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Insights into protein – DNA interactions, stability and allosteric communications: A computational study of MutS-DNA recognition complexes[1] LACRAMIOARA NEGUREANU, FREDDIE SALSBURY, Wake Forest University — DNA mismatch repair proteins (MMR) maintain genetic stability by recognizing and repairing mismatched bases and insertion/deletion loops mistakenly incorporated during DNA replication, and initiate cellular response to certain types of DNA damage. The most abundant MMR mismatch-binding factor in eukaryotes, MutS, recognizes and initiates the repair of base-base mismatches and small insertion/deletions. We performed molecular dynamics simulations on mismatched and damaged MutS-DNA complexes. A comprehensive DNA binding site analysis of relevant conformations shows that MutS proteins recognize the mismatched and platinum cross-linked DNA substrates in significantly different modes. Distinctive conformational changes associated with MutS binding to mismatched and damaged DNA have been identified and they provide insight into the involvement of MMR proteins in DNA-repair and DNA-damage pathways. Stability and allosteric interactions at the heterodimer interface associated with the mismatch and damage recognition step allow for prediction of key residues in MMR cancer-causing mutations. A rigorous hydrogen bonding analysis for ADP molecules at the ATPase binding sites is also presented. A large number of known MMR cancer causing mutations among the residues were found.

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