A local and a global view on chromosomal structure: the nucleosomal stem versus chromosome territories

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Eukaryotic genomes are organized in sets of chromosomes. Each chromosome consists of a single continuous DNA double-helix and associated proteins that organize locally in the form of a chromatin fiber. Despite the key role of the linker histone H1 in chromatin structure and dynamics, its location and interactions with nucleosomal DNA have not been elucidated. We have used a combination of electron cryomicroscopy, hydroxyl radical footprinting, and nanoscale modeling to analyze the structure of precisely positioned mono-, di-, and trinucleosomes containing physiologically assembled full-length histone H1 or truncated mutants of this protein [1]. Single-base resolution •OH footprinting shows that the globular domain of histone H1 (GH1) interacts with the DNA minor groove located at the center of the nucleosome and contacts a 10-bp region of DNA localized symmetrically with respect to the nucleosomal dyad. In addition, GH1 interacts with and organizes about one helical turn of DNA in each linker region of the nucleosome. We also find that a seven amino acid residue region (121–127) in the COOH terminus of histone H1 was required for the formation of the stem structure of the linker DNA. A molecular model on the basis of these data and coarse-grain DNA mechanics provides novel insights on how the different domains of H1 interact with the nucleosome and predicts a specific H1-mediated stem structure within linker DNA.

During cell division (mitosis) chromosomes adopt a compact form that is suitable for transport. During periods of normal cell activity (interphase), they decondense inside the cell nucleus. Being long-chain molecules (in the case of human chromosomes the contour length of the chromatin fiber is on the order of 1 mm), the random thermal motion of interphase chromatin fibers is hindered by entanglements, similar to those restricting the manipulation of a knotted ball of wool. We have studied the consequences of this effect using computer simulations [2,3]. Most importantly, we find that entanglement effects cause sufficiently long chromosomes to remain segregated during interphase and to form “territories.” Our model (1) reproduces currently avaliable experimental results for the existence and shape of territories as well as for the internal chromosome structure and dynamics in interphase nuclei as measured in Fluorescence in-situ hybridization (FISH) and chromosome conformation capture (3C) and (2) explains why entanglement effects do not interfere with the reverse process of chromosome condensation at the end of interphase. The success of our parameter-free minimal model of decondensing chromosomes suggest that the observed interphase structure and dynamics are due to generic polymer effects: confined Brownian motion conserving the local topological state of long chain molecules and segregation of mutually unentangled chains due to topological constraints.

1. *Single-base resolution mapping of H1–nucleosome interactions and 3D organization of the nucléosome*, Sajad Hussain Syeda,b, Damien Goutte-Gattata, Nils Beckerc, Sam Meyerc, Manu Shubhdarshan Shuklaa,b, Jeffrey J. Hayesd, Ralf Everaersc, Dimitar Angelovb, Jan Bednare,f,1, and Stefan Dimitrov, **Proceedings of the National Academy of Sciences (US)**, in press
2. *Structure and Dynamics of Interphase Chromosomes*, A. Rosa and R. Everaers, **PLoS Computational Biology** 4, e1000153 (2008).
3. *Looping Probabilities in Model Interphase Chromosomes,* A. Rosa, Nils B. Becker, and R. Everaers, **Biophysical Journal** 98, 2410–2419 (2010)