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Structural insights of nucleosome and the 30-nm chromatin fiber

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The eukaryotic genome is hierarchically packaged into chromatin in the nucleus. The organization and dynamics of 30-nm chromatin fibers, which is typically regarded as the secondary structure of chromatin, play a crucial role in regulating DNA accessibility for gene expression. Here we reviewed some recent progresses on the structural studies on nucleosomes, nucleosome–protein complexes, and chromatin fibers, focusing on the structural insights how the chromatin structure is regulated by different epigenetic regulation factors.

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Introduction

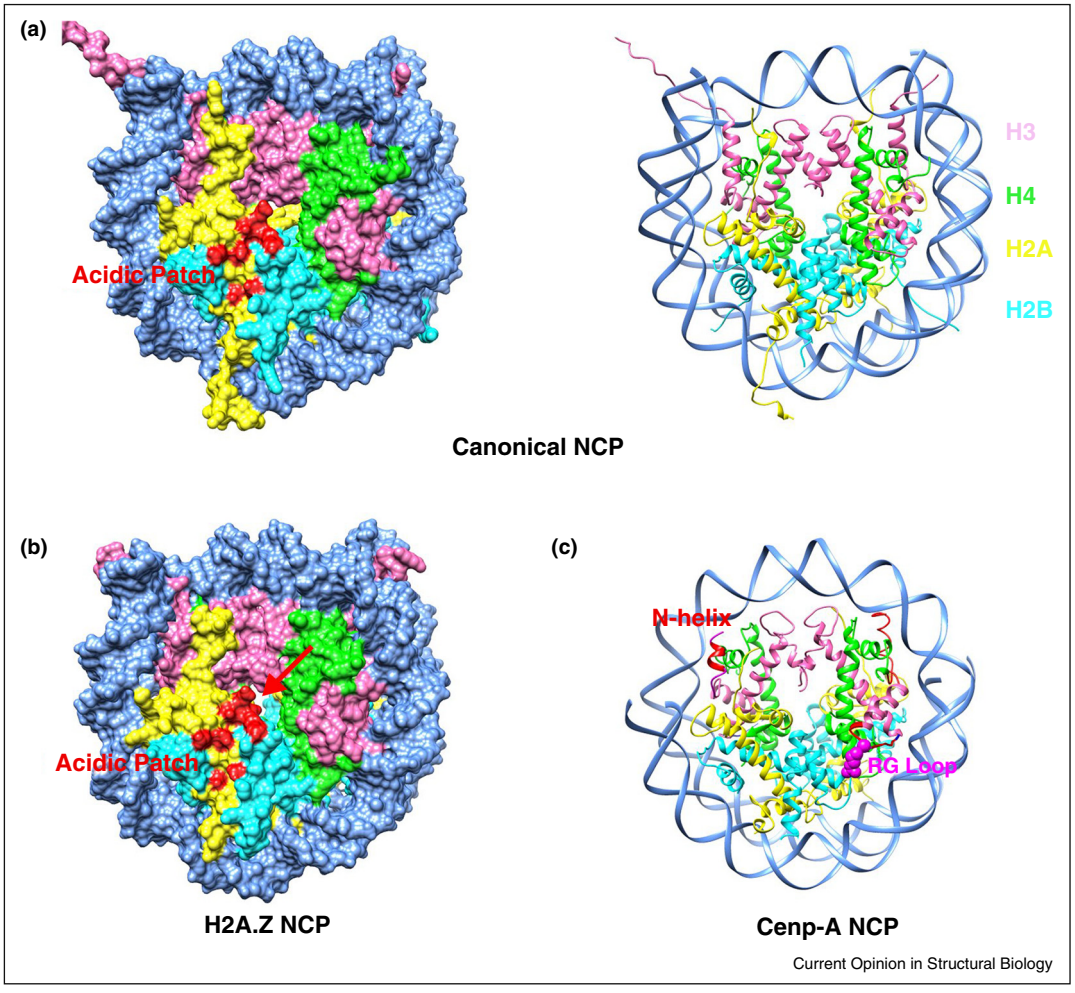
In eukaryotic cells, genomic DNA is hierarchically organized by histones into chromatin. The fundamental repeating unit of chromatin is the nucleosome, which is comprised of the core particle and linker DNA. The nucleosome core particle (NCP) comprises 146/147 base pairs (bp) of DNA wrapped in 1.7 superhelical turns around an octamer of histone proteins [1]. The nucleosome core is connected to the adjacent nucleosome core through a segment of linker DNA to form a 'beads-on-a-string' nucleosomal array with a diameter of 11 nm. The nucleosomal arrays are further organized into a more condensed 30-nm chromatin fiber, which is typically regarded as the secondary structure of chromatin, by linker histones (H1 and H5) [2]. The dynamics of chromatin fibers, that is, transitions between accessible form of nucleosomal arrays and highly compacted form of 30-nm chromatin fibers, plays a crucial role in the regulation of gene expression and other DNA-dependent activities. Numerous factors, including chromatin enzymes and chromatin binding factors, have been identified to function in these biological processes through modifying and remodeling structure and dynamics of nucleosome and/or chromatin [3,4]. Here we reviewed some recent advances on the structural studies on nucleosomes, nucleosomes–protein complexes, and 30-nm chromatin fibers by X-ray crystallography and cryogenic-electron microscopy (cryo-EM), focusing on the structural insights how the structure and dynamics of the chromatin fiber is regulated by different epigenetic factors.

Nucleosome structures

The nucleosome serves as the first level of genomic compaction. As shown in the first ground-breaking crystal structure of NCP [1], the core histones assemble into a spool-like structure onto which the core DNA is wrapped, forming a squat disc-like structure about 5.5 nm in height and 11 nm in diameter (Figure 1a). Afterwards, a generous handful of NCP structures, which contain core histones from different species, with variant histones, or with different DNA sequence (α-satellite or 601 DNA), were solved and had been reviewed extensively [5•,6,7]. Given the high degree of evolutionary conservation of the histone proteins, it is not surprising that most structures of NCPs are relatively invariant and is not much different from the earlier structure.

Histone variants are suggested to have the potential to locally alter nucleosome and chromatin structure and provide a way of epigenetic regulation. The first crystal structure [8] of NCP containing variant histone, H2A.Z, shows an extended H2A/H2B acidic patch in nucleosomal surface, which is located in regions that are essential for viability of H2A.Z in many organisms (Figure 1b). This extended acidic patch results in a subtly more unstable interaction between H2A–H2B dimer and $(H3–H4)_2$ tetramer due to the loss of a few hydrogen bonds (arrow in Figure 1b) and may potentially affect the higher order structure of chromatin [8–10]. In addition, the crystal structure of the human centromeric nucleosome containing CENP-A, a histone H3 variant specifically localizes to centromeres, shows that about 13 bp DNA from both ends are not visible, and the αN helix of CENP-A is shorter than that of canonical H3 (Figure 1c) [11•]. The structure also suggested that two extra amino acid residues (Arg 80 and Gly 81, RG loop, Figure 1c) in the loop 1 region of CENP-A may function in stabilizing the centromeric chromatin, possibly by providing a binding site for trans-acting factors [11•,12]. Interestingly, a 'hybrid structure' of nucleosome containing two H3 variant,

Figure 1



The structures of nucleosome core particles (NCPs) with the following color schemes: H3 (pink), H4 (green), H2A (yellow), H2B (cyan), and DNA (light blue). **(a)** The first atomic structure of NCP (PDB: 1AOI [1]) with canonical *Xenopus* histones. Both the surface mode (left, H2A–H2B acidic patch highlighted in red) and ribbon mode (right) are shown. **(b)** The structure of NCP containing mouse histone variant H2A.Z (PDB: 1F66 [8]). The extended H2A–H2B acidic patch (red) and subtle destabilization of the interaction (arrow) between the (H2A.Z–H2B) dimer and the $(H3–H4)_2$ tetramer are indicated. **(c)** The structure of NCP containing human histone variant CENP-A (PDB: 3AN2 [11•]). Only 121 bp central DNA is visible. In compared with canonical H3, the two extra amino acid residues (Arg 80 and Gly 81, RG loop, purple) and the shorter αN helix (red) of CENP-A are highlighted.

CENP-A and H3.3, forms an unexpectedly stable structure as compared to the CENP-A nucleosome, and allows the binding of the essential centromeric protein, CENP-C, a binding partner of CENP-A and a prime candidate to stabilize centromeric chromatin [13]. In a recent study, CENP-C was found to affect the shape and dynamics of CENP-A containing nucleosome in a manner analogous to allosteric regulation of enzymes [14]. The depletion of CENP-C leads to rapid removal of CENP-A from centromeres, indicating their collaboration in maintaining centromere identity [14].

The post-translational modifications (PTMs) of histone proteins provide another way to alter the chromatin structure for epigenetic regulation [15,16]. The evolutionarily conserved 'tail' domains in histones contain predominantly lysine and arginine residues, which are readily accessible to chromatin enzymes that carry out posttranslational modifications and important for epigenetic signaling. The histone tails are largely structurally undefined but adopted random orientations in different NCPs structure, consistent with their highly dynamics and flexibility. Importantly, these tail domains are in position to mediate inter-nucleosomal interactions within condensed chromatin structures, and, in fact, this appears to be their primary role in organizing higher-order chromatin structures. In addition, the array of PTMs further regulates the recruitment of chromatin enzymes and