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Molecular Recognition of Nucleosomes by Binding Partners

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Abstract

Nucleosomes represent the elementary units of chromatin packing and hubs in epigenetic signaling pathways. Across the chromatin and over the lifetime of the eukaryotic cell, nucleosomes experience a broad repertoire of alterations that affect their structure and binding with various chromatin factors. Dynamics of the histone core, nucleosomal and linker DNA, and intrinsic disorder of histone tails add further complexity to the nucleosome interaction landscape. In light of our understanding through the growing number of experimental and computational studies, we review the emerging patterns of molecular recognition of nucleosomes by their binding partners and assess the basic mechanisms of its regulation.

Introduction

Epigenetic signaling complexity can be achieved by the modularity and hierarchical organization of its components. Nucleosomes are the elementary building blocks of chromatin and represent points of coordination between DNA, histones and factors participating in epigenetic regulation. The nucleosome core particle (NCP, for simplicity called “nucleosome”) consists of two copies of four types of histones (H3, H4, H2A, H2B), and ~147 DNA base pairs wrapped around them in ~1.7 negative superhelical turns [1]. Nucleosomes can be affected by changes in histone and DNA sequences, by introducing covalent modifications in histones and DNA, or by the deposition of histone variants. This diverse set of nucleosome alterations may result in differences in nucleosomal structure and dynamics, and lead to the recruitment of specific chromatin components with spatiotemporal precision.

Our understanding of how the specific features of nucleosomes are recognized at the molecular level has been greatly enhanced due to the progress in experimental approaches, such as X-Ray, NMR, Cryo-EM and high-throughput and high-precision techniques, such as ChiP-Exo, DNA footprinting, and SILAC [2–11]. In addition, the hybrid approaches integrating experimental data with molecular modeling and molecular dynamics simulations

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may also provide clues about novel binding interfaces and the dynamic nature of interactions with nucleosomes [12–16]. Some of these experimental and hybrid methods can map binding sites on the nucleosome up to single-nucleotide and single-residue resolution, allowing one to start deciphering the main principles of molecular recognition of nucleosomes by epigenetic factors.

In this brief review, we assess the most recent advances in the field and provide a conceptual summary of up-to-date knowledge about binding modes and recognition motifs which are employed by the nucleosome to elicit highly specific responses upon binding to its partners. We end the review with a remark on the implications of these interactions for higher order chromatin structure.

Binding modes and motifs of the nucleosome core

The rate of deposition of complexes of nucleosomes with different binding partners into the Protein Data Bank (PDB) [17] shows an exponential increase within the last few years (Figure 1). As of writing this review, there are 36 structures of the NCP in complex with other proteins. Nucleosome-binding partners include chromatin factors, pathogen peptides, linker histones and other nucleosomes. Binding of proteins to individual NCP components may be spatially restricted by the nucleosome presence. Nevertheless many proteins can be recruited to the nucleosome by direct or indirect readout of nucleosomal DNA, by features of histone sequence and geometry [11, 18], by histone and DNA covalent modifications, or by a combination thereof (Figure 2). Pioneering transcription factors may bind and recognize distinct nucleosomal features including but not limited to: major and minor DNA grooves, the dyad region, two DNA gyres, nucleosomal DNA ends and periodic patterns on nucleosomal DNA [19, 20]. A typical nucleosome partner can contact multiple NCP components or can read more than one covalent modification to ensure the selectivity of recognition. For example, it was recently shown that the binding of kinetochore protein Mif2/CENP-C to centromeric nucleosomes involves a complex interface composed of DNA- and histone-binding domains harboring the CENP-C motif, an AT-hook, and clusters enriched in arginine and lysine residues [21].

Proteins can exclusively recognize nucleosomes while not interacting with the free DNA, free histones or histone octamers (Figure 2A). ATXR5 monomethyltransferase, for example, preferentially methylates NCPs over histone octamers (i.e., NCP without nucleosomal DNA) ensuring that H3K27me1 is not introduced on free histones and is not erroneously incorporated into active chromatin [3]. For some nucleosome binding partners, on the other hand, nucleosomal context can be preferential, but not an exclusive target. One such interactor is Spt-Ada-Gcn5 acetyltransferase (SAGA) coactivator that binds to monoubiquitinated histone H2B in nucleosomes and at the same time it binds to H2A/H2B dimers that are in complex with the histone chaperone, FACT [22]. This can be explained by the possible involvement of SAGA in the intermediate steps of nucleosomal assembly and disassembly.

Although the importance of non-random nucleosome positioning and its sequence preference has long been debated, the sequence and geometry of nucleosomal DNA can be

vital for modulating the recognition for some protein partners. Shifting the position of DNA in the nucleosome by only one base pair leads to changes in its rotational positioning of around 36°, which can affect the binding of proteins that are recruited by specific DNA motifs. Examples include A-tracts and CpG methylation of nucleosomal DNA. The location of A-tracts with respect to the nucleosomal dyad has been shown to be crucial for directing the binding of proteins of the centromere machinery because these DNA elements are known for their specific properties, such as conformational rigidity and narrow minor grooves [12, 23, 24]. Covalent modifications of nucleosomal DNA can also affect its geometry, affinity and selectivity of NCP binding to other proteins. The methyl-CpG-binding protein MeCP2 and many other proteins may bind to DNA-methylated nucleosomes more favorably than to the free methylated DNA [11]. The affinity of these interactions depends on the locations of methylated CpG dinucleotides on the nucleosomal DNA. In case of methyl-binding domain MBD1, evidence suggests its preference for the methylated CpG of the dyad region facing the histone octamers [25]. It is known that many chromatin and transcription factors may recognize specific DNA sequence motifs on the free DNA. As to their binding to the nucleosomal DNA, it was recently shown that transcription factors can recognize partial or degenerate DNA sequence motifs and this ability correlates with the flexibility of their DNA binding domains [20].

Covalent modifications, especially charge altering modifications, in histones and nucleosomal DNA influence the stability, dynamics, accessibility of DNA, and may mediate or disrupt binding of other proteins [26]. Multiple modifications can be recognized simultaneously such as in the case of 53BP1 that is recruited by both methylation of H4 and ubiquitylation of H2A in response to the DNA double-strand breaks [27]. Computational studies predict that the effects of multiple modifications can be amplified as in the case of the simultaneous acetylation of H4K79 and H3K122 [14]. Modifications can assist the recognition of another modification by altering its accessibility, as in the case for the modifications on H3 tail [15] or can act antagonistically as shown in the following examples. Lysine demethylase Fbxl11/KDM2A binds to H3K9me3-modified nucleosomes via HP1 but this interaction is disrupted by CpG methylation of nucleosomal DNA [11]. In another case, H3K56ac and the exchange of H2A with the H2A.Z variant can antagonistically influence the lifetime of “open” nucleosome conformations that could be implicated in the recruitment of nucleosome-binding proteins [28]. Namely, H3K56 acetylation makes the interface between the $(H3\text{-}H4)_2$ tetramer and the (H2A-H2B) dimer more flexible and shifts the equilibrium to a more open nucleosome state. On the other hand, H2A.Z deposition makes the dimer-tetramer interface less flexible and therefore the closed state dominates [28].

Intrinsic nucleosome dynamics and effects on binding

Nucleosomes are not static and represent the dynamic ensemble of interconverting structural substates. The intrinsic motions of nucleosomes can have implications for their geometry, stability, and solvent exposure, with further consequences for the binding of proteins to nucleosome. These motions include breathing and unwrapping of nucleosomal DNA [28], gaping of gyres [29] and conformational changes within the histone core [30]. The chromatin remodeler Snf2h, for example, illustrates how dynamic properties of the interface between histones H3 and H4 can be important for its function. Snf2h cannot slide DNA

efficiently when these two histones are covalently crosslinked to each other and their dynamics is restrained [30]. Rearrangements in the H2A-H2B dimer within a nucleosome are also necessary to maintain interactions with the unwrapping DNA upon DNA breathing motions [31]. The analysis of intrinsic nucleosome dynamics may help to understand the mechanisms by which nucleosomes partially or completely disassemble. It is especially important since partially (dis)assembled nucleosome states, observed in several experimental and computational studies [13], may represent the means to regulate the nucleosomal DNA accessibility for DNA binding partners [32].

Binding of proteins to the nucleosome can be accompanied by substantial conformational changes in the histone octamer and DNA; it can unlock novel interfaces that are otherwise buried in the nucleosome in its canonical form. Dot1L, for example, binds to nucleosomes ubiquitinated at H2B K120, and with the help of H4 tail induces an H3 conformational change such that the core residue H3 K79 becomes accessible for methylation [33]. In another case, ANP32E-ZID binding drives a conformational change in the H2A.Z αC helix such that it becomes extended twice as long compared to its counterpart in the canonical nucleosome [34]. Nucleosome binding of the Mid domain of histone chaperone FACT induces conformational changes that lead to the disruption of the H3 αN helix holding the nucleosomal DNA ends together and cause DNA unwrapping from histones [35]. Several recent Cryo-EM structures reveal that interactions between nucleosomes and chromatin remodelers are accompanied by distortions in the nucleosomal DNA, such as formation of bulges [5] and widening of the gap between the two gyres [36].

Nucleosome recognition involving intrinsic protein disorder

Nearly a quarter of NCP histone sequence and more than half of linker histone H1 sequence are intrinsically disordered [37]. Perhaps not surprisingly, disorder is equally prevalent among nucleosome interactors. The disordered regions can explore a broad ensemble of conformations according to the “fly-casting” model, speeding up the search process in a manner reminiscent of the dimensionality reduction mechanism [38]. The intrinsic disorder allows for high specificity and low affinity interactions as is the case in many signaling processes [39, 40]. Binding can either maintain disorder or it can be accompanied by a disorder-to-order transition depending on whether the stable, short-range interactions can energetically compensate for the loss in conformational entropy. For example, high mobility group nucleosome (HMGN) binding proteins maintain their disordered state even when bound to nucleosomes. These proteins regulate chromatin structure through either directly interfering with the binding of linker histone H1 to the nucleosome [4] or by altering the condensation of the disordered H1 C-terminal domain and the interactions of the histone tails with nucleosomal DNA [41]. Figure 3 illustrates examples of recent structures of nucleosome-remodeler complexes and shows how histone tails may recognize acidic patches of binding partners. The disordered histone tails do not only provide sites for binding and PTMs, but also regulate the amount of surface area on the nucleosome accessible for binding other partners. For example, H3 N-terminal tails play especially crucial roles in this process because they can bind to linker DNA and modulate its accessibility for binding of H1, HMGN and effector proteins [15, 42–45].

Mechanisms of formation of higher order chromatin structure

The molecular basis for the transformation of open arrangements of neighboring nucleosomes into compact chromatin fiber structures continues to be an active area of research. The acidic patch, spanned by H2A and H2B residues exposed at the histone core, is a binding region for many binding partners including those responsible for the formation of higher order chromatin structure [4, 46, 47]. The acidic patch is commonly recognized by the “arginine anchors” of binding partners and can be modified by introducing histone variants. H2A.Z variants have additional negatively charged residues in the acidic patch that increase the compaction of nucleosome arrays whereas the H2A.B variant lacks some of the acidic patch residues [48, 49], resulting in a decrease in chromatin compaction. These variations in the acidic patch are specifically recognized by several binding partners including ISWI-family chromatin remodeling enzymes [50]. Another important regulator of chromatin compaction is the H4 N-terminal tail, in particular a small basic patch, whose deletion or modifications disrupt the condensation of chromatin [51]. Crystal-packing interactions between the acidic patch and the H4 tail of the neighboring nucleosomes were observed in early nucleosome studies [1], later also in a twisted tetranucleosomal structure [52], and more recently in the structure of a hexanucleosomal array forming a low-packing density chromatin fiber [53]. Interestingly, not only tail-core interactions, but also histone tail-tail interactions are important in chromatin fiber folding, and this process is highly regulated by tail acetylation [16, 54].

Linker histone H1 facilitates the formation of a compact arrangement of linker DNA strands [55, 56] and is an important hub in maintaining an extensive interaction network with many different partners [57]. Recent structures of linker histones bound to nucleosomes resolved the central, folded globular domain in contact with the dyad as well as with both DNA linker strands [58, 59]. These structures differ from prior, off-dyad models [52, 60], possibly due to a small number of key interfacial residues that vary between different species and histone variants as well as differences in the experimental setups and the heterogeneous nature of linker histone binding. Computational studies suggested that the alternative binding modes of the globular domain could be due to its conformational plasticity [61]. Even more puzzling remains the disordered C-terminal tail of H1 histone which leaves a distinct, ordered protection pattern on linker DNA when treated with hydroxyl radical footprinting [55]. In solution, the H1 C-terminal tail can form complexes with DNA, and the properties of its condensate depend on the phosphorylation level of the tail, a cell-cycle-dependent modification that correlates with the degree of chromatin compaction [62]. In addition, several studies pointed out the importance of salt concentration in regulating chromatin compaction [53, 63], however the molecular details of the transitions between different chromatin states remain to be elucidated.

Conclusions and Outlook

Chromatin is highly dynamic and interactions between its components occur on different time scales spanning several orders of magnitude. How the nucleosome is recognized by a multitude of diverse interactors and how this binding is controlled in time and space still remains ambiguous. However, the rapid development of experimental and computational

techniques of high temporal and spatial precision permits a gain of more data about structure, binding kinetics and thermodynamics of different proteins to the nucleosome, including the dynamic crosstalk between histone and DNA modifications, and histone variants. The critical analysis and interpretation of this data should ultimately lead to a better conceptual understanding of how epigenetic signals can be integrated at the level of nucleosomes leading to signal amplification, enhanced response sensitivity and specificity.

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Abbreviations

NCP	nucleosome core particle
PTM	posttranslational modification
PDB	Protein Data Bank

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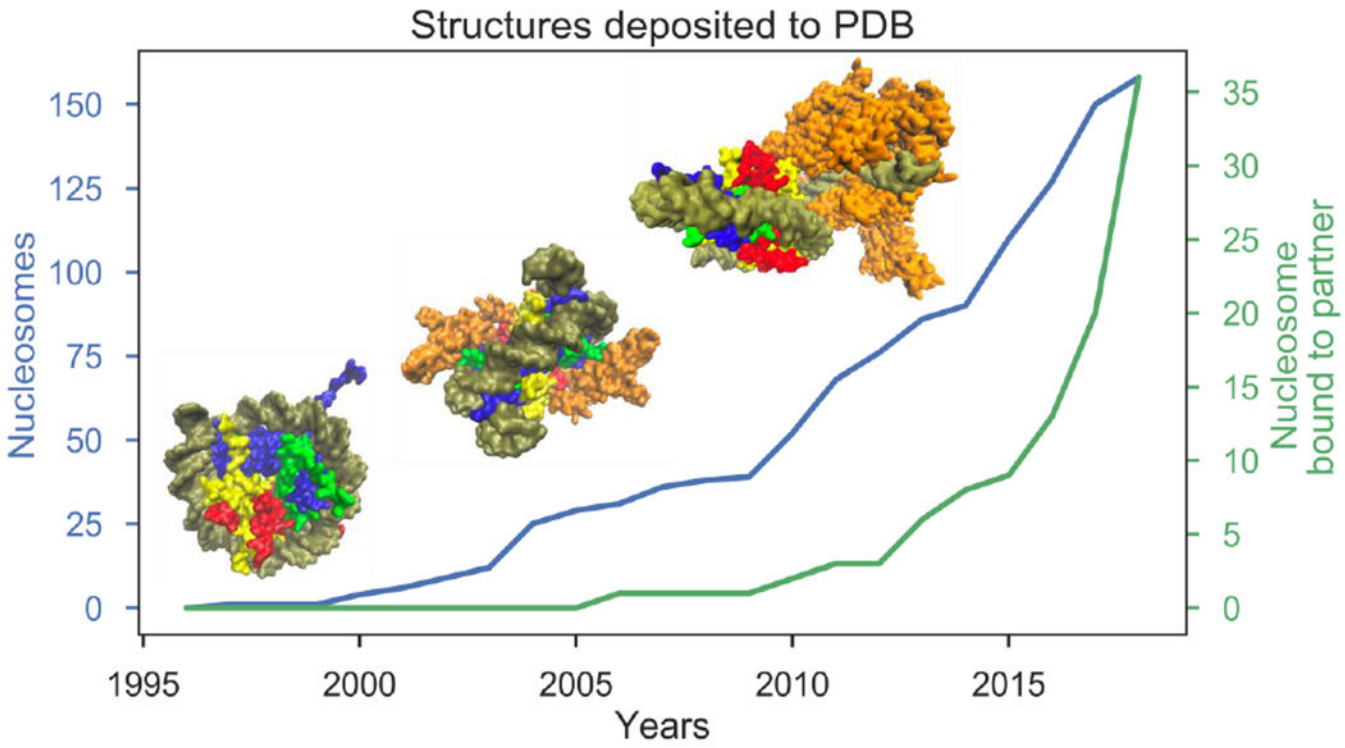

Figure 1. Growth trends in the number of nucleosome structures.

Blue graph shows the cumulative number of NCP structures in the PDB while the green graph shows the structures of the NCP in complex with a protein or peptide. From left to right, insets illustrate the first nucleosome crystal structure (1AOI, [1]), Sir3 BAH domain bound to yeast nucleosome (3TU4, [64]) and RNA Polymerase II elongation complex stalled at nucleosomal DNA SHL-2 (6A5R, [65]).

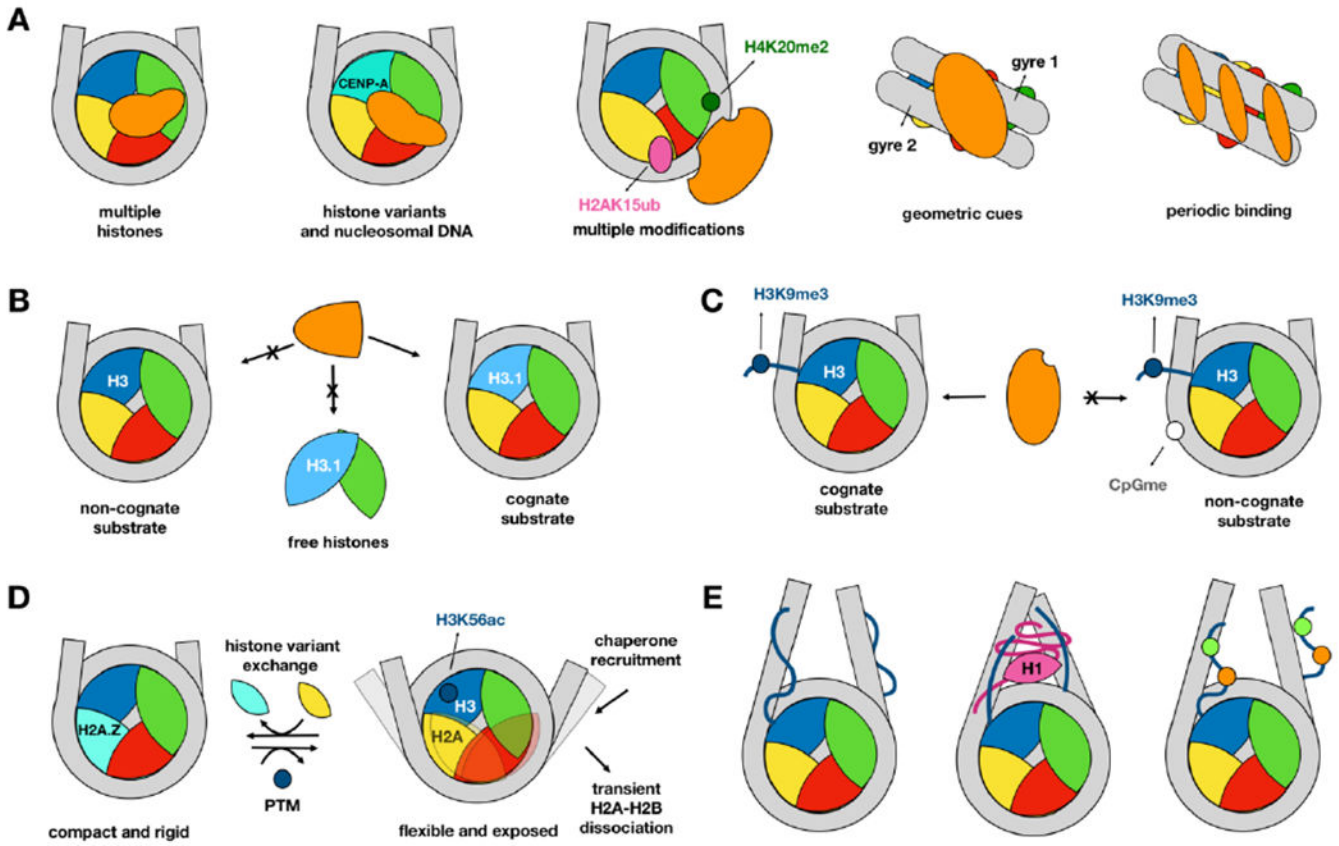

Figure 2. Features of the nucleosomal recognition.

Nucleosome binding partners are shown in orange and specific examples are given in parentheses. **A.** Multivalent recognition of the nucleosome (from left to right): through multiple histones (Sir3 BAH domain, [64]), via specific histone variants and nucleosomal DNA (CENP-N bound to centromeric nucleosome [66]), through multiple modifications (53BP1, [27]), multiple geometric cues or periodic patterns (transcription factors [19]). **B.** A binding partner recognizes variant nucleosome and does not recognize canonical nucleosome or free histones (ATXR5, [3]). **C.** Multiple modifications can antagonistically influence the recognition by binding partner (Fdxl11/KDM2A, [11]). **D.** Multiple modifications and histone variants can have opposing effects on nucleosome dynamics with consequences for recognition ([28]). **E.** Competitive binding between core histone tails, H1, linker DNA and histone modifications ([45]).

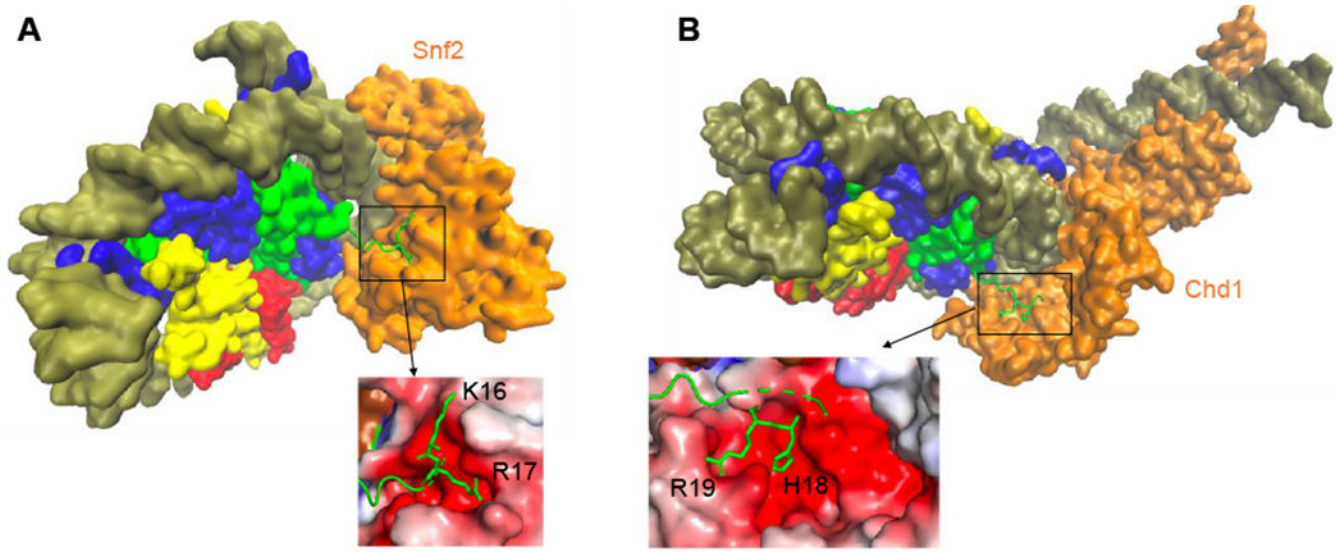

Figure 3. Interactions between the basic patch within the histone H4 tail and acidic binding pockets of chromatin remodelers.

A. Snf2 (5X0Y [5]), **B.** Chd1 (5O9G [6]). Molecular surfaces are rendered in orange (Snf2 or Chd1), blue (H3), green (H4), yellow (H2A), red (H2B), and brown (DNA), respectively. Insets show the electrostatic potential mapped of the remodelers' molecular surfaces. H4 sidechains on the binding interface are labeled.