Characterization of Arginine-Rich Binding in Protein-RNA Interactions

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The Human T-Cell Leukemia Virus Type-1 (HTLV-1) is a complex retrovirus and causative agent of adult T-cell leukemia and tropic spastic paraparesis. The Rex protein in HTLV-1 is essential for the reproduction of new viral particles, acting post-transcriptionally in the nucleocytoplasmic transport of the unspliced and partially spliced viral mRNAs, allowing for the formation of new virions. The Rex protein functions by binding to a region on the viral RNA called the Rex Response Element (RxRE), and belongs to a family of proteins that identify their RNA targets utilizing arginine-rich motifs (ARMs). A previous study characterized the NMR coordinates of a truncated 15-mer Rex peptide containing the ARM bound to an RNA aptamer (shown in Figure 1), and identified three arginine residues that, when mutated to lysine, resulted in a thirty-fold loss in binding affinity between the Rex peptide and RNA aptamer (ARG5, -7, and -13). In this study, two 100ns MD simulations were ran for each mutant peptide complex, as well as two 100ns simulations of a triple mutant complex—giving two 100ns simulations for each of the four different systems. The mutated Rex peptides exhibit displacements from the RNA aptamer due to loss of key water molecules at sites of high water density, presumably due to the lacking of the arginine "fork". The change in binding affinity due to the mutations is characterized by hydrogen bonding analysis, water density and lifetime analyses, and by monitoring displacement of the mutated peptide along the RNA aptamer. Simulations were run using modifications of the Cornell *et al.* force field and TIP4P-Ew water; analyses and visualization were conducted using AmberTools and VMD.
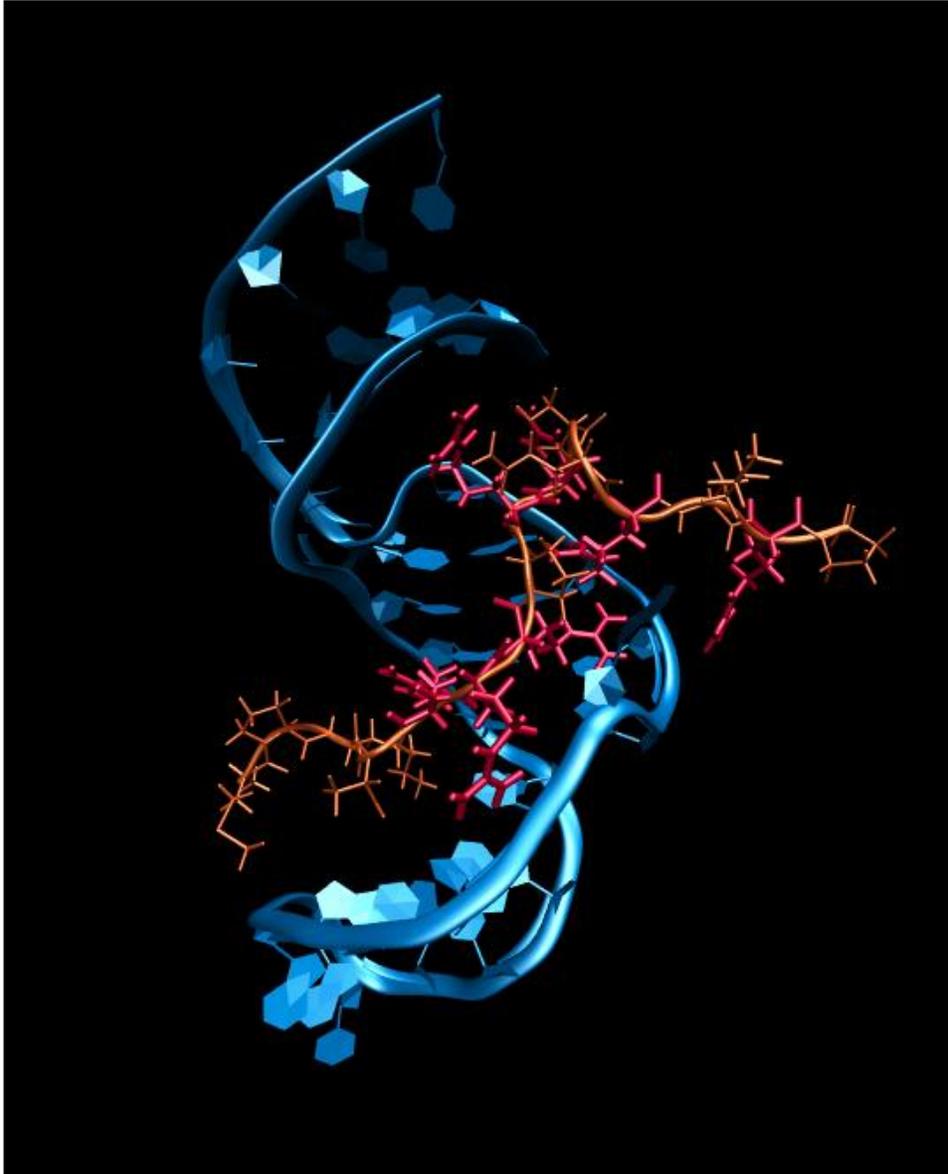
Figure 1 – A visualization of the Rex peptide (orange) bound to the RNA aptamer (blue); arginine residues are shown in red. Visualization was done using VMD.