Investigating Hydrogen Bonds in DNA Binding Sites for Tumor Suppressor Protein p53 Modeled with Amber and Visual Molecular Dynamics

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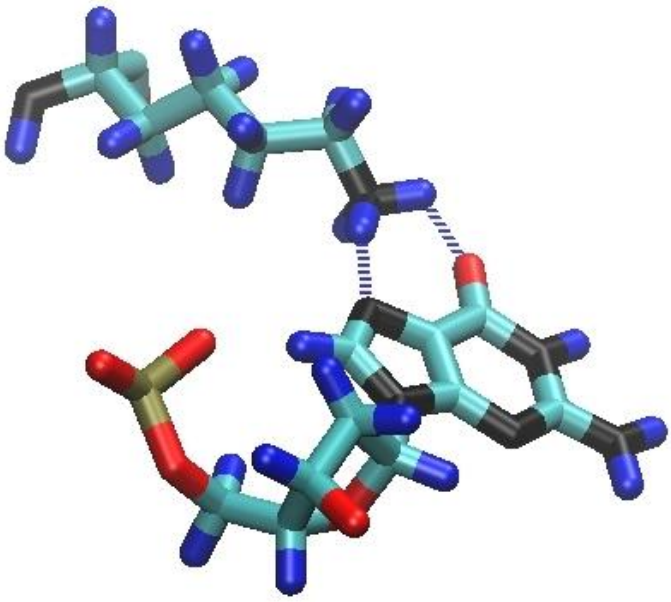
The protein p53 suppresses cancer by activating DNA repair pathways and triggering apoptosis if the DNA is beyond repair. Mutations of p53 are estimated to be present in half of all diagnosed cancer cases, the majority of which occur in the domain involved with DNA binding. In its role as a transcription factor, p53 binds to DNA by forming discriminatory hydrogen bonds with the base pairs and backbone to facilitate recognition in a sequence specific manner. However, some sequences allow for more hydrogen bonds than others. In this research, the AMBER suite adds hydrogens, mutates DNA, and energy minimizes structures, and the Visual Molecular Dynamics (VMD) program visualizes and analyzes the hydrogen bond geometry between p53 and the DNA binding site. Thus, experimental DNA sequences are engineered from the previously determined crystal structure 1TUP containing the core domain of human p53 bound to a target DNA site. These are being used to investigate which sequence allows for the maximum number of hydrogen bonds and to explore alternate hydrogen bonding networks. The information gathered from this study can be applied in the rational design of cancer therapeutics operating by compensating for bonds absent in mutated p53.



Residue Lys 120 (top) of p53 forming hydrogen bonds with a Guanine base (bottom).