

Chapter 2

PHD Fingers as Histone Readers

Jovylyn Gatchalian and Tatiana G. Kutateladze

Abstract The plant homeodomain (PHD) finger is found in proteins implicated in fundamental biological processes, including transcription, replication, DNA damage repair, cell differentiation and survival. This small double-zinc-finger domain functions as an epigenetic effector or reader that binds to posttranslationally modified and unmodified histone H3 tails and recruits transcription factors, catalytic writers and erasers, nucleosome-remodeling complexes, and other components of the epigenetic machinery to specific genomic sites. In this chapter, we review the chromatin-binding mechanisms and biological outcomes associated with binding of the PHD fingers to histone ligands and discuss the structural bases for selectivity of this reader toward histone PTMs.

2.1 Introduction

The plant homeodomain (PHD) finger was discovered in the *Arabidopsis* protein HAT3.1 in 1993 (Schindler et al. 1993) and has since been found in a variety of proteins implicated in the regulation of chromatin structure and dynamics. The PHD finger is evolutionarily conserved and is present either as a single module or in multiple copies in 218 human proteins (SMART). The ~65-residue cysteine-rich sequence of the PHD finger binds two zinc ions in a cross-braced manner. Although similar zinc-coordinating topology is seen in other double zinc fingers, including RING, FYVE, and MYND domains, the PHD finger can be distinguished by its canonical C4HC3 motif (and less common C4HC2H), as compared to the C3HC4 motif of RING, C5C/HC2 of FYVE, and C/HC4C/HHC of MYND. The primary sequences of the PHD fingers show low amino acid similarity;

J. Gatchalian · T.G. Kutateladze (✉)

Department of Pharmacology, University of Colorado School of Medicine,
Aurora, CO 80045, USA

e-mail: Tatiana.Kutateladze@ucdenver.edu

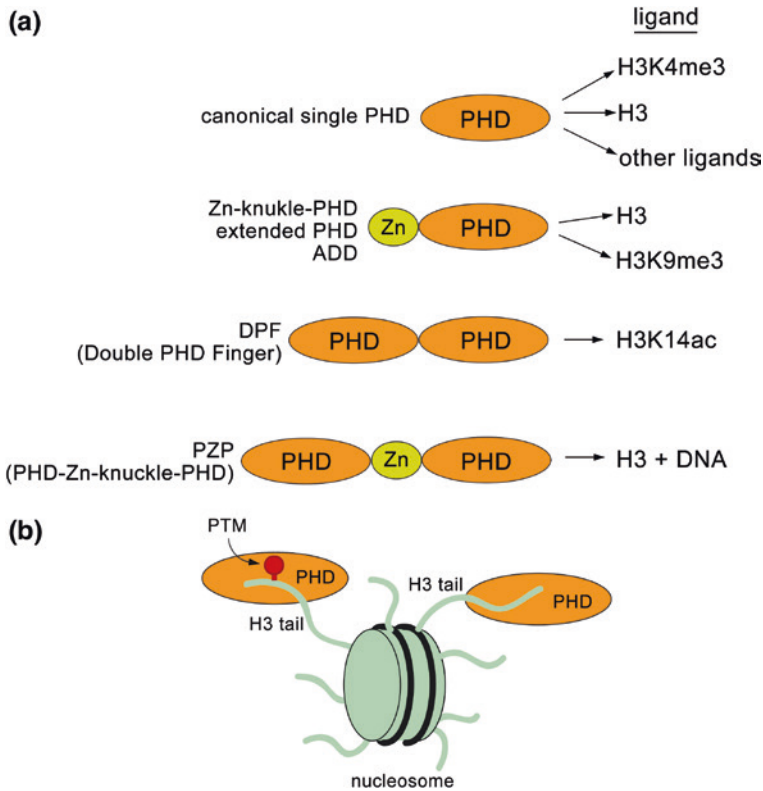


Fig. 2.1 Diverse functions and topologies of PHD fingers. **a** Shown are a canonical single PHD finger, as well as the PHD fingers adjacent to a zinc knuckle, to another PHD finger (forming the DPF domain), or to PHD–Zn knuckle (forming the PZP domain). Binding partners of the PHD fingers are indicated. **b** A model for the recognition of posttranslationally modified or unmodified histone H3 tails by the PHD fingers

however, they fold into a highly conserved globular structure, originally characterized in 2000 (Pascual et al. 2000). The typical PHD domain consists of a short double-stranded antiparallel β sheet, one or two small α helices, and several variable-length loops connecting the zinc-binding clusters.

A number of studies in the past few years reveal diverse biological roles of the PHD fingers. They recognize unmodified and modified histone H3 tails, interact with non-histone proteins, and associate with DNA (reviewed in Musselman and Kutateladze 2009, 2011; Sanchez and Zhou 2011) (Fig. 2.1). Some proteins contain only one canonical PHD finger, but some harbor several PHD fingers that act in concert or have independent functions. The PHD finger can be linked to a zinc knuckle, a zinc finger that coordinates one zinc ion and is characterized by either C4 or C2HC sequence (Fig. 2.1a). The closely coupled tandem PHD fingers create a distinct fold, the double PHD finger (DPF), whereas two PHD fingers connected by a zinc knuckle are assembled into the PZP (PHD–zinc knuckle–PHD) domain.

The various combinations of coupled modules greatly influence the overall function and dynamics of the PHD finger. The biological activity of the PHD finger can be further altered through the action of adjacent domains, such as histone readers (bromodomain (BD), chromodomain (CD), Tudor, etc.) or catalytic PTM (postranslational modification) writers, and erasers [reviewed in the Chap. 7 of this book].

In this chapter, we discuss the molecular mechanisms and biological consequences of chromatin targeting by the PHD fingers and analyze the structural basis for the selectivity of this epigenetic reader toward histone PTMs.

2.2 General Functions of PHD Fingers

2.2.1 Subsets of PHD Fingers

The biological function of the PHD finger was uncovered thirteen years after the initial isolation and characterization of this module. In 2006, the PHD fingers of BPTF and ING2 were found to recognize trimethylated lysine 4 of histone H3 (H3K4me3) (Li et al. 2006; Peña et al. 2006; Shi et al. 2006; Wysocka et al. 2006). The PHD fingers of numerous proteins have since been shown to bind H3K4me3 with high specificity and affinity. Together the readers of H3K4me3 comprise one of the well-established subsets of PHD fingers, and epigenetic readers in general, that are highly specific for a particular PTM (Table 2.1). The second major subset, exemplified by the PHD fingers of BHC80 and DNMT3L, binds to unmodified histone H3 tail (Lan et al. 2007; Ooi et al. 2007).

Table 2.1 Specificities of the PHD fingers for modified and unmodified H3

Histone ligand	PHD finger protein	Chromatin function (host complex)	References
H3K4me3	BPTF	Chromatin remodeling, transcription (NURF)	Li et al. (2006), Ruthenburg et al. (2011), Wysocka et al. (2006)
	Bye1 (S.c.)	Transcription	Kinkelin et al. (2013), Shi et al. (2007)
	Cti6 (S.c.)	(Rpd3/HDAC)	Shi et al. (2007)
	Dido	Transcription	Gatchalian et al. (2013)
	ING1	Transcription, cell cycle regulation, DNA repair (mSin3a/HDAC)	Peña et al. (2006, 2008)
	ING2	Transcription, cell cycle regulation, DNA repair (mSin3a/HDAC)	Peña et al. (2006, 2009), Shi et al. (2006)
	ING3	Transcription, cell cycle regulation, DNA repair (NuA4/Tip60 KAT5)	Peña et al. (2006)

(continued)

Table 2.1 (continued)

Histone ligand	PHD finger protein	Chromatin function (host complex)	References
	ING4	Transcription, cell cycle regulation, DNA repair (HBO1 KAT7)	Hung et al. (2009), Palacios et al. (2008), Peña et al. (2006)
	ING5	Transcription, cell cycle regulation (MOZ/MORF KAT6) (HBO1 KAT7)	Champagne et al. (2008), Peña et al. (2006)
	JARID1A (KDM5A)	Transcription H3K4 KDM	Wang et al. (2009)
	JARID1B (KDM5B)	Transcription H3K4 KDM	Klein et al. (2014), Zhang et al. (2014)
	Jhd1 (S.c.)	H3K36 KDM	Shi et al. (2007)
	KDM7A (C.e.)	KDM	Yang et al. (2010)
	KIAA1718 (KDM7A)	Transcription H3K27 KDM	Horton et al. (2010)
	MLL1 (KMT2A)	Transcription H3K4 KMT	Chang et al. (2010), Park et al. (2010), Wang et al. (2010)
	MLL2 (KMT2B)	Transcription H3K4 KMT	Ali et al. (2014), Wang et al. (2010)
	MLL5 (KMT2E)	Transcription H3K4 KMT	Ali et al. (2013), Lemak et al. (2013)
	PHF2	Transcription H3K9 KDM (ARID5B)	Wen et al. (2010)
	PHF8	Transcription, cell cycle regulation H3K9 (also H3K27 and H4K20) KDM	Feng et al. (2010), Horton et al. (2010), Qi et al. (2010)
	PHF13	Chromosome separation in mitosis	PDB:3O7A, Min et al. (unpublished)
	PHO23 (S.c.)	(Rpd3/HDAC)	Peña et al. (2006), Shi et al. (2007)
	PYGO1/2	Transcription, Wnt signaling (PYGO1/2/BCL9/ β -catenin/TCF)	Fiedler et al. (2008), Miller et al. (2013, 2010)
	RAG2	Recombination (RAG1/2V(D)J)	Liu et al. (2007), Matthews et al. (2007), Ramon-Maiques et al. (2007), Yuan et al. (2012)
	Spp1 (S.c.)	(Set1c KMT)	Shi et al. (2007)
	Set3 (S.c.)	(Set3c/HDAC)	Shi et al. (2007)
	TAF3	Transcription, differentiation (TFIID)	van Ingen et al. (2008), Vermeulen et al. (2007)
	YNG1 (S.c.)	(NuA3 KAT)	Martin et al. (2006), Peña et al. (2006), Shi et al. (2007), Taverna et al. (2006)
	YNG2 (S.c.)	(NuA4 KAT)	Peña et al. (2006), Shi et al. (2007)

(continued)

Table 2.1 (continued)

Histone ligand	PHD finger protein	Chromatin function (host complex)	References
H3K4	AIRE PHD1	Transcription, autoimmune regulator	Chakravarty et al. (2009), Chignola et al. (2009), Koh et al. (2008), Org et al. (2008)
	BHC80	Transcription (LSD1/KDM1A)	Lan et al. (2007)
	BRPF1/2 PHD1 of PZP	Transcription, cell cycle regulation (MOZ/MORF KAT6)	Lalonde et al. (2013), Qin et al. (2011)
	CHD5	Chromatin remodeling	Oliver et al. (2012), Paul et al. (2013)
	DNMT3A	DNA methylation	Otani et al. (2009)
	DNMT3L	Regulatory factor/DNA methylation	Ooi et al. (2007)
	JADE1 PHD1 of PZP	Transcription, cell cycle regulation (HBO1 KAT7)	Avvakumov et al. (2012), Saksouk et al. (2009)
	JARID1B (KDM5B)	Transcription H3K4 KDM	Klein et al. (2014)
	TRIM24	Transcription, E3-Ub ligase	Tsai et al. (2010)
	UHRF1	Transcription, cell cycle control, DNA-methylation regulation, E3-Ub ligase	Arita et al. (2012), Cheng et al. (2013), Lallous et al. (2011), Liu et al. (2013), Rajakumara et al. (2011), Rothbart et al. (2012, 2013), Wang et al. (2011), Xie et al. (2012)
H3K9me3	ATRX ADD	Chromatin remodeling, cell cycle regulation, mitosis	Dhayalan et al. (2011), Eustermann et al. (2011), Iwase et al. (2011)
	CHD4 PHD2	Chromatin remodeling, transcription (NuRD/HDAC)	Mansfield et al. (2011), Musselman et al. (2009)
	TRIM33	Transcription, TGF β signaling, E3-Ub ligase	Xi et al. (2011)
H3K14ac	DPF3b DPF	Transcription, chromatin remodeling (BAF)	Lange et al. (2008), Zeng et al. (2010)
	MORF DPF	MORF KAT6B	Ali et al. (2012)
	MOZ DPF	MOZ KAT6A	Dreveny et al. (2014), Qiu et al. (2012)

A smaller number of PHD fingers displays preference for the histone H3 tail trimethylated at lysine 9 (H3K9me3) (Dhayalan et al. 2011; Eustermann et al. 2011; Iwase et al. 2011; Mansfield et al. 2011; Musselman et al. 2009; Xi et al. 2011). The DPF module selects for histone H3 acetylated at lysine 14 (H3K14ac) (Ali et al. 2012; Dreveny et al. 2014; Lange et al. 2008; Qiu et al. 2012; Zeng et al. 2010), and the PHD2 finger of BRPF1/2 associates with DNA (Lalonde et al. 2013; Liu et al. 2012).

In addition to recognizing histone tails, PHD fingers have been implicated in binding to non-histone proteins and self-association. For example, the third PHD finger (PHD3) of MLL1 is capable of binding both H3K4me3 and the nuclear cyclophilin Cyp33, while the second PHD finger (PHD2) of MLL1 forms a dimer and shows E3 ubiquitin ligase activity in the presence of the E2-conjugating enzyme CDC34 (Chang et al. 2010; Fair et al. 2001; Hom et al. 2010; Park et al. 2010; Wang et al. 2010, 2012).

The mechanistic outcome of histone or non-histone recognition by PHD fingers is the recruitment or stabilization of their host proteins, i.e., transcription factors, PTM writing and erasing and nucleosome-remodeling enzymes, and other elements of the epigenetic machinery, at chromatin; however, the physiological consequence of these interactions is highly context dependent and is often determined by the overall function of the chromatin-modifying complex in which the PHD finger resides.

2.2.2 Regulation of Gene Transcription

Interaction of the PHD finger with histone H3 tail is required for a variety of cellular processes; however, transcriptional regulation is by far the most common function of the PHD finger-containing proteins. The transcriptional co-activator TAF3 has been shown to anchor basal transcription factor TFIID to H3K4me3-enriched chromatin through its PHD finger (van Ingen et al. 2008; Vermeulen et al. 2007). Recognition of H3K4me3 by the PHD finger of histone demethylase PHF8 increases the enzymatic activity necessary for transcriptional activation (Feng et al. 2010; Horton et al. 2010; Qi et al. 2010). The DPF domain of DPF3b associates with H3K14ac, and this interaction plays an important role in transcriptional activation of DPF3b/BAF target genes, critical for the heart and skeletal muscle development (Lange et al. 2008; Zeng et al. 2010). The DPF module of the MOZ HAT cooperates with the catalytic MYST domain of this protein to enhance H3K9 and H3K14 acetylation and *HOXA9* gene expression (Dreveny et al. 2014; Qiu et al. 2012).

Conversely, in response to DNA damage, binding of the PHD finger of the tumor suppressor ING2 to H3K4me3 recruits the repressive mSin3a/HDAC1 complex, promoting histone deacetylation and acute repression of actively transcribed genes (Peña et al. 2006; Shi et al. 2006). Histone demethylase LSD1 is also stabilized at promoters of target genes through binding of the PHD finger of the BHC80 subunit with unmodified H3 (Lan et al. 2007). Whereas this interaction plays a role in LSD1-mediated transcriptional repression, similar recognition of H3 by the JADE1 PHD1 finger is essential for recruitment of the activating HBO1 HAT complex (Avvakumov et al. 2012; Lalonde et al. 2013; Saksouk et al. 2009). Collectively, these studies demonstrate that the downstream effect of the interaction between a PHD finger and histone tail depends on the enzymatic function of the host protein or the host complex.

2.2.3 Crosstalk to DNA Methylation and Chromatin Remodeling

Transcriptional regulation is often linked to other DNA-related events, including DNA methylation and chromatin remodeling, and a number of PHD finger-containing proteins are implicated in both. The non-canonical (a C4C4 topology) PHD fingers of DNA (cytosine-5)-methyltransferases recognize unmodified H3, coupling histone tail association with DNA methylation, necessary for gene repression (Ooi et al. 2007). A more complex interplay between the unmodified H3-binding PHD finger and the neighboring H3K9me3-binding tandem Tudor domain (TTD) of UHRF1 is required for epigenetic inheritance of DNA methylation (Arita et al. 2012; Cheng et al. 2013; Lallous et al. 2011; Liu et al. 2013; Rajakumara et al. 2011; Rothbart et al. 2012, 2013; Wang et al. 2011; Xie et al. 2012). Binding of the BPTF PHD finger to H3K4me3 stabilizes the nucleosome-remodeling NURF complex at chromatin, enhancing NURF-catalyzed nucleosome sliding and activation of developmental genes (Li et al. 2006; Wysocka et al. 2006). The nucleosome remodeling and repressive activities of the deacetylase NuRD complex depend on concurrent binding of two PHD fingers of the CHD4 ATPase subunit to H3 or H3K9me3 (Mansfield et al. 2011; Musselman et al. 2009, 2012b; Ramirez et al. 2012). Interaction of the non-canonical PHD finger with H3K9me3 promotes localization of another ATP-dependent chromatin remodeler, ATRX, with heterochromatin (Dhayalan et al. 2011; Eustermann et al. 2011; Iwase et al. 2011).

2.2.4 Nuclear Signaling

The PHD finger-containing proteins play a key role in nuclear signaling, mediating cell cycle, cell growth and differentiation, and tumor-suppressive responses. Dysregulation of these signaling pathways is associated with a number of human diseases, including cancer and neurological and immunodeficiency disorders. Concomitant contacts of the PHD finger of Pygo1 with H3K4me3/2 and BCL9 control β -catenin-mediated transcription within the Wnt signaling pathway (Fiedler et al. 2008; Miller et al. 2013). Stem cell differentiation and expression of a set of stemness genes are modulated by the H3K4me3-specific Dido PHD finger (Gatchalian et al. 2013). Binding of the PHD-BD cassette of TRIM33 to H3K9me3K14acK18ac is necessary for switching the poised chromatin state and triggering stem cell differentiation (Xi et al. 2011). The histone-binding activity of the PHD finger also regulates E3-ubiquitin ligase activity of TRIM33 (Agricola et al. 2011).

The PHD finger of MLL5 functions as a switch in the chromatin recruitment and exclusion of MLL5 (Ali et al. 2013; Lemak et al. 2013). Phosphorylation of H3T3 or H3T6 during mitosis abolishes the interaction of the MLL5 PHD finger

with H3K4me3, resulting in the release of MLL5 from mitotic chromosomes (Ali et al. 2013). The PHD finger of RAG2, a component of the RAG1/2 V(D)J recombinase, associates with H3K4me3 at actively rearranging gene segments, and this binding is important for the V(D)J recombination activity (Liu et al. 2007; Matthews et al. 2007; Ramon-Maiques et al. 2007). Disruption of the interaction of the autoimmune regulator AIRE PHD1 finger with H3 reduces localization of AIRE at specific genomic sites, leading to an inhibition of ectopic expression of peripheral tissue-specific antigens in thymic cells (Chakravarty et al. 2009; Chignola et al. 2009; Koh et al. 2008; Org et al. 2008).

Loss of the histone-binding activity of the PHD finger-harboring proteins due to mutations, deletions, and translocations is implicated in oncogenesis. Interaction of the PHD fingers with histone H3 is required for suppression of cellular transformation by CHD5 (Oliver et al. 2012; Paul et al. 2013) and for activation of oestrogen-dependent genes associated with cell proliferation and tumor development by TRIM24 (Tsai et al. 2010). Dysregulation of the H3K4me3-binding PHD finger of JARID1A is linked to the development of haematopoietic malignancies (Wang et al. 2009). Specific recognition of H3K4me3 by the PHD fingers of tumor suppressors ING1-5 is essential in DNA damage repair, cell growth and apoptosis and tumor-suppressive mechanisms (Avvakumov et al. 2012; Champagne et al. 2008; Hung et al. 2009; Peña et al. 2006, 2008; Saksouk et al. 2009; Shi et al. 2006).

Such functional versatility of the PHD finger-containing proteins and their ability to recognize histone tails with relatively high specificities and affinities underscore the important role of this PTM reader in many nuclear events, making it a critical component of the epigenetic machinery.

2.3 Molecular Basis for the Association with Chromatin

2.3.1 Recognition of H3K4me3

Over a dozen atomic-resolution structures of the PHD fingers in complex with H3K4me3 have been determined, revealing a highly conserved mechanism for the recognition of this histone tail (Fig. 2.2). The H3K4me3 peptide is bound in an extended conformation in a large binding site that encompasses nearly one-third of the PHD finger surface. The peptide forms the third antiparallel β -strand, pairing with the existing double-stranded β -sheet of the PHD finger. Numerous intermolecular hydrogen bonds, including characteristic backbone contacts between the β 1-strand of the protein and R2-T6 residues of H3K4me3, stabilize the complex. The fully extended side chain of trimethylated K4 occupies a well-defined binding pocket, consisting of one to four aromatic residues and named the ‘aromatic cage’ (colored red in Fig. 2.2a, b). The aromatic rings are usually positioned almost perpendicular to the protein surface and to each other and are engaged in cation- π , hydrophobic, and van der Waals contacts with the trimethylammonium

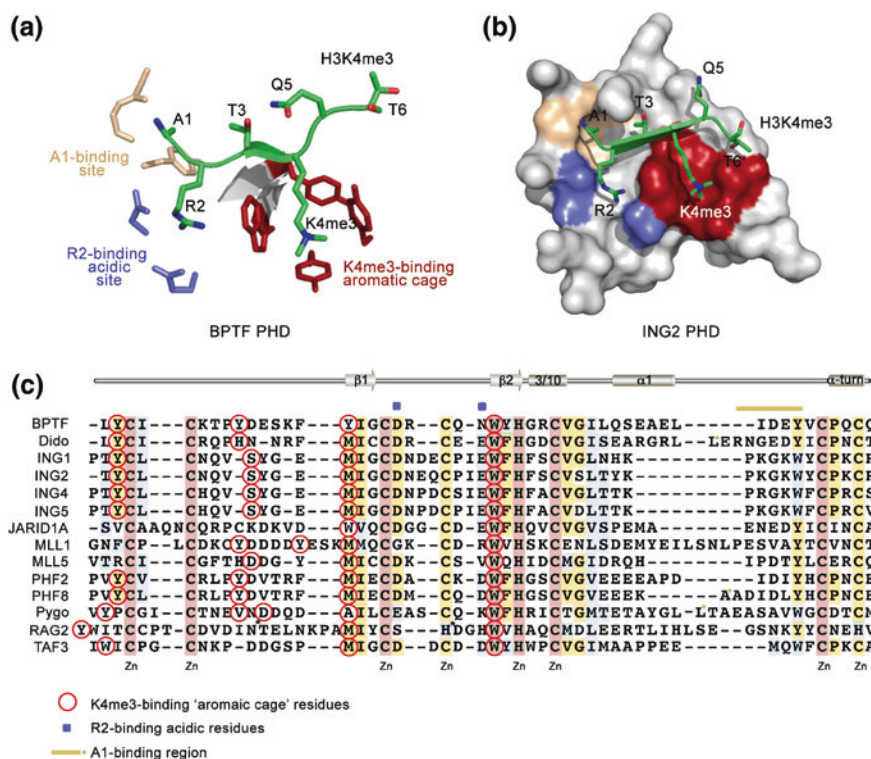


Fig. 2.2 The molecular basis for H3K4me3 recognition by the PHD finger. **a, b** Crystal structures of the H3K4me3-bound PHD fingers of BPTF (2F6J) and ING2 (2G6Q). The bound H3K4me3 peptide is shown as a ribbon diagram and colored green. The binding sites for A1, R2, and K4me3 of the peptide are colored wheat, blue, and red, respectively. **c** Alignment of sequences of the H3K4me3-specific PHD fingers: absolutely, moderately, and weakly conserved residues are colored *pink*, *yellow*, and *light blue*, respectively. The K4me3-binding aromatic cage residues, the R2-binding acidic site residues, and the A1-binding region are indicated by *red circles*, *blue squares*, and a *yellow line*, respectively. Secondary structure elements of the BPTF PHD finger are shown at the *top*. For simplicity, eight residues in RAG2 are deleted, as indicated by *asterisks*

moiety of K4. This mode of Kme recognition through the aromatic cage is a widespread mechanism utilized by many methyllysine readers, including CD, MBT, and Tudor [reviewed in the Chaps. 3, 4, and 5 of this book and (Musselman et al. 2012a; Taverna et al. 2007)]. Substitution of the aromatic cage residues disrupts or significantly diminishes binding of the PHD fingers to H3K4me3.

An invariable tryptophan residue at the position-2 with respect to the zinc-coordinating histidine (note that the W is present in all known H3K4me3-recognizing PHD fingers) separates the K4me3-aromatic cage from the adjacent R2-binding groove. This groove is commonly made of acidic residues that constrain the guanidinium group of R2 through hydrogen bonding and ionic interactions (colored blue in Fig. 2.2a, b). Another distinguishable feature of the H3K4me3 recognition

is the conserved coordination of A1. The N-terminal primary amino group of A1 is hydrogen bonded to one, two, or three backbone carbonyls located in the loop connecting the sixth and seventh zinc-coordinating residues of the PHD finger (colored wheat in Fig. 2.2a, b). The methyl group of A1 occupies a cavity lined with the hydrophobic core residue, a tryptophan or a tyrosine in the position-2 with respect to the seventh zinc-coordinating residue of the PHD finger. Overall, the PHD-H3K4me3 interaction typically involves the first six N-terminal residues of the histone tail with T3, Q5, and T6 uniquely contributing to each interaction.

The PHD fingers exhibit a high nM to low μ M binding affinity for H3K4me3 as measured by isothermal titration calorimetry, tryptophan fluorescence, fluorescence anisotropy, and NMR. Such moderate affinity reflects the fact that the PHD finger-containing proteins are involved in regulatory processes and must be recruited to and released from chromatin on demand. This requires a delicate balance of affinities high enough to attract and at the same time low enough to dismiss them when no longer needed. Similar affinities have been reported for other histone-binding modules (Musselman et al. 2012a; Taverna et al. 2007), reiterating the physiological importance of the low μ M range interactions.

2.3.2 Recognition of Unmodified H3

The second largest subset of PHD modules includes canonical and non-canonical PHD fingers that are capable of recognizing unmodified H3 tail. These PHD fingers bind unmodified H3 peptide with the same low μ M affinity as the PHD fingers that bind H3K4me3, and structural analysis of the PHD-H3 complexes suggests some similarities in the histone-binding mechanisms. Like H3K4me3, the unmodified H3 peptide adopts an extended β -strand conformation and lays antiparallel to the β 1-strand of the protein (Fig. 2.3). The N-amino group of H3A1 donates hydrogen bonds to two or three backbone carbonyl groups of the protein, and the guanidinium moiety of R2 is usually bound through hydrogen bonds and ionic contacts. The differences between the two mechanisms arise from the distinct coordination of unmodified K4 and in some cases of other basic residues, including R8 and K9. The H3-specific PHD fingers lack the aromatic cage, which is required for the recognition of K4me3, and instead contain a stretch of acidic residues N-terminal to the first zinc-coordinating Cys1. The acidic residues form hydrogen bonds and salt bridges with the positively charged side chains of K4 and sometimes R8 and K9. Recognition of unmodified K4 is important for the H3-specific PHD fingers, as methylation of this residue decreases or abolishes the binding. Further significant contacts at the interface are provided by the hydrophobic residue preceding Cys3 of the protein that inserts between K4 and R2 of the peptide, replacement of which also disrupts the interaction with H3.

The extended PHD finger of UHRF1 utilizes a distinct mechanism to bind unmodified H3 (Arita et al. 2012; Cheng et al. 2013; Lallous et al. 2011; Liu et al. 2013; Rajakumara et al. 2011; Rothbart et al. 2012, 2013; Wang et al. 2011; Xie

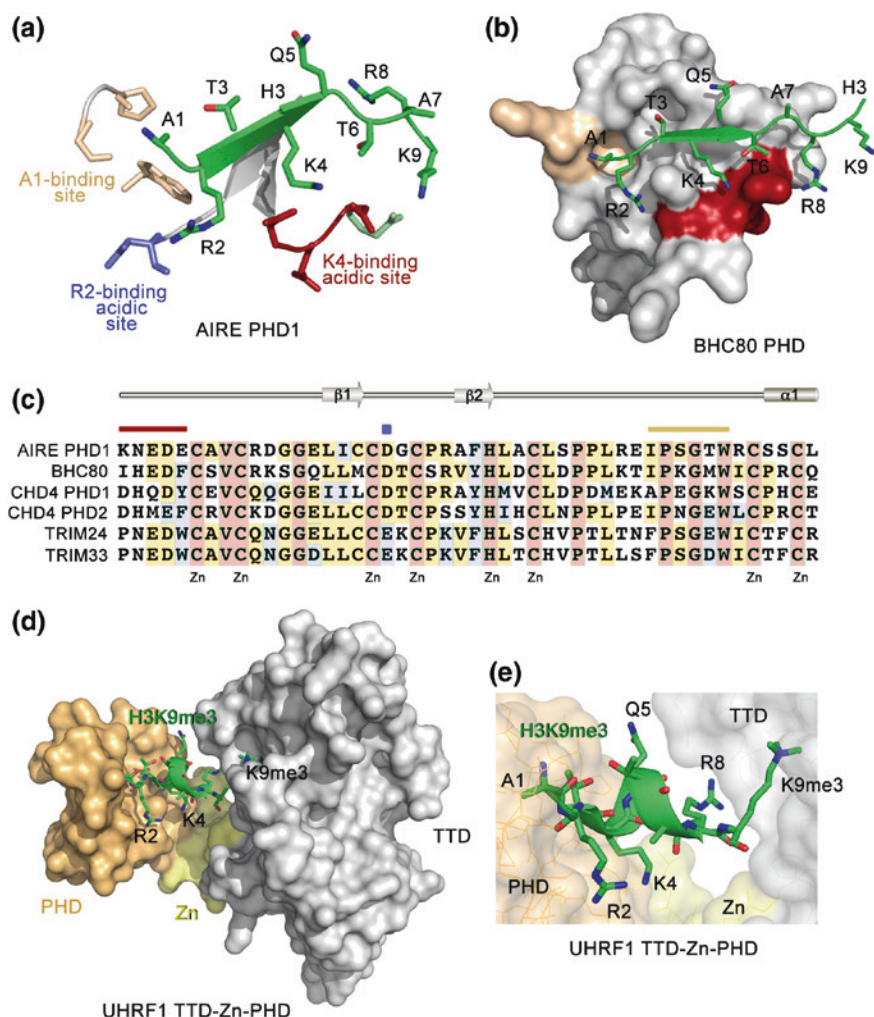


Fig. 2.3 The molecular mechanism of binding of the PHD finger to unmodified H3 tail. **a, b** The solution and crystal structures of the PHD fingers of AIRE (2KE1) and BHC80 (2PUY) in complex with unmodified H3 peptide. The binding sites for A1, R2, and K4 of the histone peptide are colored *wheat*, *blue*, and *red*, respectively. The bound H3 peptide is shown as a ribbon diagram and colored *green*. **c** Alignment of sequences of the H3-binding PHD fingers: absolutely, moderately and weakly conserved residues are colored *pink*, *yellow*, and *light blue*, respectively. The K4-binding acidic region, the R2-binding acidic residue, and the A1-binding region are indicated by a *red line*, a *blue square*, and a *yellow line*, respectively. Secondary structure elements of the BHC80 PHD finger are shown at the *top*. **d** The crystal structure of the linked tandem Tudor domains (gray), Zn knuckle (yellow), and PHD (orange) (TTD–Zn–PHD) of UHRF1 (3ASK). **e** A zoom-in view of the H3K9me3 binding site of UHRF1 (3ASK)

et al. 2012). The crystal structure of the TTD–Zn knuckle–PHD region of UHRF1 in complex with H3K9me3 peptide shows that the three modules are adjacent to each other and form a ring-shaped assembly with a central hole between TTD and PHD (Arita et al. 2012; Cheng et al. 2013) (Fig. 2.3d, e). The PHD finger and TTD interact with the A1–K4 portion and the R8–K9me3 portion of the peptide, respectively, and the residues K4–R8 fold into a short α -helix. Much like in the canonical PHD finger complex, the β 1-strand of UHRF1 and the residues R2–K4 of the histone peptide form an intermolecular β -sheet; the N-terminal amino group of A1 is hydrogen bonded to two backbone carbonyl groups of the protein; and R2 is restrained by the carboxyl groups of two aspartate residues. However, the side chain of K4 is relatively solvent exposed and forms only one hydrogen bond with the carbonyl group of a zinc knuckle cysteine. No additional contacts are seen between the PHD finger and the histone residues beyond K4, allowing K4 to be posttranslationally modified without significantly disrupting this interaction. Indeed, trimethylation of K4 reduces binding of the UHRF1 PHD finger ~two- to threefold, whereas asymmetric dimethylation of R2 decreases this interaction ~sixfold, and acetylation of A1 completely abrogates it (Arita et al. 2012; Cheng et al. 2013).

2.3.3 Recognition of H3K9me3

A combination of a GATA-like (C4) zinc knuckle and a non-canonical (C4C4) PHD finger comprises the ADD (ATRX–DNMT3–DNMT3L) domain. Whereas the ADD domains of DNMT3L, DNMT3A, and ATRX interact robustly with unmodified H3, the latter shows preference for methylated K9 ($K_{dS} = 3.7$ and $0.5 \mu\text{M}$ for the interaction with H3 and H3K9me3, respectively) (Dhayalan et al. 2011; Eustermann et al. 2011; Iwase et al. 2011; Ooi et al. 2007; Otani et al. 2009). The crystal and solution structures of the ATRX ADD domain in complex with H3K9me3 peptide demonstrate that the side chain of K9me3 inserts between the zinc knuckle and the PHD finger (Eustermann et al. 2011; Iwase et al. 2011) (Fig. 2.4a). The trimethylammonium group is uniquely coordinated through hydrophobic and cation- π contacts with a single aromatic residue, Y203, and a set of non-conventional carbon-oxygen hydrogen bonds, which together may account for the observed ~sevenfold increase in binding affinity.

Trimethylation of K9 enhances interaction of the TRIM33 PHD finger with unmodified H3 ~twofold (Xi et al. 2011). The crystal structure of the PHD–BD region of TRIM33 bound to H3K9me3K14acK18ac peptide shows that the PHD finger associates with the A1–S10 residues of the peptide, whereas BD recognizes K18ac (Xi et al. 2011) (Fig. 2.4b). The trimethylated K9 forms a cation- π contact with W889 and a non-conventional carbon-oxygen hydrogen bond with the carbonyl oxygen of the PHD finger. Similarly, the cation- π and hydrophobic interactions between F451 and K9me3 stabilize the CHD4 PHD2–H3K9me3 complex, as this module binds to H3K9me3 ~20-fold stronger than it binds to unmodified H3 (Mansfield et al. 2011; Musselman et al. 2009) (Fig. 2.4c).

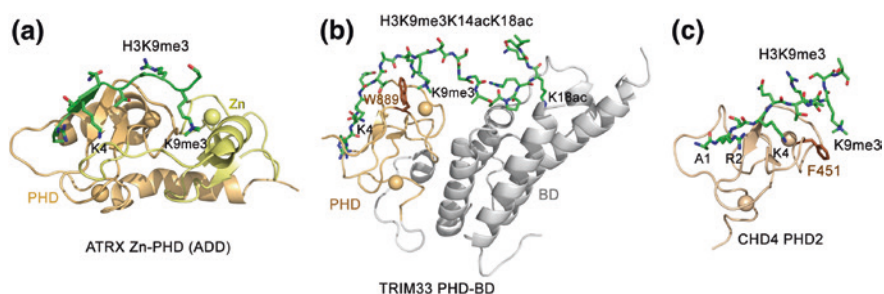


Fig. 2.4 Methylation of K9 enhances binding of a set of PHD fingers to H3. **a** The crystal structure of the ATRX ADD domain in complex with H3K9me3 peptide (3QL9). The histone peptide is shown as a ribbon diagram and colored *green*. **b** The crystal structure of the linked PHD finger and bromodomain (BD) of TRIM33 in complex with H3K9me3K14acK18ac peptide (3U5O). **c** The solution structure of the CHD4 PHD2 finger in complex with H3K9me3 (2L75)

2.3.4 Recognition of H3K14ac

The DPF module of DPF3b, MOZ, and MORF has been shown to associate with H3K14ac and other acetylated histone tails (Ali et al. 2012; Dreveny et al. 2014; Lange et al. 2008; Qiu et al. 2012; Zeng et al. 2010). Analyses of binding affinities and NMR chemical shift perturbations reveal that acetylation enhances the histone binding ~2- to fourfold; however, this at first glance only a slight increase in binding affinity has significant implication for activities of the DPF-containing proteins.

The NMR and crystal structures of the DPF3b and MOZ DPF modules in complex with H3K14ac peptide provide insight into the selectivity of this reader toward acetyllysine substrates (Dreveny et al. 2014; Qiu et al. 2012; Zeng et al. 2010) (Fig. 2.5). Both PHD fingers in DPF possess a typical zinc-finger scaffold, but the two overlap substantially and form a unique bean-shaped structure (Fig. 2.5a, b). The first four *N*-terminal residues of H3K14ac peptide are bound in the acidic groove of the second PHD2 finger. Notably, the side chains of R2 and K4 are restrained through numerous intermolecular hydrogen bonds. As a result of such stringent coordination, methylation of either histone residue disrupts binding to H3. Additionally, intermolecular hydrogen bonds constrain the side chains of R8 and R9 in the MOZ and DPF3b complexes, respectively (Dreveny et al. 2014; Zeng et al. 2010).

The first PHD1 module of DPF, however, is unique as it contains an acetyllysine-binding pocket (Dreveny et al. 2014; Zeng et al. 2010). This pocket consists of primarily hydrophobic residues, indicated by orange ovals in Fig. 2.5c, and it accommodates the entire side chain of K14ac. The residues K4-T11 of the H3K14ac peptide exist in an α -helical conformation in the MOZ complex or form a bulge-containing loop in the DPF3b complex. The H3K14ac docking is accompanied by a conformational change mediated through the double-glycine (G11–G12) hinge of the peptide (Dreveny et al. 2014).

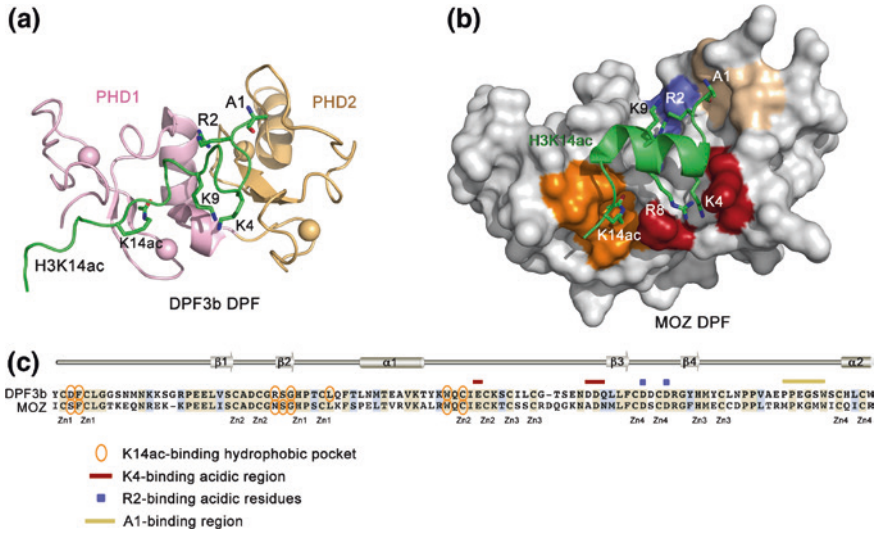


Fig. 2.5 DPF prefers acetylated histones. **a, b** The solution and crystal structures of DPF of DPF3b (2KWJ) and MOZ (4LLB) in complex with H3K14ac peptide. The binding sites for A1, R2, K4, and K14ac of the histone peptide are colored *wheat*, *blue*, *red*, and *orange*, respectively. **c** Alignment of the DPF sequences: identical and similar residues are colored *gray* and *light blue*, respectively. The K14ac-binding hydrophobic site residues, the A1-binding region, the R2-binding acidic residues, and the K4-binding acidic site are indicated by *orange ovals*, a *yellow line*, *blue squares*, and *red lines*, respectively. Secondary structure elements of DPF3b DPF are shown at the *top*

2.3.5 Binding to DNA

A conserved arrangement of two PHD fingers linked by a zinc knuckle, termed the PZP domain, is found in various eukaryotic proteins, including BRPF1/2/3, Jade1/2/3 and AF10/17 (Avvakumov et al. 2012; Saksouk et al. 2009). Although structural information regarding the entire PZP domain is not yet available, the structures of the individual PHD fingers of BRPF2 and biochemical studies of PZP show that the first PHD1 finger is highly specific for unmodified H3, with methylation of K4 or R2 abolishing or considerably reducing this interaction (Lalonde et al. 2013; Qin et al. 2011) (Fig. 2.6).

Unlike PHD1, the second PHD2 finger of BRPF1/2 associates with DNA (Lalonde et al. 2013; Liu et al. 2012). This atypical PHD finger has two zinc-coordinating histidine residues in its sequence (C4HC2H) and contains an additional long β3–β4 hairpin. The BRPF2 PHD2 finger has a saddle-like structure with a large positively charged patch spread throughout the concave surface (Liu et al. 2012) (Fig. 2.6b). This patch, formed by lysine and arginine residues of the β1–β2 loop and the β3–β4 hairpin, is centrally involved in the interaction with double- and single-stranded DNA though no apparent nucleotide sequence preference is observed. Substitution of these basic residues of PHD2 disrupts binding to DNA.

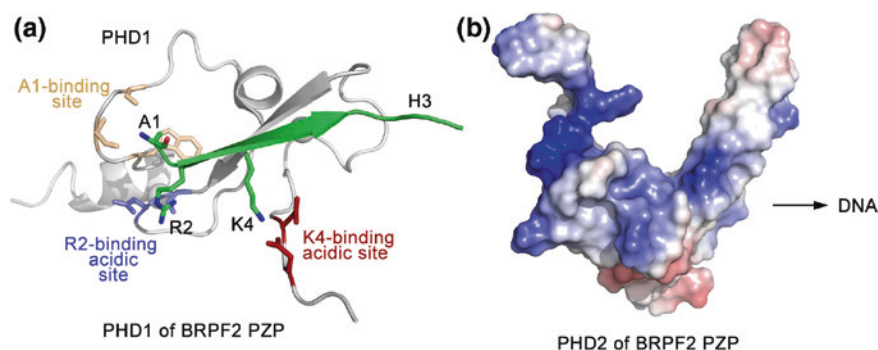


Fig. 2.6 The histone- and DNA-binding activities of PZP. **a** The solution structure of the H3-bound BRPF2 PHD1 finger (2L43). **b** Electrostatic potential surface of the BRPF2 PHD2 finger (2LQ6)

2.4 Concluding Remarks

The abundance of the PHD finger-containing proteins in the human genome and the ability to recognize various PTMs underscore a pivotal role of this epigenetic reader in cell biology. The PHD fingers act in a multifaceted manner to modulate chromatin properties and regulate fundamental processes such as transcriptional activation and repression, cell differentiation, division, and survival. In this chapter, we have focused on the mechanistic details and biological functions of individual PHD fingers; however, these domains are frequently found adjacent to other chromatin-binding modules, including histone readers, writers and erasers, and DNA-binding domains. The interplay between multiple readers and the DNA-binding domains creates an intricate network of contacts with nucleosomes and adds another layer of complexity to the chromatin-targeting mechanisms. Furthermore, many nuclear enzymes and components of multisubunit enzymatic complexes contain PHD fingers, which through histone binding bridge the catalytic activities to specific genomic regions. The recruited enzymes then further alter the chromatin structure through removing epigenetic marks, depositing new PTMs on histones and DNA, or modulating nucleosome position and dynamics. Thus, the biological outcome of histone recognition by PHD fingers is highly context dependent and is often the result of a combinatorial readout of multiple PTMs by a combination of epigenetic effectors present in the protein or the protein complex (reviewed in Musselman et al. 2012a; Ruthenburg et al. 2007).

Aberrant histone-binding activity of the PHD finger impairs proper localization of the host proteins and chromatin-associating complexes. This can cause genomic instability and lead to misregulation of gene transcription and other DNA-templated processes, triggering a range of human diseases including cancer, genetic disorders, immunodeficiency, and neurological abnormalities (reviewed in Baker et al. 2008; Chi et al. 2010). The link between aberrant functions of PHD

fingers and diseases suggest a novel therapeutic opportunity, particularly for the use of the PHD finger-containing proteins as diagnostic markers. In-depth molecular analysis of the PHD–histone interactions can be essential for further advancing the cutting-edge epigenetic-driven therapeutic strategies.

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