

THE EFFECT OF DIVALENT IONS ON THE INTERACTIONS BETWEEN HISTONES AND DNA

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ABSTRACT

In eukaryotes, ~147 bp of DNA is packaged around histones (H2A, H2B, H3, H4) corresponding to helices ($\alpha 1$, $\alpha 2$, and $\alpha 3$). These helices interact to form the octamer called nucleosome, the basic repeating unit of chromatin. The anchoring of basic lysine and arginine side chains inside the histones into the minor grooves of DNA facilitates the interaction between DNA and histones. The epigenetic substitutions inside the histones, such as bulky arginine to compact lysine substitution in H3 (CENP-A formation), might fine-tune the affinities of histones to DNA. The interactions for the folding of nucleosomes might depend on magnesium concentration inside the cell. To analyze the effect of this concentration on the interaction between DNA and lysine and arginines inside the helices, we prepared two Widom601 sequence regions interacting with a CENP-A region and a canonical H3 region, respectively, via Pymol. Then, the energies of these molecules were minimized and the molecules were resolved in the cubic OPC water box for 1 μ s, separately, via CHARMM36 force field and Gromacs, while Na⁺, Cl⁻, and Mg⁺⁺ ions were providing a physiological condition. The simulations were replicated in a condition with excess Mg⁺⁺. The trajectories were obtained and analyzed via VMD and Python. It was revealed by contact analysis that magnesium induces the detachment of histones, especially CENP-A, from DNA. Moreover, the distance of CENP-A to DNA is increasing significantly in a high divalent environment, compared to canonical H3. Lastly, root mean square fluctuation analysis of histones shows that the stability of canonical H3 is less than CENP-A in both physiological and high divalent conditions, and increased magnesium concentration decreases the stability of these histones. This study reveals that an excess amount of divalent ions affects the stability of histones with regards to sequence, and the binding interactions of these histones and DNA.