Eukaryotic genomes are presented to cellular factors in the form of chromatin, wherein a nucleosome serves as the fundamental subunit, which consists of DNA wrapped around a core of histone proteins. Access to genetic information is controlled in part by the posttranslational modification of histones and 5-methylcytosine methylation of DNA. Distinct sets of these chromatin marks are associated with most DNA transactions and have been implicated as carriers of epigenetic identity, although precise mechanisms connecting the marks to functional consequences are only beginning to emerge.

Combinations of histone posttranslational modifications and DNA methylation appear to regulate the physical properties of the chromatin fibre, either directly or via specific protein adaptors termed 'effectors'. Recent studies have shown that these effector modules bind to histone tails in a modification state-specific manner. Emerging hints that many putative effector modules coexist within the same protein complex suggest that multivalent engagement of chromatin substrates may be a functionally important phenomenon.

### Marks, modules and multivalency

Histones can be covalently modified by the addition of a variety of chemical appendages that create binding sites for specific protein modules. The top panel illustrates the chemical structures of the small modifications that have been most intensively studied. Many examples of histone-binding, or effector, modules are known, shown in the middle panel, and are representative examples of each different class of protein fold (grey) in complex with its cognate modified histone-binding partner (yellow). See also Table 1.

In most cases, resolution of the binding pocket (red) of a module dictates the modification state of a mark that is preferentially bound, while residues outside the binding pocket contribute to both of the histone sequence specificity. In several instances, similar folds bind different marks; for example, tudor domains can bind Kme2 (H3K4me2) or Kme3 (H3K4me3), and PHD fingers can bind exclusively Kme2 (H3K4me2) or Kme3 (H3K4me3). The structural underpinnings of this multistate specific readout (Kme1, Kme2, Kme3 on Kme2, Kme3) are shown by the four different structures displayed in the ‘Different methyl state recognition’ panel. In those cases where the inhibitor is not in contact to the single histone peptide, and its function. For example, the Kme1, Kme2, or the context of the N terminus of H3 (Kme1), can be bound by PHD fingers of proteins or antibodies that other activate (for example, the BPTF subset of the NURF complex in human gene remodeling substituting transcription or promote gene expression for example, the INGA subset of the Hoxa-Enhancer complex is involved in repression following DNA damage). Analyses of native histone modification states has increased our appreciation that histone PTMs occur as protein complexes rather than in isolation which may help account for this paradox. Perhaps multivalent interactions with diverse patterns dictate composite specificity and enhance the affinity of histone-associated complexes.

### Themes of recognition

Emerging themes in the molecular recognition of modified histones are illustrated in the context of the PHD finger of BPTF, and appear to reflect the product of convergent evolution.

- The histone peptide often engages the binding module in an induced cation-π cage as also depicted in the ‘Different methyl state recognition’ panel.
- Residues in the N- or C-terminus with respect to the histone mark are often crucial determinants of binding sequence specificity.
- Additional specificity may be recognized by the sequence of a free N terminus.

### Modes of multivalent chromatin engagement

Histone-binding modules are often found in the same protein with other binding modules, suggesting a means to simultaneously interact with many different histone tails. Multiple modules engage marks on different histone tails.

- Discontinuous bridging: Multiple modules engage marks on different histone tails.
- Adjacent bridging: Multiple modules engage marks on adjacent histone tails.

### Module connectivity

Module connectivity is driven by different aspects of the bound module pocket and the chemical nature of the bound chromatin mark. The top panel illustrates the chemical structures of the small modifications that have been most intensively studied. Many examples of histone-binding, or effector, modules are known, shown in the middle panel, and are representative examples of each different class of protein fold (grey) in complex with its cognate modified histone-binding partner (yellow). See also Table 2.

### Known chromatin marks

- Chromatin marks are illustrated in the context of the PHD finger of BPTF, and appear to reflect the product of convergent evolution.
- Discontinuous bridging: Multiple modules engage marks on different histone tails.
- Adjacent bridging: Multiple modules engage marks on adjacent histone tails.

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