Drosophila melanogaster linker histone (dH1) binding to the nucleosome

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Linker histone proteins are key players in the structuring of chromatin for the packing of DNA in eukaryotic cells. The common fruit fly (*Drosophila melanogaster*) has a single isoform of the linker histone (dH1). It is thus a useful model organism to investigate the effects of the linker histone (LH) on nucleosome compaction and the configuration of the chromatosome, the complex formed by binding of a LH to a nucleosome. The structural and mechanistic determinants of how LH proteins bind to nucleosomes are not fully understood. Here, we apply Brownian dynamics simulations to compare the binding of dH1 and the chicken (*Gallus gallus*) LH H5 isoform to identify residues in the LH that critically affect the configuration of the chromatosome.

1 Introduction

In eukaryotic cells, DNA is packed by formation of nucleosomes consisting by stretches of ~ 146 bp of DNA wrapped around a core histone protein octamer. Compaction and various cellular

processes, including gene expression are regulated by the binding of linker histone (LH) proteins to nucleosomes, forming chromatosomes. While many organisms have more than one LH isoform, the model organism *Drosophila melanogaster* has a single H1 isoform (dH1) which facilitates experimental studies on the phenotypic effects of dH1. LHs are $\sim$ 200 amino acid (aa) proteins composed of a short flexible N-terminal tail ($\sim$ 25 aa), a globular DNA binding domain ($\sim$ 80 aa), and a long C-terminal domain ($\sim$ 100 aa). Previous experiments have shown that nucleosome binding is primarily determined by the LH globular domain and removal of the N- and C-domains affects the affinity of the binding but not the binding site on the nucleosome. In this report, we investigated the effect of single mutations on globular domain dH1 - nucleosome binding by means of Brownian dynamics simulations. The results are compared with the nucleosome binding configurations of the globular domain of a chicken (*Gallus gallus*) H5 mutant isoform.

2 Methods

8 different structures of a nucleosome, previously generated by molecular dynamics simulation and representing a range of linker DNA (L-DNA) conformations, were used for Brownian dynamics simulation-based docking of dH1 and H5 globular domains to the nucleosome [1]. The structures of the globular domains of dH1 (kindly provided by Dr. Yawen Bai, [2]) and *Gallus gallus* H5 (Chain B PDB ID: 1hst, [3]) shown in Figure 1 were used. Docking was performed as described in Öztürk et al. [1] for the wild-type (WT) globular domains and for the single point mutants shown in Figure 1. The mutations are at sites that are important for DNA binding or have very different physiochemical properties in the two proteins.

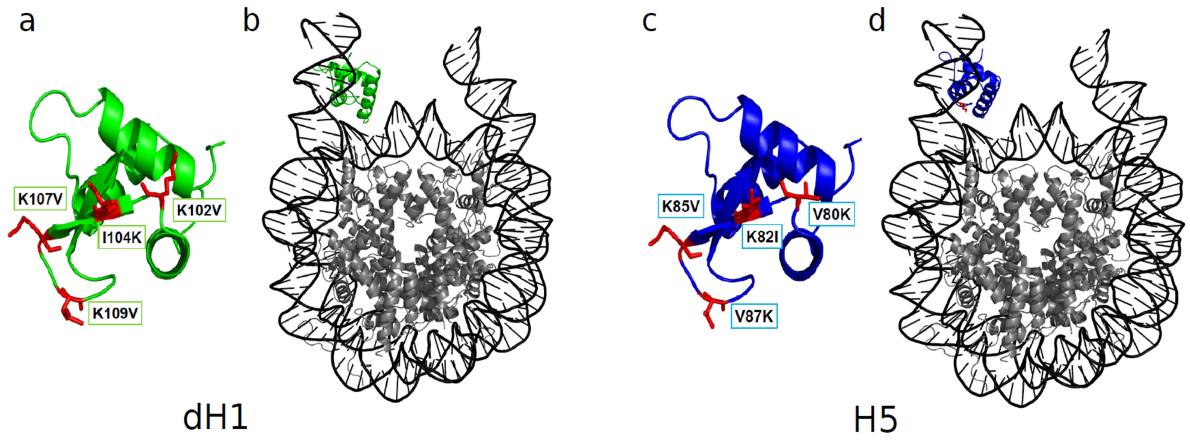

Figure 1: Structures of the globular domains of the linker histone proteins, dH1(a-green) and H5 (c-blue), and the locations of the mutations (red) evaluated by computational docking to a nucleosome. Selected Brownian dynamics docking simulation results for WT dH1(b) and V87K mutant of H5 (d) bound to nucleosome (gray) in off-dyad form.

3 Results

Experiments have revealed structures of the chromatosome with gH5 bound in an on-dyad configuration and dH1 bound in an off-dyad configuration. Docking of the WT and mutant

variants of the globular domains of dH1 and H5 to the nucleosome revealed that, depending on the extent of opening of the linker-DNA arms, a range of configurations of the chromatosome is possible. Of the single-point mutations, K107V and I104K resulted in the most significant changes in configurations compared to WT dH1, whereas K82I and V87K had the greatest effects compared to WT H5. Interestingly, for a subset of nucleosome conformations, the V87K mutant of H5 docked in similar configurations to WT dH1.

4 Conclusions

Our Brownian dynamics simulations reveal that chromatosome configurations depend on the extent of opening of the linker DNA arms. Certain single residue mutations of dH1 and H5 can significantly change the binding mode. These results may help to explain the evolutionary emergence of various LH isoforms having different cellular functions and provide a basis for mutagenesis experiments to understanding the mechanisms of chromatin packing.

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References

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