Molecular dynamics study on the effect of As(III) ion on human uracil DNA glycosylase enzyme

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Mutations in DNA occur due to exposure to chemicals, toxins, and radiation. The presence of uracil in DNA is a modification that occurs due to the misincorporation and spontaneous deamination of cytosine. Glycosylases can repair mutated DNA, and human uracil DNA glycosylase (hUNG) is one such DNA repair enzyme that initiates the base excision repair pathway. However, the activity of these enzymes gets affected when exposed to toxic metals. Therefore, it is essential to study the mechanism of action of the toxic metals with these enzymes. Experimental investigations have revealed that Cd(II) ions can inhibit the activity of hUNG. These studies suggest that the inhibition takes place due to the replacement of the catalytic water molecule found in the active site of the enzyme by the Cd(II) ion. Other than Cd(II) ion, As(III) is also considered a toxic metal ion categorized under human carcinogens. Therefore, the work here has focused on the accumulation of As(III) with the hUNG enzyme, and the intension of this work was to study the effect of As(III) ion on hUNG. The study was done using CavityPlus web server and computational analysis based on molecular dynamic (MD) simulations considering two systems of the enzyme; in the presence and absence of the As(III) ion. The CavityPlus web server results showed that the number of cavities of the enzyme changes for the two situations of the enzyme. Further, the ability of a ligand to bind with a cavity of the hUNG was comparatively studied using the ligandability results obtained from the server. The root means square deviation and total energy analysis done using the simulation trajectories showed that the enzyme and the system with As(III) obtain high stability compared to the free enzyme and the system, respectively. The localization of the residues of the enzyme in the Ramachandran plot showed that a high percent of residues of the enzyme with As(III) lie in the favorable region of the plot. Based on the analysis of these results, it is concluded that As(III) ion can reduce the activity of the enzyme by forming a stable enzyme-metal ion system.

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