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Histone tails as signaling antennas of chromatin

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Abstract

Histone tails, representing the N- or C-terminal regions flanking the histone core, play essential roles in chromatin signaling networks. Intrinsic disorder of histone tails and their propensity for post-translational modifications allow them to serve as hubs in coordination of epigenetic processes within the nucleosomal context. Deposition of histone variants with distinct histone tail properties further enriches histone tails' repertoire in epigenetic signaling. Given the advances in experimental techniques and *in silico* modelling, we review the most recent data on histone tails' effects on nucleosome stability and dynamics, their function in regulating chromatin accessibility and folding. Finally, we discuss different molecular mechanisms to understand how histone tails are involved in nucleosome recognition by binding partners and formation of higher-order chromatin structures.

Keywords

histones; nucleosome; histone tail; chromatin

Introduction

Packing of eukaryotic DNA into chromatin engages the basic building blocks called nucleosomes. Nucleosome core particles (NCP) consist of an octamer of four types of histones (H2A, H2B, H3, H4), and ~147 DNA base pairs wrapped around them [1]. The N- and C-terminal intrinsically disordered (IDP) regions flanking histone cores represent histone tails that do not have well determined tertiary structure but rather exist in a dynamic conformational ensemble. In addition, a linker histone H1, comprising a globular domain and disordered N-and C-terminal tails, can bind to nucleosome to form so called chromatosome. The variability in histone tails can be introduced through post-translational modifications (PTM) and deposition of histone variants. The roles of histone tails in the epigenetic regulation have been elucidated through the advances in experimental approaches

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such as nuclear magnetic resonance (NMR) spectroscopy, cryo-electron microscopy (cryo-EM), fluorescence resonance energy transfer (FRET), chemical crosslinking and mass spectrometry (MS) [2*,3,4**,5,6,7]. A large variety of histone tail PTMs, histone modifying enzymes and reader proteins has been identified and characterized to unravel their roles in various regulatory processes [8,9]. With a rapidly increasing number of histone and nucleosome complex structures deposited in the Protein Data Bank (PDB) [10], atomic details of histone tail mediated interactions have been revealed [11*,12**,13**].

Histone tails participate in various chromatin functions. They moderate nucleosome stability and dynamics, DNA accessibility, nucleosome sliding and repositioning [14,15]. One of the most important roles of histone tails is associated with nucleosomal function to ensure the coordination in time and space of different pathways of epigenetic regulation. Indeed, nucleosomes represent hub points in chromatin signal flow and form a dense set of interactions with other macromolecules [16,17*]. This requires modularity, a crosstalk between signaling components, proofreading capability and redundancy which in turn yields high response sensitivity and robustness. In this review, we summarize the distinct biological and physico-chemical properties of histone tails which allow them to perform these above-mentioned functions in the context of the full nucleosome and chromatin.

Physico-chemical properties of histone tails are essential for chromatin signaling

IDPs are characterized by certain physico-chemical properties which are explored by histone tails. Intrinsic disorder in histone tails may speed up the search for nucleosome targets and facilitate their interactions with partners. To achieve it, according to the fly-casting mechanism, intrinsically disordered proteins use an increased capture radius for specific binding compared to folded proteins [18]. It has been known for a long time that histone tails affect nucleosome thermodynamic stability and dynamics. Removing tails may induce a more rapid nucleosome unwrapping but the long-lived DNA detachments may lead to structural rearrangements of the H3 tails delaying of DNA re-wrapping [19,20*,21] (Figure 2c). Histone tail dynamics is correlated with the DNA unwrapping although this coupling strongly depends on the salt concentration [7,22]. The energetic barrier in nucleosome unwrapping mainly arises from the electrostatic interactions between DNA and histone core. However, according to the recent study, the unwrapping of DNA from histone core abolishes the tail-DNA interactions and results in an increased conformational entropy of histone tails. Thus, the energetic barrier arising from the electrostatic interactions can be significantly offset by such entropic contribution from histone tails (enthalpy-entropy compensation) [20*]. The same study suggested that histone modifications may modulate the stability of nucleosomes through fine-tuning of histone tails' entropic contributions to the free energy of nucleosome unwrapping [20*].

Growing evidence demonstrates the functional importance of so-called fuzzy interactions [23] mediated by histone tails when a high conformational heterogeneity of tails can be maintained in the bound state [12**,13**,24*,25]. It has been suggested that such interactions may provide high on- and off-rates, thereby enabling rapid signaling response in

chromatin [24*,25]. Moreover, high conformational flexibility maintained on interaction interfaces minimizes the conformational entropy loss upon tail binding and facilitates the binding of histone modifying enzymes to multiple PTM sites [13**,24*,25]. The following example illustrates how interactions between two disordered regions of chaperone Vps75 and H3 N-terminal tail allow H3 tail to stay in close proximity to the acetyltransferase Rtt109 active site. As a consequence, different H3 acetylation sites, K9, K23 or K27, can be all dynamically exposed to the catalytic pocket with the minimal entropic penalty [13**]. Such mechanism can, in turn, promote the cooperativity between nearby epigenetic marks of different types. Finally, disordered histone tails may promote the formation of complexes, as was observed in the case of H1 C-terminal tail which stays disordered, bridges together and stabilizes the complex between importin7 and importinβ [12**] (Figure 1a).

Disordered histone tails can fold upon binding undergoing so called disorder-order transitions. In such cases, the dynamic intrinsically disordered tails lose entropy, which may result in high specificity recognition even if the binding affinity is rather low. The following roles of disorder-order transitions may be directly connected to histone tails' functions in chromatin signaling. First, disorder-order transitions may maintain the spatial clustering of residues. Recent simulation study showed that N-terminal tail of H1 was completely unstructured in the free unbound state but folded upon binding to nucleosome [26*]. Such disorder-order transition allowed to preserve clustering of basic residues (K14, K17, K20 and K21) and provided concerted positive charges on one face of the formed alpha helix promoting interactions between H1 N-terminal tail and DNA [26*]. Second, disordered tails may adopt different stable conformations upon binding to different partners. This could confer functional promiscuity enabling tails to bind to a wide range of different chromatin factors. Third, disorder-order transitions may modulate and drive the signal transduction by allosteric coupling. Multiple studies pointed to the allosteric regulation of chromatin factors by histone tails [11*,27,28]. One representative example includes an allosteric activation of de novo methyltransferase DNMT3A by H3 tails (Figure 1b). Interactions between ATRX–DNMT3–DNMT3L (ADD) domain and catalytic domain (CD) of DNMT3A cause autoinhibition of its enzymatic activity. The disordered H3 tails can interact with residues located on the ADD-CD binding interface and form an anti-parallel β sheet with the two β-strands in ADD domain, leading to a conformational change of ADD domain, thus inducing the activation of DNMT3A [11*].

The deposition of reversible PTMs and histone variants enhances the functional diversity of histone tails. The distinct patterns of covalent histone modifications form a "histone code" which offers a dynamic way to mediate the regulatory processes in chromatin on the nucleosomal scaffold. IDPs are usually enriched with modification sites and histone tails represent extreme cases with the very high density of PTMs (methylation, acetylation, ubiquitination, phosphorylation, ADP-ribosylation, crotonylation and succinylation), although recent studies point to the importance of PTMs in histone cores as well [29]. The flexibility of histone tails provides relatively easy access to their sites for chromatin factors, modifications in histone tails are recognized by various reader domains, allowing for recruitment of regulatory proteins to nucleosomes [30]. PTMs can orthosterically disrupt the interaction if the modified residue is directly located on binding interface. At the same time, post-translational modifications in tail residues can play roles of covalent allosteric effectors

and modulate binding of histone tails to partners by shifting the IDP's conformational ensembles and/or equilibrium between ordered and disordered states. For example, it was shown that charge-reducing modifications may trigger the disorder-order transitions of H1 tails in solvent and induce the formation of secondary structures [26*].

Histone tails carry multiple PTMs sites that can be modified simultaneously or in sequential time order. Previously we showed for multiple phosphorylation events that they can expand the repertoire of the recognition patterns, provide more accurate modulation of the strength of the signal and lead to cooperative binding effects [31]. All these mechanisms could be attributed to histone tail signaling. For example, it has been shown that H3S28 phosphorylation leads to the recruitment of the HP1 protein to the H3K9 methylated H3-tail since the negative charge of the phosphate group increases the H3-tail dynamics [32**]. At the same time, the enhanced conformational sampling study of H4 tail showed that progressive sequential acetylation had a cumulative effect, decreased conformational heterogeneity, and increased tail's helical propensity [33]. Finally, it was demonstrated that H4K16ac worked cooperatively with the other three acetylated lysines on the same tail to disrupt the chromatin folding: while H4K5ac, H4K8ac and H4K12ac showed little effect on folding, the acetylation of all four lysines on the H4 tail disrupted chromatin folding significantly more than H4K16ac alone [34].

Besides the covalent modifications in histone tails, the deposition of diverse histone variants into nucleosomes brings another layer of regulatory mechanism [35]. Histone variants may have shortened or extended N- and C-terminal tails with altered physico-chemical properties compared to the canonical histones and in some cases (like H3.3 and H2A.X) may carry variant-specific PTMs [36,37]. For instance, H1 variant tails vary in sequence lengths and carry different numbers of charged amino acids and certain sequence motifs, like S/TPKK motifs [38,39]. It may fine-tune the disorder-order transitions upon DNA binding leading to different binding affinity values of H1 variants to nucleosome [26*]. Another Micrococcal nuclease digestion experiment showed that the extended C-terminal tail in H2A.W variant interacted with the linker DNA which increased the stability of nucleosome and affected the binding of linker histone H1 to nucleosome [40*]. Several "short H2A variants" including H2A.B, H2A.L, H2A.P and H2A.Q lack the portions of C-terminal tails and deposition of these variants into a nucleosome leads to unwrapping of DNA ends from the histone octamer and an increase in DNA accessibility [41,42].

Histone tail-DNA interactions modulate nucleosome recognition by chromatin factors

In eukaryotic cells the genetic material is tightly packed into the nucleus but at the same time, in many cases it should remain dynamically accessible during transcription and replication processes. To overcome such challenge, eukaryotic cells have different means to regulate chromatin and DNA accessibility, and intrinsic disorder of histone tails may provide a basis for such dynamic regulation. Histone tails have long been shown to have high conformational flexibility and solvent accessibility, giving an impression that they extend into the solvent and are fully accessible to binding partners. However, a growing pile of

evidence points to the extensive and transient interactions of histone tails with nucleosomal and linker DNA [4**,5,7] (Figure 2a). Recent NMR studies, for example, have shown that interactions of H3 tails with DNA lead to the decreased nucleosomal and linker DNA solvent accessibility [2*,4*,15]. Moreover, the removal of histone tails causes an enhanced binding of many chromatin factors to nucleosome, most likely resulting from the increased solvent accessibility of nucleosomal and linker DNA [17*]. These findings altogether point to the fact that tail-DNA interactions within and between nucleosomes regulate the amount of surface area on histone tails and nucleosomal or linker DNA accessible for binding to other partners. The tail-DNA interactions have been suggested to compete with binding of chromatin factors to histone tails and/or to nucleosomal and linker DNA [4**,15,17*].

Recently a tail displacement model has been proposed according to which the association of one protein or domain with the nucleosomal or linker DNA can potentially displace histone tails from DNA and increase tails' accessibilities to other binding partners [2*,8] (Figure 2a). One recent example supporting this view includes the nucleosome recognition by LSD1-CoREST complex, where the interaction between the SANT2 domain and nucleosomal DNA displaces the H3 tails from DNA and facilitates tails' interactions with the LSD1 active site [2*]. Moreover, PTMs and mutations can directly modulate tail-DNA interactions in the context of nucleosome [5,43] (Figure 2b). Charge-changing modifications, for instance, can affect the binding of histone tails to DNA by perturbating their electrostatic interactions. In concordance with this, recent NMR studies demonstrate that phosphorylation and acetylation in H3 tail can weaken the tail-DNA interactions, enhance the tail dynamics and solvent accessibility thereby facilitating the binding of reader proteins to histone tails [4**,5].

Chromatin signaling by histone tail cleavage

Besides the reversible covalent histone modifications, the structure and dynamics of chromatin can also be regulated by irreversible proteolytic processing of histone tails [44,45] Due to the critical roles of histone tails in chromatin function summarized above, not surprisingly that histone tail cleavage has profound effects on nucleosome dynamics and interactions. It is expected that compared to covalent modifications, clipping of histone tails should lead to more drastic and long lasting changes to chromatin and plays essential roles in gene expression, cell differentiation, aging and cancer development [44,45]. As shown in the previous section, histone tails may interact with the nucleosomal and linker DNA, therefore proteolytic cleavage of histone tails may enhance the DNA accessibility to nucleosome-binding proteins. Moreover, histone tail cleavage may result in irreversible deletion of critical PTM sites and disrupt the inter-nucleosomal interactions affecting chromatin compaction [3,44].

Histone tail cleavage is performed by histone proteases which clip histone tails at particular sites [44,45]. Although histone tail cleavage occurs among all core histones, clipping of H3 tail has been mostly investigated, and a comprehensive list of cleavage sites and their functional relevance has been compiled. For instance, matrix metalloproteinase 9 (MMP-9) primarily cleaves H3K18-Q19 sites in histone H3 N-terminal tail during the osteoclast

differentiation [46] and Jumonji-C (JmjC) domain-containing protein 5 (JMJD5) clips the H3 N-tail at monomethyl-lysine (Kme1) sites in the DNA damage response pathways [47].

Roles of histone tails in the formation of higher order chromatin structures

Histone tails moderate the inter-nucleosomal interactions and induce chromatin compaction as they contain a myriad of basic residues which contribute to the attractive electrostatic interactions between neighboring nucleosomes [48]. Without histone tails nucleosomes cannot self-associate and compact into higher order chromatin structures due to the increased DNA-DNA electrostatic repulsion [49,50**]. It has been revealed that H3, H4 and H1 tails mostly contribute to the cooperative chromatin folding process. Recent cryo-EM structures of nucleosome core particle, biochemical and small-angle X-ray diffraction experiments suggested that the H3 tail participated in the initial contact with the neighboring nucleosomal DNA and made essential contacts between two nucleosomes [51,52]. As for the H4 tails, chemical cross-linking experiments showed that H4 tails from an adjacent nucleosome formed the inter-nucleosomal interactions by docking onto a negatively acidic patch exposed by the core H2A/H2B dimers [53]. Further evidence was provided by another cryo-EM experiments showing the involvement of the H4 and H1 tails in inter-nucleosomal interactions [54,55]. It was, for example, identified that the C-terminal tail of H1.2 was essential for interacting with H3K27me3 to trigger the chromatin compaction and gene silencing in cancer cells [55].

The roles of histone tails in chromatin folding are further aggrandized by PTMs, which can create binding sites for chromatin-associated proteins or directly modulate chromatin fiber dynamics. Of all known histone tail modifications, lysine acetylation is the most widely studied modification in relation to chromatin compaction, whose direct physico-chemical role is believed to neutralize the basic charge of lysine residue. Lysine acetylation results in a reduction of the electrostatic attraction between tails and the negatively charged DNA and thus directly impacts the nucleosome stability and chromatin folding [34]. For example, it has been observed that the acetylation of H4K16 has a negative effect on nucleosome array compaction in vitro and is associated with transcriptionally active chromatin [56]. A subsequent study demonstrated that H4K16ac lead toa more open chromatin in vivo [57]. Studies of H4 tail using molecular dynamics simulations have suggested that the H4K16ac impairs and weakens the H4 tail-acidic patch binding and reduces the inter-nucleosome interaction [3]. However, it should be noted that the outcome of histone tail acetylation depends on histone type and the locations of modified sites, and a recent study using reconstituted nucleosome arrays found that acetylation of H3K18 and H3K27, unlike H4K16ac, had no impact on higher-order chromatin structure [58*].

Conclusions and outlook

Disordered histone tails are essential components in epigenetic regulatory networks. PTMs along with histone variants dramatically enhance the functional diversity of disordered histone tails and enable them to modulate a variety of signaling processes through different molecular mechanisms. The high flexibility of histone tails is necessary for their signaling functions but poses major difficulties in characterizing their dynamics and interactions.

Recent developments in experimental approaches along with the increased computational power and advances in *in silico* simulations using improved water models and forcefields for IDP and DNA have helped to elucidate the mechanisms of histone tails in mediating intra-/inter-nucleosome interactions (Figure 3). Notably, many hybrid methods that integrate experimental data with the molecular modelling have deliverednovel insights into how histone tails modulate nucleosome recognition by partners. However, the functional importance of histone tails merits more extensive studies focusing on their kinetics and dynamics in providing chromatin signaling with high spatio-temporal precision.

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Highlights

- Intrinsic disorder empowers histone tails' diverse roles in chromatin signaling.
- Introducing PTMs and histone variants dramatically enhances the functional diversity of histone tails.
- Interactions of histone tails with nucleosomal and linker DNA modulate the nucleosome recognition by binding partners.
- Histone tail cleavage regulates chromatin structure and function.
- Histone tails play critical roles in the formation of higher-order chromatin structure.

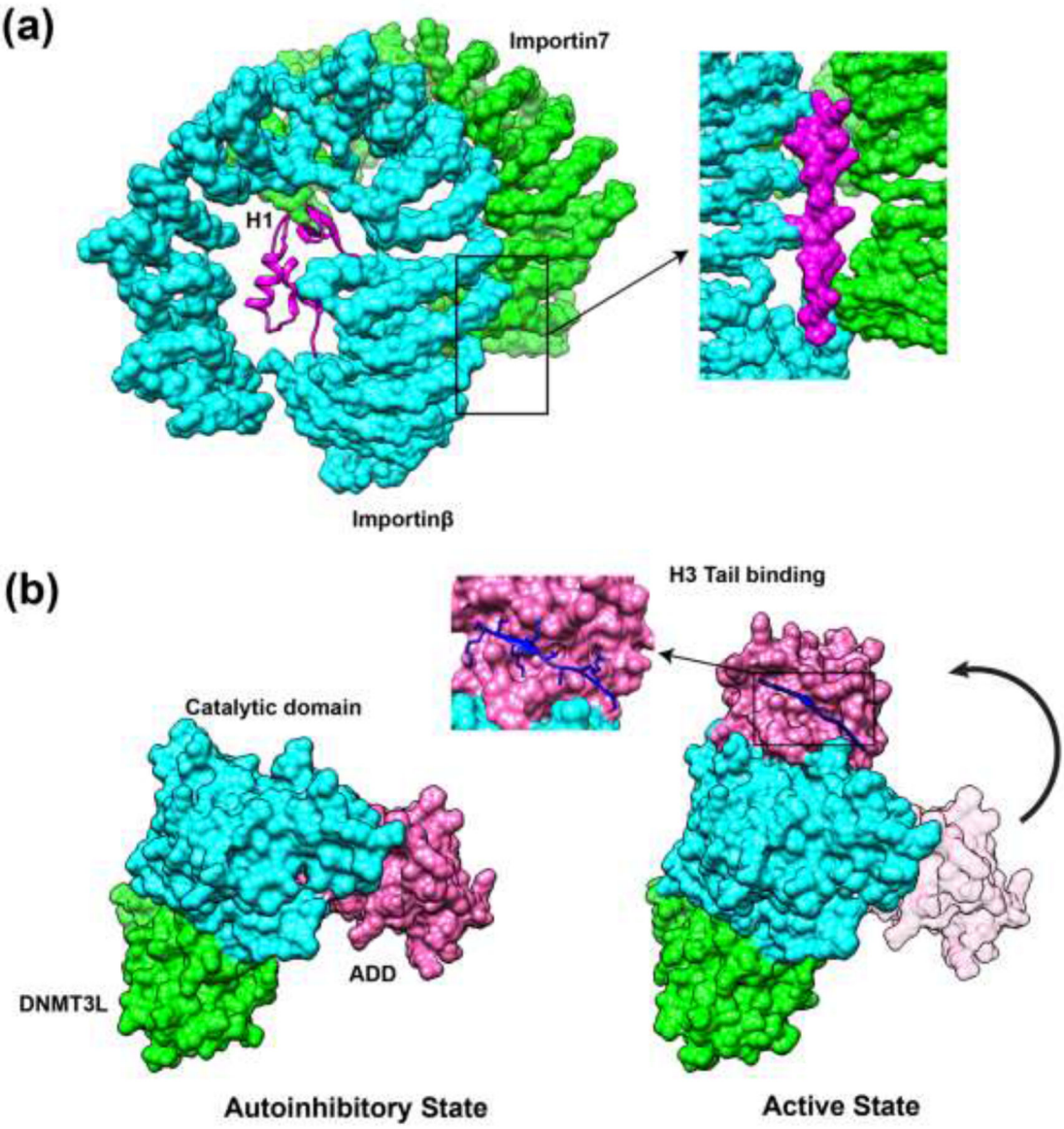

Figure 1.

Intrinsically disordered histone tails perform their functions through different molecular mechanisms. (a) Fuzzy interactions of H1 tails stabilize the importin7-importinβ complex in histone transport (PDB: 6N88). H1 C-terminal domain can bind to acidic residues located near the importin7-importinβ binding interfaces through transient and non-specific electrostatic interactions. (b) Binding of H3 tails to ADD domain of DNMT3A allosterically induces the transition of DNMT3A from autoinhibitory state to the active state (PDB: 4UTP, 4U7T). Molecular surfaces are rendered in magenta (ADD domain of DNMT3A), cyan (catalytic domain of DNMT3A) and green (DNMT3L).

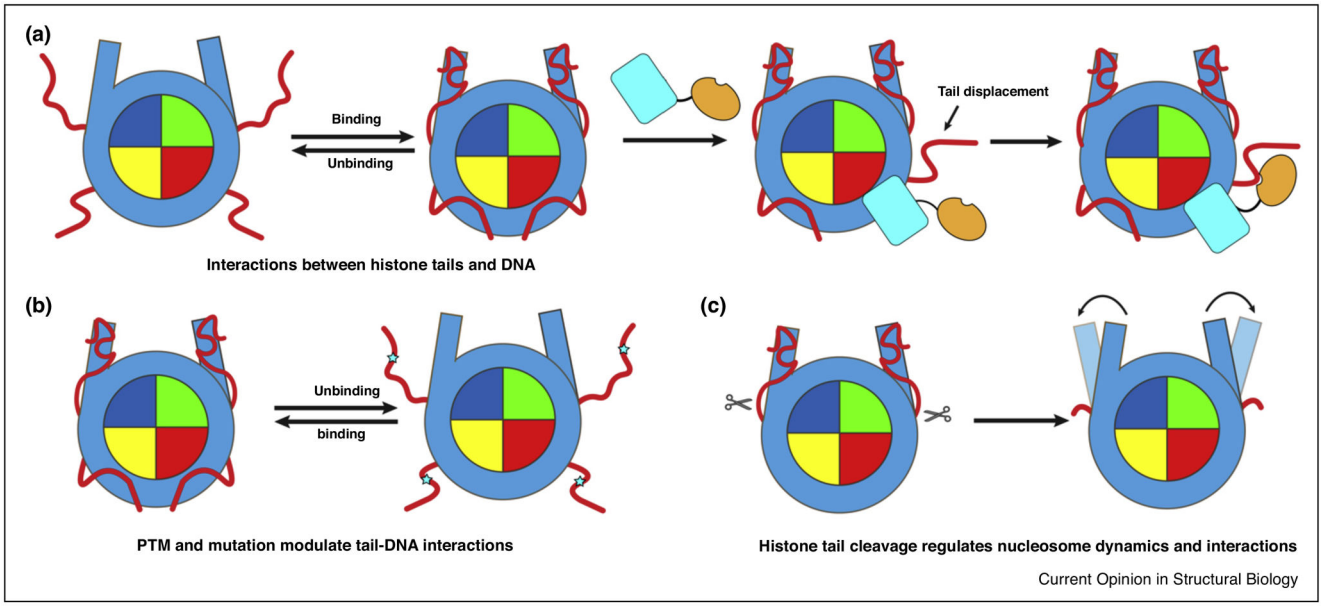

Figure 2.

Mechanisms of regulation of nucleosome dynamics and interactions through histone tails. (a) Extensive and transient tail-DNA interactions in nucleosome and tail displacement mechanism of nucleosome recognition. (b) PTMs and mutations in histone tails modulate tail-DNA interactions and accessibility of DNA and tails in nucleosome. (c) Histone tail cleavage regulates nucleosome dynamics and interactions.

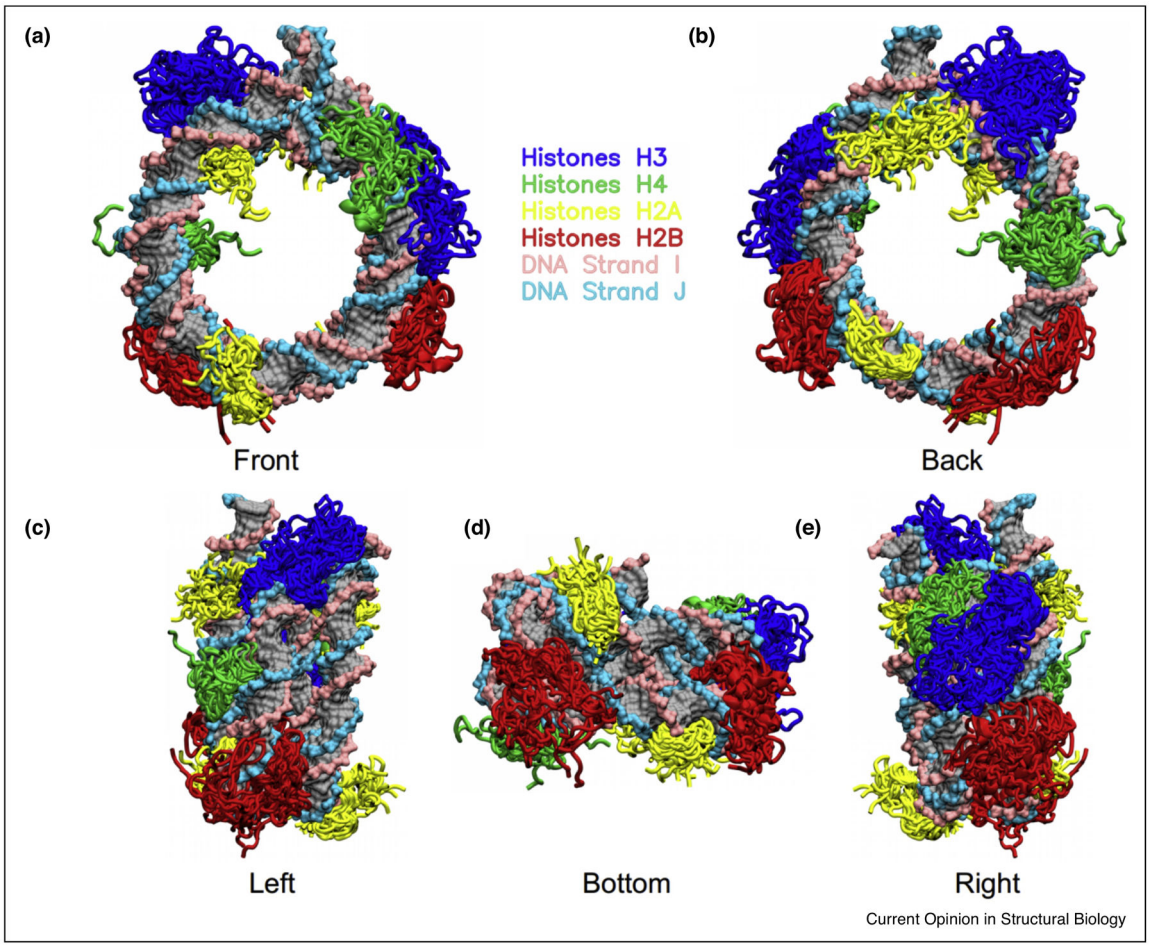

Figure 3.

Representative binding modes between disordered histone tails and nucleosomal DNA observed in molecular dynamics simulations. The cartoon representations of histone core domains are hidden for clarifications.