Computational Models Exploring the Role of Flexibility in Binding Tat Peptide to TAR RNA

Viral-encoded regulatory proteins interacting with RNA target sequences control the gene expression of lentiviruses, notably the human immunodeficiency virus (HIV) and bovine immunodeficiency virus (BIV). The latter provides a simpler interaction model between the viral trans-activator protein (Tat) and trans-activation response RNA element (TAR), including Tat peptides binding to TAR RNA fragments. This model may offer insights into clinical approaches for treatment, initially through theoretical consideration of the role of peptide flexibility in binding as evidenced from literature-based binding assays and NMR. It has more recently been suggested that DNA-protein binding may also be enhanced by increases in conformational entropy. Here, we identified the hinge region of the BIV TAR-Tat complex, where K75 and R78 are considered possible residue positions for substitution by a more local-flexible glycine; these substitutions allow for alternative RNA-peptide interactions. Initially we generated 294 possible RNA structures that bind Tat peptides. Then, molecular modeling by DOCK6 and GROMACS indicated, for single and double substituted K75G and R78G 14-mer peptides, conformations partially excluded from the major groove of the RNA. Interestingly, the binding energies indicate mutants being more stable than the native peptide. Future studies should include a broader exploration of starting structures and simulation time.