the most suitable nucleotides for high-affinity binding with A1. These insights will be useful in the rational design of nucleotide-analogs for targeting A1 RRMs.

Keywords : hnRNPA1, molecular docking, molecular dynamics, RNA-binding proteins
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