Using Virtual Reality to Study the Effects of Mutations on BET Protein Interactions

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Bromodomain and extra-terminal (BET) proteins play essential roles in regulating gene expression and immune responses. In fact, BET proteins have been associated with diseases such as cancer and osteoarthritis. There are four BET proteins, BRD2, BRD3, and BRD4, and each BET protein has two bromodomains (BD), which are responsible for binding to DNA and one extra-terminal domain (ET), which is responsible for recruiting proteins. In this research study, BRD3's ET and its interactions with a specific peptide were studied with the goal of attempting to create a mutation in the peptide that would increase the binding strength between the peptide and the BRD3 ET. The four main factors that were evaluated were hydrogen bonding, steric clashing, root mean square deviation, and changes in secondary structure. In this study, a total of 42 mutations were proposed and evaluated. Of those 42 mutations, 16 were determined to be beneficial, and seven were determined to be highly beneficial. These seven highly beneficial mutations resulted in significant improvements in hydrogen bonding and steric clashing, and they also resulted in little secondary structure change. These findings are important because they can be used to create BET inhibitors and other proteins that may aid in regulating BET proteins. However, further research is needed to evaluate the effects of multiple mutations on BET proteins.

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