Molecular Dynamics Simulations of the Structural Effects of Oncogenic Mutations in the Nucleosome

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Abstract

The information available to the cell to initiate, control or stall metabolic processes is housed in the genome whose monomeric unit is the nucleosome core particle (NCP). The dynamics of the NCP together with DNA binding proteins drive cellular processes including replication and transcription. However, these dynamics are biochemically exploited by tumor cells to aid their proliferation in different cancer types including glioblastoma, leukemia, lung carcinoma, and chondroblastoma [1]. Mutations in the core histone proteins (H2B and/or H4) seen in uterine cancer have been shown to destabilize the H2B-H4 protein interface [2]. We ran hundreds of nanoseconds of all-atomistic simulation of different mutations of amino acid residues in the core histones of the NCP at different concentrations of NaCl[3]. We noticed a destabilization of some helix interfaces in the histone core characterized by a decrease in interhelical hydrogen bonds in the mutant systems when compared to the wild type. We also observed that the strong interhelical hydrogen bonds favor the formation of π- π interaction between the aromatic rings of aromatic amino acids at the helix interface. The binding free energy of the wild-type system was lower and hence more stable when compared to the mutant systems. Furthermore, some leucine and histidine at the histone interface were the main contributors to this free energy. We intend to run longer simulations to understand the stability of the helix interfaces in the mutant systems. Observing the structural effects of oncogenic mutations in the histone may shed light on how mutations affect the stability of the histone core proteins.

Reference:

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