Characterization of the Readout Mechanism and the L1 Loop's Role in the p53 Tumor Suppressor Protein Binding Event via Molecular Dynamics Simulations

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A primary target in cancer research, the p53 tumor suppressor protein, is a transcription activator playing an integral role in the regulation of the cell cycle. Through binding to DNA, the protein has the ability to "turn on" other repair proteins to mend damaged DNA, inhibit cellular division, and initiate apoptosis in cells that are damaged beyond repair. Most inactive p53 mutants contain changes primarily localized to the DNA binding domain (DBD). While intensive research has been conducted on different p53 mutants, previous studies have not yet focused on the capability for the system to exhibit direct and indirect readout among various genomic sites. Consequently, the L1 loop's role in binding to sequences exhibiting differences in the readout also remains obfuscated. This study aims to characterize these two aspects of the p53 binding event. Hydrogen bonding as direct readout will be ascertained from additive energy models and DNA deformation mechanics will be explored as indirect readout from molecular dynamics (MD) simulations. Additionally, this experiment illuminates the contribution of the L1 loop to the p53/DNA binding interface. Molecular models of p53 with DNA expected to have differing hydrogen bonding patterns are constructed and simulated using the Amber12 MD suite. Results from this study will inform rational design of novel therapeutics to combat the changes that are hypothesized to cause over 50% of tumorous cancers.