Modeling p53 Protein Interactions with Genomic DNA Binding Sites

Noah N. Trueblood and Kelly M. Thayer
Department of Chemistry
Vassar College
124 Raymond Avenue
Poughkeepsie, NY 12604

Fifty percent of human cancers have been found to have missense point mutations in the p53 gene, and thus the p53 protein has become the subject of intensive scientific investigation. Most commonly, mutations occur in p53's core domain, the portion involved in interaction with target DNA. If the mutations eliminate any interactions involved with the DNA or if they compromise the structural stability of the protein, p53 will be unable to bind to DNA and thus will be unable to act as a tumor suppressor. Development of small molecule therapeutics could arise from a deeper structural understanding of the protein and its intricacies. If a therapeutic can be developed that can effectively restore function to a p53 protein that can no longer differentially interact with DNA, literature studies suggest that it will resume normal binding resulting in either initiating the process of repairing damaged DNA or triggering apoptosis.

Experimentally determined genomic p53 binding sites have been categorized on the basis of structural properties including hydrogen bonding potential and mechanical bending at a central TG step, yielding four groups in addition to the well studied consensus binding. The non-consensus groups may contain examples of novel binding mechanisms which may exhibit both direct and indirect readout as a result of the DNA mechanical properties. To investigate the structural diversity of the p53 DNA binding sites, the current research encompasses modeling of these 482 sequences. This undertaking entails using the AMBER molecular dynamics package to model the binding site sequences into the 1TUP crystal structure, and they are analyzed with AmberTools as well as the Visual Molecular Dynamics software. Hydrogen bonding between p53 and DNA and the geometrical properties of the DNA are being examined in consensus and non-consensus binding sites.