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Centromere chromatin: a loose grip on the nucleosome?

Yuri L Lyubchenko

Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, Nebraska, USA

Yuri L Lyubchenko: ylyubchenko@unmc.edu

To the Editor

Centromeres are specialized segments of chromosomes that aid in chromosomal segregation after DNA replication. The kinetochore is a protein complex that interacts specifically with the centromere to allow the separation of sister chromosomes into the daughter cells. If the centromere becomes damaged or removed, the chromosomes segregate randomly. This suggests that centromeres contain specific characteristics that allow their selection by kinetochores. However, the structural details of centromeres and the mechanism underlying this recognition process remain unclear. It is known that all centromeric nucleosomes contain modified H3 histones (CENP-A; reviewed in ref. 1). An analysis of the CENP-A–nucleosome array by atomic force microscopy (AFM) revealed that CENP-A nucleosomes have a considerably lower height than do regular H3 nucleosomes². The authors therefore suggested that CENP-A nucleosomes consist of one set of each histone (tetrasome) rather than the histone duplicates observed in regular H3 nucleosomes (octasomes). However, subsequent crystallographic data did not confirm this finding³, revealing instead that both types of nucleosomes are octameric. The controversy was reconciled in a recent publication by Miell *et al.*⁴ in which a thorough AFM analysis was combined with biochemical tests, showing that CENP-A nucleosomes had a lower height than did H3 nucleosomes and that both were octameric particles. Miell *et al.*⁴ suggest that CENP-nucleosomes are structurally different from H3 nucleosomes, and this conclusion is in agreement with crystallographic models for both types of nucleosomes³. Indeed, terminal DNA segments of CENP-A nucleosomes (13 bp) are detached from the histone core, and this partial unwrapping decreases the volume and hence the height of the nucleosome⁵. The crystallographic data for CENP-A and H3 nucleosomes³ can be used to generate models for nucleosome arrangements for both types of nucleosomes. The flanking DNA sequences emerging from H3 nucleosomes cross each other at an ~90° angle (Fig. 1a), whereas in CENP-A nucleosomes the flanking sequences are nearly parallel (~0°) because the wrapped DNA is 26 bp shorter (Fig. 1b). This arrangement generates the well-known zig-zag model for H3 nucleosomes (Fig. 1c), whereas CENP-A nucleosomes form a parallel array (Fig. 1d). The possibility that these nucleosomal arrangements lead to different higher-order structures of centromeric and regular chromatin is a crucial question that needs to be addressed in future studies.

At present, however, additional issues need to be considered. Two recent reports^{6,7} challenge the finding that CENP-A nucleosomes have reduced heights because their analysis of mononucleosomes⁶ and arrays⁷ made with both types of H3 histones did not reveal a height difference. These studies and the response by Miell *et al.*⁸ provide a number of

explanations for these differences, including experimental problems related to use of AFM. The data reported by Miell *et al.*^{4,8} imply that CENP-A nucleosomes are more dynamic than H3 nucleosomes. To validate this claim, structural studies should be combined with single-molecule biophysics approaches capable of characterizing dynamic states of biological systems. In this respect, it might be attractive to consider high-speed AFM, which is capable of visualizing structural features at nanometer resolution and which was successfully used to study the dynamics of mononucleosomes⁹.

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Figure 1.

The models of nucleosomes and nucleosomal arrays, projected on a plane. (**a–d**) Schematic structures of H3 and CENP-A mononucleosomes (**a** and **b**, respectively) and their arrangements into arrays (**c** and **d**, respectively). Histone cores are shown as yellow and green disks.