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Unraveling chromatin structure using magnetic tweezers

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The compact, yet dynamic organization of chromatin plays an essential role in regulating gene expression. Although the static structure of chromatin fibers has been studied extensively, the controversy about the higher order folding remains. The compaction of eukaryotic DNA into chromatin has been implicated in the regulation of all DNA processes. To understand the relation between gene regulation and chromatin structure it is essential to uncover the mechanisms by which chromatin fibers fold and unfold. We used magnetic tweezers to probe the mechanical properties of individual nucleosomes and chromatin fibers consisting of a single, well-defined array of 25 nucleosomes. From these studies five major features appeared upon forced extension of chromatin fibers: the elastic stretching of chromatin's higher order structure, the breaking of internucleosomal contacts, unwrapping of the first turn of DNA, unwrapping of the second turn of DNA, and the dissociation of histone octamers. These events occur sequentially at the increasing force. Neighboring nucleosomes stabilize DNA folding into a nucleosome relative to isolated nucleosomes. When an array of nucleosomes is folded into a 30 nm fiber, representing the first level of chromatin condensation, the fiber stretched like a Hookian spring at forces up to 4 pN. Together with a nucleosome-nucleosome stacking energy of 14 kT this points to a solenoid as the underlying topology of the 30 nm fiber. Surprisingly, linker histones do not affect the length or stiffness of the fibers, but stabilize fiber folding up to forces of 7 pN. The stiffness of the folded chromatin fiber points at histone tails that mediate nucleosome stacking. Fibers with a nucleosome repeat length of 167 bp instead of 197 bp are significantly stiffer, consistent with a two-start helical arrangement. The extensive thermal breathing of the chromatin fiber that is a consequence of the observed high compliance provides a structural basis for understanding the balance between chromatin condensation and transparency for DNA transactions. The kinetics of force induced nucleosome unstacking was resolved using a Hidden Markov analysis. Overall, our results reveal a highly dynamic structure that combines high level of compaction of DNA with transient accessibility.