Combinatorial Readout of Dual Histone Modifications by Paired Chromatin-associated Modules*

The study of histone modifications and their interaction with effector modules/proteins has attracted increasing attention in recent years. Accumulating evidence indicates that epigenetic regulation, which involves post-translational modification on histones and DNAs or the participation of RNAs, plays an important role in many cellular processes. Histone modifications can function individually but are also capable of functioning combinatorially as a pattern. Recently, much attention has focused on interpreting combined histone patterns by their downstream effectors. Structure/function-based studies on paired module-mediated histone cross-talk have greatly enhanced our understanding of the plasticity of the “histone code” hypothesis.

The nucleosome core particle, composed of a histone octamer wrapped by 146 bp of DNA (1) and visualized as small beads under the electron microscope (2), constitutes the building block of chromatin structure. The flexible and unstructured N-terminal tails of histone proteins that protrude from the central core of the nucleosome are post-translationally modified at various positions. In addition, the wrapped DNA bases and some residues located within the rigid histone core can also be modified, indicating that not only the flexible histone tails but also the nucleosome as a unit can be the target of post-translational regulation by effector proteins. The type, pattern, and distribution of histone modifications constitute a “histone code” (3), whose alphabet can be specifically “written,” “read,” and “interpreted” by effector proteins through a series of downstream events, thereby regulating multiple cellular processes, including transcription, cell cycle progression, cell growth and differentiation, and apoptosis.

Many post-translational modifications (PTMs)3 have been identified on histones, displaying a wide variety both in the types of modification and in the states of the same kind of modification. There has been considerable recent progress in the identification of PTMs, as well as the effector modules associated with their specific readout. Generally, the binding modules are small domains (50–150 residues) containing binding pockets that accommodate these PTMs in a chemical type- and histone sequence-specific manner (4, 5). These binding modules are called “readers.” Similarly, domains that are responsible for specifically adding or removing these PTMs are called “writers” or “erasers.” The readout of single histone modifications by effector modules has been extensively investigated, and the rules underlying molecular recognition are outlined in several reviews (4, 6). Regulatory events involving two or more epigenetic marks usually require two or more effector modules to function together. Long-range histone cross-talk usually involves several proteins that either function in a particular pathway or alternately form a complex (7, 8), thereby adding additional levels of complexity to efforts aimed at characterization of molecular details associated with recognition events.

Short-range histone cross-talk can be monitored on closely positioned paired modules. These paired chromatin-associated modules appear in multiple combinations, ranging from reader-reader pairs to reader-writer and reader-eraser pairs. They represent simplified models for studying short-range communication between histone and/or non-histone modifications. Furthermore, these paired chromatin-associated modules usually exhibit new functions that are distinct from their individual components. This minireview focuses mainly on paired modules that have been structurally characterized or biochemically implicated in chromatin-mediated processes, with the discussion focusing on their distinct functions as a combined unit, as part of an effort to reveal the molecular basis underlying paired module-mediated histone cross-talk impacting on epigenetic regulation.

Combinatorial Readout by Reader-Reader Pairs

More than 10 families of reader modules have been identified that are capable of specifically recognizing histone marks in different sequence contexts, and the list would be even longer if one took into account readers of DNA modifications and RNA regulators. The diversity of histone mark recognition is further enhanced by pairs of reader modules, such as PHD-PHD, PHD-Bromo, and Bromo-Bromo pairs, where PHD is the PHD finger module and Bromo is the bromodomain module (Table 1). When each module recognizes a specific histone mark, the dual modules can display a combinatorial effect that is reflected in the cooperativity of the binding event during readout of the pattern of histone marks. A positive combinatorial effect associated with reading of two or more histone modifications was first reported for the double Bromo of TAF1 (9), a subunit of the TFIID complex. The TAF1 double Bromo exhibits a much higher binding affinity for di/tetraacetyllysine-modified H4 peptide, with the different combinations consistently exhibiting 7–27-fold higher binding affinity over a singly H4K16ac-modified peptide. The structure of the TAF1 double Bromo shows that each domain possesses an acetyllysine-binding pocket. The 25-Å distance between the two acetyllysine-binding pockets enables the double Bromo to simultaneously read two acetyllysines separated by 7 or more amino acids (Fig. 1A), thereby providing a structural explanation of the higher affinity.

* This is the third article in the Thematic Minireview Series on Epigenetics. This minireview will be reprinted in the 2011 Minireview Compendium, which will be available in January, 2012.
1 To whom correspondence may be addressed. E-mail: wangz@mskcc.org.
2 To whom correspondence may be addressed. E-mail: pateld@mskcc.org.
3 The abbreviations used are: PTM, post-translational modification; PHD, plant homeodomain; Bromo, bromodomain; TF, transcription factor; RRM, RNA recognition motif.
MINIREVIEW: Readout of Dual Histone Modifications

TABLE 1
| Protein name | Paired domains | Histone patterns | Histone-binding features | Selected PDB codes |
|--------------|----------------|------------------|-------------------------|--------------------|
| TAF1         | Bromo-Bromo    | H4K5/8/12/16ac   | Combinatorial reading of two or four acetylation marks; also interacts with C/EBP/AS1F | 1EQF, 3AAD |
| TRIM24       | PHD-Bromo      | H3K4me0, H3K23ac, H4ac | Combinatorial reading of H3K4me0 and H3K23ac on a single H3 tail | 3O34, 3O36 |
| DPF3b        | PHD1-PHD2      | H3(1–9), H3K14ac, H4-Nac | Combinatorial reading of unmodified N-terminal H3 and H3K14ac | 2KWJ, 2KWN |
| BPTF         | PHD-Bromo      | H3K4me3, H4Kac   | Combinatorial reading (needs validation) of H3K4me3- and H4Kac-containing marks at the nucleosome level | 2F6J |
| MLL1         | PHD3-Bromo     | H3K4me3         | Binding H3K4me3 and CytP33 simultaneously | 3LQJ, 2KU7 |
| PHF8         | PHD-JmC        | H3K4me3, H3K9me2 | Binding H3K4me3 enhances demethylase activity on H3K9me2 | 3KV4 |
| KIAA1718     | PHD-JmC        | H3K4me3, H3K27me2 | Binding H3K4me3 enhances demethylase activity on H3K27me2 but reduces activity on H3K9me2 | 3KV5, 3KV6 |
| Rsc4         | Bromo-Bromo    | H3K14ac, self-K25ac | Binding self-K25ac inhibits binding H3K14ac | 2ROY, 2ROV |
| Kap1         | PHD-Bromo      | No histone binding | PHD as a SUMO E3 ligase | 2RO1 |
| CHD1         | Chromo-Chromo  | H3K4me3         | Two modules cooperate to bind one mark | 2BW |
| 53Bp1        | Tudor-tudor    | H3K20me2        | One effective binding module | 2IG0 |
| Crb2         | Tudor-tudor    | H3K20me2        | One effective binding module | 2FHD |
| JMJD2A       | Tudor-tudor    | H3K4me3, H4K20me3 | One effective binding module; displays binary binding substrates | 2GFA, 2QGS |
| MDC1         | BRCT-BRCT      | H2AX S139ph     | One effective binding module | 2AZM |
| SCML2        | MRT-MRTF       | Kme1            | One effective module; no sequence specificity | 2VYT |

for multiple acetylysine-containing histone tails. TFIIID is an important protein component required for RNA polymerase II activity and functions to initiate assembly of the transcription machinery. Transcriptionally active genes are usually hyperacetylated at promoter regions, suggesting that the TFIIID complex uses the double Bromo of TAF1 to specifically select hyperacetylated active genes to facilitate transcriptional initiation. Given that the structure of the complex is not yet available, the details of the combinatorial readout mechanism remain to be elucidated. Indeed, a single Bromo of Brd4, the mouse homolog of TAF1, has been shown recently to combinatorially bind two acetylysine marks (10), demonstrating that a pair of acetylysines can be read by a single Bromo module or that four acetylysines could be simultaneously read by a pair of Bromo modules.

For the case of reading two histone modifications by two reader modules in a positive combinatorial manner, one would expect the two binding events to function in cis, namely that one binding event is facilitated by the other. An illustrative example of cis action on a single histone tail bearing two marks was recently provided by studies on the TRIM24 PHD-Bromo dual cassette (11). TRIM24 is a chromatin-associated protein whose cellular levels are closely related to the onset of multiple human cancers. The C-terminal region of this large protein contains a PHD-Bromo cassette that is responsible for chromatin association. The TRIM24 PHD finger specifically targets the unmodified H3K4 (H3K4me0) histone mark, whereas the TRIM24 Bromo targets a series of acetyllysine-containing H3/H4 peptides, with a preference for the H3K23ac mark. Structural studies revealed several features that contribute to the combinatorial readout of the TRIM24 PHD-Bromo cassette for dual-marked H3(1–35)K4K23ac peptide. First, the H3K4-binding pocket on the TRIM24 PHD finger extends smoothly toward the acetyllysine-binding pocket of the TRIM24 Bromo. Second, H3K4- and H3K23ac-containing peptides are aligned in the same orientation. (By contrast, H3K4me0- and H3K27ac-containing peptides are aligned in opposite orientations.) Third, the distance between the two binding pockets is long enough (36.4 Å) so that only the H3K4me0-H3K23ac pair but not the H3K4me0-H3K9ac and H3K4me0-H3K14ac pairs can bind simultaneously within a single histone tail (Fig. 1B).

The combinatorial effect is strongly supported by isothermal titration calorimetry binding data, in which TRIM24 PHD-Bromo showed an ~90-fold higher binding affinity for the dual-marked H3K4me0-H3K23ac-containing peptide than for short peptides containing either single mark. What is the basis for TRIM24 PHD-Bromo recognition of such a non-canonical histone signature? Genome-wide ChIP sequencing identified that H3K4me0 and H3K23ac marks (or other H3ac and H4ac marks) appear in abundance within the distal region of estrogen response elements, where TRIM24 binds and functions as a coactivator of estrogen receptor α. The estrogen response elements coexist alongside many TRIM24-regulated genes, providing a unique platform for histone modification-directed recruitment of TRIM24.

Single PHD fingers have been identified to specifically interact with two kinds of histone modifications: H3K4me0 and H3K4me3. In addition, the PHD-PHD pair of DPF3 has been
reported to bind acetyllysine-containing histones (12), thereby expanding the binding partners of PHD fingers to include acetylated lysines. An NMR-based structure/function study of the PHD-PHD pair of DPF3b showed that both domains are in close contact, such that the histone-binding surface of the two PHD fingers combines to form an extended surface groove, which interacts extensively with the H3K14ac-containing peptide (13). In the solution structure, the acetylated Lys-14 and the N-terminal residues of H3 interact with PHD1 and PHD2, respectively, thereby displaying a combinatorial effect for the recognition event (Fig. 1C). In the absence of Lys-14 acetylation, DPF3b interacts only with N-terminal H3(1–9) through its PHD2 finger in the structure of this complex, resulting in a 4-fold reduction in binding affinity. DPF3 also associates with BAF chromatin-remodeling complexes, displaying tissue-specific expression, and plays an essential role in muscle development (12). The combinatorial readout feature would greatly enhance its specificity and affinity, allowing for a site-directed recruitment of the BAF chromatin-remodeling complex.

All of the above examples of systems identified or implicated in combinatorial readout of two or more histone modifications occurred for cases in which all modifications are positioned on the same histone tail, so precise thermodynamic parameters and structural information can be conveniently obtained using a single synthesized peptide as the substrate. What happens if two histone modifications occur on different histone tails, and in such a case, should one expect some cooperativity when being read simultaneously? A structure-based study on the BPTF PHD-Bromo cassette addressed this issue, given that this dual domain has the potential for reading the H3K4me3 mark by its PHD finger and an acetyllysine-containing H4 mark by its Bromo in a combinatorial manner (14–16). Similar to the TRIM24 PHD-Bromo cassette, the BPTF PHD-Bromo cassette shows specificity toward H3K4me3 modification by its PHD finger while exhibiting a broad binding spectrum for acetyllysine-containing H4 tails by its Bromo. As the targets of the dual domain reside on two different histone tails, either a single nucleosome or a dinucleosome containing these specific modifications would be required to test for combinatorial binding readout. Structure-based modeling suggests that the BPTF PHD-Bromo cassette can be snugly docked onto a single nucleosome, with both domains recognizing adjacent positioned H3 and H4 tails simultaneously (Fig. 1D) (15). Experiments on the BPTF PHD-Bromo cassette aimed at biochemical and in vivo verification are in progress, with the emphasis on exploring the effect of combinatorial readout at the nucleosome level.

Linking Histone Readout to Other Regulatory Events

Not all of the paired readers function in a combinatorial manner, with exceptions reflecting loss-of-reading functions typical of individual reader families. Thus, neither domain of the KAP1 PHD-Bromo cassette binds histones, with this dual domain functioning instead as an intramolecular E3 ligase that facilitates sumoylation of the linked Bromo (17, 18). Some tandem readers function together to read a single histone modification, as seen for the CHD1 double chromodomains (19), thereby functioning in a similar manner to single reader modules. Some of these paired modules have only one effective binding module, as observed for JMJD2A double tudor domains (20), 53BP1 double tudor domains (21), MDC1 tandem BRCT domains (22), and SCML2 tandem MBT (malignant brain tumor) domains (23) (Table 1). For many of these paired modules, despite the ineffective binding module contributing as a structural component, their functional role remains poorly understood.

Recently, structural studies on the MLL1 PHD3-Bromo cassette (24) revealed that the Bromo plays a regulatory role in the recognition of a cyclophilin protein, CyP33. The MLL1 PHD3-Bromo cassette displays an elaborate regulation mechanism that involves both histone binding and non-histone protein-mediated regulation. In the MLL1 PHD3-Bromo cassette, the PHD3 finger is responsible for specific recognition of the H3K4me3 mark, whereas the Bromo has lost its acetyllysine-binding ability. Although the function of the MLL1 Bromo remains to be identified, it does play an important role in regulating the function of MLL1 PHD3. First, interaction with the MLL1 Bromo increases the affinity of MLL1 PHD3 for H3K4me3-containing histone peptides. Second, MLL1 PHD3 interacts with the RNA recognition motif (RRM) domain of CyP33 through a distinct surface adjacent to the H3K4me3-binding surface. This RRM-interacting surface on PHD3 is blocked by the Bromo in the MLL1 PHD3-Bromo cassette due to a cis-configured proline within the linker connecting these two domains (Fig. 2A), but this blocked surface is released in the presence of full-length CyP33, which utilizes its peptidylprolyl isomerase domain to isomerize the linker proline from cis to trans. This isomerization induces a conformational change between PHD3 and the Bromo, so the RRM-binding surface on PHD3 becomes exposed for targeting by the RRM of CyP33 (Fig. 2A). Third, H3K4me3-containing histone and the RRM domain of CyP33 can bind the PHD3 finger of the MLL1 PHD3-Bromo cassette simultaneously so as to generate a ternary complex. This cis,trans-proline isomerization-mediated regulation by CyP33 correlates with the transcriptional switch between activation and repression (25, 26). In this sense, the effective Bromo plays a key role in regulating the interaction between PHD3 and the regulator CyP33. This example also indicates that the H3K4me3-reading event can be associated with both activation and repression, thereby supporting the concept that histone modification-associated regulations are closely related to their cellular context (7).

Histone readers that interact with non-histone proteins have also been reported for the Pygo1 PHD finger (27) and TAF1 double Bromo (28) modules. The TAF1 double Bromo not only shows combinatorial readout for di/tetraacetylated histone tails as discussed above but also interacts directly with the ASF1 chaperone using a surface different from the acetyllysine-binding surface. ASF1 can bind the heterodimeric H3-H4 complex (29, 30), which has been proposed to function in the nucleosome assembly/disassembly pathway. ASF1-TAF1 (double Bromo) and ASF1-histone (H3-H4) complexes are mutually exclusive. The structural information, complemented with biological assays, suggests that transfer of ASF1, bound initially to the TAF1 double Bromo at the promoter region, to the histone (H3-H4), tetramer complex results in the disassembly of the nucleosome structure. In this example, hist-
The individual functions of the Gcn5p Bromo and the histone acetyltransferase domain are not directly coupled but are both required for the full-length protein to function properly. This study points out the difficulty in studying the reading and writing-erasing relationship in large multimodular proteins, especially for cases in which the two domains are separated in primary sequence and critical three-dimensional structural information is not available.

For those cases in which the reader and writer-eraser modules do show direct interaction based on structural information, the relationship between reading and writing events is prone to be correlated, as has been shown for PHF8 and KIAA1718 demethylases (36). PHF8 is an H3K9me1/2 and H4K20me1 demethylase (37, 38), which contains the typical catalytic JmjC domain together with a proximally positioned PHD finger that reads the H3K4me3 modification. The demethylase activity of PHF8 on H3K9me2 is modulated by methylation at H3K4, with PHF8 demethylase activity enhanced 12-fold in the presence of the H3K4me3 mark. How does H3K9me2-specific demethylase activity connect to the H3K4me3 modification? The structure of the PHF8 PHD-JmjC paired domain in complex with the dual-modified H3(1–24)K4me3K9me2 peptide provides a molecular explanation for the coordinated interplay between these histone modifications and the PHF8 PHD-JmjC pair (36). The PHD finger and JmjC domain are in close contact so that the H3K4me3-binding pocket in the PHD finger and the H3K9me2-specific demethylase pocket in the JmjC domain are positioned in close proximity. A single H3 peptide bearing both the K4me3 and K9me2 marks is positioned optimally within the extended binding surface of the paired module such that each modification is inserted into its respective binding pocket (Fig. 2B). As the PHF8 PHD finger is responsible mainly for recognition of the H3K4me3 mark, one anticipates that the enhanced binding affinity will increase the local concentration of the H3K9me2 mark, thereby leading to the enhanced demethylase activity. For the case of the KIAA1718 demethylase, whose PHD finger reads H3K4me3 and also makes close contacts with the JmjC domain, the binding pockets between these two domains are too far apart to accommodate both K4me3 and K9me2 modifications simultaneously on a single H3 peptide (36). Thus, for the KIAA1718 demethylase, the presence of the H3K4me3 modification inhibits the demethylase activity for H3K9me2 but enhances the activity for H3K27me2. The demethylase preferences of PHF8 and KIAA1718 are dictated by the reading/phd finger and the JmjC PHD JmjC pair (36). The PHD finger and JmjC domain are in close contact so that the H3K4me3-binding pocket in the PHD finger and the H3K9me2-specific demethylase pocket in the JmjC domain are positioned in close proximity. A single H3 peptide bearing both the K4me3 and K9me2 marks is positioned optimally within the extended binding surface of the paired module such that each modification is inserted into its respective binding pocket (Fig. 2B). As the PHF8 PHD finger is responsible mainly for recognition of the H3K4me3 mark, one anticipates that the enhanced binding affinity will increase the local concentration of the H3K9me2 mark, thereby leading to the enhanced demethylase activity. For the case of the KIAA1718 demethylase, whose PHD finger reads H3K4me3 and also makes close contacts with the JmjC domain, the binding pockets between these two domains are too far apart to accommodate both K4me3 and K9me2 modifications simultaneously on a single H3 peptide (36). Thus, for the KIAA1718 demethylase, the presence of the H3K4me3 modification inhibits the demethylase activity for H3K9me2 but enhances the activity for H3K27me2. The demethylase preferences of PHF8 and KIAA1718 are dictated by the reading module when the H3K4me3 mark is present (Fig. 2C), a concept validated by the available structural information, thereby providing a good example for understanding the coupled function of reading and erasing events on a specific histone pattern.

Reading beyond Histone Modifications

Many of the interactions between histone modifications and their effector modules display sequence specificity, i.e. residues flanking the modification are also important for the interaction. There are also some readers, such as most bromodomains, that show broad binding specificity for acetylysine-containing peptides (39, 40). Those histone reader modules that exhibit broad binding specificity may also be expected to bind non-histone...
proteins, as shown by the CBP Bromo and L3MBTL1 MBT domains (41, 42). If so, what is the mechanism for choosing between histone and non-histone modifications? A study on the Rsc4 tandem Bromo provides some clues about the regulation between reading histone and non-histone modifications (43). Both bromodomains of Rsc4 can read acetylated peptides, with the second Bromo of the pair specifically recognizing the H3K14ac mark, whereas the first Bromo reads its own K25ac modification (Fig. 2D). More interestingly, Rsc4 Lys-25 acetylation inhibits binding to H3K14ac, suggesting an autoregulatory mechanism of action by the tandem Bromo. This is also an example of negative cooperativity in reading two modifications. Although a structural explanation for this negative cooperativity is not readily apparent, the autoregulatory mechanism is strongly supported by both in vivo mutational assays and in vitro pulldown measurements. This example indicates that non-histone modifications can also play an important role in regulating the function of effector proteins. In fact, these non-histone PTMs exist in abundance in many regulatory proteins, such as p53, G9a, and RNA polymerase II, many of which can also be potential targets of histone modifications. For the TRIM24 PHD-Bromo cassette, simultaneous binding of H3K4me0 and H3K23ac is greatly facilitated by a smoothly extended binding surface. Another feature of paired modules is that there are hundreds of combinations of effector modules in nature, our understanding of histone communication is still at a preliminary stage. In addition, most of the paired modules are only part of large multimodular proteins or of complexes they reside in. What happens when three or more histone modifications are involved, and will these histone modifications be read simultaneously or in a sequential order?

Another question relates to the extent to which DNA or RNA components are involved in epigenetic regulation. Research on DNA methyltransferases revealed that Dnmt3L is able to read unmethylated Lys-4 on H3, which connects the histone-binding event to de novo DNA methylation through the link between Dnmt3L and Dnmt3a (49, 50). In addition, there are also quite a few paired chromatin-associated modules containing both potential DNA-binding domains and histone-binding domains such that research on these proteins could provide insights into the cross-talk between histone and DNA. Small siRNAs and noncoding RNAs are also well known epigenetic regulators, with potential connections between histone recognition and RNA regulation, and are likely to become a fascinating area for future research (51, 52). Furthermore, considering that histone modification patterns can also change during different stages of the cell cycle and cell development, an understanding of dynamic histone communication events as a function of the cell cycle or different cell lineage may help in the depiction of a four-dimensional model of histone communication networks with their regulators.

Structural biology and cell biology methods have long been shown to play an important role in studying both the in vitro and in vivo binding processes between histone modifications and their effector proteins. Like ChIP-on-chip and ChIP sequencing, ChIP-based bioinformatics analysis has enabled the mapping and understanding of histone modifications at the genomic level. When combined with new technology, classical methods have greatly enhanced our understanding of the complexities associated with the histone code.
MINIREVIEW: Readout of Dual Histone Modifications

extent, in vivo and/or genetics analysis indicates that dysregulation of PTMs may be the causal reason for the onset of multiple human diseases (53, 54). Recently, pioneering research on the role of inhibitors of the BRD4 Bromo in cancer therapy has indicated that histone readers can also serve as targets for drug design (55, 56). A deeper understanding of the mechanism of histone cross-talk and its regulation, especially at the nucleosome level, may help in structure-based rational design of drugs to treat histone dysregulation-related human diseases.

Acknowledgment—We thank Dr. Htaitao Li for helpful comments.

REFERENCES

1. Luger, K., Mader, A. W., Richmond, R. K., Sargent, D. F., and Richmond, T. J. (1997) Nature 389, 251–260

2. Thoma, F., Koller, T., and Khug, A. (1979) J. Cell Biol. 83, 403–427

3. Jenuwein, T., and Allis, C. D. (2001) Science 293, 1074–1080

4. Seet, B. T., Dikic, I., Zhou, M. M., and Pawson, T. (2006) Nat. Rev. Mol. Cell Biol. 7, 473–483

5. Taverna, S. D., Li, H., Ruby, T. J., Allis, C. D., and Patel, D. J. (2007) Nat. Struct. Mol. Biol. 14, 1025–1040

6. Kouzarides, T. (2007) Cell 128, 693–705

7. Lee, J. S., Smith, E., and Shilatifard, A. (2010) Mol. Cell 37, 927–932

8. Suganuma, T., and Workman, J. L. (2008) Nat. Rev. Mol. Cell Biol. 9, 438–446

9. Fair, K., Anderson, M., Bulanova, E. M., Hi, T., Tropschug, M., and Diaz, M. O. (2001) Mol. Cell. Biol. 21, 3589–3597

10. Morinie`re, J., Rousseaux, S., Steuerwald, U., Soler-Lo´pez, M., Curtet, S., Andra, F. B., Gonzales, M., Lan, F., Ongusaha, P. P., Huarte, M., Yaghi, N. K., Lim, H., Garcia, B. A., Brizuela, L., Zhao, K., Roberts, T. M., and Shi, Y. (2010) Nature 466, 503–507

11. Akai, Y., Adachi, N., Hayashi, Y., Eitoku, M., Sano, N., Natsume, R., Kudo, M. J., Zhou, M. M., and Rauscher, F. J., 3rd (2007) Mol. Cell 28, 682–685

12. Wu, L., Tanasa, B., Tyurina, O. V., Zhou, T. Y., Gassmann, R., Liu, W. T., Ohgi, K. A., Benner, C., Garcia-Bassets, I., Aggarwal, A. K., Desai, A., Dorrestein, P. C., Glass, C. K. and Rosenfeld, M. G. (2010) Nature 466, 508–512

13. Zeng, L., Zhang, Q., Li, S., Plotnikov, A. N., Walsh, M. J., and Zhou, M. M. (2010) Nature 466, 258–262

14. Li, H., Ilin, S., Wang, W., Duncan, E. M., Wysocko, J., Allis, C. D., and Patel, D. J. (2006) Nature 442, 91–95

15. Morinie`re, J., Rousseaux, S., Steuerwald, U., Soler-Lo´pez, M., Curtet, S., Vitte, A. L., Govin, J., Gaucher, J., Sadoul, K., Hart, D. J., Kriegsveld, I., Khochbin, S., Mu¨ller, C. W., and Petosa, C. (2009) Nature 461, 664–668

16. Xia, Z. B., Anderson, M., Diaz, M. O., and Zeleznik-Le, N. J. (2003) J. Biol. Chem. 278, 823–837

17. Akai, Y., Adachi, N., Hayashi, Y., Eitoku, M., Sano, N., Natsume, R., Kudo, M. J., Zhou, M. M., and Rauscher, F. J., 3rd (2007) Cell Biol. 1025–1040

18. Liu, W., Tanasa, B., Tyurina, O. V., Zhou, T. Y., Gassmann, R., Liu, W. T., Ohgi, K. A., Benner, C., Garcia-Bassets, I., Aggarwal, A. K., Desai, A., Dorrestein, P. C., Glass, C. K. and Rosenfeld, M. G. (2010) Nature 466, 508–512

19. Qi, H. J., Sarkissian, M., Hu, G. Q., Wang, Z., Bhattacharjee, A., Gordon, D. B., Gonzales, M., Lan, F., Ongusaha, P. P., Huarte, M., Yaghi, N. K., Lim, H., Garcia, B. A., Brizuela, L., Zhao, K., Roberts, T. M., and Shi, Y. (2010) Nature 466, 503–507

20. vanDemark, A. P., Kasten, M. M., Ferris, N., Heroux, A., Plattner, W., Brizuela, L., Zhao, K., Roberts, T. M., and Shi, Y. (2010) Nature 466, 503–507

21. vanDemark, A. P., Kasten, M. M., Ferris, E., Plattner, W., Brizuela, L., Zhao, K., Roberts, T. M., and Shi, Y. (2010) Nature 466, 503–507

22. Ruthenburg, A. J., Allis, C. D., and Patel, D. J. (2007) Mol. Cell 28, 682–685

23. Li, H., Fischle, W., Wang, W., Duncan, E. M., Liang, L., Murakami-Ishibe, S., Allis, C. D., and Patel, D. J. (2007) Mol. Cell 28, 677–691

24. Botuyan, M. V., Lee, J., Ward, I. M., Kim, J. E., Thompson, J. R., Chen, J., Spooner, E., Li, E., Zhang, G., Coliaocavo, M., and Shi, Y. (2006) Cell 125, 467–481

25. Lee, J., Thompson, J. R., Botuyan, M. V., and Mer, G. (2008) Nat. Struct. Mol. Biol. 15, 109–111