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Mechanistic similarities in recognition of histone tails and DNA by epigenetic readers

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Abstract

The past two decades have witnessed rapid advances in the identification and characterization of epigenetic readers, capable of recognizing or reading posttranslational modifications in histones. More recently, a new set of readers with the ability to interact with the nucleosome through concomitant binding to histones and DNA has emerged. In this review, we discuss mechanistic insights underlying bivalent histone and DNA recognition by newly characterized readers and highlight the importance of binding to DNA for their association with chromatin.

Keywords

reader; PTM; histone; DNA; chromatin

Introduction

In eukaryotic cells, the genomic material is tightly packaged in the nucleus, forming a protein-DNA complex named chromatin. The fundamental unit of chromatin, the nucleosome or nucleosome core particle (NCP), consists of an octamer of four histone proteins (H2A, H2B, H3, H4) around which the double stranded DNA wraps almost twice [1]. NCPs are further compacted into the higher-order chromatin structures, including chromatin fiber, self-associating domains and loops, and ultimately chromosomes. Despite the high level of compaction, the chromatin structure is dynamic, allowing for DNA to be readily accessible when needed and recruit chromatin-modifying and chromatin-remodeling complexes to facilitate the DNA-templated processes, such as DNA damage repair, transcription, replication and recombination. The chromatin structure, dynamics and DNA accessibility are modulated by covalent epigenetic modifications found in DNA and histones. While DNA can be methylated or hydroxymethylated on cytosine, histones

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Conflict of Interest

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undergo a wide array of posttranslational modifications (PTMs). These include methylation, acylation and ubiquitination of lysine residues, methylation and citrullination of arginine residues, and phosphorylation of serine and threonine residues. The nature and position of the modified residue is essential and often correlates with a particular chromatin state. For instance, acetylation of lysine is generally associated with open chromatin and active gene transcription, whereas methylation of lysine could lead to either activation or repression of transcription. In addition to altering direct electrostatic contacts between DNA and histones within the nucleosome, either destabilizing or stabilizing the nucleosome, histone PTMs are recognized or 'read' by protein domains termed readers [2–4].

Over the past decade, a considerable effort was put forward to identify histone PTMs and combinations of these modifications and characterize their cognate readers. Binding of readers to histone PTMs helps recruiting and stabilizing various chromatin remodeling complexes and transcription factors at specific chromatin sites [5–9]. Chromatin-associating proteins often contain multiple copies of readers specific for different PTMs as well as DNA-binding modules which together ensure proper localization of these proteins and thus a proper biological response. A set of epigenetic readers has recently been found to recognize not only histone PTMs but also DNA [10–15]. The bivalent engagement of readers enhances their binding affinity to the nucleosome and can also augment their selectivity if the reader recognizes specific PTM and DNA sequences.

The first examples of readers capable of simultaneous binding to histone PTMs and DNA, such as chromodomains of MSL3 [10] and Chp1 [11], the PWWP domains of Pdp1 [12] and PSIP1/LEDGF [13,14], and the Tudor domain of PHF1 [15], were reported ten years ago. Since then, the list of readers with the dual histone/DNA binding activity has grown fast and now includes bromodomains of BRDT [16], BRM and BRG1 [17], the CW domain of MORC4 [18], the DPF domain of MORF [19], the PZP domain of BRPF1 [20,21] and the YEATS domain of AF9 [22]. We refer to the detailed overview of well-characterized readers by Weaver et al. [23], and in this report highlight mechanistic insights underlying bivalent histone/DNA recognition by new members of this set of epigenetic readers.

Bromodomain

Bromodomain (BD) was the first reader discovered in 1999 [24]. BDs of many proteins, although not all, bind acetylated lysine (acetyllysine) containing sequences, including acetylated histones, most of the time weakly and promiscuously. A few BDs however show selectivity for acetylated sites in histones that arises from the interactions involving adjacent to acetyllysine histone residues [25]. Despite little sequence similarity, all BDs share the same structure, consisting of four a-helices arranged into a bundle (Fig. 1a). A deep hydrophobic cavity formed between the helices serves as a binding site for acetyllysine, which is restrained through a hydrogen bond with a highly conserved asparagine of BD and a water-mediated hydrogen bond with tyrosine.

Recently, Miller et al. characterized the association of a tandem of BDs in BRDT and other BET proteins with acetylated on histone H4 and H3 (H4K5ac/K8ac and H3K18ac/K23ac) nucleosomes [16]. Miller et al. found that despite both BDs of BRDT bind to

the acetylated histone tail peptides, in the context of acetylated NCP, only the first BD (BD1) shows binding to the nucleosome, whereas the second BD (BD2) does not bind. Histone tails within the nucleosome are known to be less available to readers as they are involved in electrostatic interactions with DNA [26], therefore it is plausible that the weak association of BD2 with acetylated NCP becomes undetectable. In contrast, binding affinity of BD1 toward the acetylated nucleosome is increased ~6-fold compared to its affinity toward the acetylated peptide owing to the additional non-specific interaction of BD1 with nucleosomal DNA. NMR experiments identified a basic patch on the surface of BD1 which is perturbed upon binding of DNA and likely represents the DNA-binding site of BD1 (Fig. 1a). The acetyllysine-binding site and the DNA-binding site of BD1 do not overlap, indicating that BD1 can simultaneously bind both ligands within the nucleosome, and such bivalent engagement would enhance binding affinity of BD1. Mutation of the DNA-binding site residues in BD1 of BRDT leads to a decrease in the association of overexpressed BRDT with chromatin in cells, suggesting that the DNA binding function of BD1 is essential for subcellular localization of this protein. In addition to BD1 of BRDT, some BDs of other BET family members and BDs from BRM and BRG1 were found to have similar dual histone/DNA binding activity, implying that the bivalent binding mechanism is conserved in a subset of BDs [16,27].

CW domain

The CW (four cysteine residues and two tryptophan residues) domain folds into a double-stranded antiparallel β-sheet and a 3_{10}-helical turn connected by a single zinc-binding cluster of four cysteines [18,28–31]. This reader binds histone H3 tail, selecting for methylated lysine 4 of histone H3 (H3K4me) [28,29,32]. In the complex, the H3K4me3 tail occupies the acidic groove of CW and pairs with the β-sheet of the protein forming the third antiparallel β-strand. The CW domain of the MORC4 ATPase has been shown to interact with H3K4me3 and the adjacent ATPase domain through the same elongated acidic binding groove [18]. Electrostatic surface potential of the MORC4 CW domain reveals that the side of this domain, which is opposite to the H3K4me3/ATPase-binding site, is highly positively charged (Fig. 1b). This observation suggested that in addition to forming the complex with H3K4me3 or ATPase, the CW domain can simultaneously be engaged with the negatively charged DNA. Indeed, EMSA experiments and mutagenesis studies confirmed that the MORC4 CW domain has the DNA-binding function, which plays a role in promoting the catalytic activity of the MORC4 ATPase as well as binding of CW to H3K4me3 [18]. Furthermore, binding of the MORC4 ATPaseCW cassette to the nucleosome enhances the nucleosome stability and impedes interactions of DNA-binding proteins, such as transcription factors and co-activators.

DPF domain

The double PHD finger (DPF) domain has been shown to recognize histone H3 tail acylated at lysine 14 (H3K14acyl) [33–37]. DPF adopts a bean-shaped double zinc finger fold with a well-defined groove that accommodates 15 N-terminal residues of H3K14acyl. Upon binding, residues K4-T11 of H3K14acyl form an a-helix and acylated K14 inserts into a hydrophobic cavity of DPF (Fig. 1c). The DPF domain of the histone acetyltransferase

(HAT) MORF has the ability to bind both H3K14acyl and DNA [19]. The histone and DNA binding sites of DPF are in close proximity which provides a fine-tuned balance of electrostatic contacts with the nucleosome (Fig. 1c). Notably, while both interactions of DPF with DNA and histone are essential for binding this reader to the H3K14acyl-nucleosome, interaction with DNA contributes greater [19]. The DPF mutant with impaired histone binding activity causes a moderate decrease in binding to the nucleosome, whereas the mutant defective in DNA binding is unable to associate with the nucleosome.

PZP domain

Structural studies of the PZP (PHD-zinc-knuckle-PHD) domain of BRPF1, a core component of the acetyltransferase MOZ/MORF complex, show that this module contains two integrated PHD fingers linked by a zinc finger [20,21]. While the first PHD finger (PHD1) binds to unmodified histone H3 tail, the second PHD finger (PHD2) associates with DNA [20] (Fig. 1d). Interestingly, the isolated PHD1 and PHD2 fingers of the homologous protein BRPF2 have been shown to retain their binding functions [38–40]. The PZP domain of BRPF1 prefers nucleosomes containing extra-nucleosomal linker DNA, and two molecules of PZP can bind to the single NCP [20]. Simultaneous contacts of PZP with H3 and DNA within the nucleosome impacts the NCP dynamics. The bivalent engagement shifts the DNA unwrapping/rewrapping equilibrium of the nucleosome toward a more open conformation and thus increases DNA accessibility within the nucleosome to transcription factors. This finding suggests that functionally active PZP of BRPF1 might be important in stabilization of the MOZ/MORF complex at chromatin with accessible DNA, such as euchromatin. In vitro and in cell experiments with mutants defective in binding to H3 or DNA show that although bipartite H3/DNA interaction of the PZP domain is required for tight binding to the nucleosome and for acetylation of the nucleosome by the MOZ/MORF HAT complex, interaction with extra-nucleosomal DNA predominates [21].

YEATS domain

The YEATS (Yaf9-ENL-AF9-Taf14-Sas5) domain is an evolutionarily conserved module found in yeast and human proteins. The YEATS domains are highly selective for acylated H3K9 (H3K9acyl) or acylated H3K27 (H3K27acyl) and this selectivity mediates diverse and non-redundant functions of the YEATS domain-containing proteins [41–48]. The YEATS domain adopts a canonical immunoglobin β-sandwich structure, consisting of eight β-strands connected by variable loops and capped with a short α-helix at one of the open ends of the β-sandwich (Fig. 1e). The loops at the opposite end of the β-sandwich create the acetyllysine binding site. The bound histone H3K9/27acyl tail lays perpendicular to the β-strands allowing the acetyllysine side chain to insert between two aromatic residues of the YEATS domain and be constrained through a set of hydrogen bonds. Structural and biochemical studies show that the YEATS domain of AF9 is capable of binding to DNA [22]. This reader contains several patches of positively charged residues in one of the β-sheets and near the α-helix, which could contact DNA, and it also prefers a more accessible, free DNA to the DNA wrapped around the nucleosome. Although YEATS domains of other human proteins have not been experimentally tested, a high conservation of

the DNA binding residues suggests that the bivalent histone/DNA binding function is likely conserved at least in the YEATS domain of ENL.

Concluding remarks

A large number of epigenetic readers has been identified in the past two decades. Selective binding of a reader to a histone PTM or combinatorial readout of multiple PTMs by a set of readers, which are present in the host protein or its cognate complex, provide a mechanism for targeting and/or stabilization of the protein/complex at particular genomic sites and for producing precise biological responses. Since epigenetic readers bind histones within the nucleosome, it is not entirely surprising that some readers also bind DNA. This is particularly evident when the PWWP domain or the Tudor domain bind H3K36me3 positioned right between two gyres of DNA, so contact of these readers with DNA is unavoidable. The cryo-EM structure of the LEDGF PWWP domain bound to the nucleosome containing a methyllysine analogue mimicking H3K36me3 confirmed the bivalent interaction with the methylated histone tail and both gyres of nucleosomal DNA [49]. The dual engagement increases affinity of these readers due to the avidity effect and can also enhance specificity. For instance, binding of the PWWP domain of PSIP1/LEDGF to DNA enhances a very weak (~2–3 mM-range) association of this reader with histone H3K36me3 four orders of magnitude [13,14], whereas a relatively weak DNA binding of bromodomain, Tudor and YEATS augments association with NCPs by a few fold [15,16,50]. The examples of readers discussed in this work further demonstrate that relative contribution of the contacts with histones and DNA vary substantially. The DNA binding function could be critical for tight association of readers with chromatin as histone tails are not easily accessible within the nucleosome [23]. The intra-nucleosomal interaction between H3 tail and DNA reduces the accessibility of unmodified H3 tails compared to free H3 peptides by up to a factor of ~10 in physiologically relevant conditions [26]. The DNA binding activity of readers can also facilitate the accessibility of the histone tails by impeding the intra-nucleosomal DNA-histone tail contacts. We expect that the set of readers capable of simultaneous binding to histones and DNA will be further expanded and more readers will be discovered for which binding to DNA is critical in their functions.

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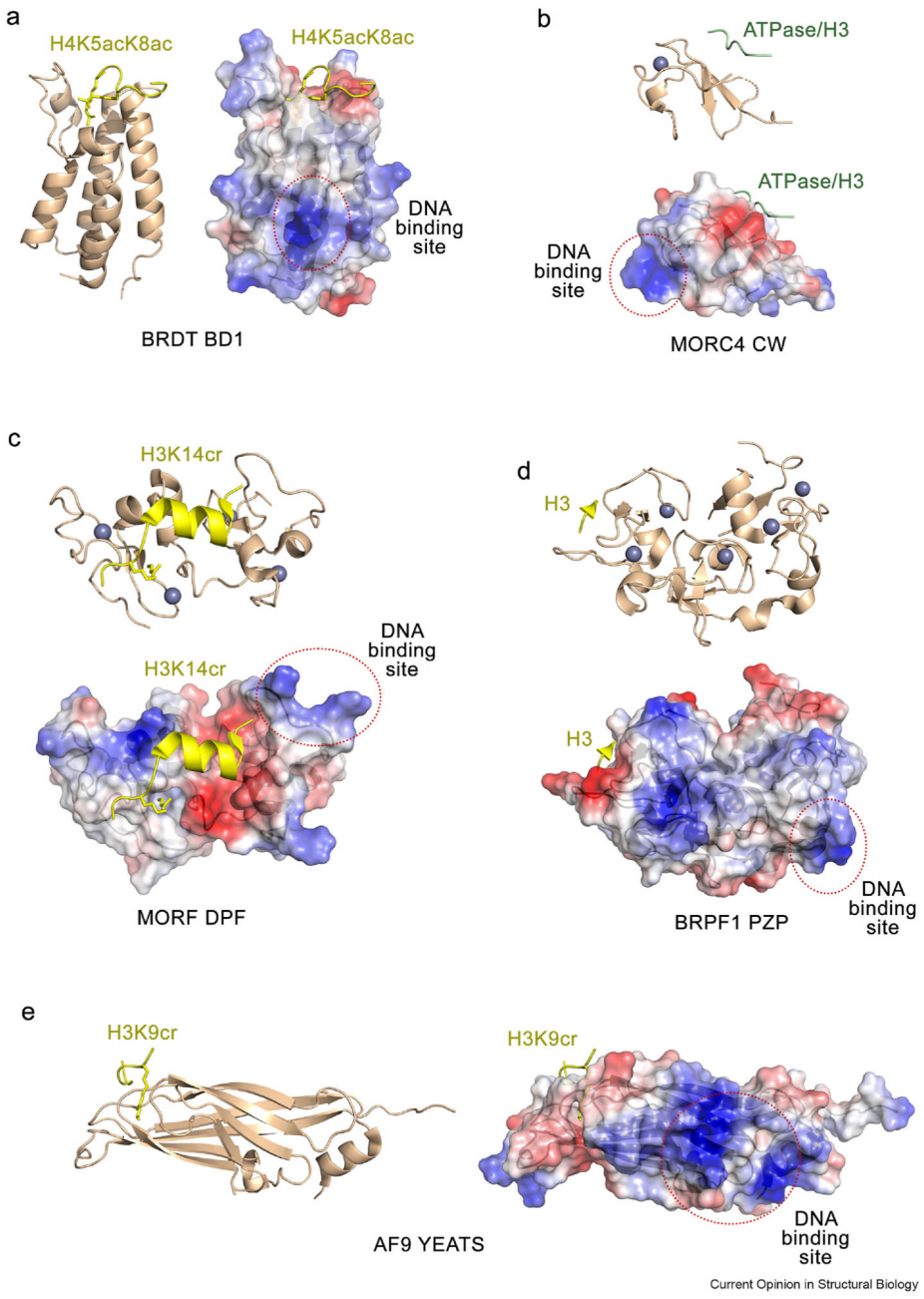

Figure 1:

Molecular basis for the bivalent histone/DNA engagement of epigenetic readers with the nucleosome. Ribbon diagram and surface representations of (a) BD of BRDT (PDB 2WP2), (b) the CW domain of MORC4 (PDB 7K7T), (c) the DPF domain of MORF (PDB 6OIE), (d) the PZP domain of BRPF1 (PDB 6U04) and (e) the YEATS domain of AF9 (PDB 5HJB) in complex with indicated ligands. Electrostatic surface potential of each reader is shown with blue and red colors representing positive and negative charges, respectively. Bound histone peptides and a loop of the ATPase domain (for CW) are shown as yellow

and green ribbons, and zinc ions are shown as grey spheres. DNA binding sites, mapped by mutagenesis, EMSA and NMR, are indicated by red dotted ovals.